Mathematics and Physics of Cancer: Questions

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KITP Colloquium

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1) Cancer statistics and the multi-stage model.

2) Cancer microevolution and clonal expansion.

3) Metastasis: “Weinberg model” and homeostatic pressure.

I)

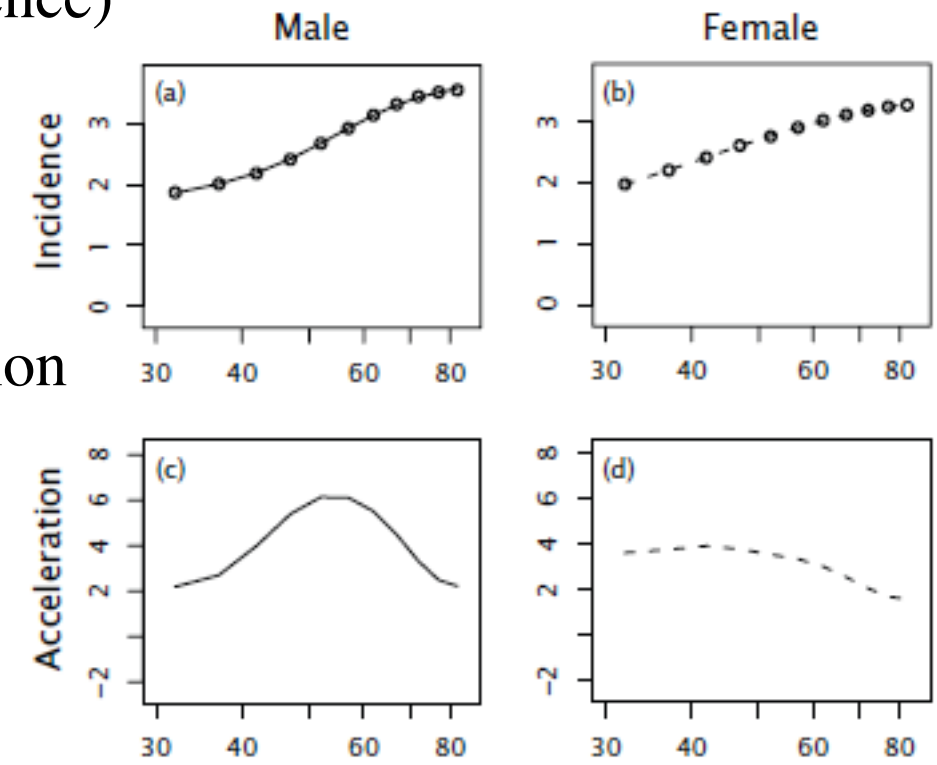
Cancer Statistics

All cancer types,
US citizens, Caucasian

Incidence ≡ total # US cancer cases/10^5 citizens

Acceleration ≡ Incidence/age slope on log-log scale.

log(Incidence)



Acceleration

log(Age)

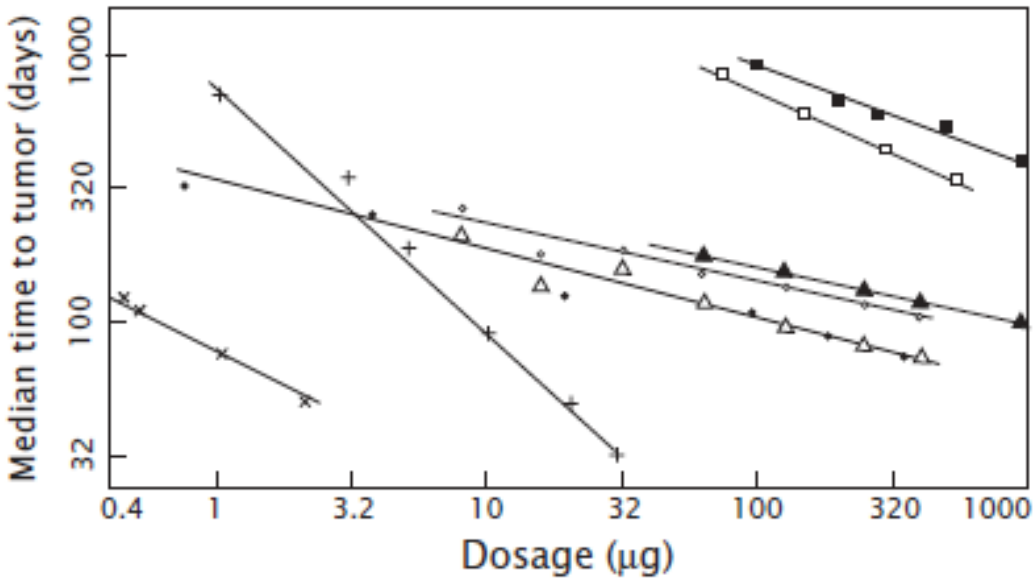
Frank, Dynamics of cancer

Power-Law: $I(t) \propto nb(D)t^{n-1}$ Acceleration = n-1

$D \equiv$ amount of carcinogen/day

$M \equiv$ median duration to tumor onset

$$b(D) = \frac{\ln 2}{M(D)^n}$$



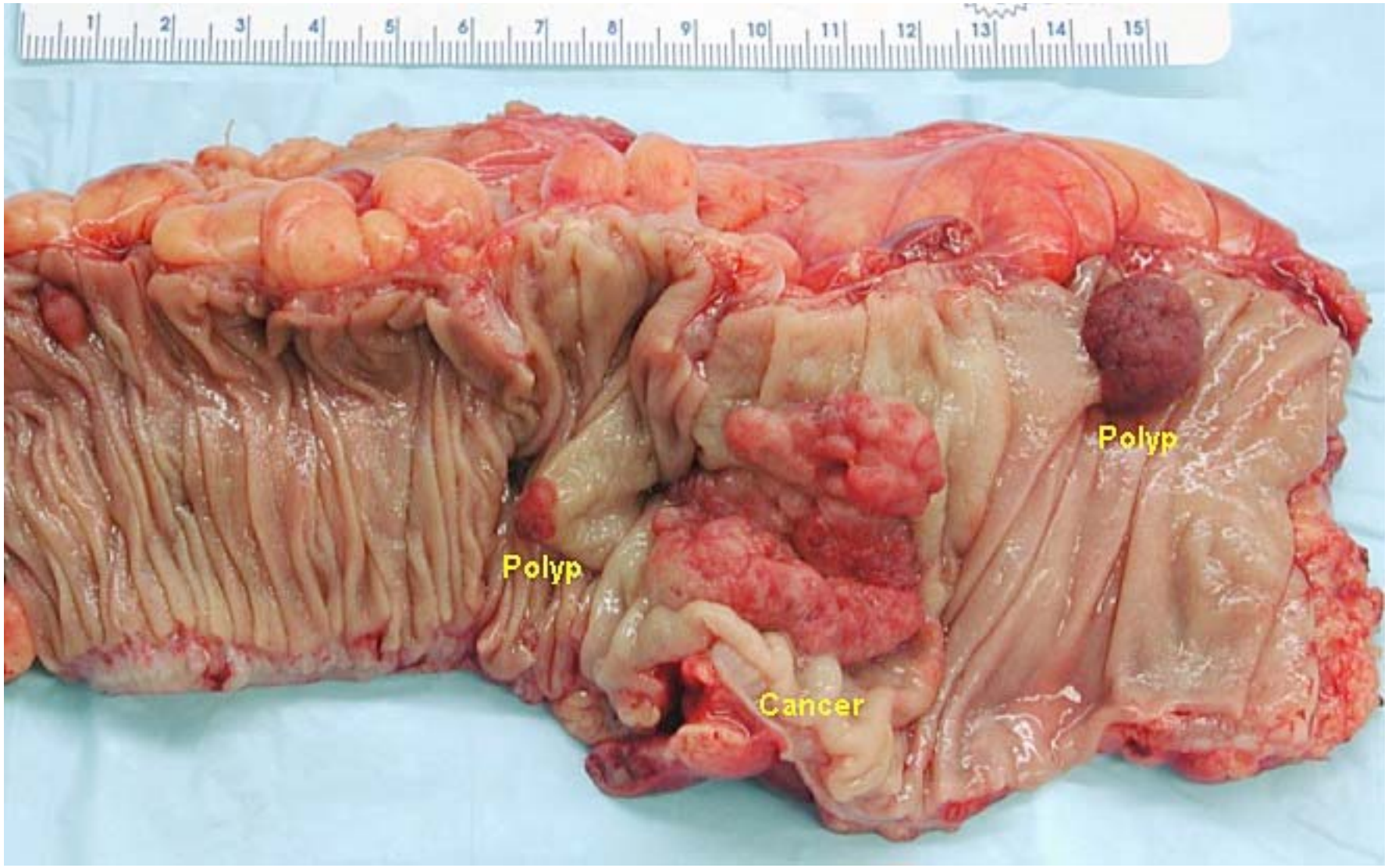
"dose-response"

"Druckney Formula" $DM^s = k$

Colorectal cancer

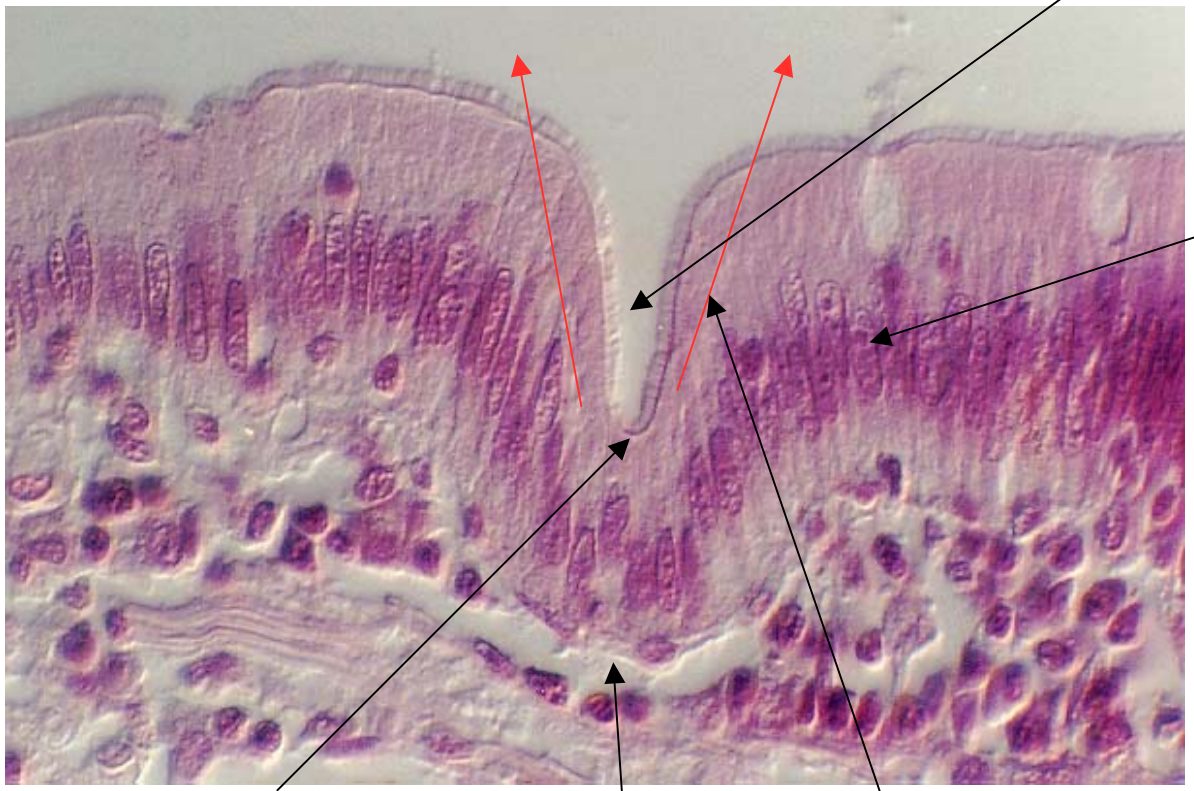
pedunculated polyp

sessile polyp



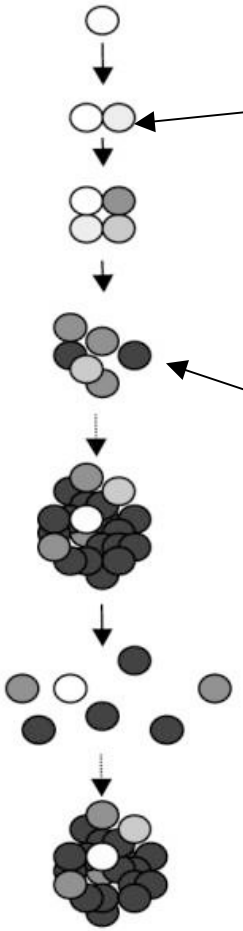
Polyp (“adenoma”) ⟶ Carcinoma ⟶ Metastasis (liver)

Normal colon epithelial tissue: highly organized



- Each crypt*: separate lineage of epithelial cells*.
- Normal epithelial cells respond to anti-growth signals.
- Cells with damaged DNA and "misplaced" cells: commit suicide. ("apoptosis")

