"What is Evolution? Bicentennial of Charles Darwin's Birth"
October 16, 2009, Coop-in Kyoto

Cancer as a mini-evolutionary process.

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Evolution: slow change of organisms

mutation:

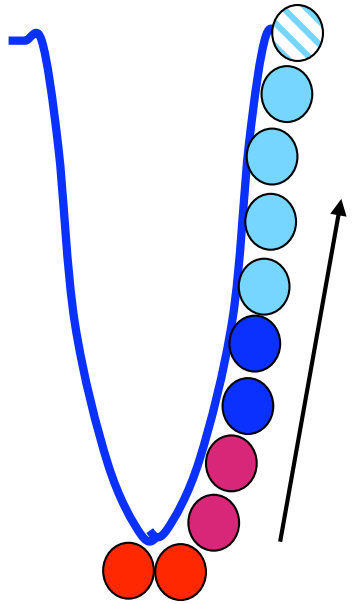
mistake of reproduction

natural selection:

mutant with a higher survival
and a faster reproductive rate
will replace the old type.

Colon cancer arises in a crypt

A crypt consists of 1000-4000 cells.



Apoptosis on top of crypt

36 hours

A small number of stem cells replenishes the whole crypt.

The colon contains 10^7 crypts.

Tumorigenesis includes multiple steps of mutations of stem cells:

- loss of tumor suppressors
- oncogenes
- angiogenesis (induction of blood vessels)
- metastasis
- etc.

Carcinogenesis is an Evolutionary Process.

(1) Chromosomal Instability

(2) Tissue structure

(3) Chronic myeloid leukemia

Tumor Suppressors

p53

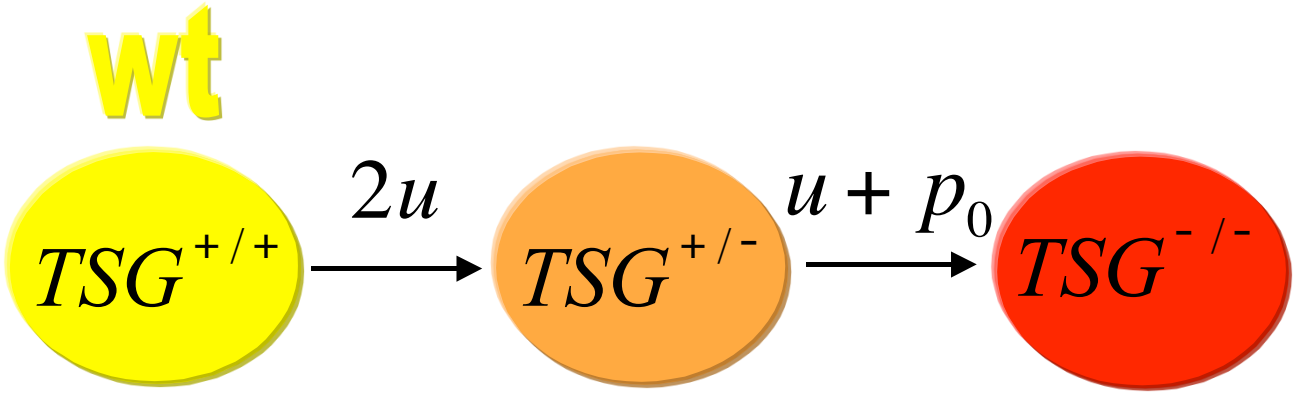
Rb

APC

. . . . .

Tumor Suppressors prevents cell division and causes apoptosis, if something is wrong.

Loss of Both Copies of a Tumor Suppressor Gene is the First Step toward Cancer.



Cancer initiation

Escape apoptosis

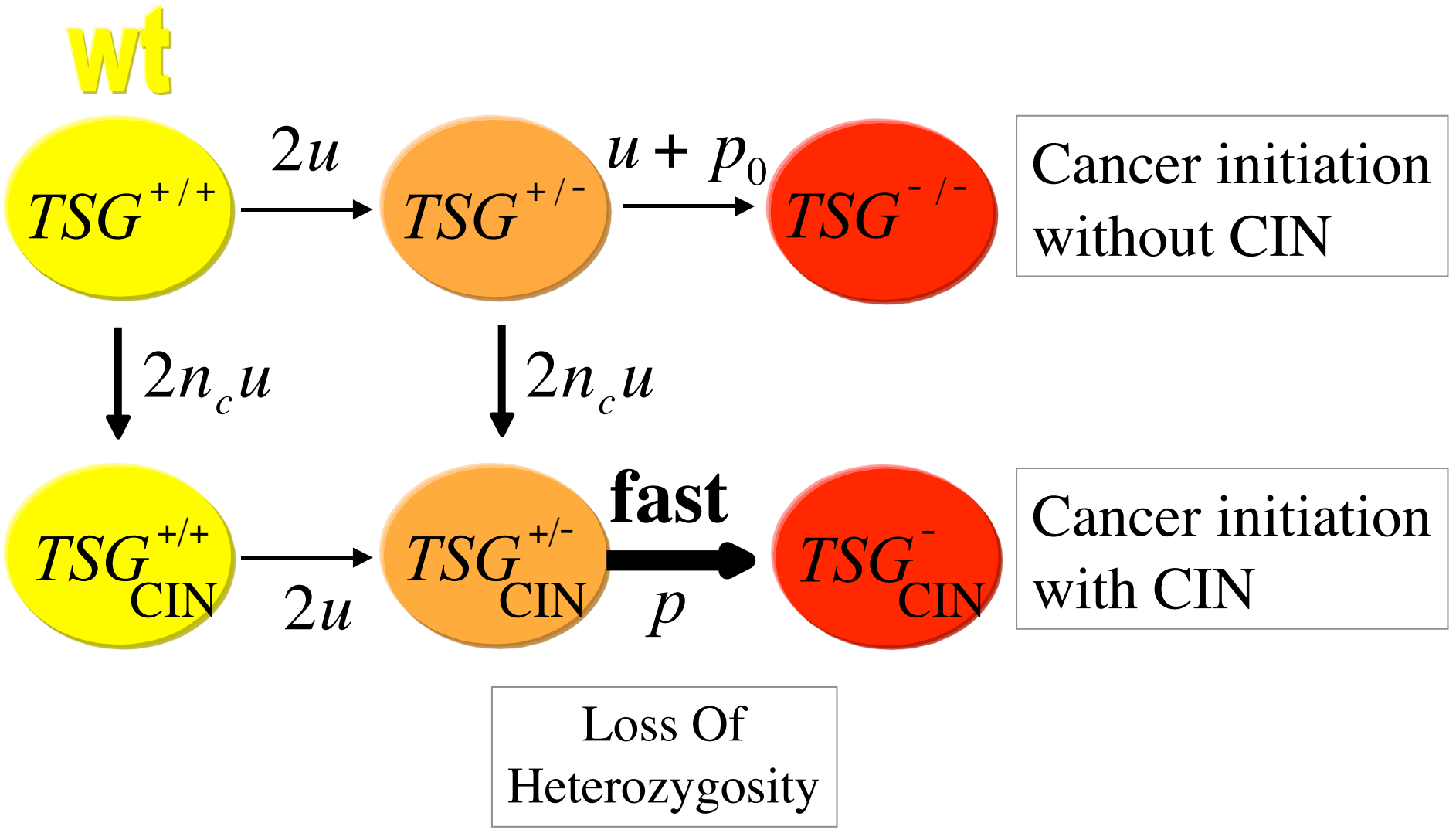
Chromosomal Instability (CIN)

Normal cells

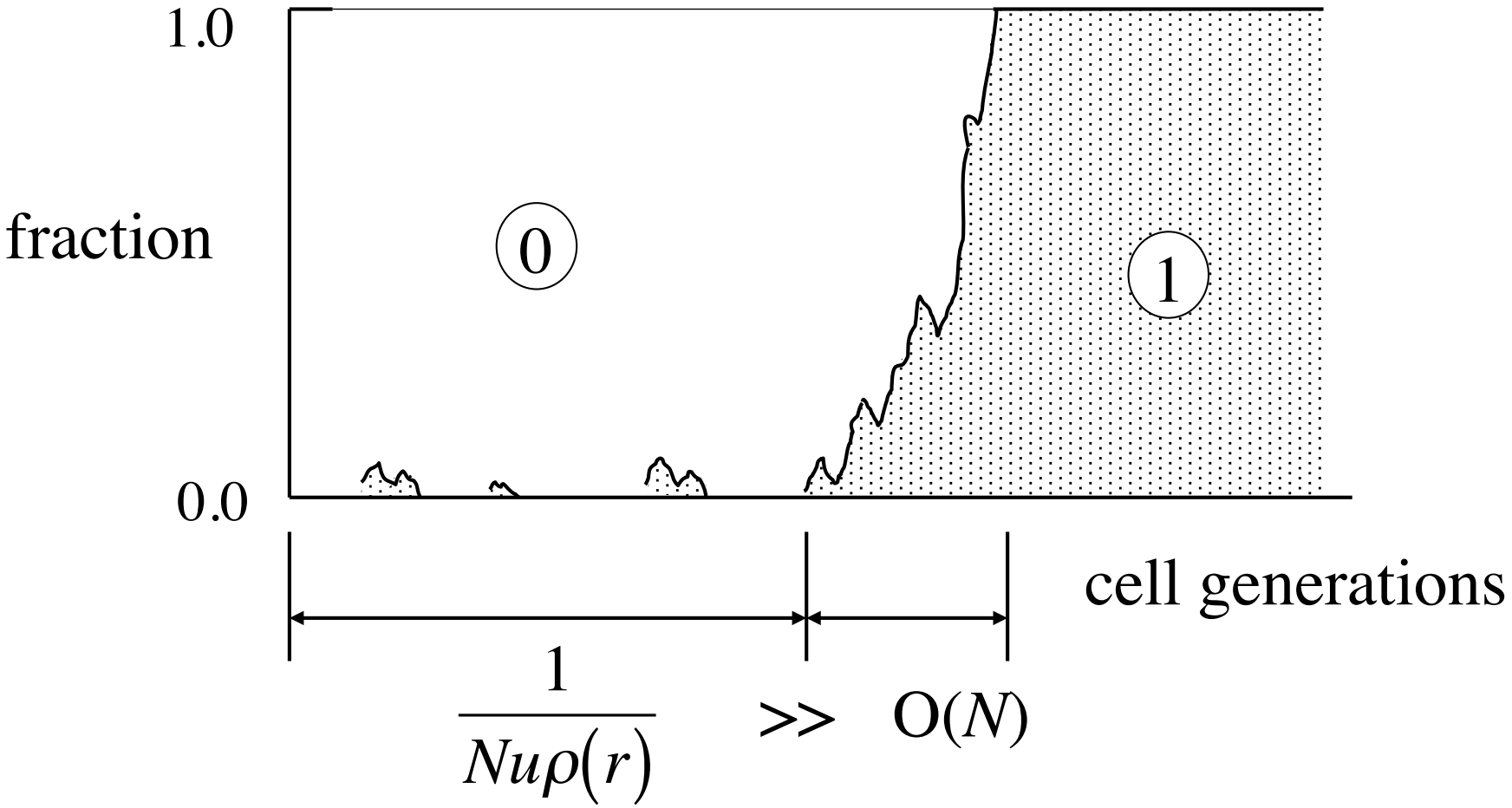
CIN cells

Can Chromosomal Instability Enhance the Risk of Cancer?