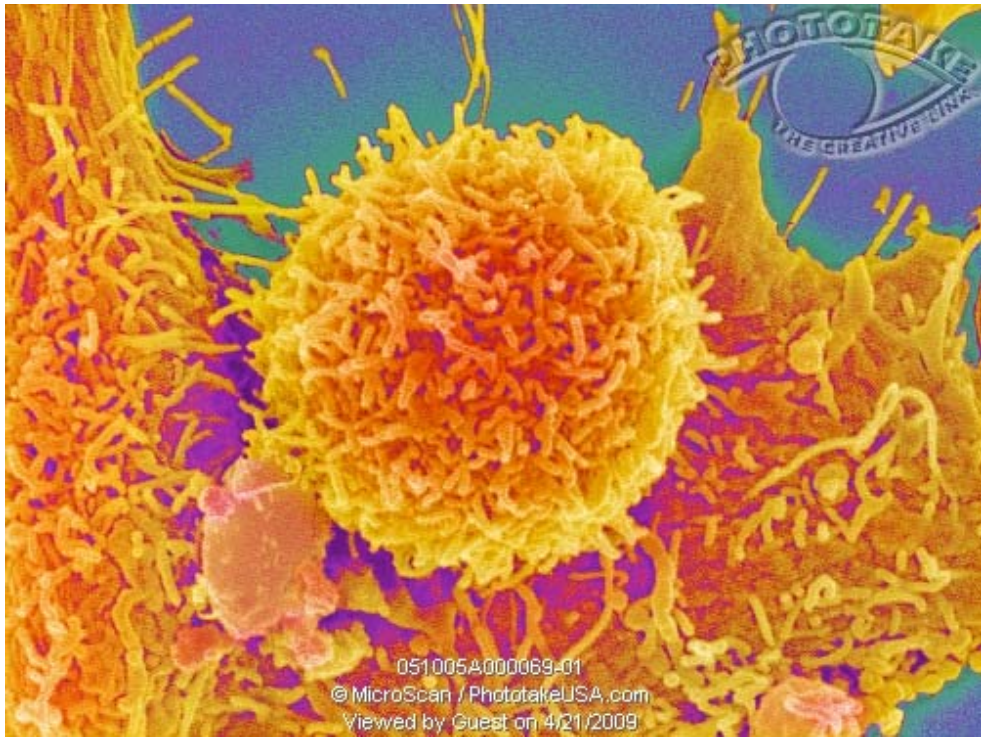
stem cell: *unlimited* number of divisions

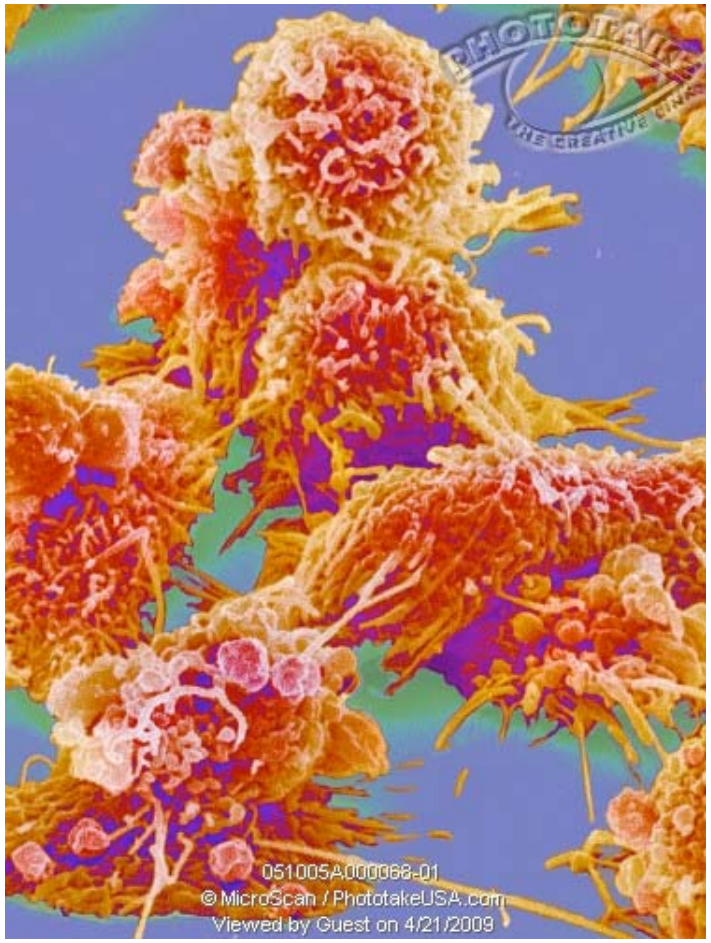


progenitor cell: large but *limited* number of divisions.

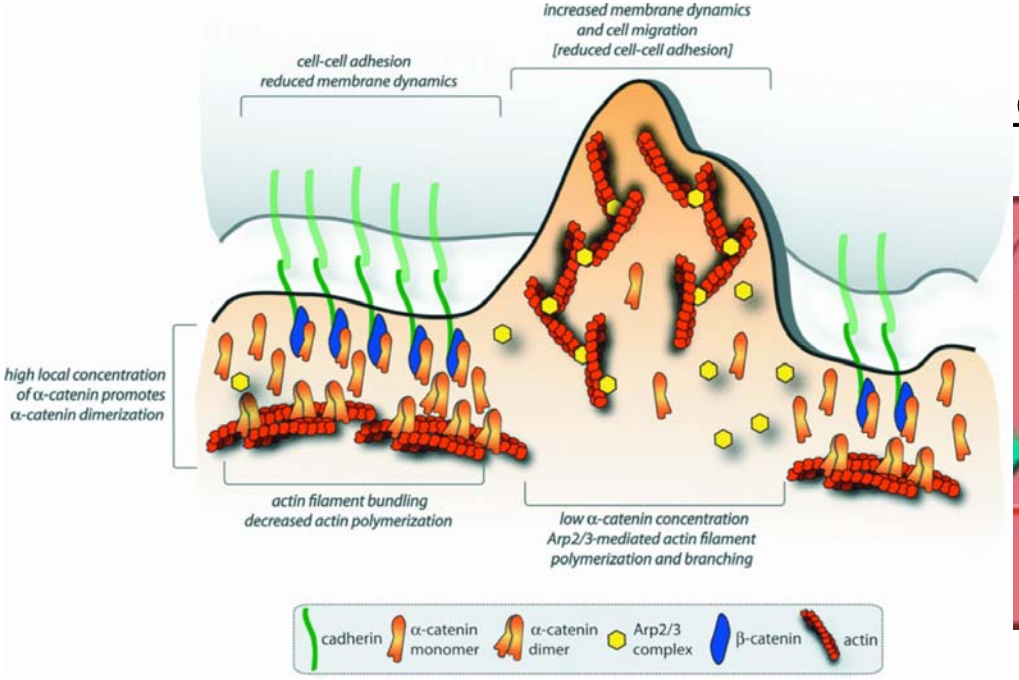
differentiated cell: few divisions

colon cancer cells: disorganized (x 3000, SEM)

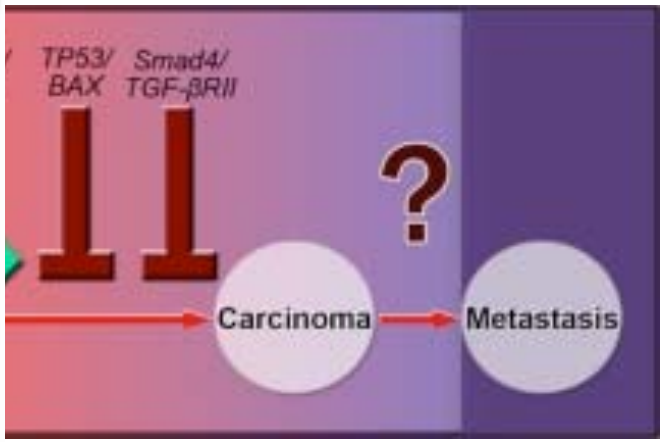




- Cells do not respond to anti-growth signals.
- Cells with damaged DNA do not undergo apoptosis.
- Cells can carry *hundreds* of mutations.



<u>colorectal cancer</u> (Vogelstein group)



 80%

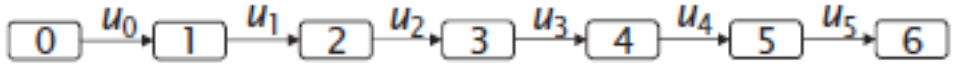
APC/β-catenin: Regulates # cell divisions. Cell adhesion

K-Ras: "*oncogene*" Activates cell growth and division.

p53: "*tumor suppressor gene*". Repairs mutations, initiates apoptosis of cells with damaged DNA

Armitage-Doll Multistage Model

Cancerous lineage: accumulate sequence of specific mutations ("hits").

No mutations 

← Cancer

$x_i(t)$ = # stem cells having i mutations at time t.
$x_i(0) = x_0(0)\,\delta_{i,0}$: # initial cell lineages/stem cells

u = mutation rate of a gene (~10^{-7} per generation for colorectal cancer)

"Master Equation"

$$\frac{dx_0(t)}{dt} = -ux_0(t)$$
$$\frac{dx_j(t)}{dt} = ux_{j-1}(t) - ux_j(t)$$
$$\frac{dx_n(t)}{dt} = ux_{n-1}(t)$$

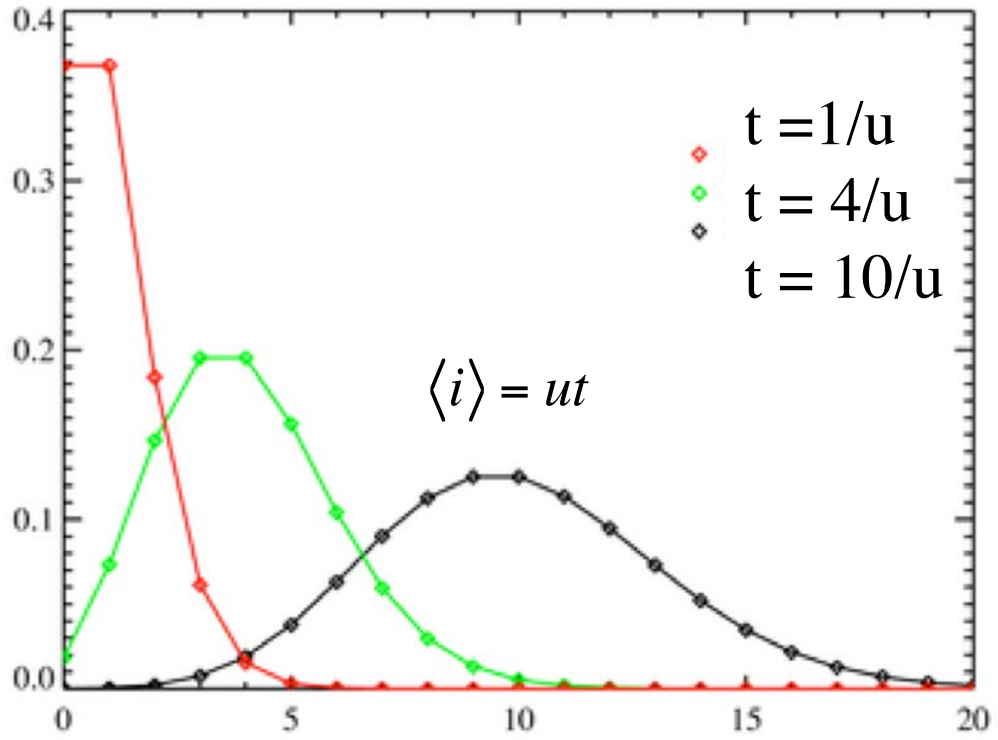
Frank, Dynamics of cancer

* *Size* lineage: not important.

Solution: $x_i(t)/x_0(0) = \dfrac{e^{-ut}(ut)^i}{i!}$ *Poisson Distribution*

sequential

x_i



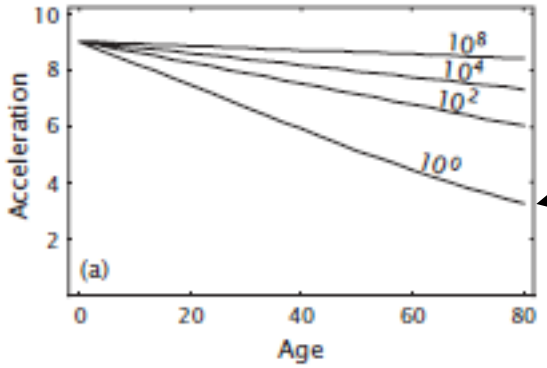
i

i) Incidence :

$$I(t) = \frac{dx_n(t)/dt}{\sum_{i=0}^{n-1} x_i(t)} = \frac{u(ut)^{n-1}}{(n-1)!\sum_{i=0}^{n-1}\frac{(ut)^i}{i!}}$$

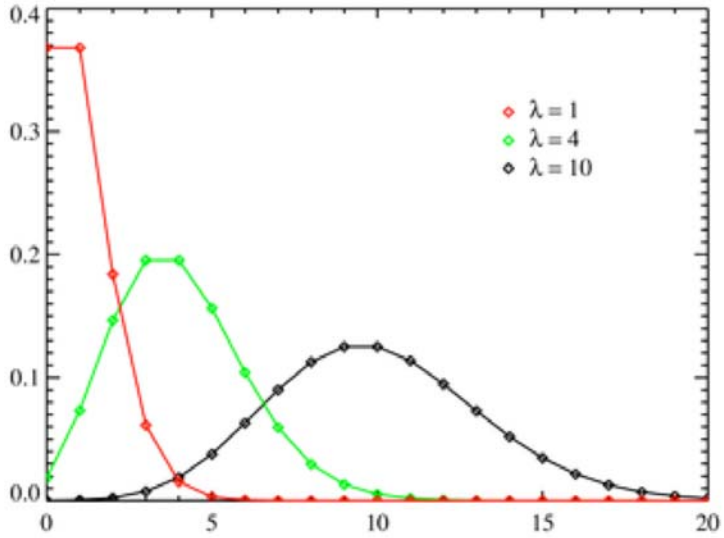
Early times: power-law, Acceleration = n-1

ii) Late times: *acceleration decreases monotonically with age.*



u = 0.008/year

u = 0.08/year



* Tests of the Multistage Model:

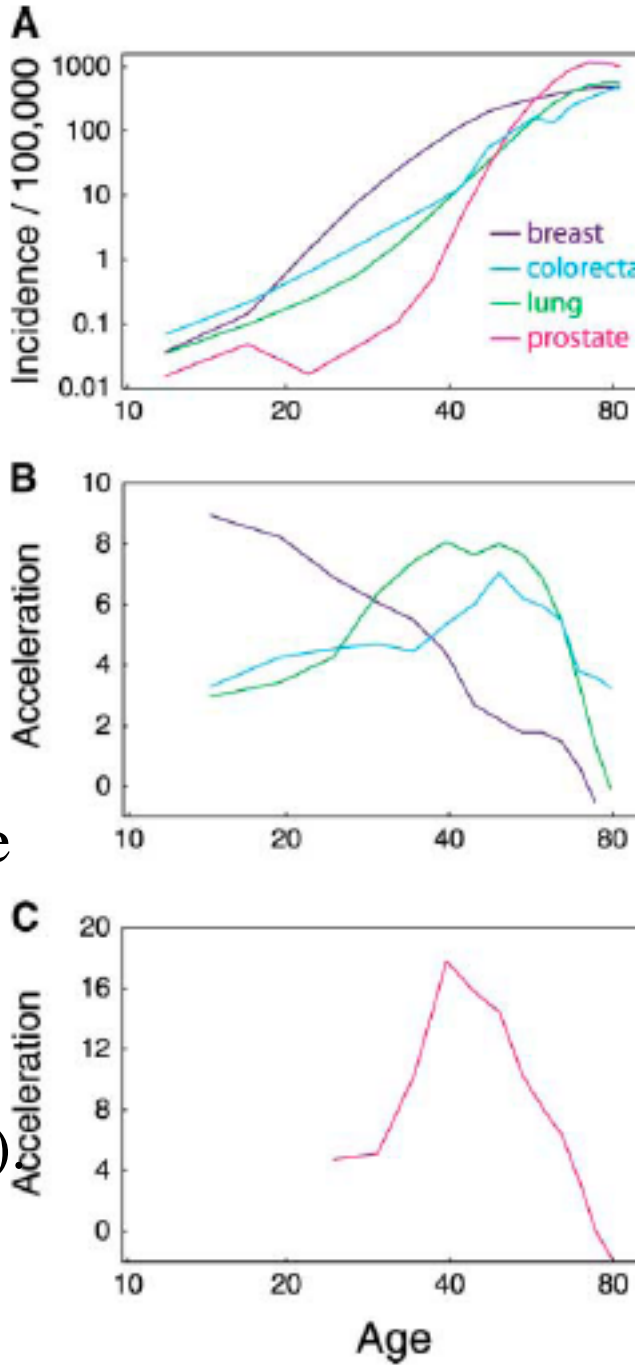
i) Inherited vs. sporadic tumors: n->n+1
ii) Retinablastoma: n=2

(Knudson, 1970-1990)

* Problems with the Multistage Model:

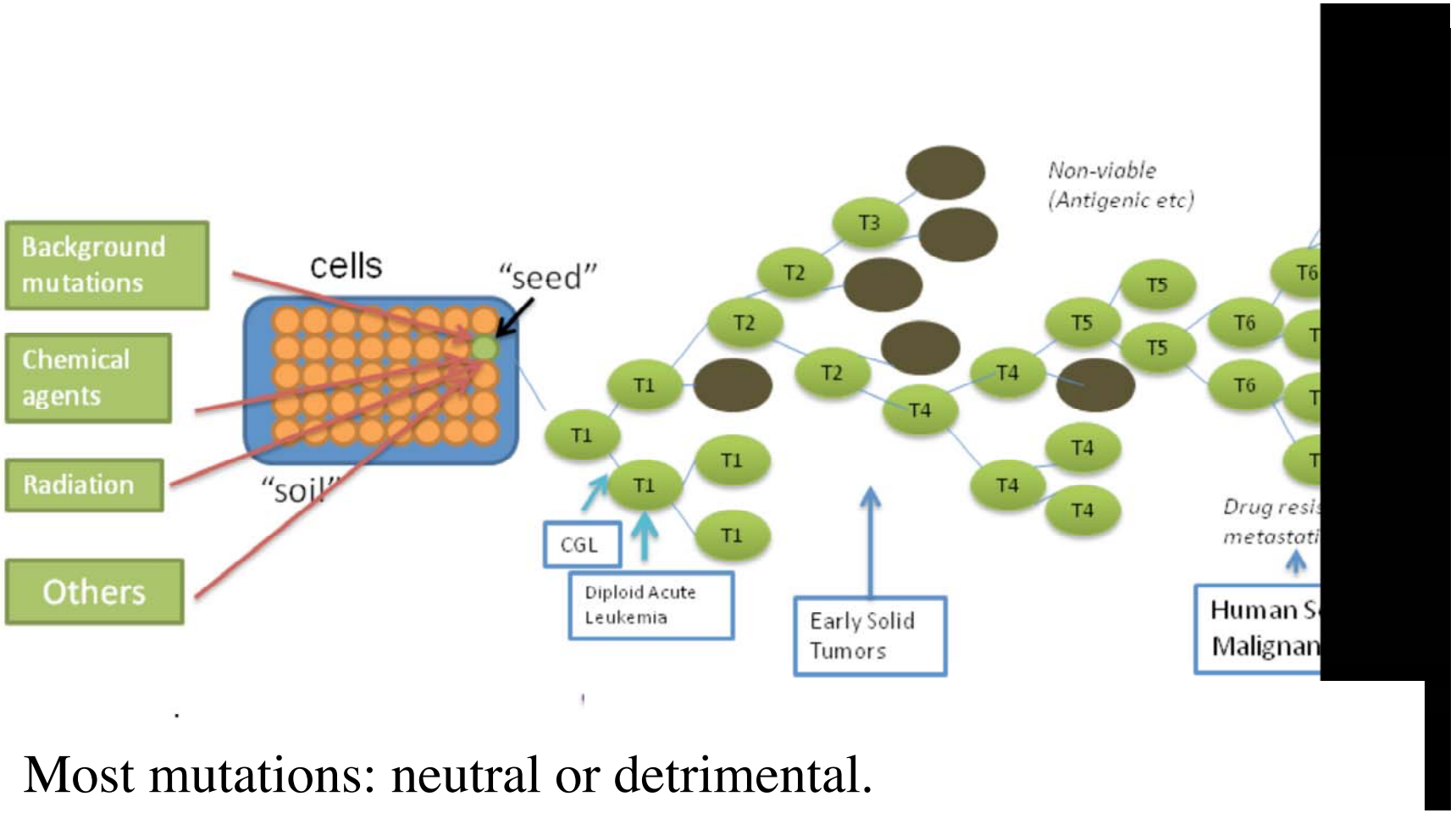
1) For *u* of about 10^{-7} per gene per generation, an incidence of $(ut)^{n-1}$ is *much too low* for large n (6, 7...) cancers (Loeb, 2001)

2) Acceleration of certain cancers show pronounced *maxima*. (colorectal, prostate, lung)



II) Microevolution and Clonal Expansion

Nowell, 1970

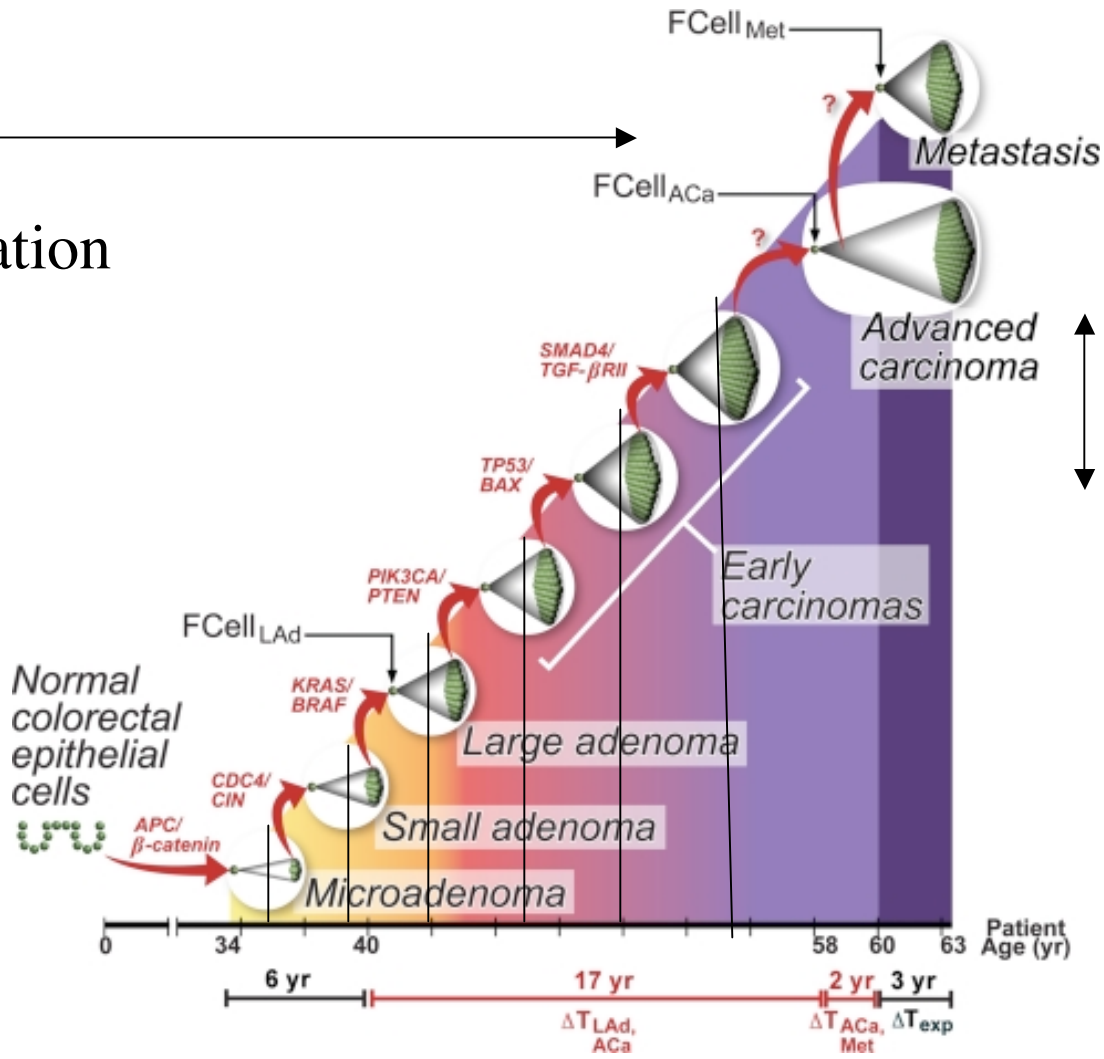


- Most mutations: neutral or detrimental.
- Some rare mutations are "beneficial": *increased division rate*.
- Number of cells with that mutation grows: *clonal expansion*.
- *Cancer clones evolve by Darwinian natural selection.*

Colorectal cancer clonal expansions : "lesion sequencing" all mutations

- From *total #* of mutations of clone k compared to k-1: estimate founding date of clone k: "*molecular clock*"

no clear mutation signature



(Jones et al., 2008)

clone size

Generalized Multistage Model

Current Biology, Vol. 14, 242–246, February 3, 2004,

$$\frac{dx_0(t)}{dt} = -u_0(t)x_0(t)$$

$$\frac{dx_j(t)}{dt} = u_{j-1}(t)x_{j-1}(t) - u_j(t)x_j(t)$$

$$\frac{dx_n(t)}{dt} = u_{n-1}(t)x_{n-1}(t)$$

lineage transition rates: proportional to mean lineage size $\langle N_k \rangle$

$u_k(t) \sim u \langle N_k(t) \rangle$ averaged over clone foundation times

$N_k(t-s)$: *size* of cell lineage/clone at time t with k mutations.

Stochastic quantity: time s of clone foundation is random.

$$\frac{d}{dt}N_k = r_k N_k\left(1 - N_k / K_k\right)$$

r_k = clone division rate

K_k = maximum size

time of foundation of lineage k.

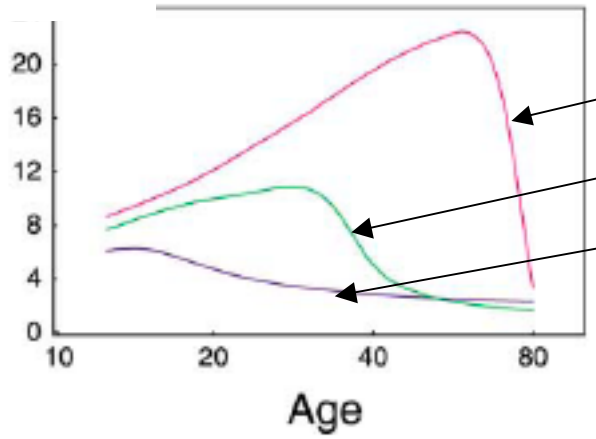
lineage size at t

$$x_k(t)\langle N_k(t)\rangle = \int_0^t u_{k-1}(s)\,x_{k-1}(s)\exp\left(-u\int_s^t N_k(\alpha)\,d\alpha\right) N_k(t-s)\,ds$$

probability *no* transition
k -> k+1 between times s & t

* recursive definition, "mean-field"

Acceleration



3 expansions

2 expansions

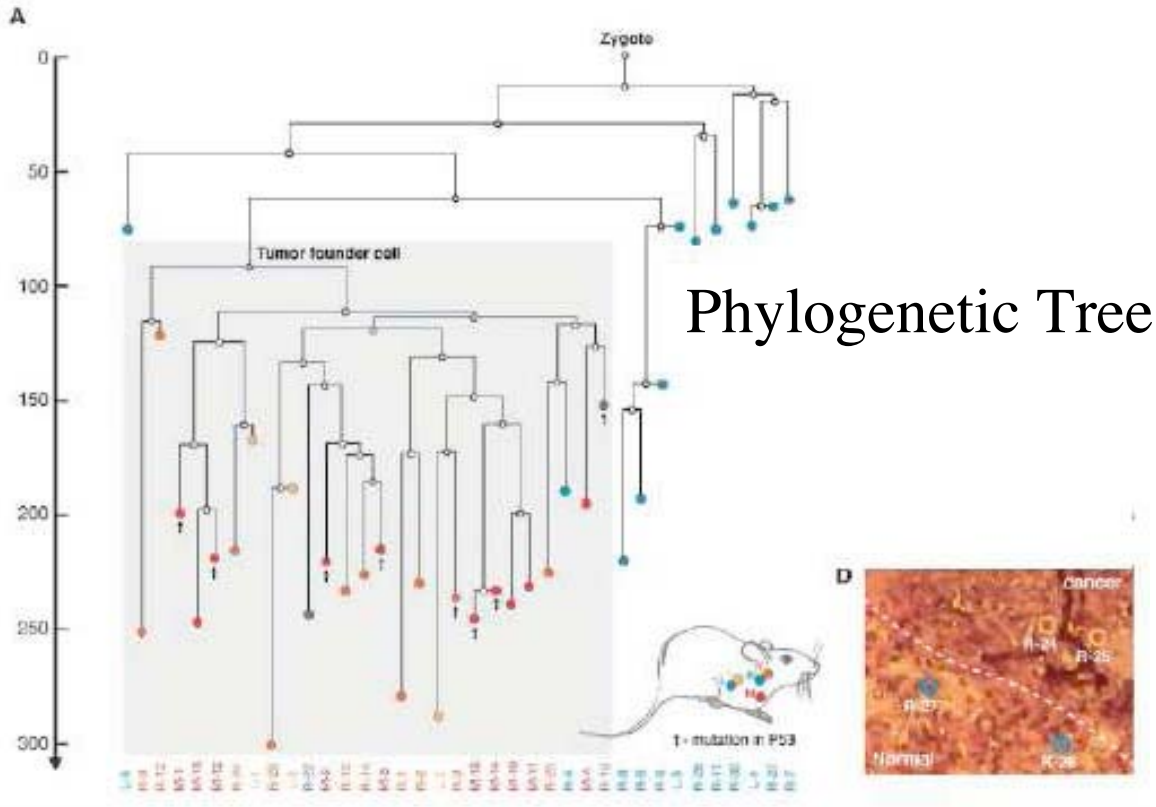
1 expansion

Clone size matters.