Effect of Chromosomal Instability (CIN)

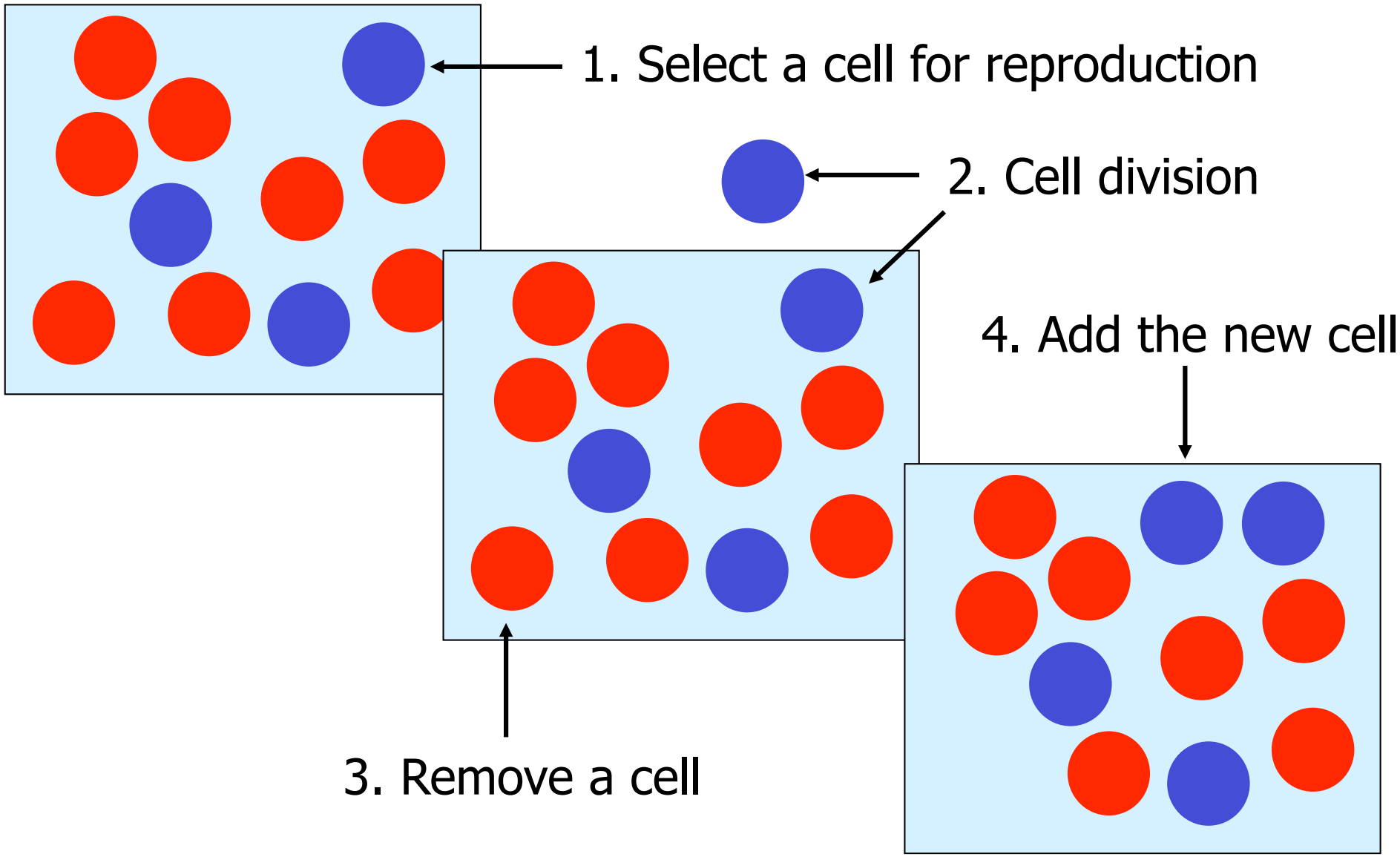


Fixation of mutant

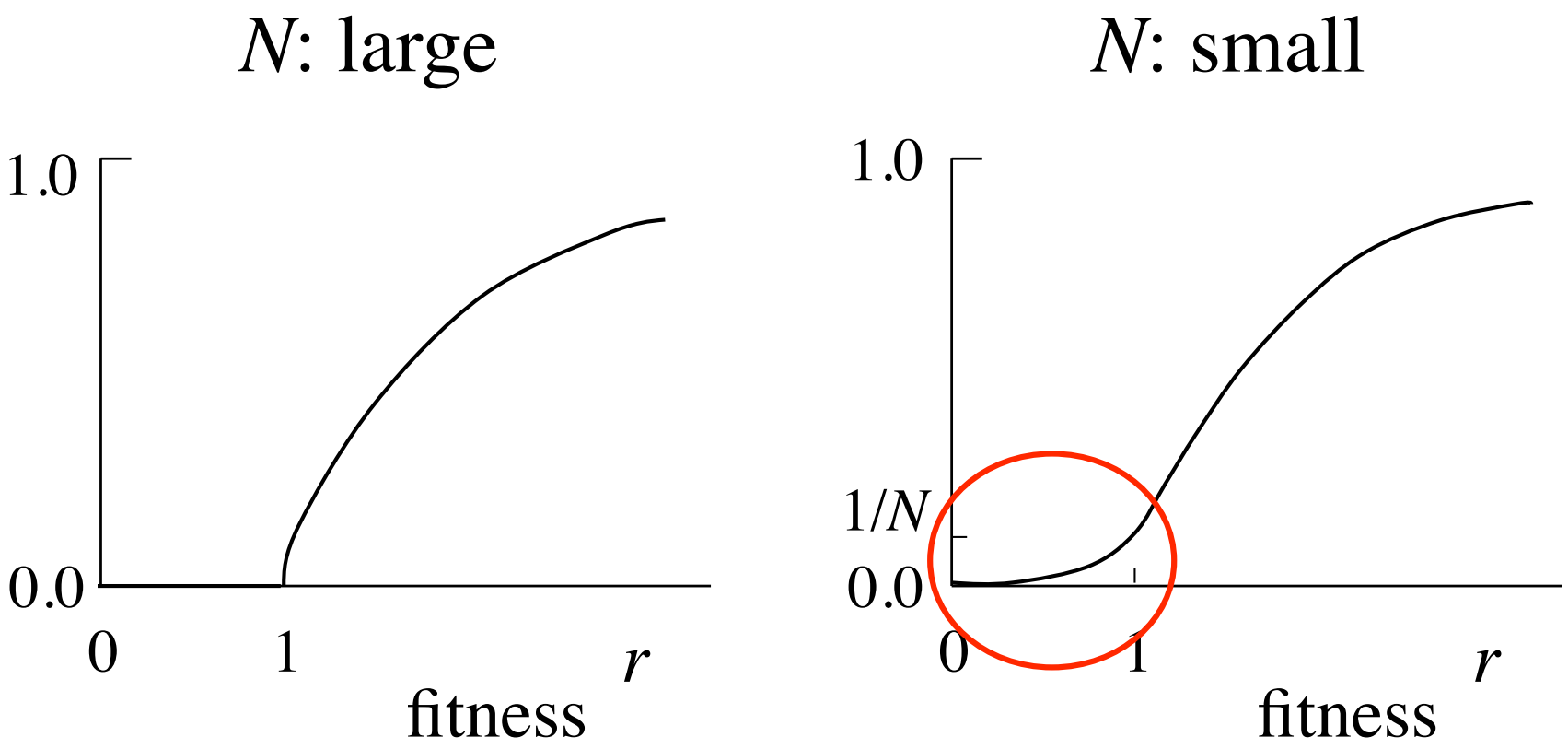


can be approximated by a Markovian transition

Moran Process

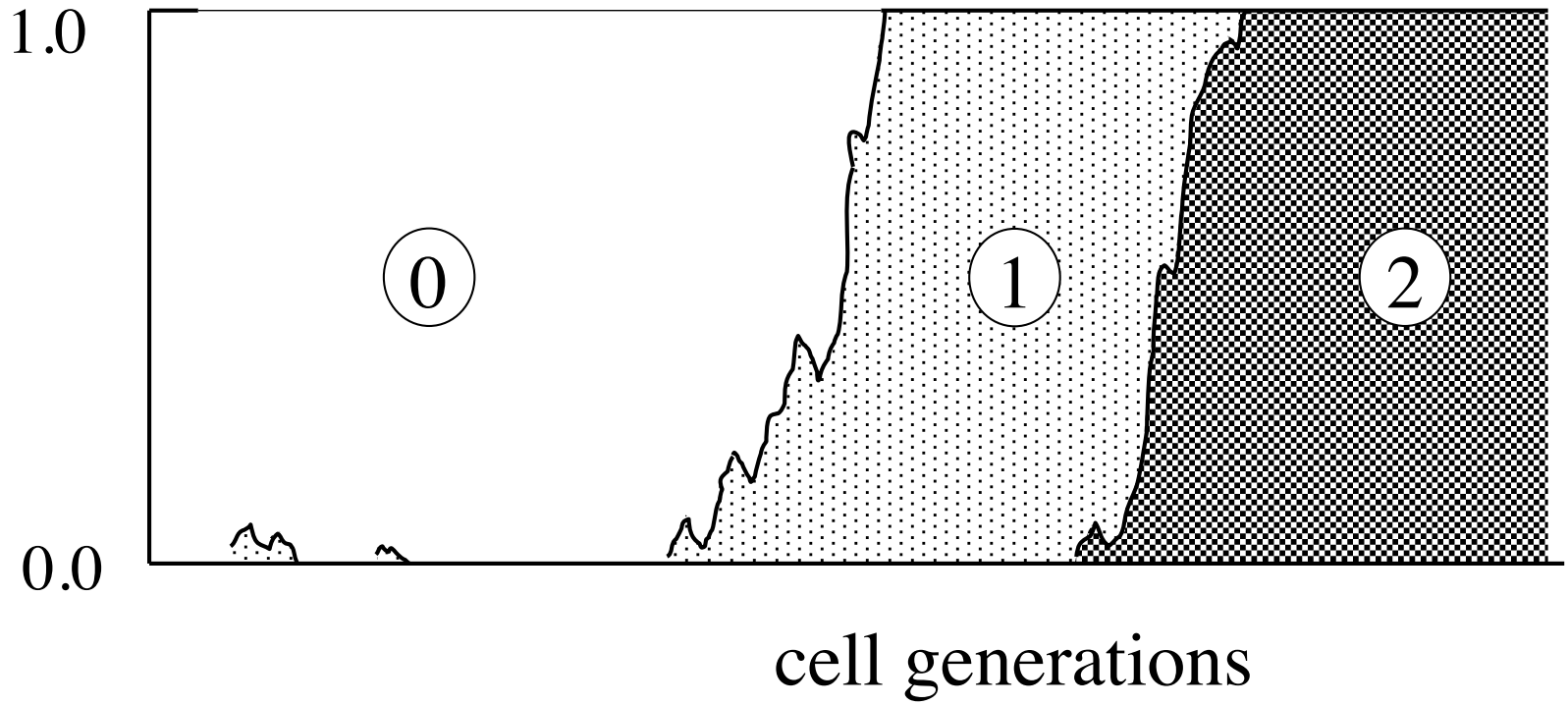


Fixation probability $\rho(r)$



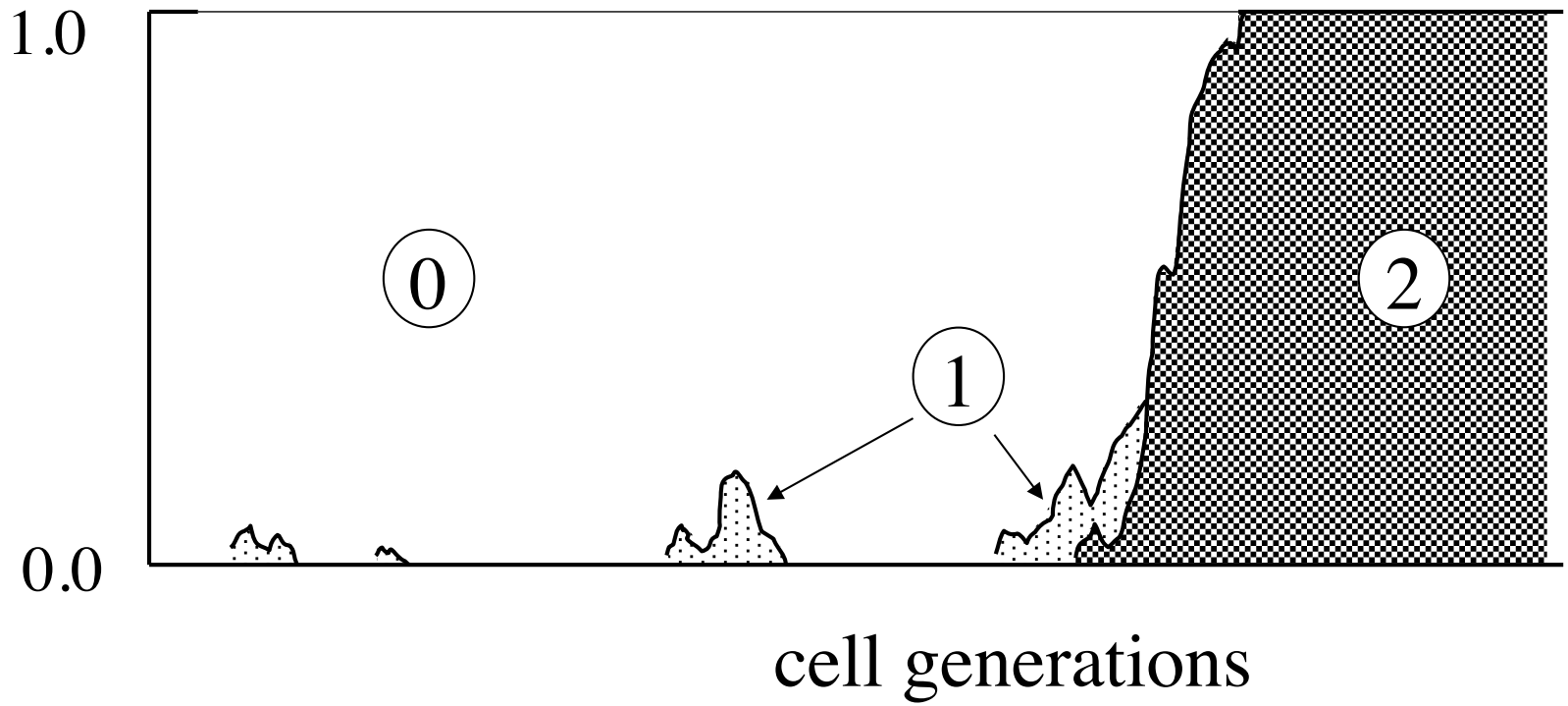
Deleterious mutations can be fixed,
if N is small.

Fixation of an intermediate mutant



Tunneling:

The Second Mutation Spreads without the Fixation of the First One



explicit formula for tunneling rate

$$R_{tunnel} \approx Nu_1\left[\frac{-(1-r)+\sqrt{(1-r)^2+2(1+r)ru_2\rho(a)}}{1+r}-\rho(r)\right]_+$$

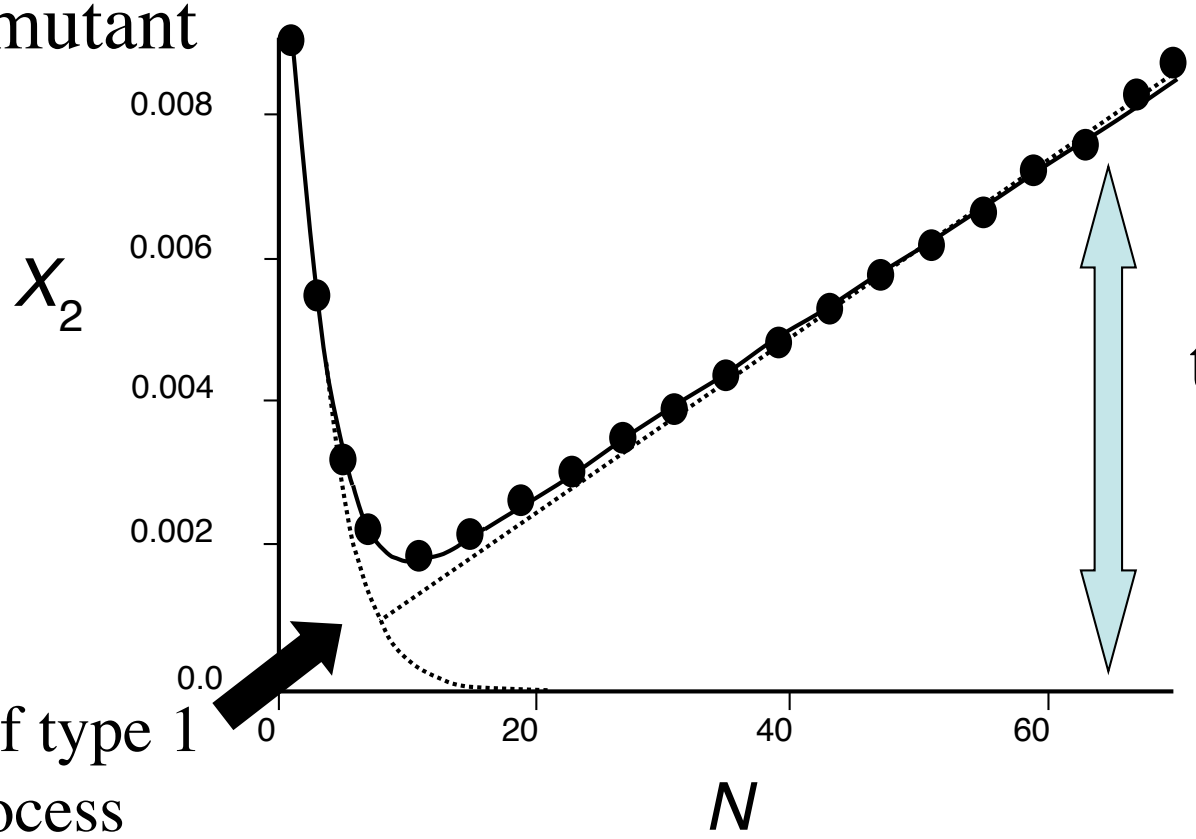
deleterious mutation

$$\approx \begin{cases} Nu_1\left[\dfrac{ru_2}{1-r}\rho(a)-\rho(r)\right]_+ & \text{if } 1-r >> 2\sqrt{u_2\rho(a)} \\ Nu_1\left[\sqrt{u_2\rho(a)}-\dfrac{1}{N}\right]_+ & \text{if } 1-r << 2\sqrt{u_2\rho(a)} \end{cases}$$

neutral mutation

Intermediate mutant is deleterious

Fixation probability of
Type 2 mutant



tunneling
1-step process

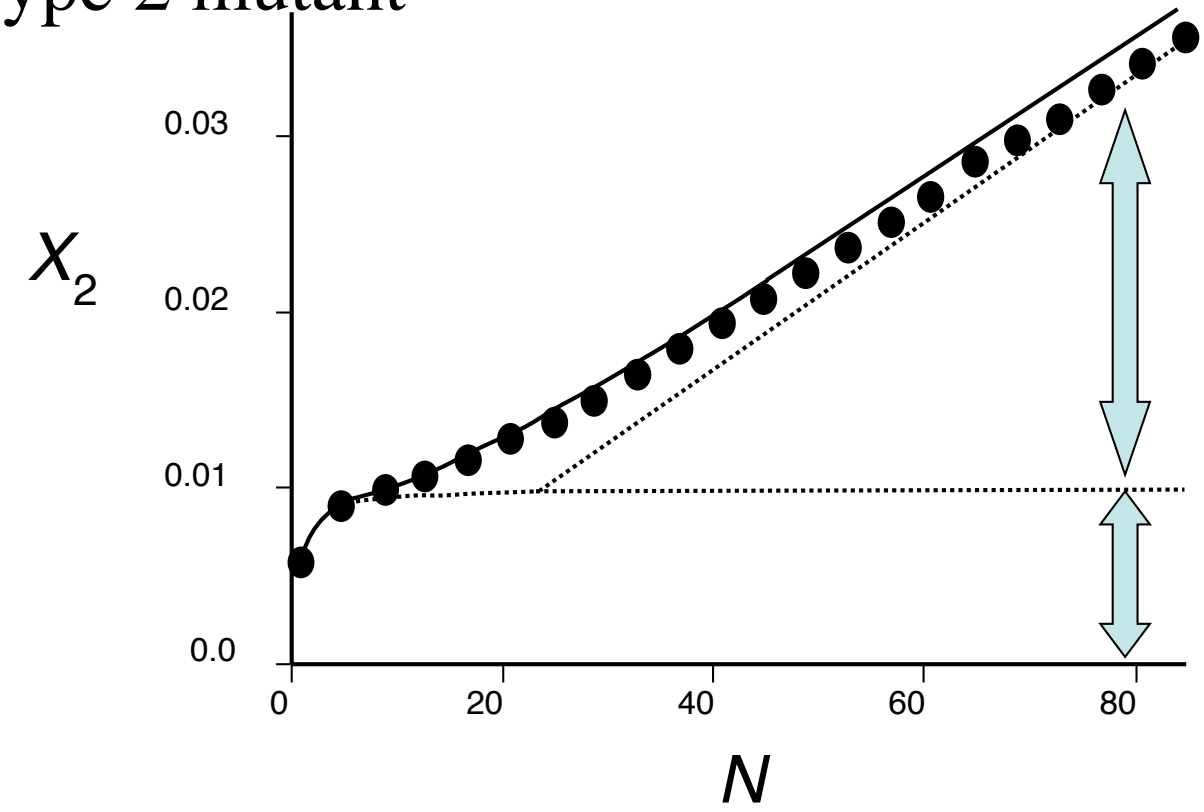
fixation of type 1
2-step process

Small compartment: 2-step evolution

Large compartment: Tunneling (1-step evolution)