Small u and acceleration problems solved?

Question:

* Measure # generations/clone (“micro-satellite mutations” clock)



(Frumkin et al., 2009)

Phylogenetic Tree (mouse lung cancer)

* Assumption of unrestricted cancer cell division: *cancer much too large*.

* What fraction of tumor cells are “stem-like”?

    * Can early progenitor cells start clonal expansion?

      Probably not for early colorectal cancer: Nature Reviews Cancer 9, 2 (01 February 2009)

* Is clonal expansion important *not* because of size but because it increases stem-cell division rates? $u_k(t) \propto \frac{d}{dt} \log \langle N_k(t) \rangle$

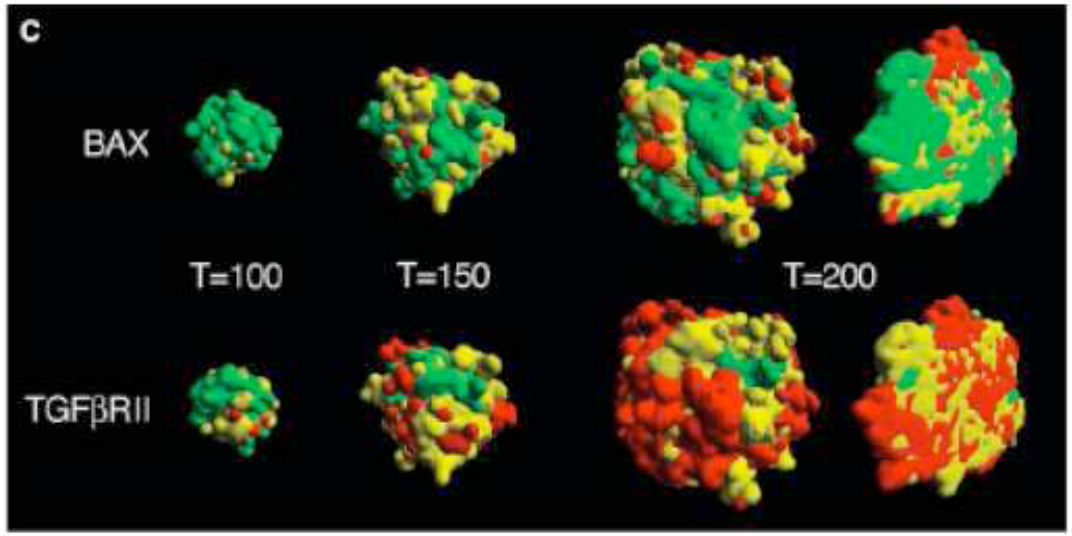
* Healing after repeated tissue insult accelerates cancer development.

Ganguly R, Puri IK (February 2006). "Mathematical model for the cancer stem cell hypothesis". Cell proliferation 39 (1): 3–14

Natural Selection

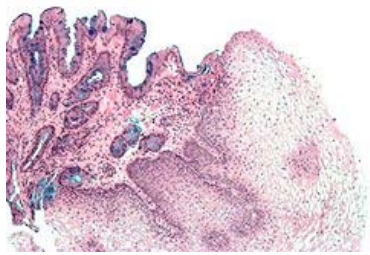
* Multistage models neglect *competition* between clones for space and nutrient. Important? (Gatenby and Vincent, 2003)

* Cancer: an ecological community of clones?



Ecological Diversity

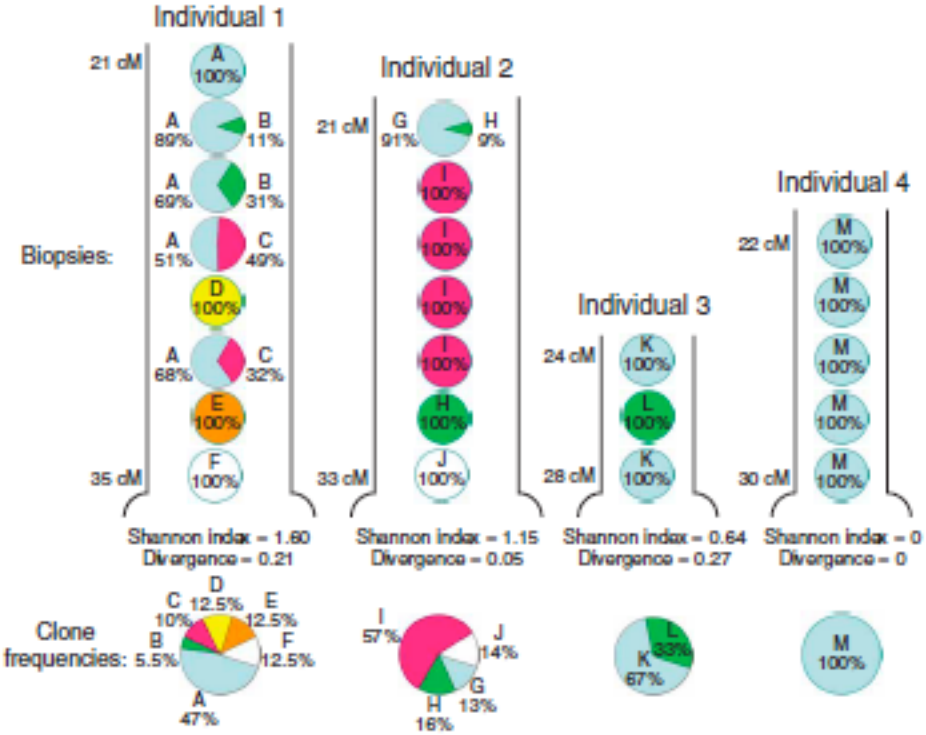
"Barrett's esophagus"



- Growth of esophagus ("neoplasm").
- risk of transition to cancer: 0. 5% per patient per year.

A: p53 & D9S1121 mutations.
B: A + chromosome abnormality.
C: A + tetraploidy.
D: A + 2 other D9S mutations.

Biopsy clonal population:
(Maley et al., 2004)

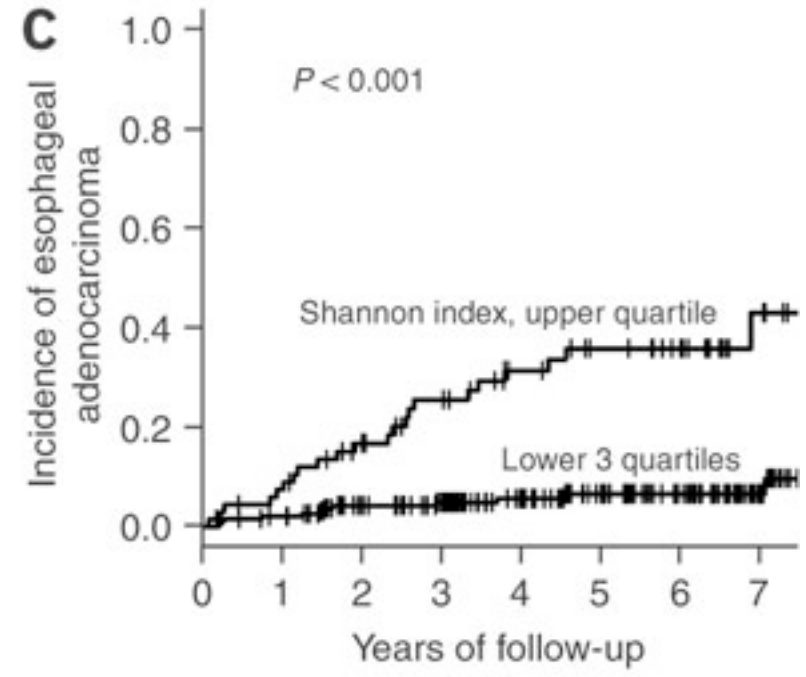


Measure *frequency* p_k of clone k:

Shannon Diversity Index: $H = -\sum_k p_k \ln p_k$

* maximized if (i) there are many clones (ii) all of similar size.

"Kaplan-Meier Plot"



- Diversity index: good predictor for transition to cancer for Barrett's.
- Number of clones, genetic divergence between clones also work.

Question:

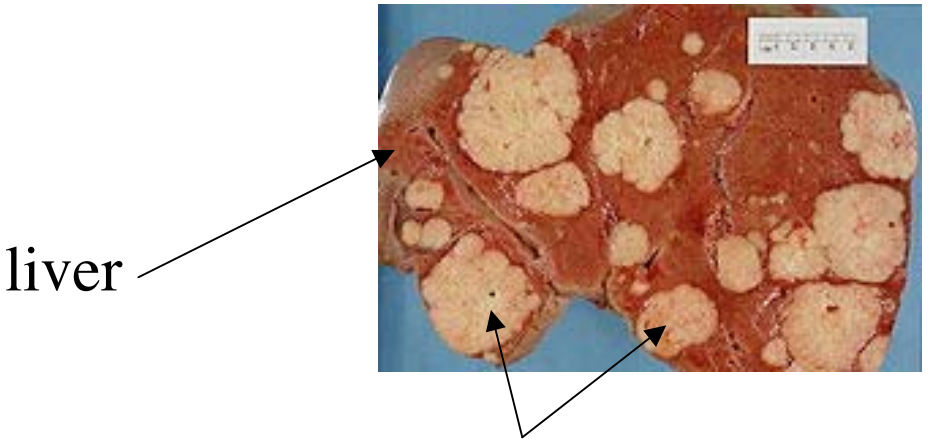
What is the optimal game strategy for a cancer?
(Shibata, commentary)

A) Maximize clonal diversity: more efficient search for combinations of mutations that have high cell division rate. **Low clone size**. Minimal clonal competition.

or

B) Maximize clone size: larger clone size increases probability for making the *next* hit of the mutation sequence. **Low diversity**.

III) Metastasis



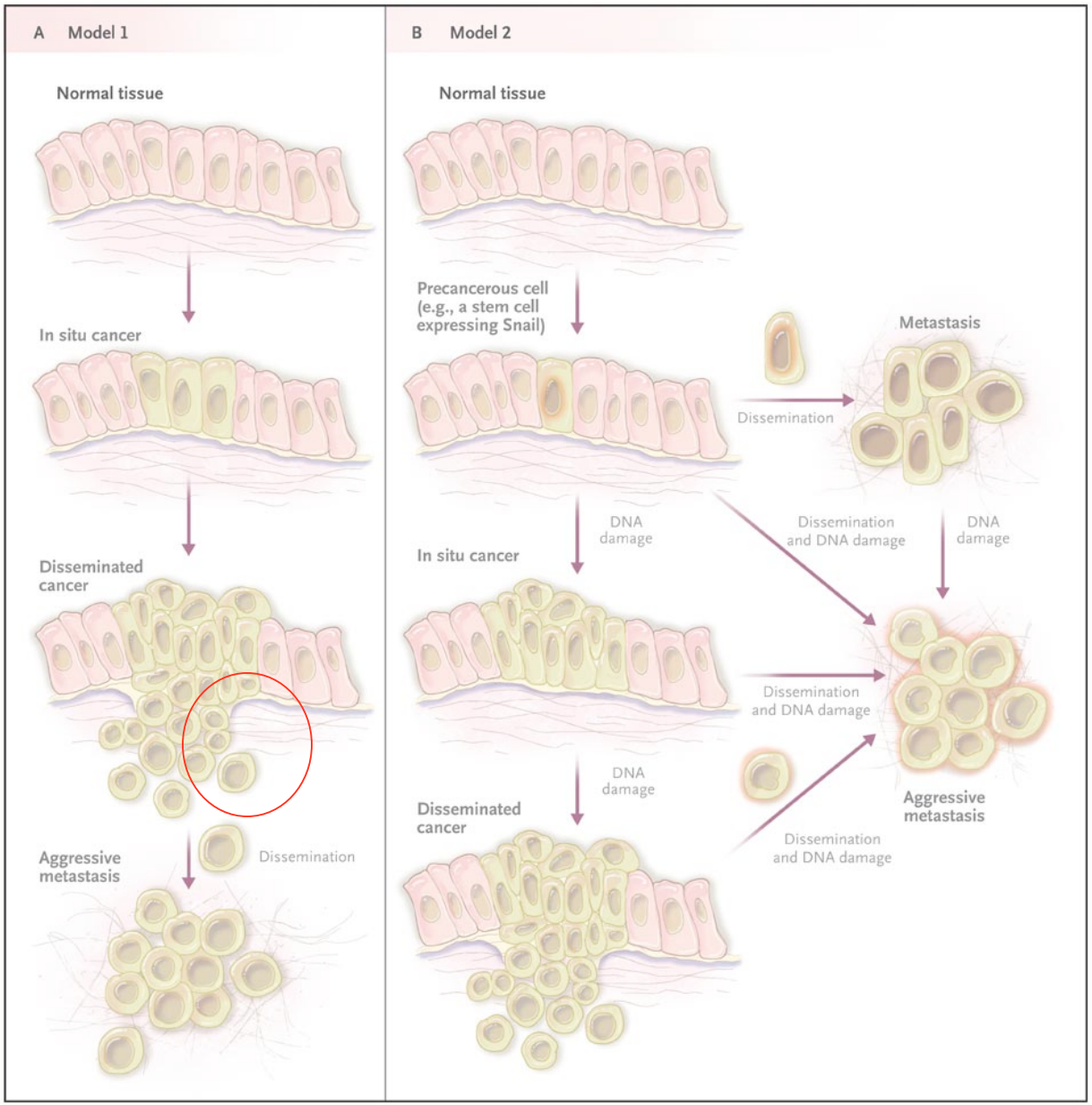
liver tumors, from a pancreatic tumor

- Metastasis main cause of cancer mortality. No clear mutation signature.
- Many cancer cells leave a colorectal cancer: “seeds”.
- *Small fraction* (1/1000) grow new tumors on *specific* organs: “soil”.
- Cells secreted by a tumor are *motile*. ***No longer epithelial cells***. Resemble cells of “loose connective tissue” (mesenchyme).