Intermediate mutant is neutral

Fixation probability
of Type 2 mutant

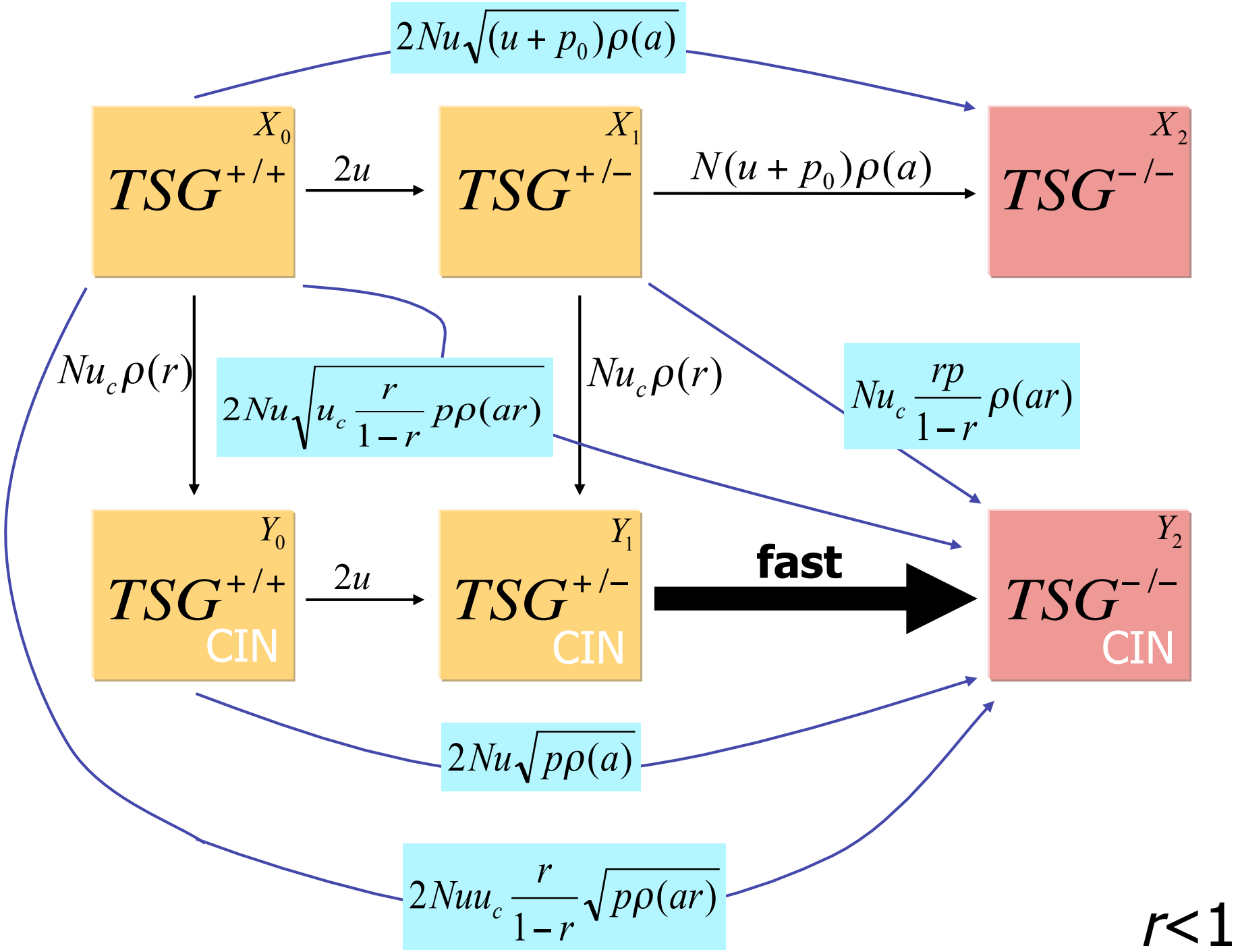


tunneling
1-step process

fixation of type 1
2-step process

Small compartment: 2-step evolution

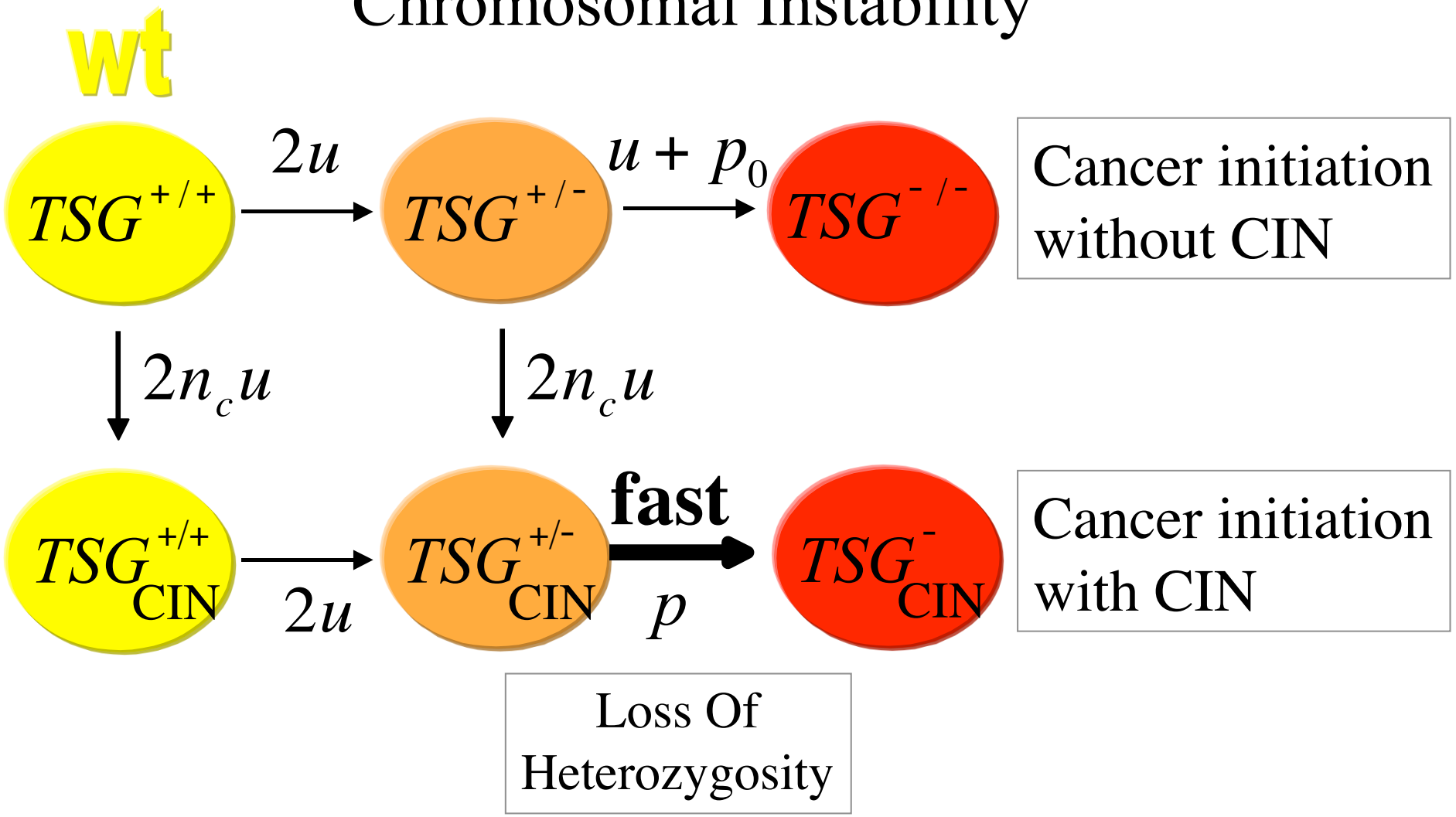
Large compartment: Tunneling + 2-step evolution


$2Nu\sqrt{(u+p_0)\rho(a)}$
X_0
$TSG^{+/+}$
$2u$
X_1
$TSG^{+/-}$
$N(u+p_0)\rho(a)$
X_2
$TSG^{-/-}$
$Nu_c\rho(r)$
$2Nu\sqrt{u_c\frac{r}{1-r}p\rho(ar)}$
$Nu_c\rho(r)$
$Nu_c\frac{rp}{1-r}\rho(ar)$
Y_0
$TSG^{+/+}$
CIN
$2u$
Y_1
$TSG^{+/-}$
CIN
fast
Y_2
$TSG^{-/-}$
CIN
$2Nu\sqrt{p\rho(a)}$
$2Nuu_c\frac{r}{1-r}\sqrt{p\rho(ar)}$

$r<1$

Can Chromosomal Instability Enhances the Risk of Cancer?

Chromosomal Instability



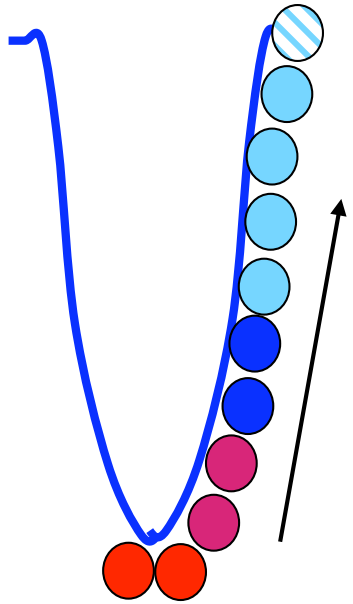
CIN occurs before the loss of TSG.

Does the Tissue Structure

Change the Cancer Risk?

Colon cancer arises in a crypt

A crypt consists of 1000-4000 cells.



Apoptosis on top of crypt

36 hours

A small number of stem cells replenishes the whole crypt.

The colon contains 10^7 crypts.

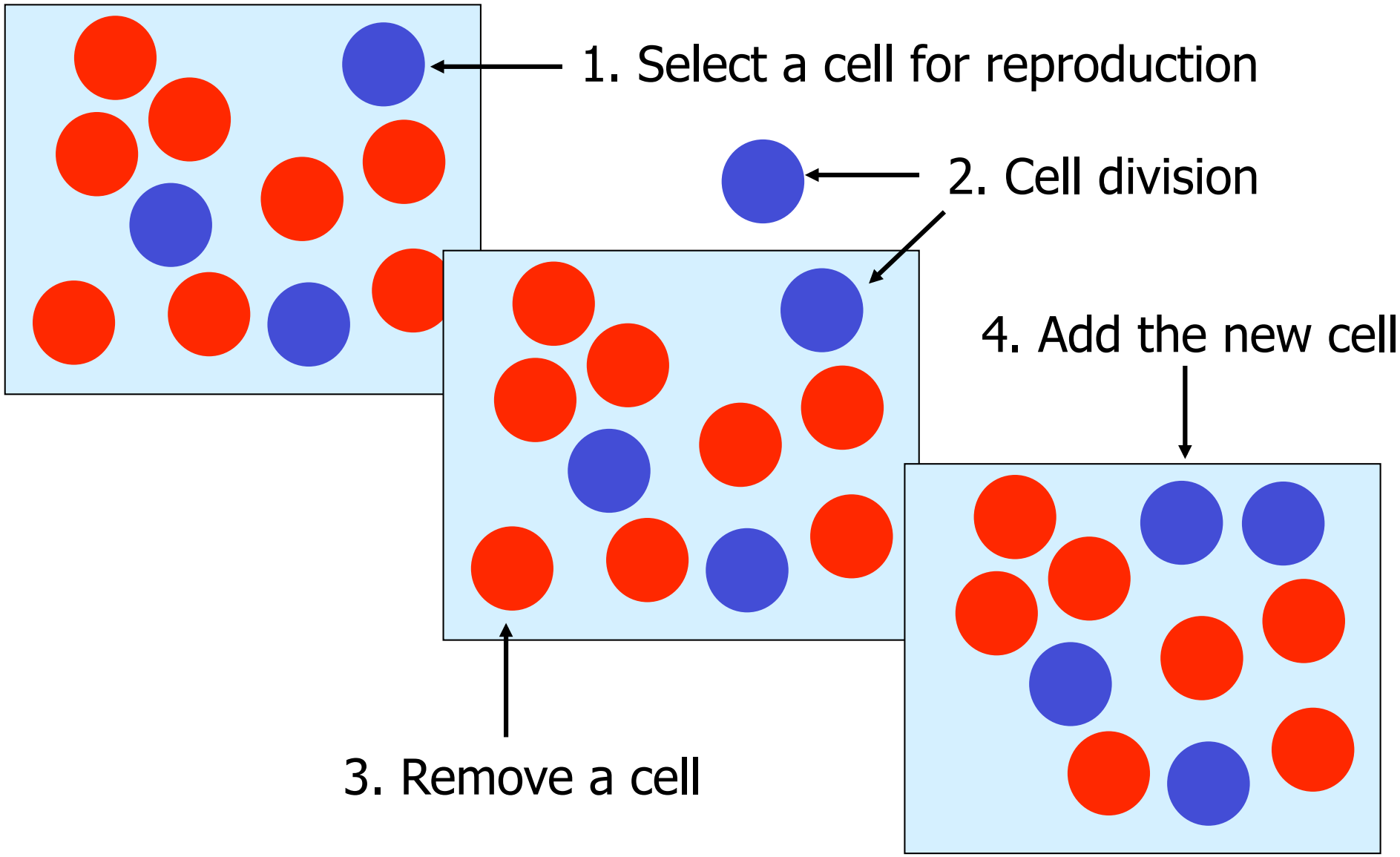
Small Compartments Large Compartments

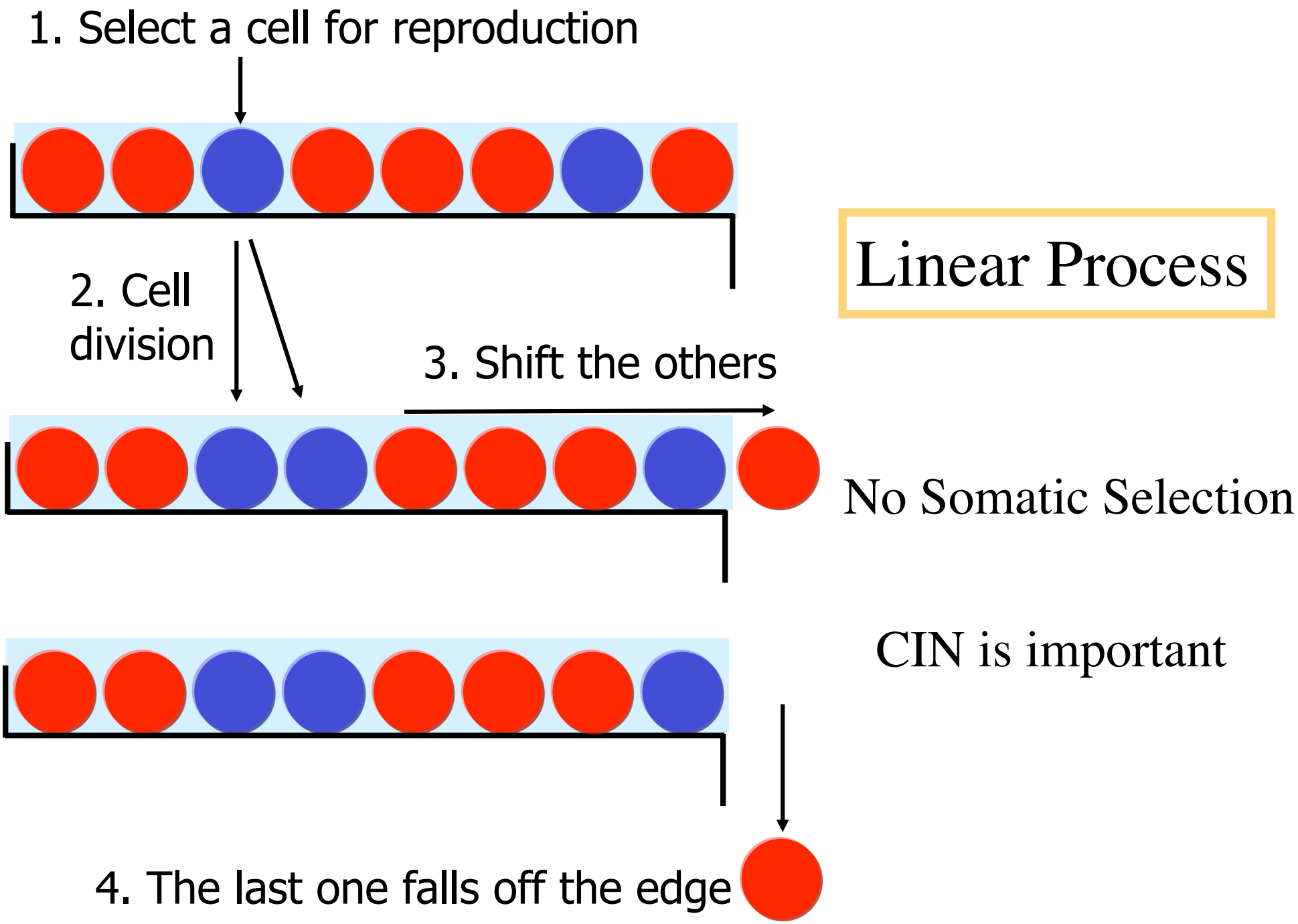
Mutants with higher fitness (gate-keeper)

Mutants with lower fitness (care-taker)

Small compartments
reduce the risk of mutants with higher fitness,
but enhance the risk of CIN.