Classical model

time

mutations



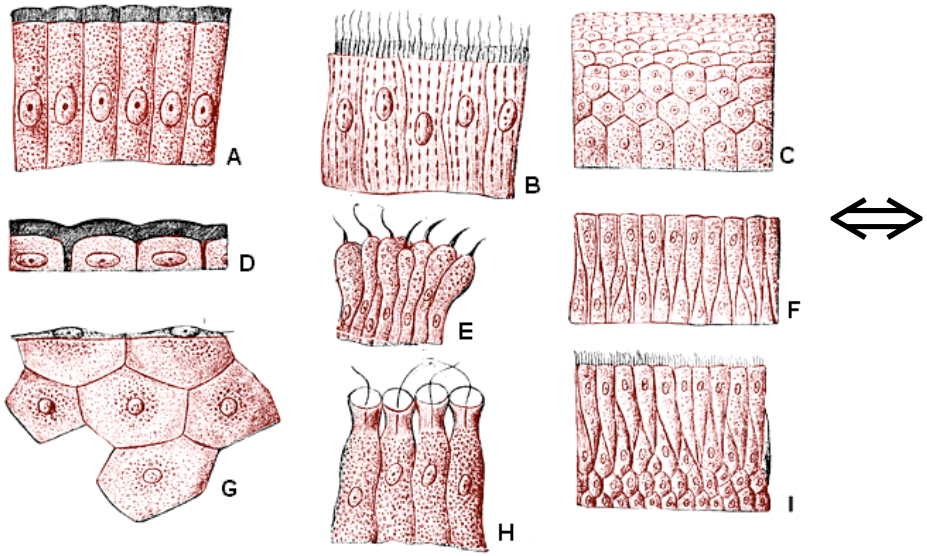
Weinberg model.

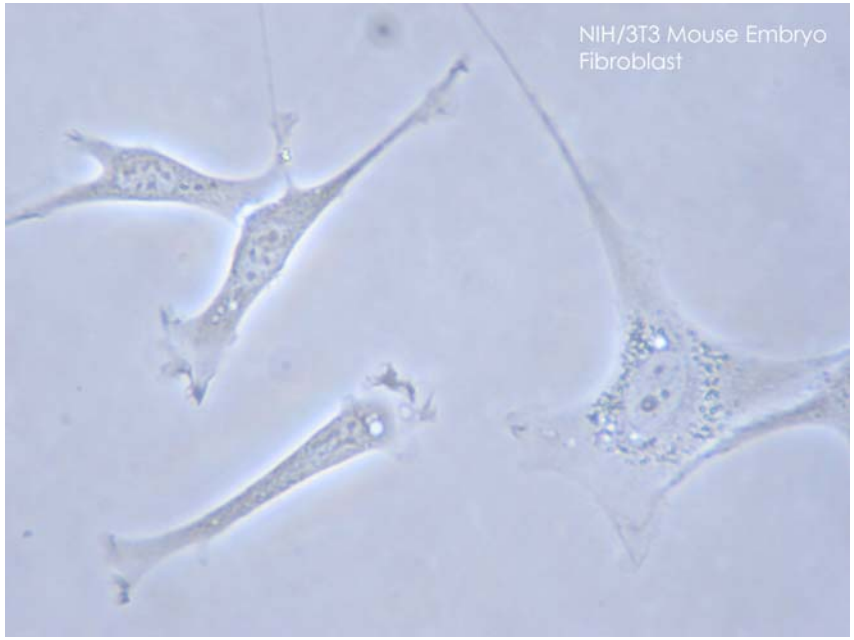
I. Sanchez-Garcia, NEJM, **360**, 297, 2009

Epithelial-to-Mesenchymal Transition: EMT

Mesenchymal-to-Epithelial Transition: MET

Reversible



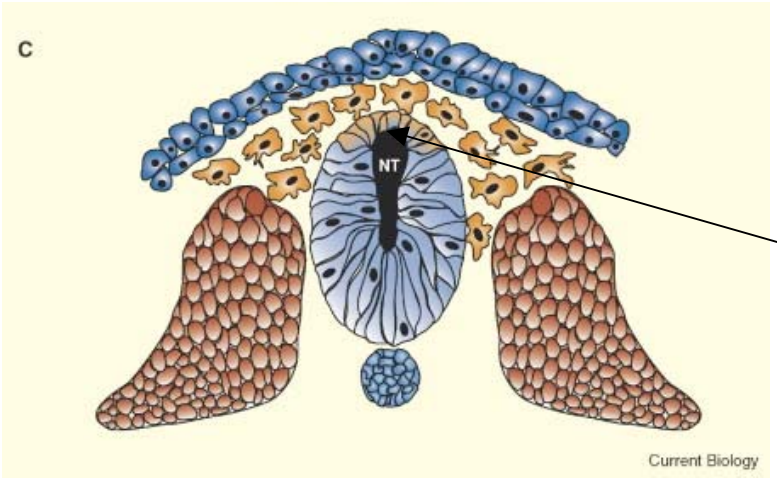


epithelial tissue

differentiated, sessile

fibroblasts

weakly differentiated, motile



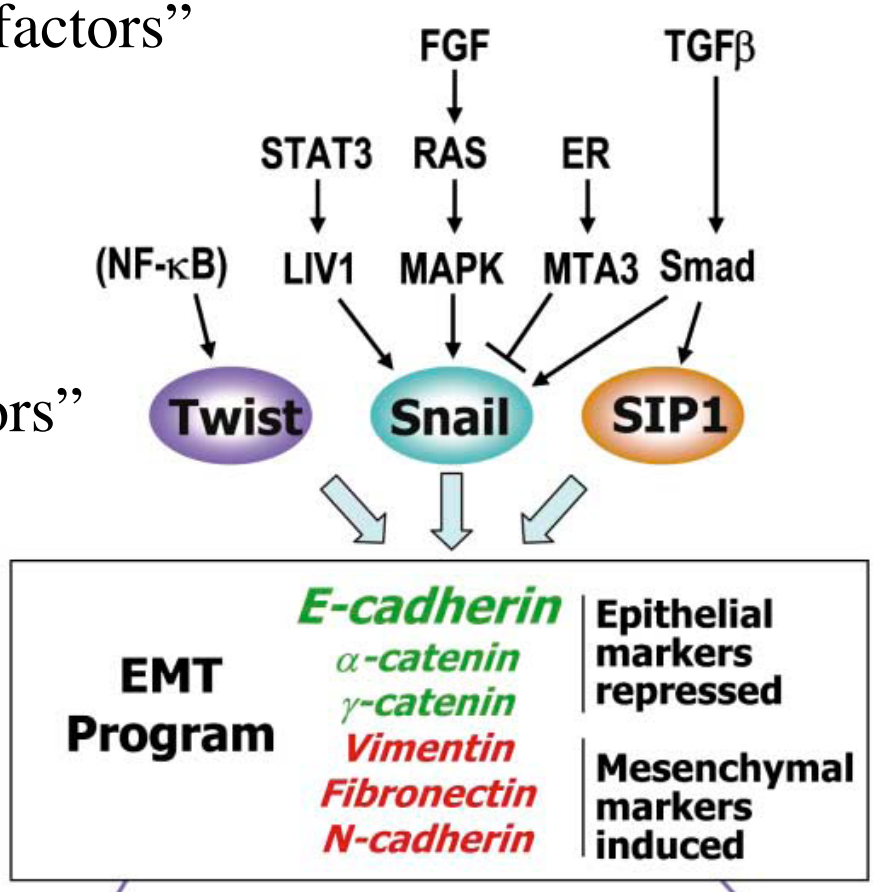
embryo development:
EMT and MET

expression of Snail, Twist,..

What triggers EMT?

External: "growth factors"

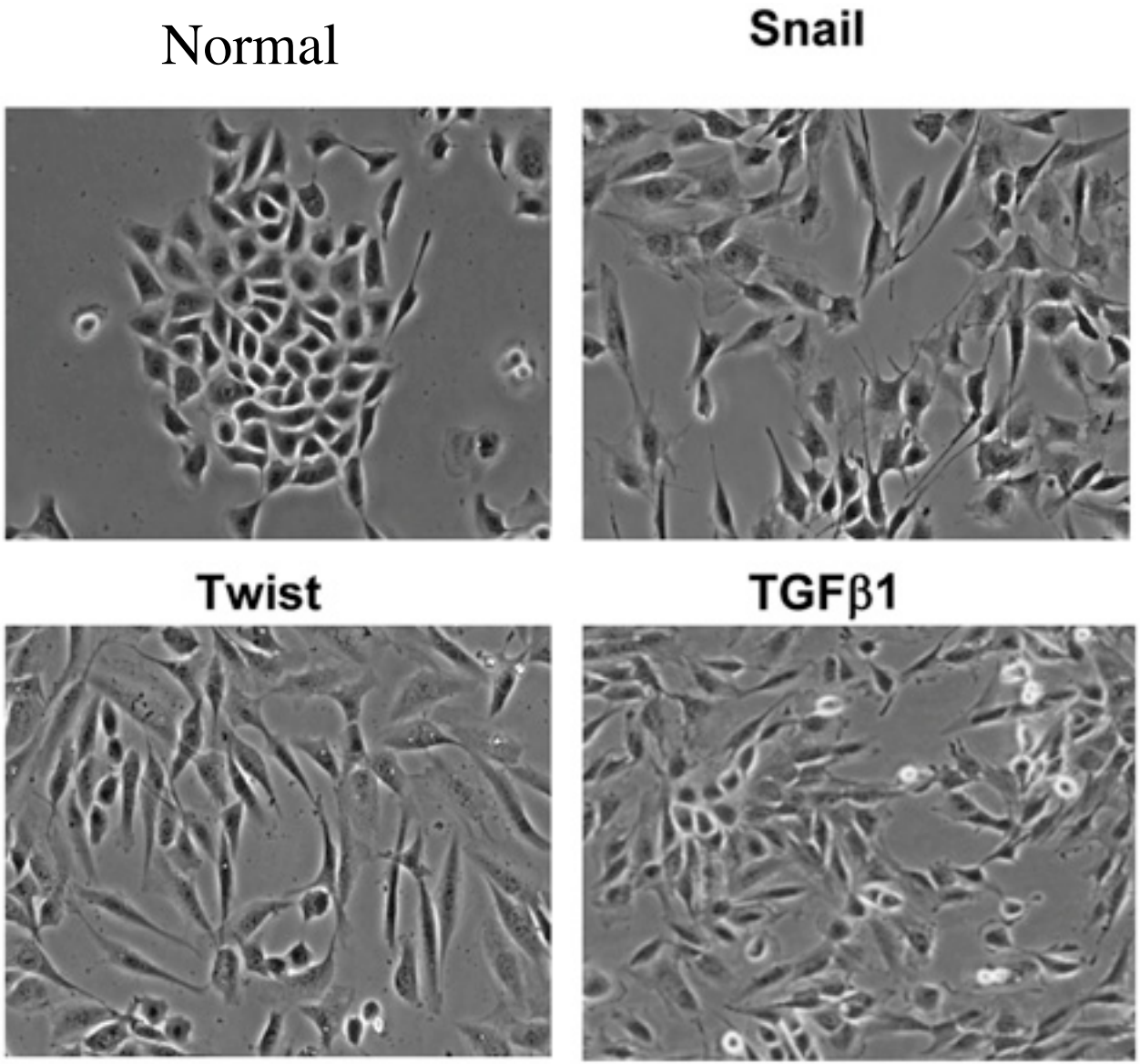
"transcription factors"



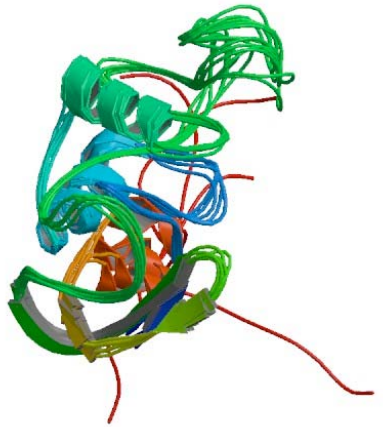
Y .Kang & J.Massague
Cell, 118, 2777, 204

* Could the Twist, Snail, .. proteins *trigger metastasis*?