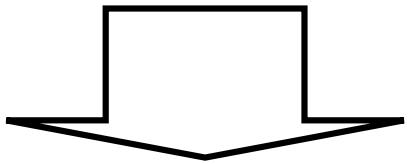
Moran Process




1. Select a cell for reproduction
2. Cell division
3. Shift the others
4. The last one falls off the edge
Linear Process
No Somatic Selection
CIN is important

(1) Compartmentalization

(2) Stem cells/non-stem cells



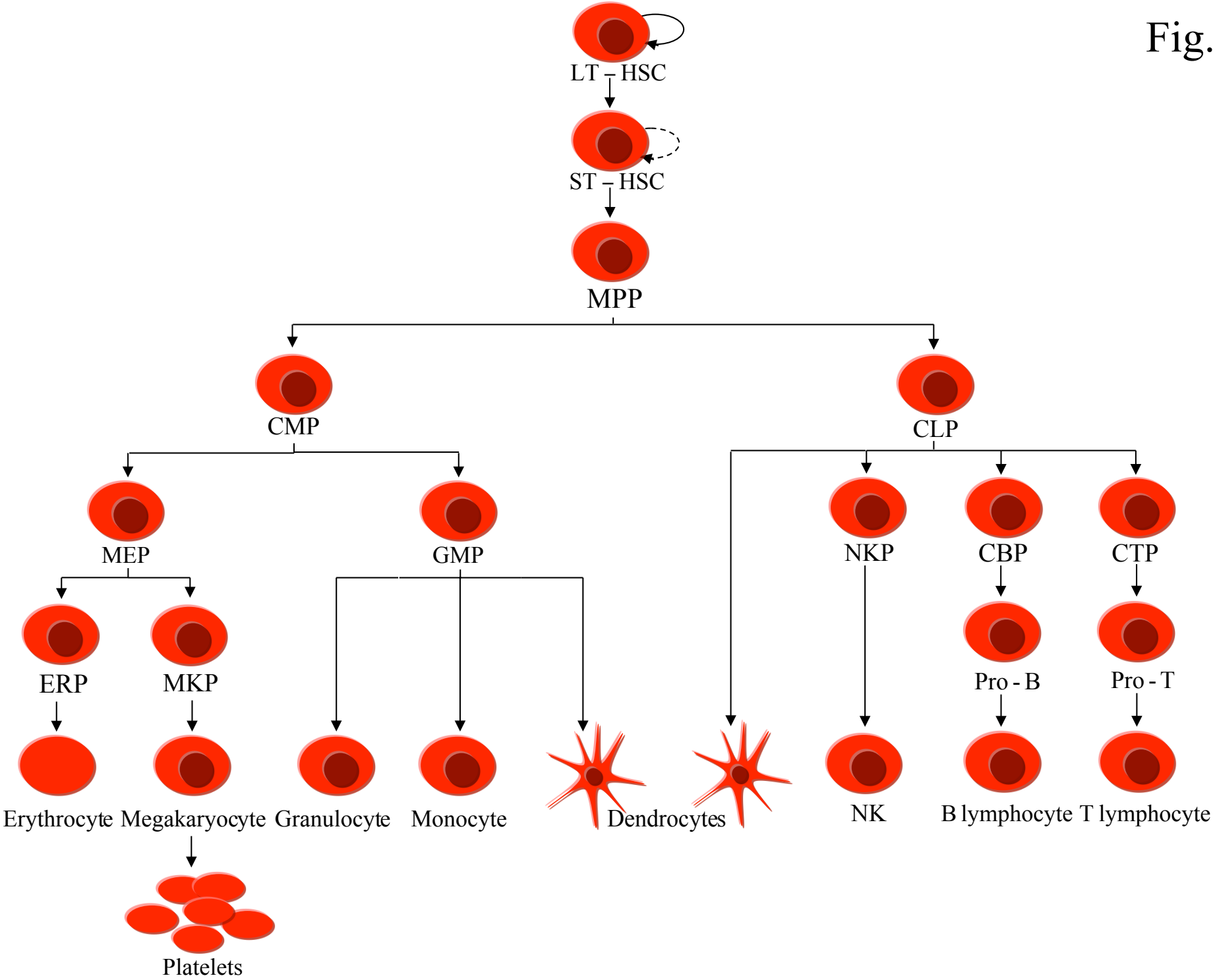
Somatic Selection is Suppressed

Risk via High Fitness Mutants is Reduced

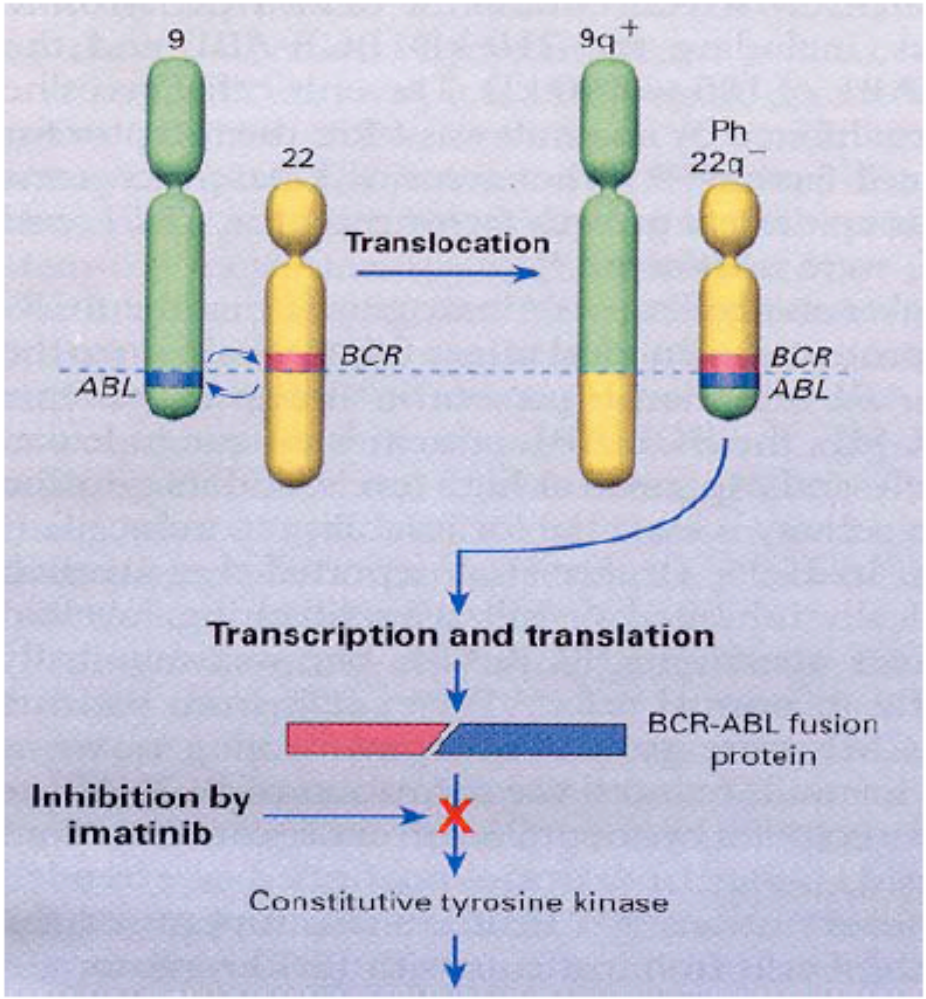
Risk via Low Fitness Mutants is Enhanced
(e.g. CIN)

Dynamics of Chronic Myeloid Leukemia (CML)

Fig. 1

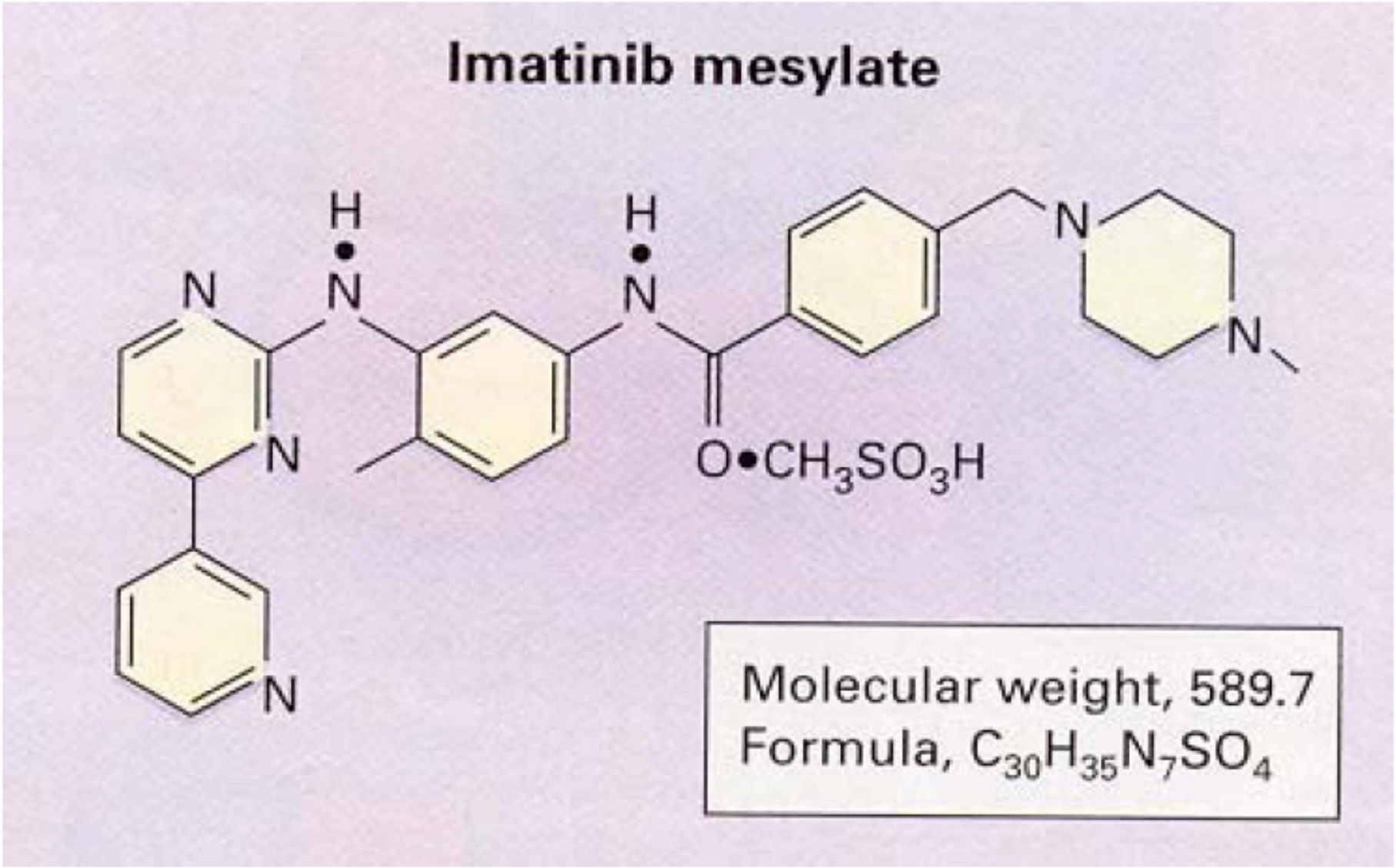

LT – HSC
ST – HSC
MPP
CMP
CLP
MEP
GMP
NKP
CBP
CTP
ERP
MKP
Pro - B
Pro - T
Erythrocyte
Megakaryocyte
Granulocyte
Monocyte
Dendrocytes
NK
B lymphocyte
T lymphocyte
Platelets