* Over-express “Snail” and “Twist” in immortal mammary epithelial cells

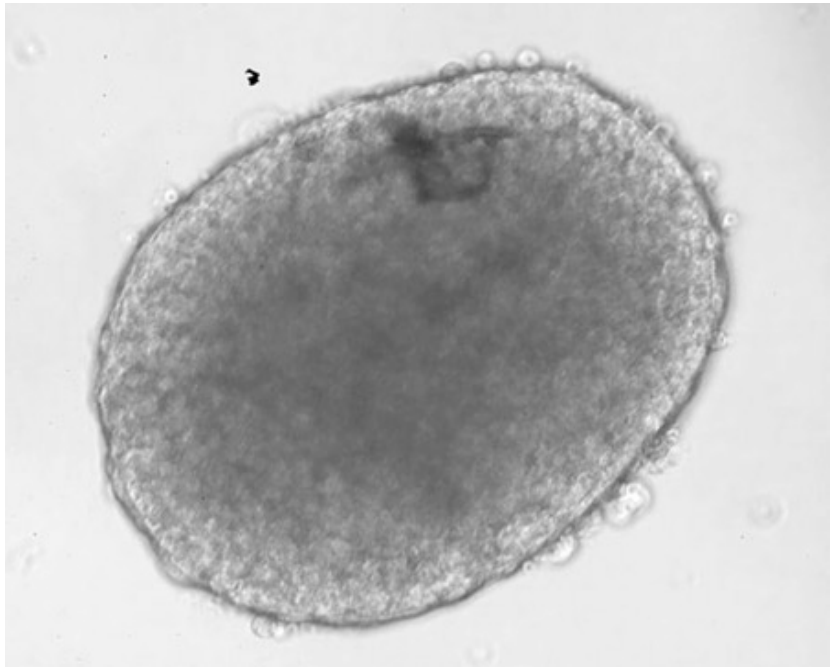


(Mani et al, 2008)



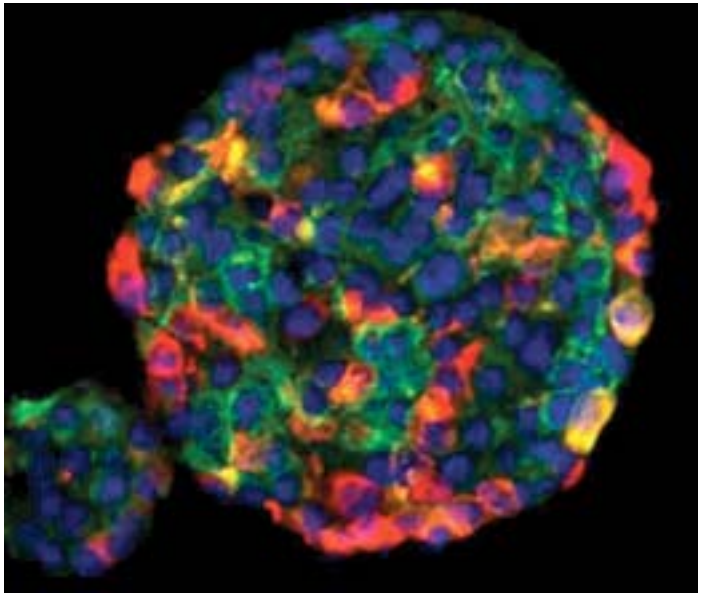
- CD44 adhesion molecule appears on cell surface.
  cancer stem-cell “marker”

1) Cells spontaneously self-assemble into “mammospheres”
2) Revert back to epithelial cells: *in-vitro metastasis*!



(Mani et al, 2008)

surface markers

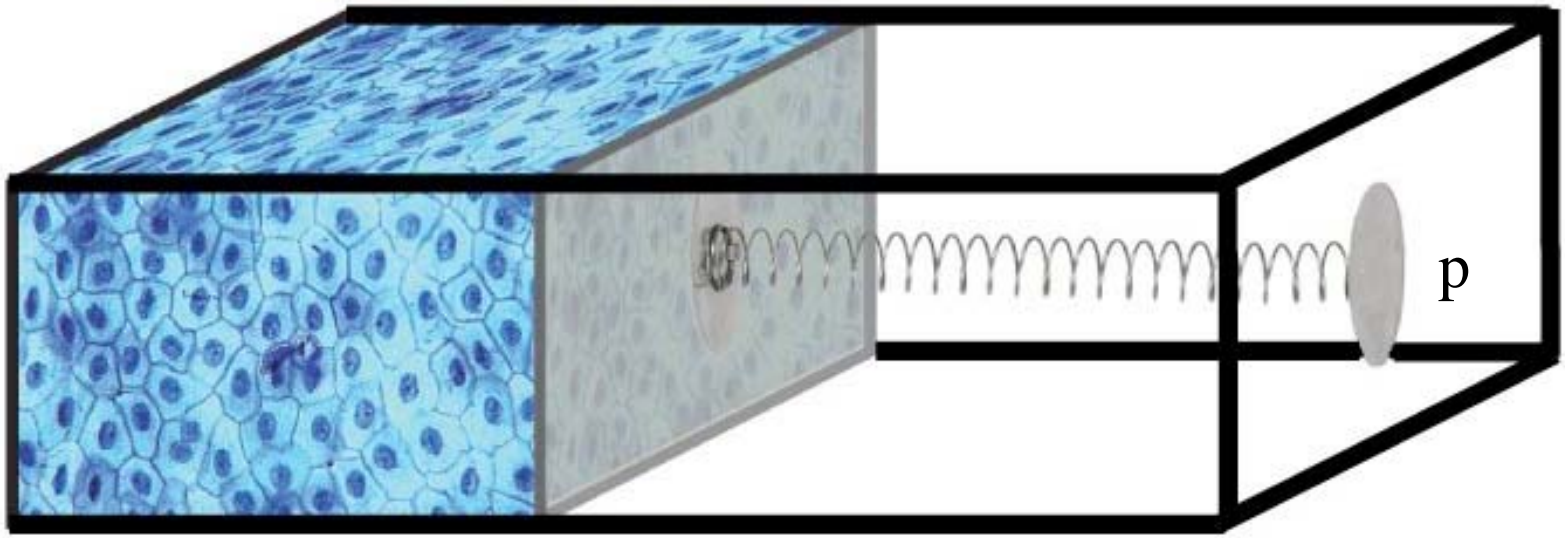


yellow: pluripotent mammary cells
blue: differentiated cells. MET

Why are metastatic nuclei so rare and so organ selective?

Basan, Risler, et al, 2009

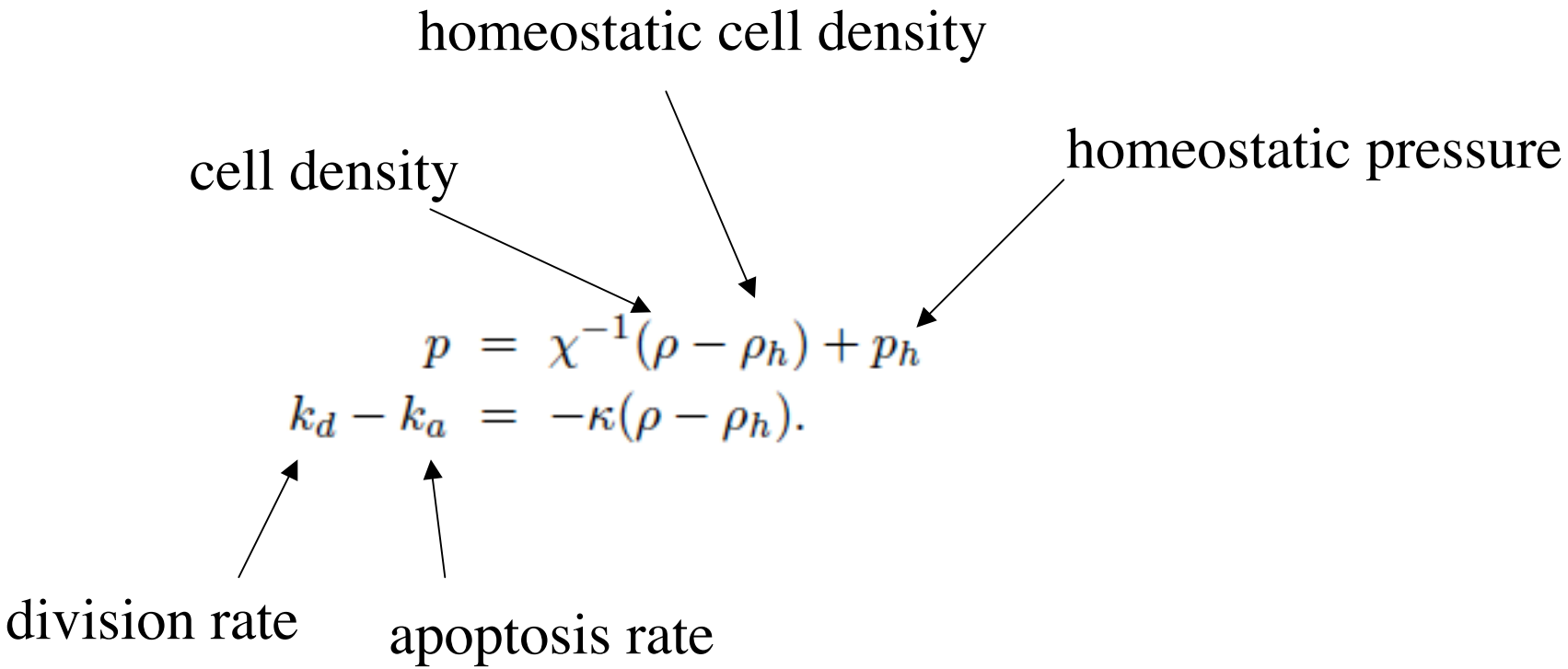
* Interaction between tissue samples with different growth rates.



fluid exchange

"Homeostatic pressure"

• p *not* hydrostatic pressure; generated by *cell division*
200 nanoNewton/(50μ)^2 ~ 100 Pa ~ blood pressure



$$\frac{\partial}{\partial t}\rho + \nabla \cdot (\rho \mathbf{v}) = (k_d - k_a)\rho,$$

non-conserved, viscous fluid flow

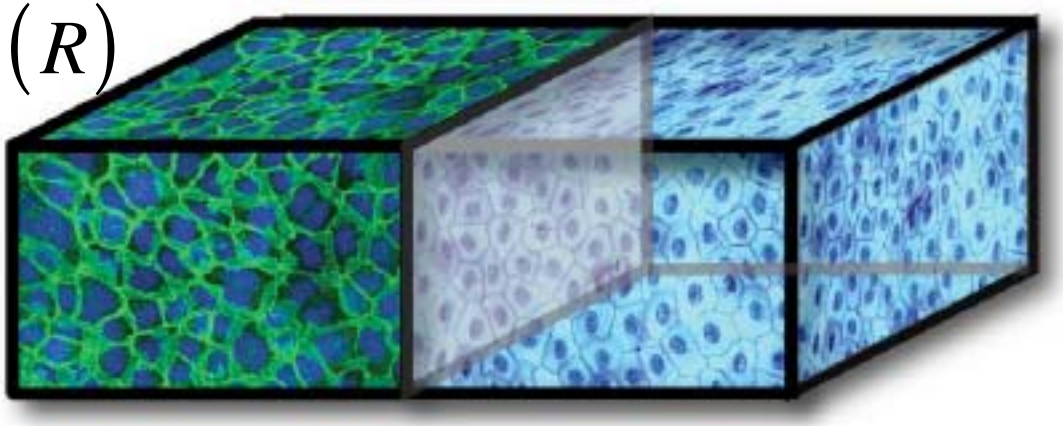
$$\eta \Delta \vec{v} = \vec{\nabla} p$$

* System evolves to the homeostatic state: $p = p_h$; $\rho = \rho_h$

Two tissue samples in contact with different homeostatic pressures

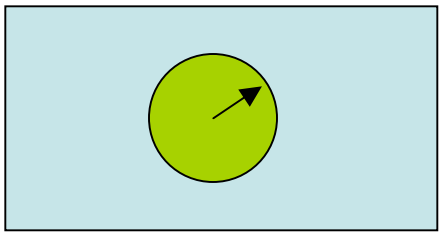
tissue-tissue "interfacial energy" γ $(\sim 10^{-3} J/m^2)$

$p_h(L) > p_h(R)$



net division → net apoptosis

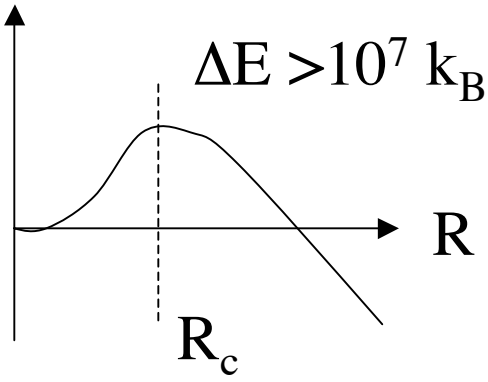
Spherical nuclei: *activation barrier*



$$\frac{2\gamma}{R_c} = p_h(L) - p_h(R) < 100\ \text{Pa}$$

critical radius $> 10\ \mu$

$$E(R) \approx \gamma R^2 + \left(p_h(R) - p_h(L)\right)R^3$$



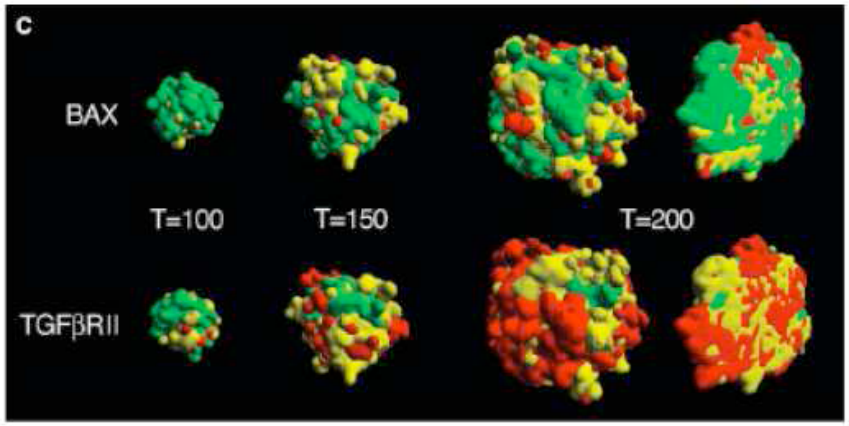
* exponentially sensitive to interface energy/geon

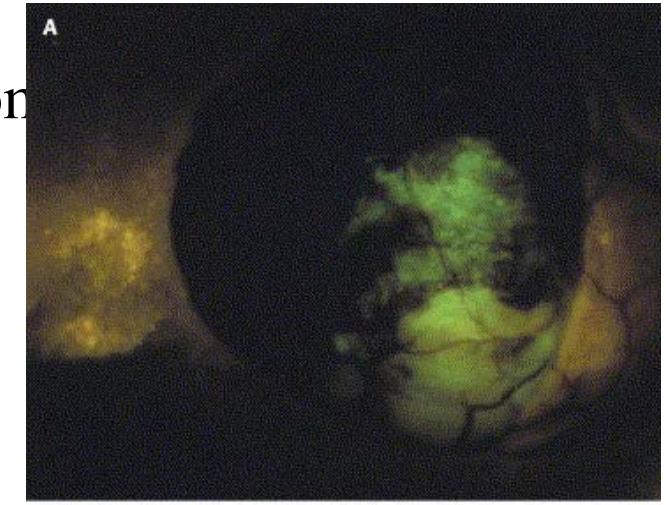
Question: *Angiogenesis*

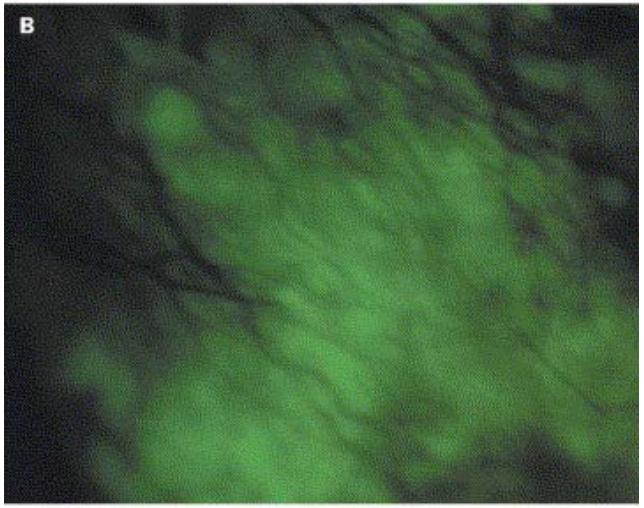
Larger tumors (R >1mm) grow channels open to the blood circulation system.