The Philadelphia chromosome arises by a translocation between chromosomes 9 & 22

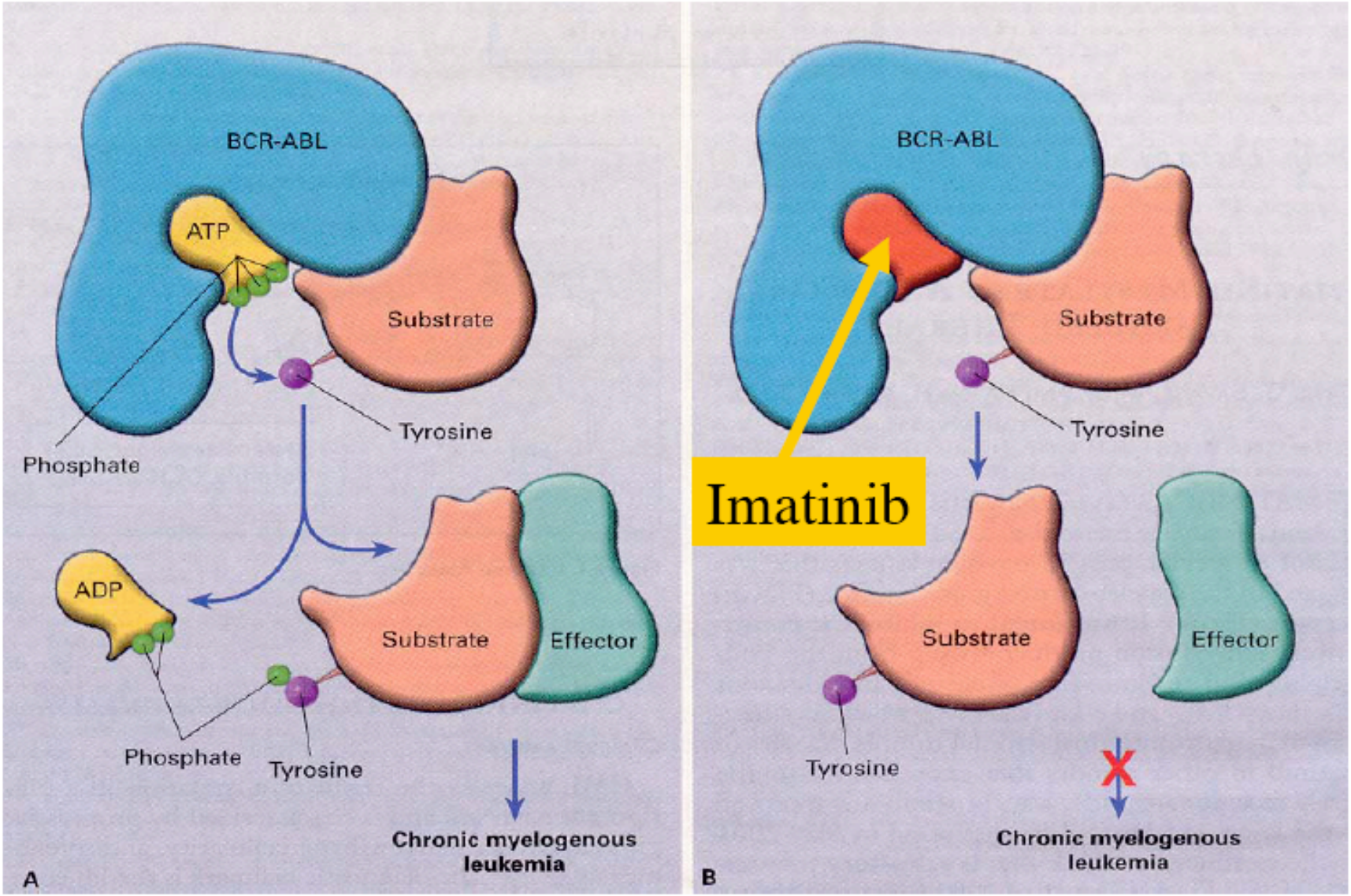


Chronic myeloid leukemia

Imatinib (Gleevec) is an inhibitor of BCR-ABL

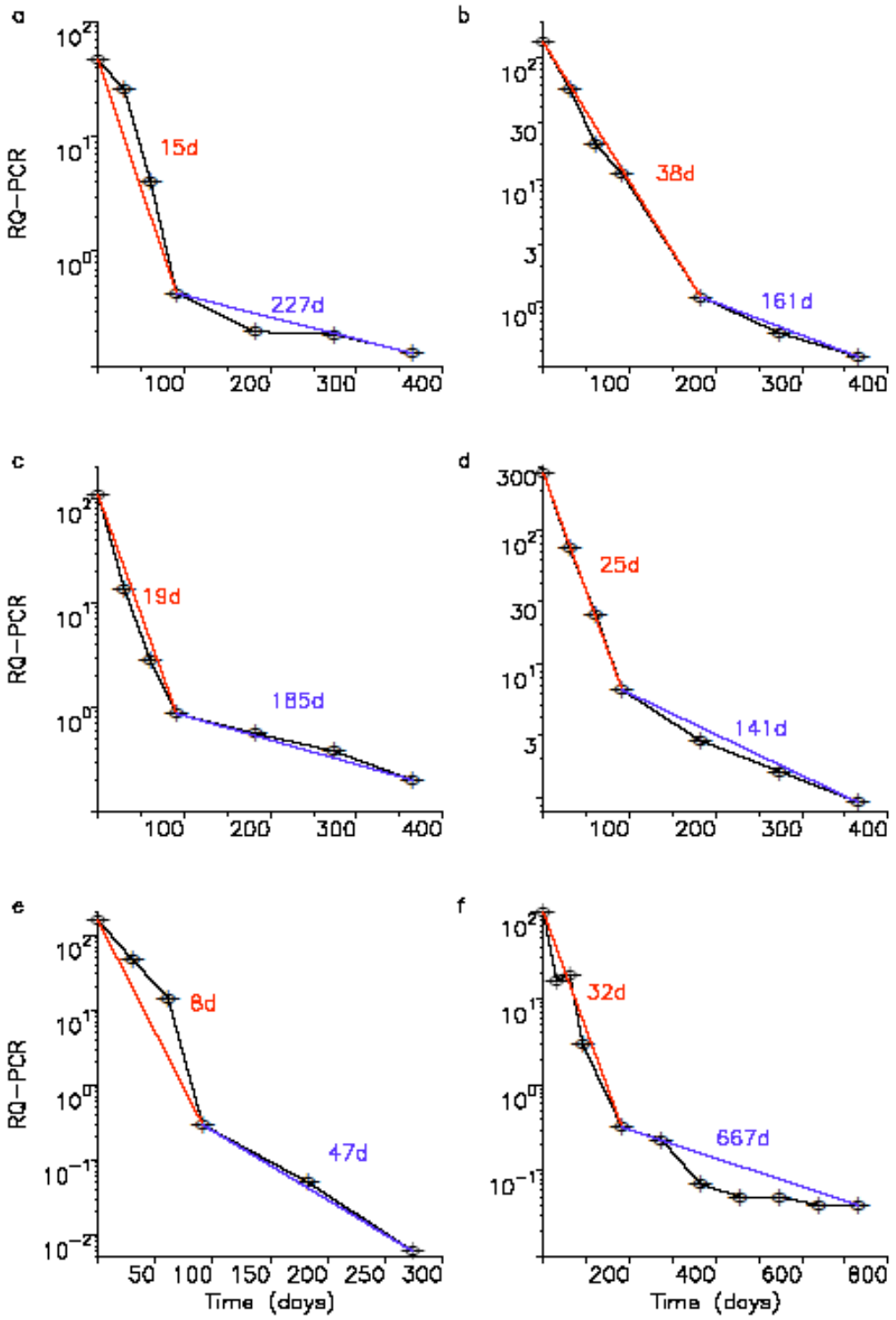


Imatinib is an inhibitor of BCR-ABL

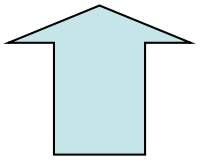


Imanitib is a very effective drug.

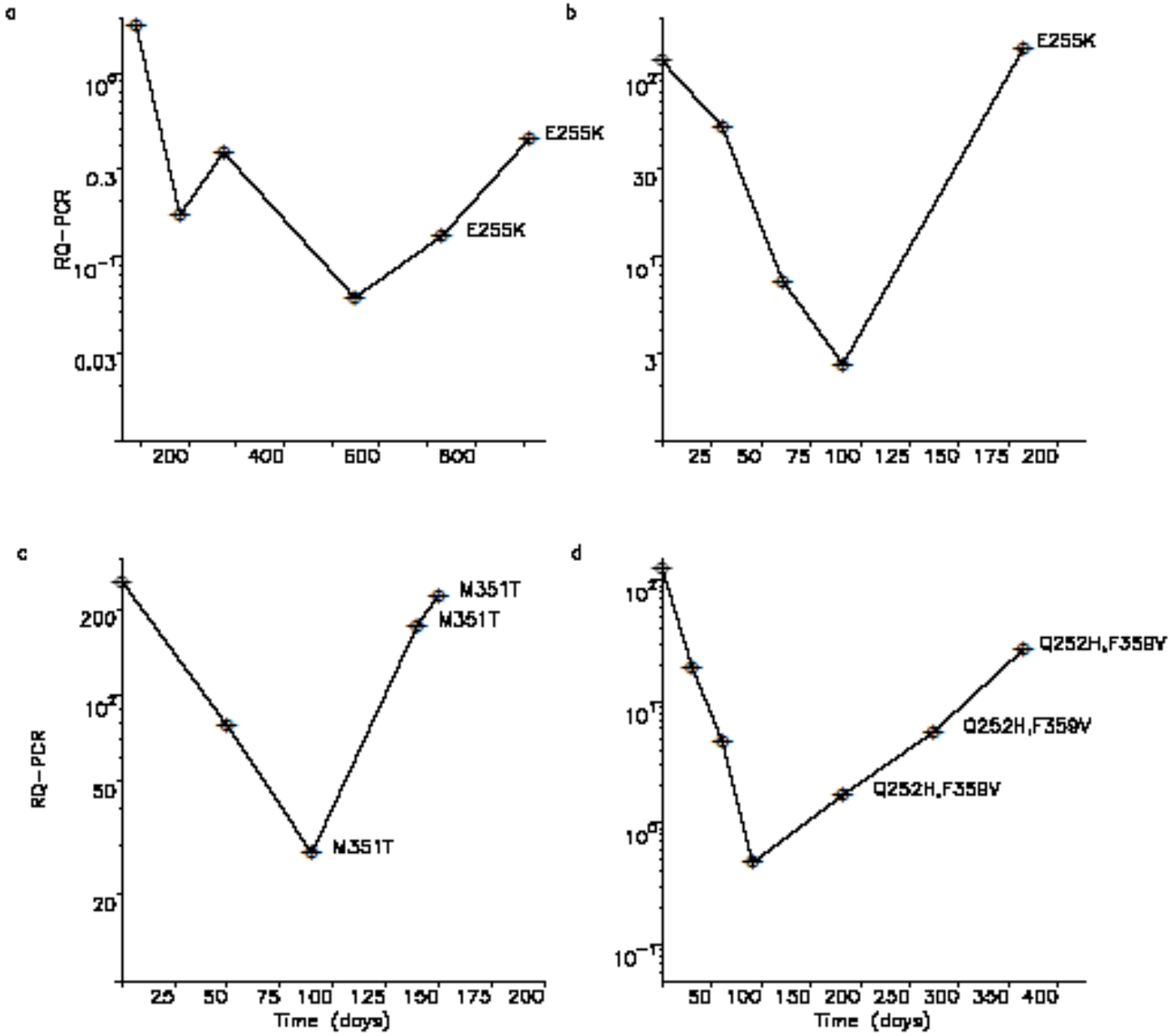
Under treatment cancer cells decrease in two phases



Resurgence

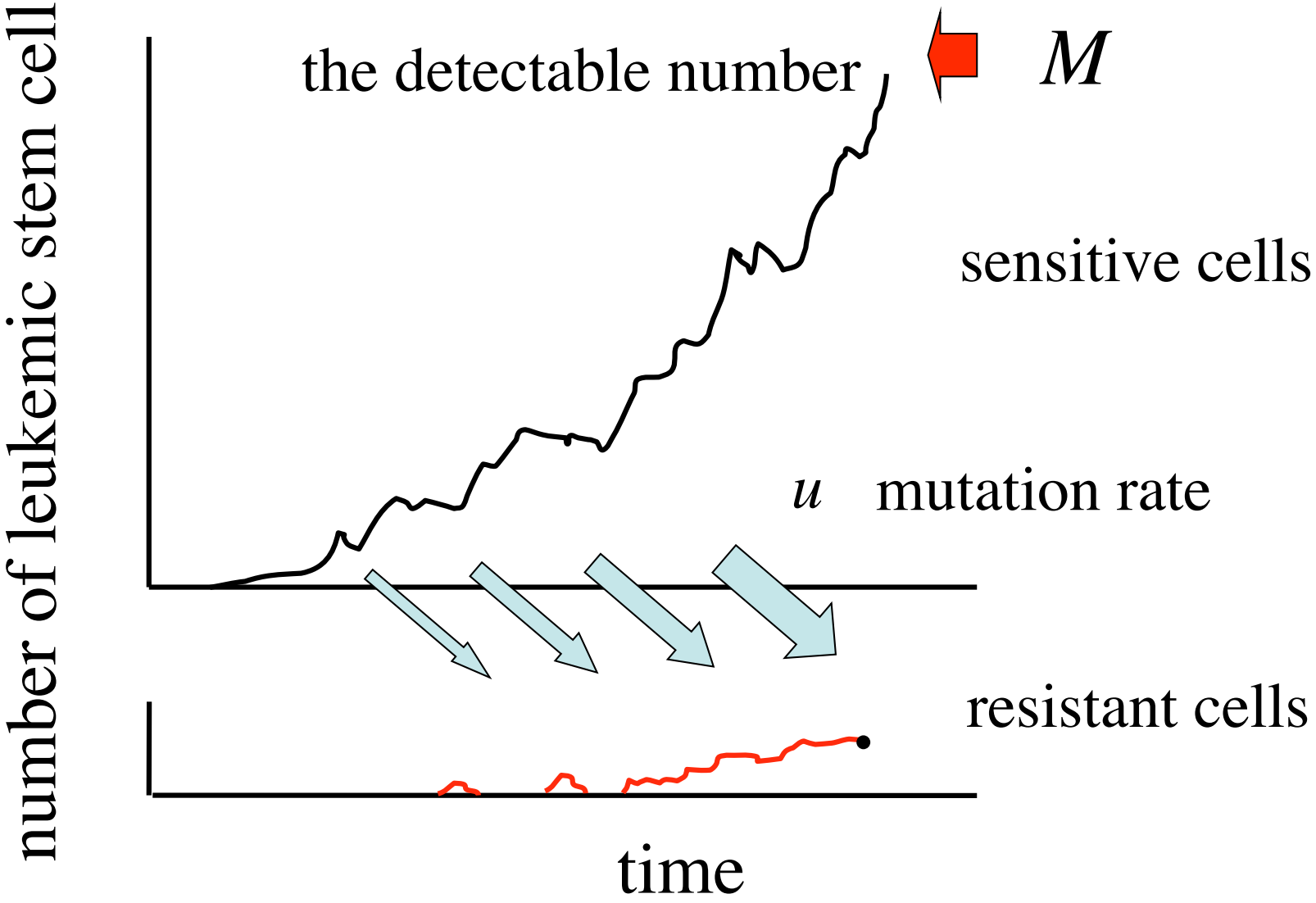


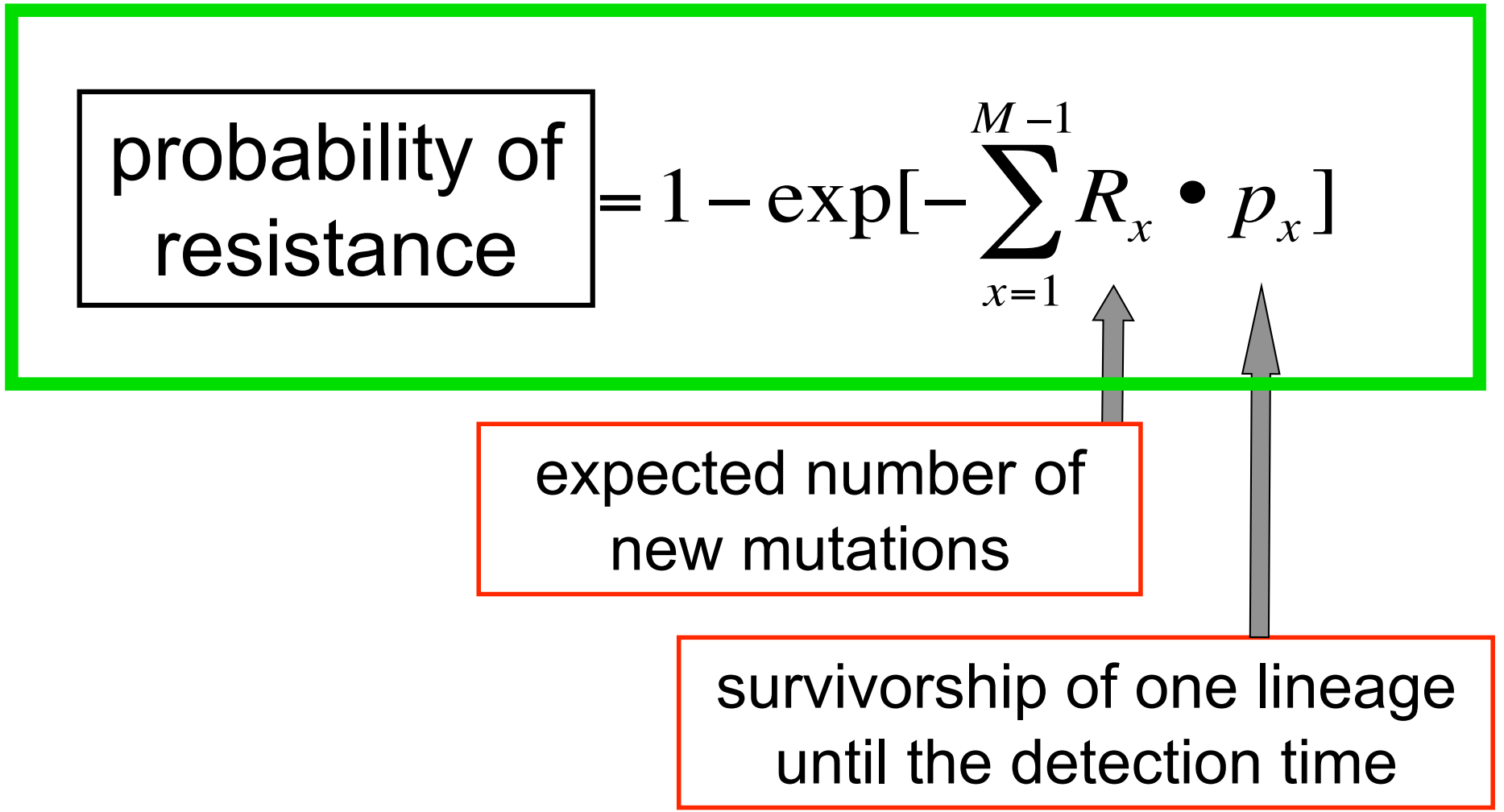
Resistant cells



What is the probability
for one or more stem cells to
be resistant to the drug
at the time of diagnosis?

Model for the number of resistant cells when sensitive cell number reaches *M*





x :the number of sensitive cells when the mutant is produced

R_x is the expected number of new mutations when the number of sensitive cells is x .

$$R_x = \frac{rux}{1 - d/r} \int_0^\infty f_x(t)\,dt$$

r: division rate
d: death rate
u: mutation rate

the probability
that there are x sensitive cells at time t

$$f_1(0) = 1, \quad f_x(0) = 0 \qquad \text{for } x = 2, 3, ..., M-1$$

$$\frac{df_1}{dt} = 2df_2 - (r+d) f_1$$

$$\frac{df_x}{dt} = r(x-1) f_{x-1} + d(x+1) f_{x+1} - (r+d) x f_x$$

$$\frac{df_{M-1}}{dt} = r(M-2) f_{M-2} - (r+d)(M-1) f_{M-1}$$

generating function:

$$\bar{g}(\xi,t) = E[\xi^{Z(t)} \mid Z(0) = 1] \Rightarrow \bar{g}(\xi,0) = \xi$$

$$\bar{g}(\xi,t+\Delta t) = a\Delta t\bar{g}(\xi,t)^2 + b\Delta t \bullet 1 + (1-(a+b)\Delta t)\bar{g}(\xi,t)$$

$$\Leftrightarrow \frac{\partial \bar{g}}{\partial t} = (a - b\bar{g})(1-\bar{g})$$

$$\Leftrightarrow \bar{g}(\xi,t) = \frac{(\xi-1)(b/a)e^{(a-b)t} - (\xi - b/a)}{(\xi-1)e^{(a-b)t} - (\xi - b/a)}$$

$$M = x\exp[(r-d)t] \quad \Rightarrow \quad t = \frac{1}{r-d}\log(\frac{M}{x})$$

$$p_x = \left(1-\frac{b}{a}\right) \Bigg/ \left[1-\frac{b}{a}\left(\frac{x}{M}\right)^{(a-b)/(r-d)}\right]$$

a: division rate *b*: death rate *M*: detection size

Probability of Resistance

$$P = 1 - \exp\left[-\frac{MuF}{1 - d/r}\right]$$

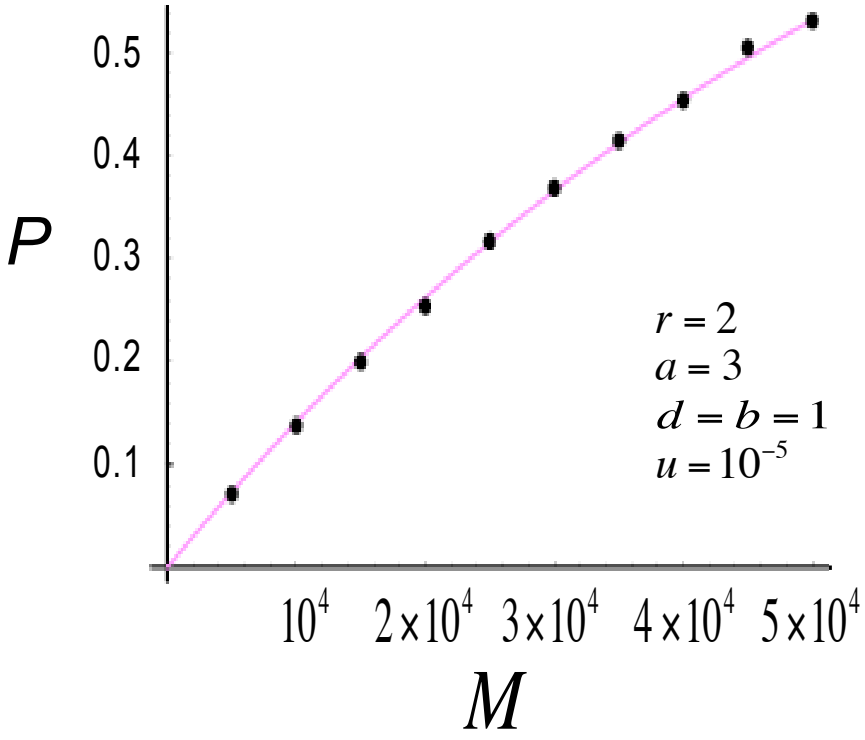
where $$F = \int_0^1 \frac{1 - b/a}{1 - (b/a)\, y^{(a-b)/(r-d)}}\, dy$$

M : detection size u : mutation rate

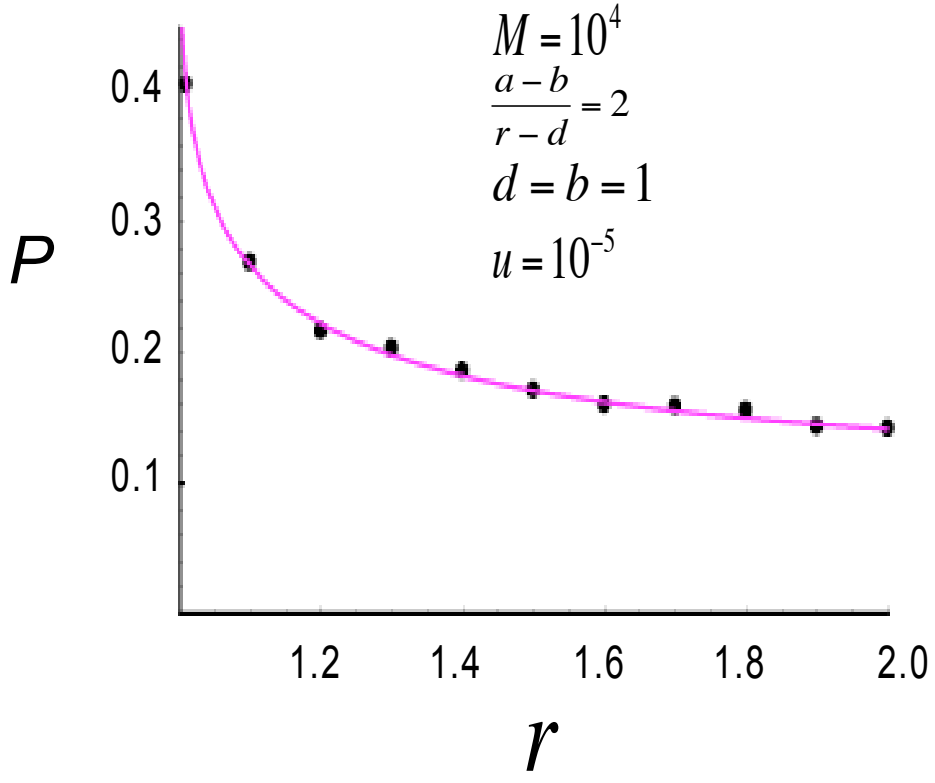
r, d : division/death rate (sensitive cells)

a, b : division/death rate (resistant cells)

Simulation results fit the formula.