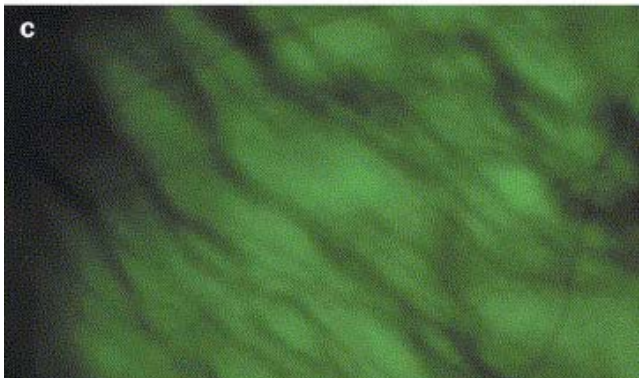
* Is homeostatic pressure of large tumors *fixed*?

* Homeostatic pressure competition between clones?



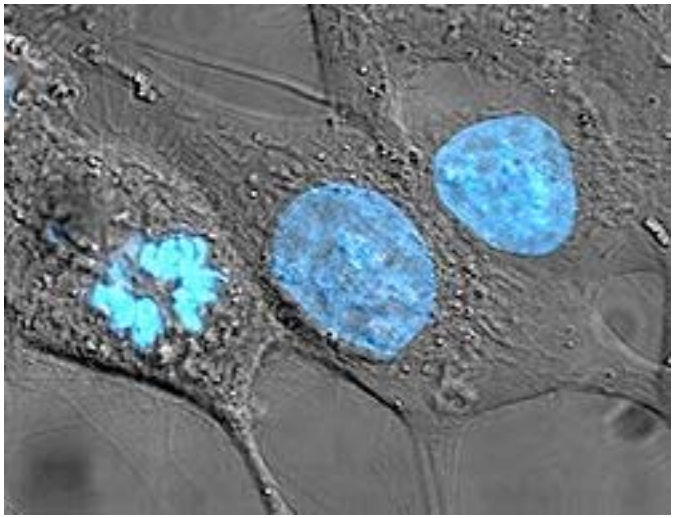






• Can mutations really speed up division rates?

Current champions: “HeLa” cells

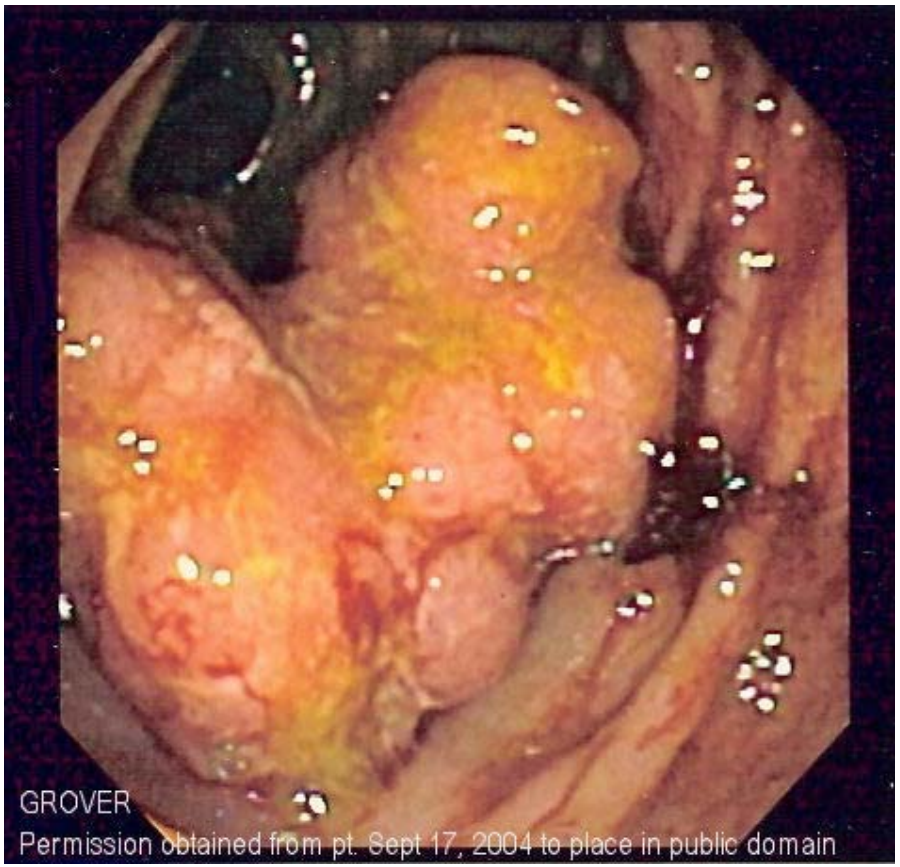


• no apoptosis.
• division rate 1/hour
• *robust*: contaminate laboratory cell lines !

Colorectal Cancer

Vogelstein

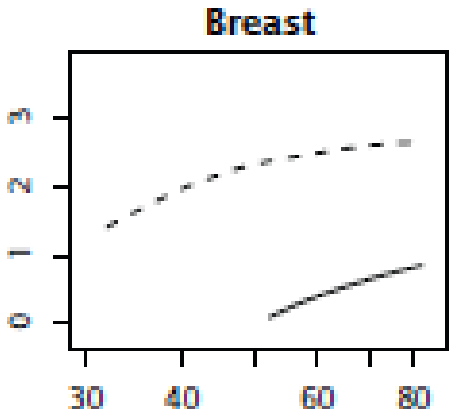
Colonoscopy
(Crohn's disease)

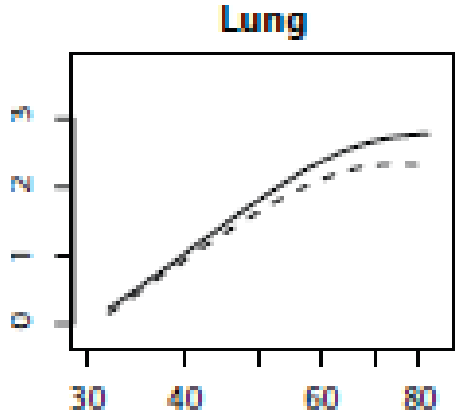


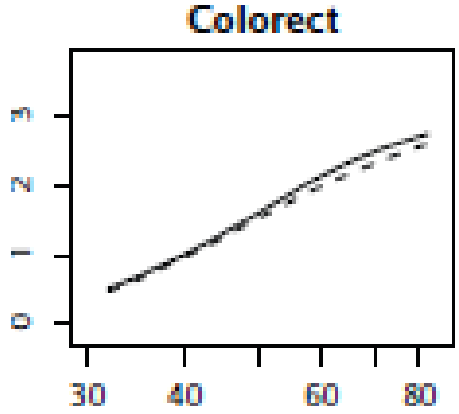
Epithelial Cancers

*decrease with age of acceleration.

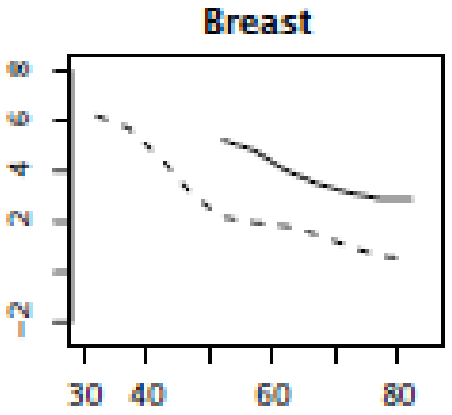
Incidence

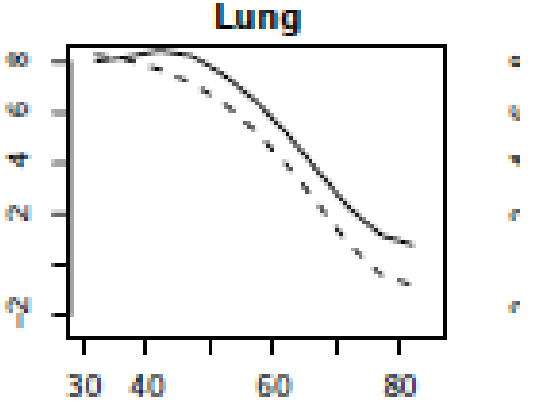


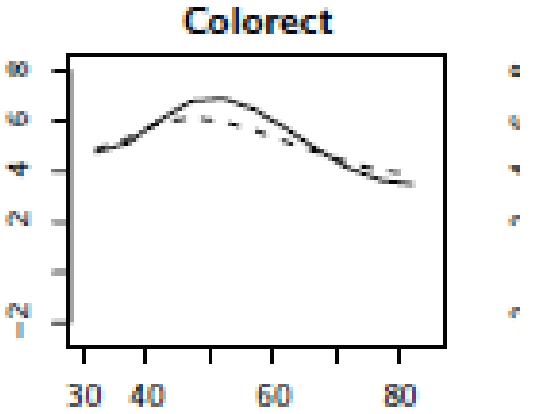




Acceleration





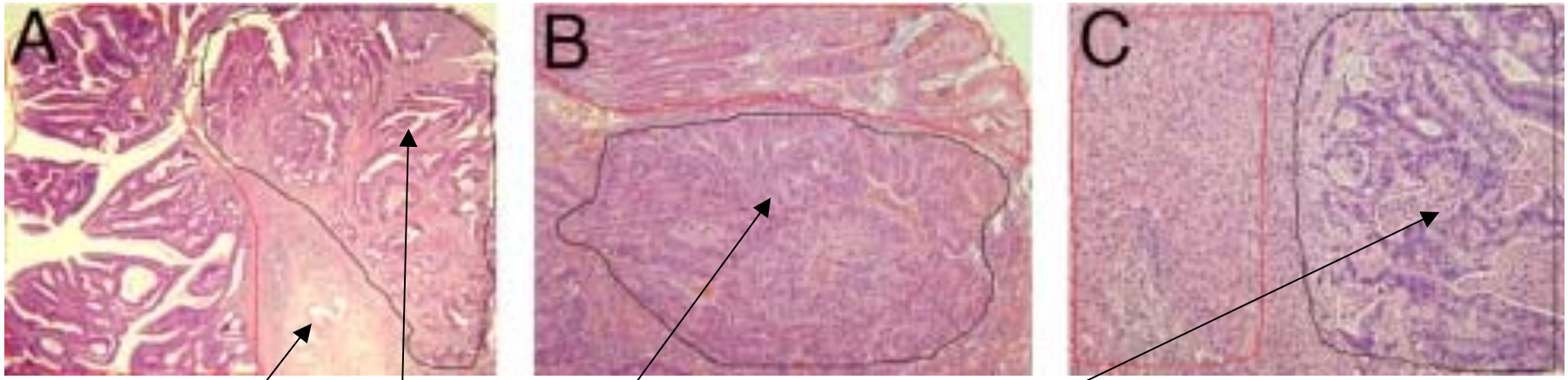


H&E stains

metastasis

normal tissue

liver



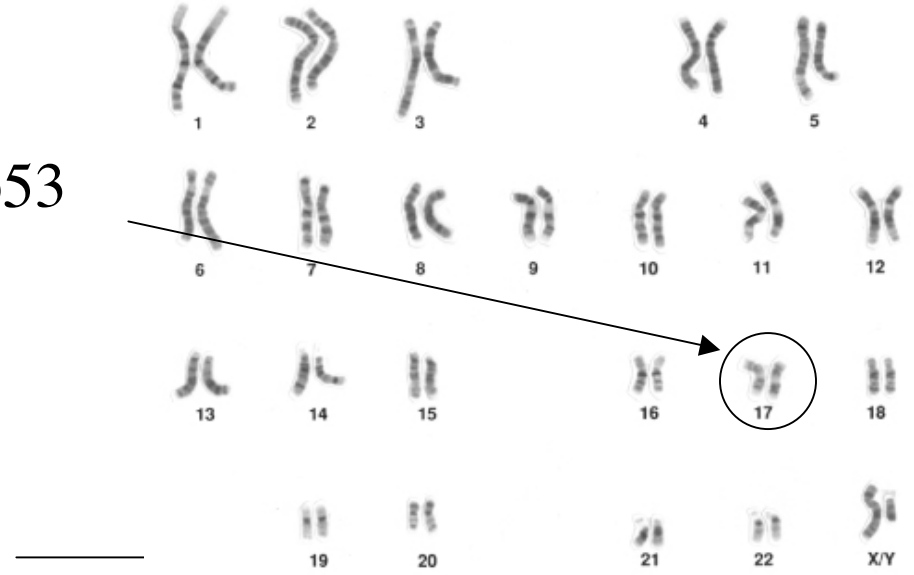
adenoma

carcinoma

same patient

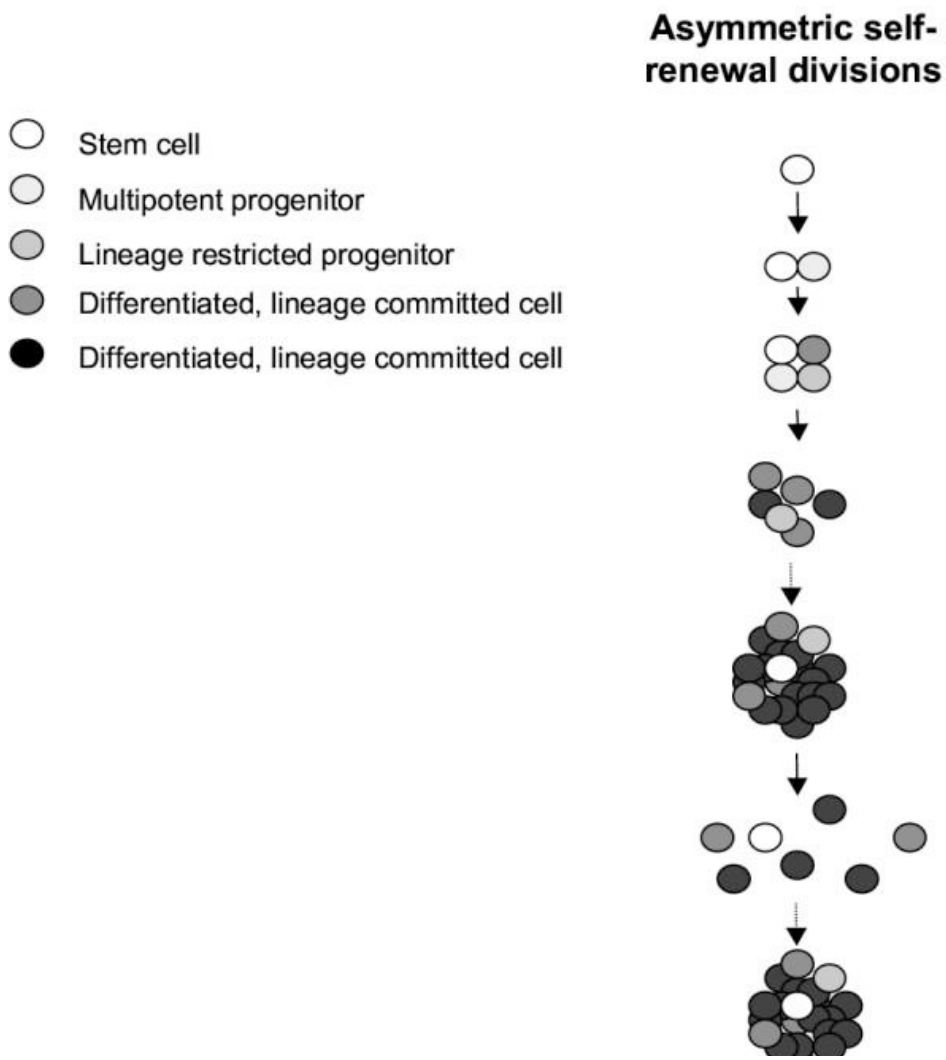
Chromosomal Instabilities

p53



Diploid

* Breakage: section of chromosome 17 - with p53 - broken off.
* Tetraploidy: 4 sets of chromosomes.



* What fraction of tumor cells are stem-like?
* Can early progenitor cells start clonal expansion? Mutate into stem cells

Probably not for early colorectal cancer: Nature Reviews Cancer 9, 2 (01 February 2009): Size does not matter?

Unresolved issue:

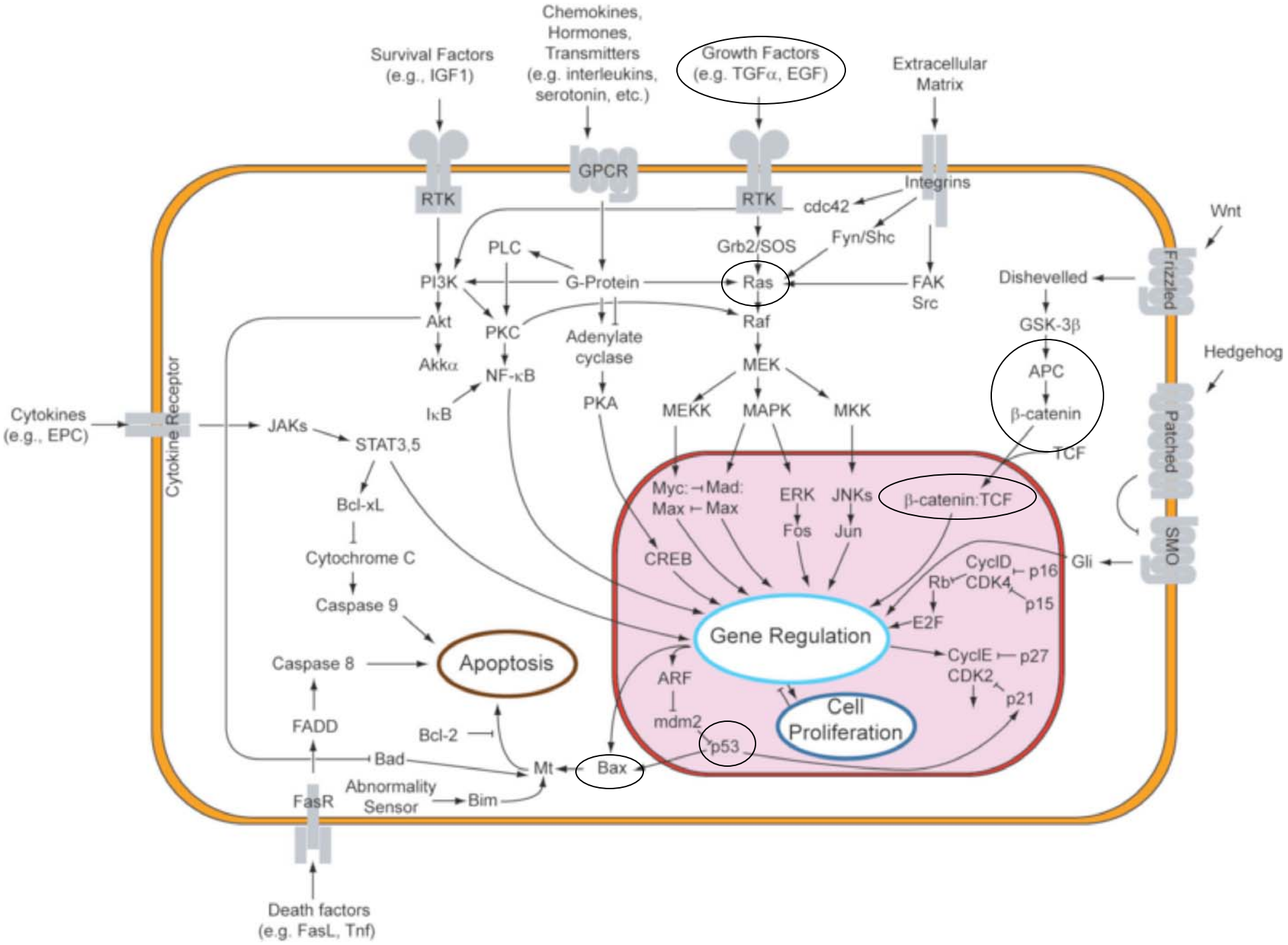
1) What is the optimal game strategy for a cancer?
(Shibata, commentary)

A) Maximize clonal diversity: more efficient search for combinations of mutations that have high cell division rate. **Low clone size**. Minimal clonal competition.
B) Maximize clone size: larger clone size increases probability for making the *next* hit of the mutation sequence. **Low diversity**.

2) What is the role of epigenesis and phenotypic persistance?
The same clone can have regions of cells with different DNA methylation patterns altering gene expression.

Colorectal cancer: 10^2 mutations/cell

3) Apart from the major mutations (APC, p53, K-Ras, PTEN,..), do a *large* number of mutations with a *small* differential advantage have important effects? Diversity produce "mutational robustness"?
(Beerenwinkel et al., 2007)


Survival Factors
(e.g., IGF1)
Chemokines,
Hormones,
Transmitters
(e.g. interleukins,
serotonin, etc.)
Growth Factors
(e.g. TGFα, EGF)
Extracellular
Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Wnt
Frizzled
Dishevelled
GSK-3β
APC
β-catenin
TCF
β-catenin:TCF
Hedgehog
Patched
SMO
Gli
Akt
PKC
Adenylate
cyclase
Raf
Akkα
NF-κB
IκB
PKA
MEK
MEKK
MAPK
MKK
Cytokines
(e.g., EPC)
Cytokine Receptor
JAKs
STAT3,5
Myc: ⊣ Mad:
Max ⊢ Max
ERK
JNKs
Fos
Jun
CREB
Bcl-xL
Cytochrome C
Caspase 9
Caspase 8
Apoptosis
CyclD
p16
Rb
CDK4
p15
E2F
Gene Regulation
CyclE
p27
CDK2
p21
ARF
mdm2
p53
Cell
Proliferation
FADD
Bcl-2
Bad
Mt
Bax
FasR
Abnormality
Sensor
Bim
Death factors
(e.g. FasL, Tnf)

Does clonal expansion matter ?

Example:

* n=5

A -> B -> C -> D -> E

1) Growth Rate: non-linear dependence on # mutations

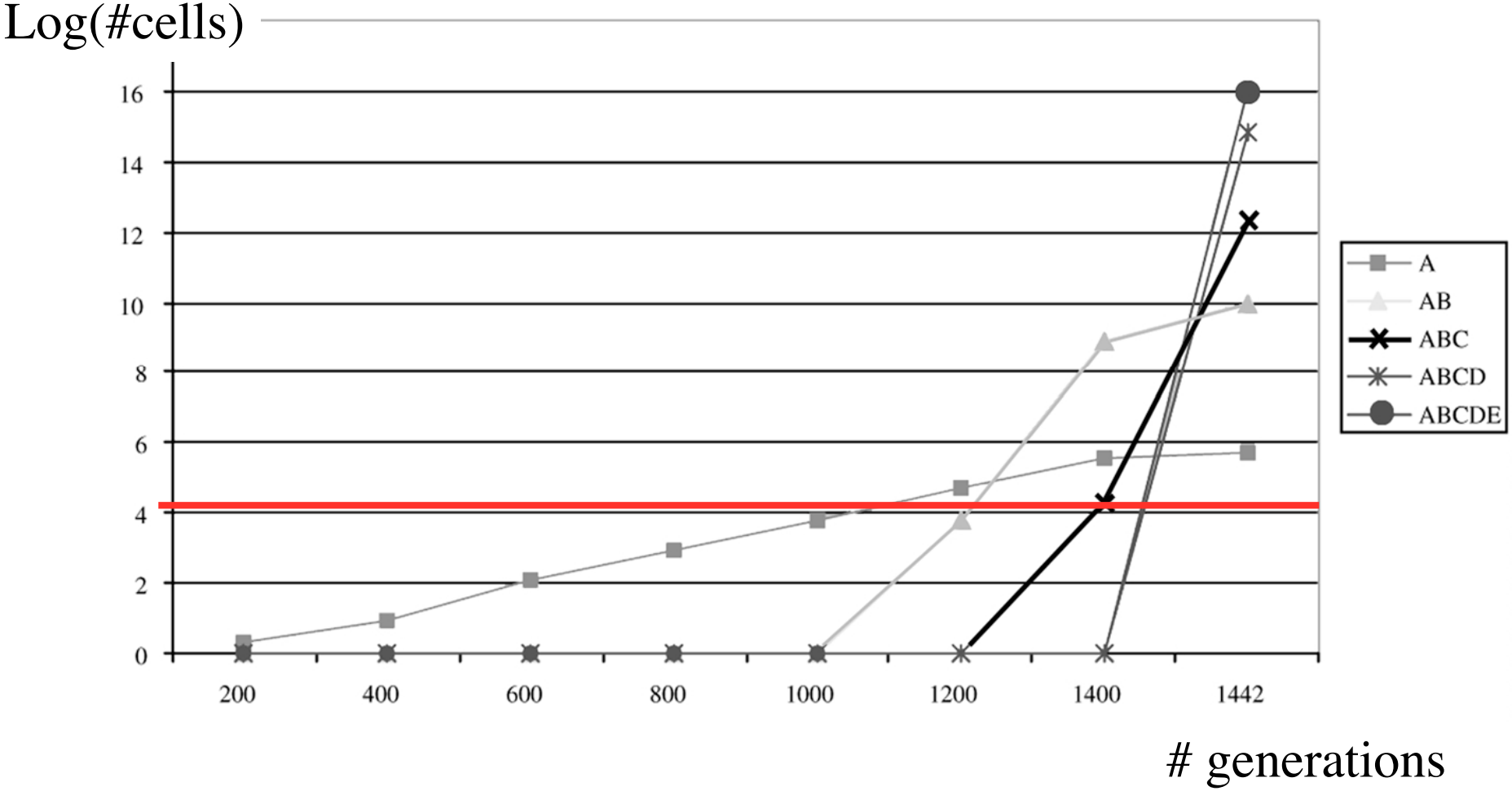
A cell: 1.01. A + B cell: 1.05. A + B+ C cell: 5.
A+ B+ C + D cell : 20. A + B + C + D + E: 100.

2) Let *all* cancer cells undergo an unlimited number of divisions.

numerical simulation

* Mutation rate: u = 2×10^{-7} per generation per gene

Tomlinson Breast Cancer Res. 2001 3:299



* Solves small-u problem? *Clone size amplifies mutation probability.*