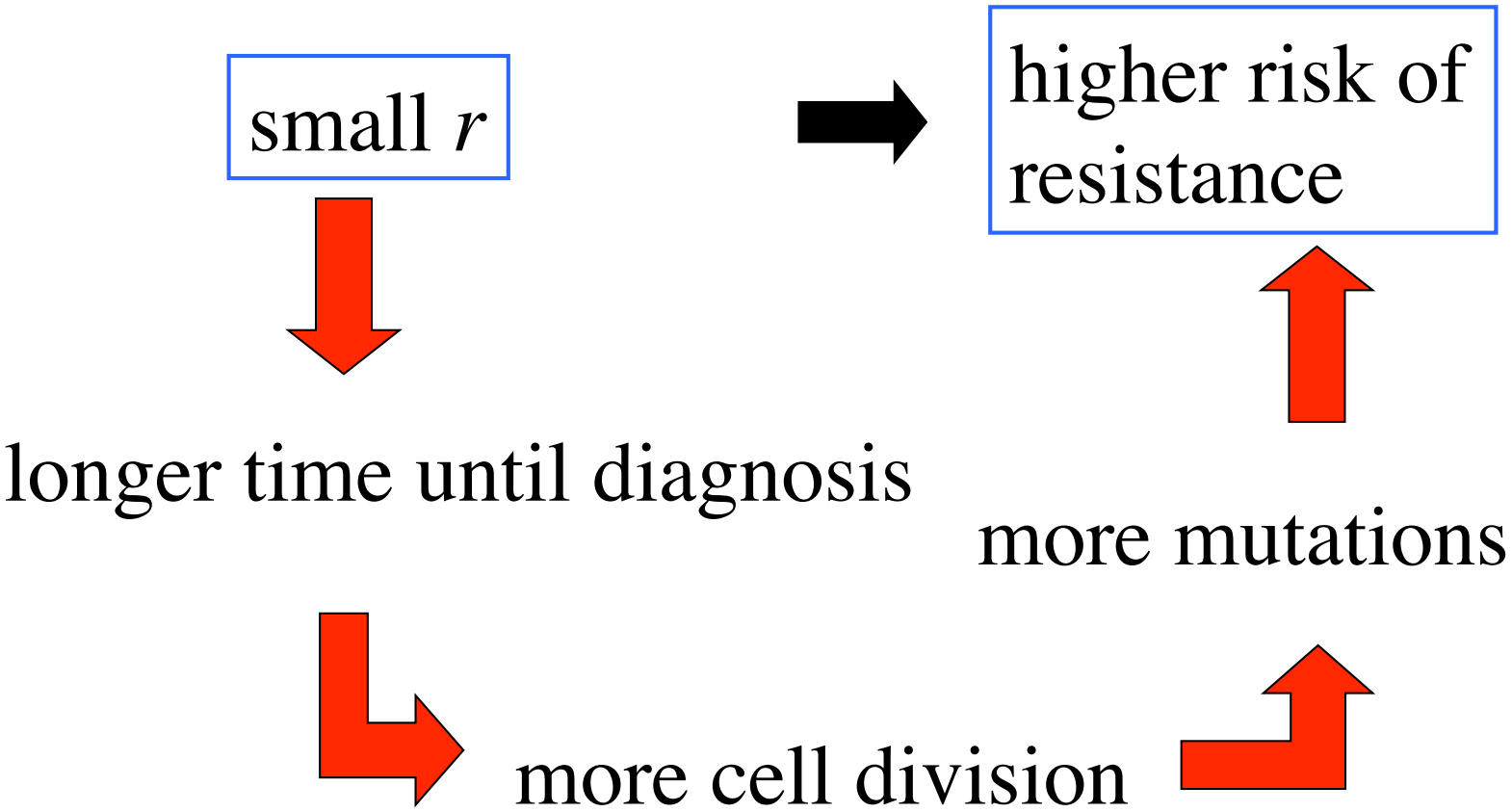


(detection size)



(division rate)

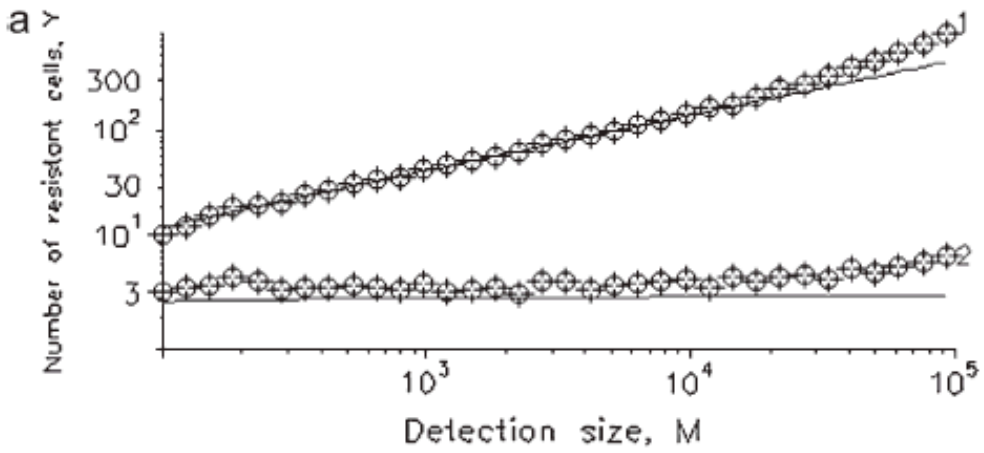
Slow growth implies higher risk of resistant cells

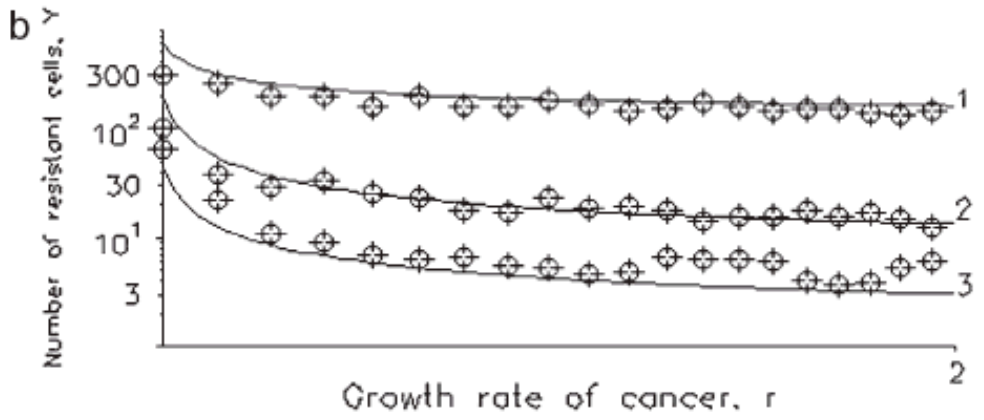


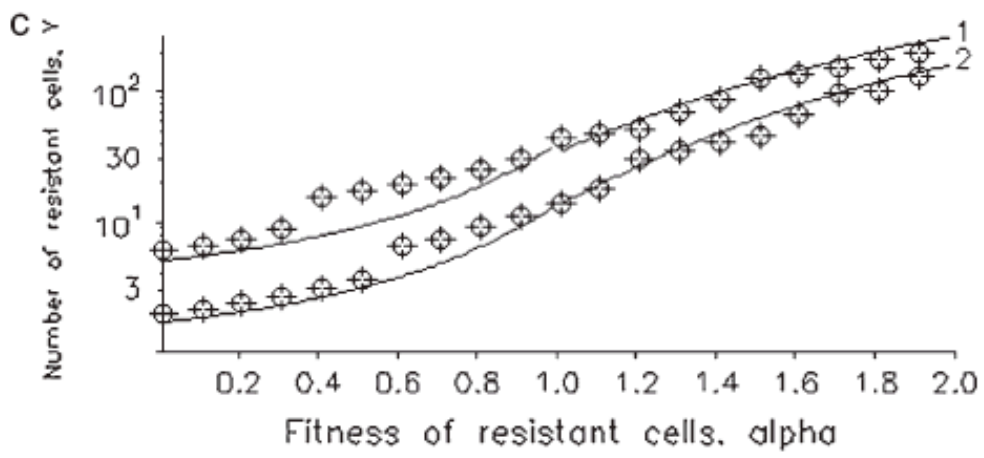
Mean number of resistant cells (conditional to one or more resist. cells)

$$\bar{Y} = \frac{G'(1)}{P} = \frac{u}{P(1-d/r)} \sum_{x=1}^{M-1} \left(\frac{M}{x}\right)^{\alpha}$$
$$\approx \frac{Mu\left(1 - 1/M^{1-\alpha}\right)}{P(1-d/r)(1-\alpha)}.$$

$$\bar{Y} = \frac{1}{M}\left(\frac{M}{2}x_c + \sum_{x=x_C}^{M-1} (M/x)^{\alpha}/F\right)$$
$$\approx \frac{\alpha(M/2)^{1-1/\alpha}}{(\alpha-1)F^{1/\alpha}} - \frac{1}{(\alpha-1)F}.$$







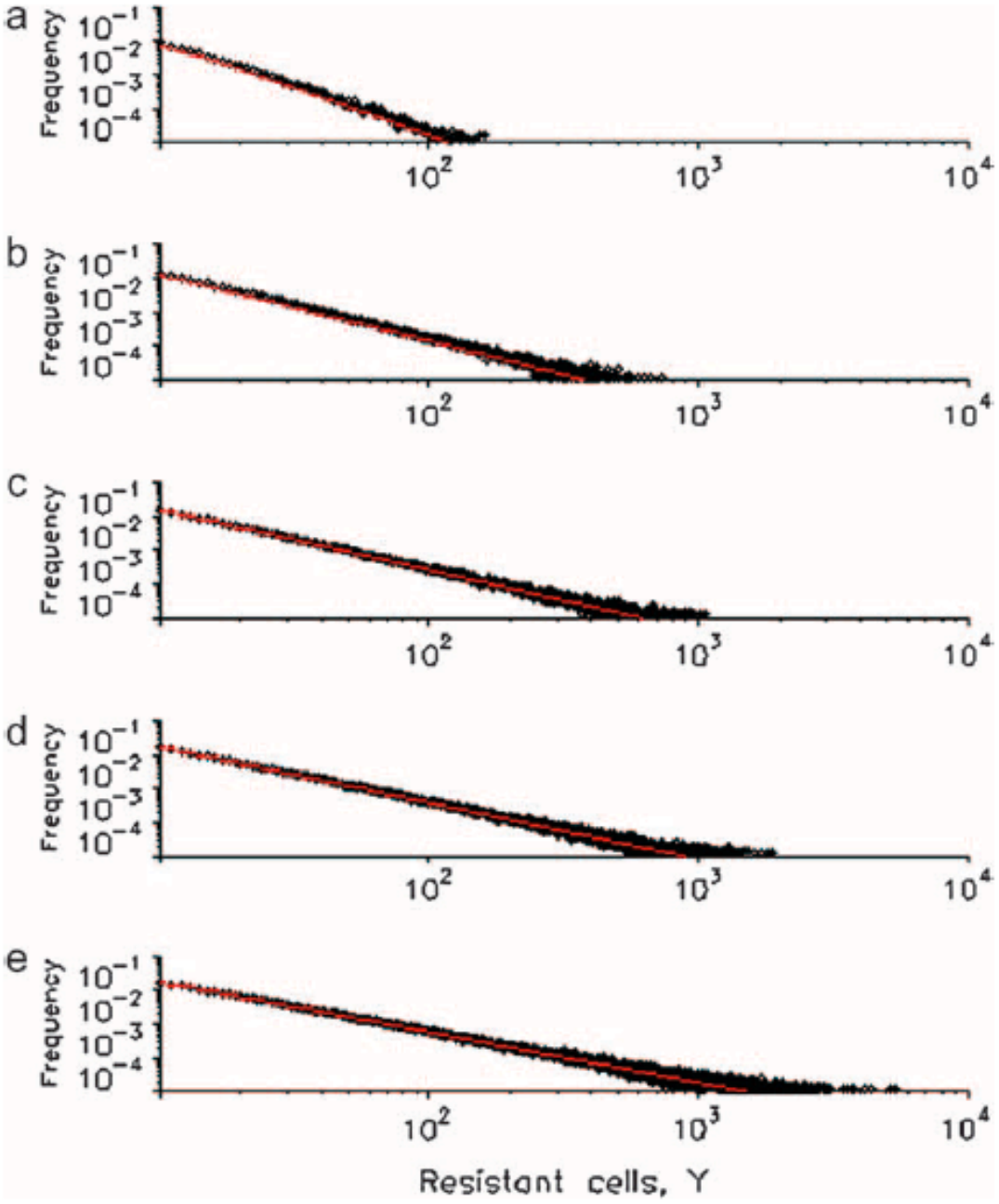
Distribution of resistant cell number

z: large

$$\Pr[y_1 < Y \le y_2] = \frac{1}{(Fy_1)^{1/\alpha}} - \frac{1}{(Fy_2)^{1/\alpha}}$$

z: small

$$\Pr[Y = y] = \frac{(1-b/a)^2}{\alpha F} \int_0^1 \frac{z^{1/\alpha}(1-z)^{y-1}}{(1-(b/a)z)^{y+1}} dz$$



Cancer Progression

is

Somatic Evolution.

Collaborators

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