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Evolutionary dynamics of cancer

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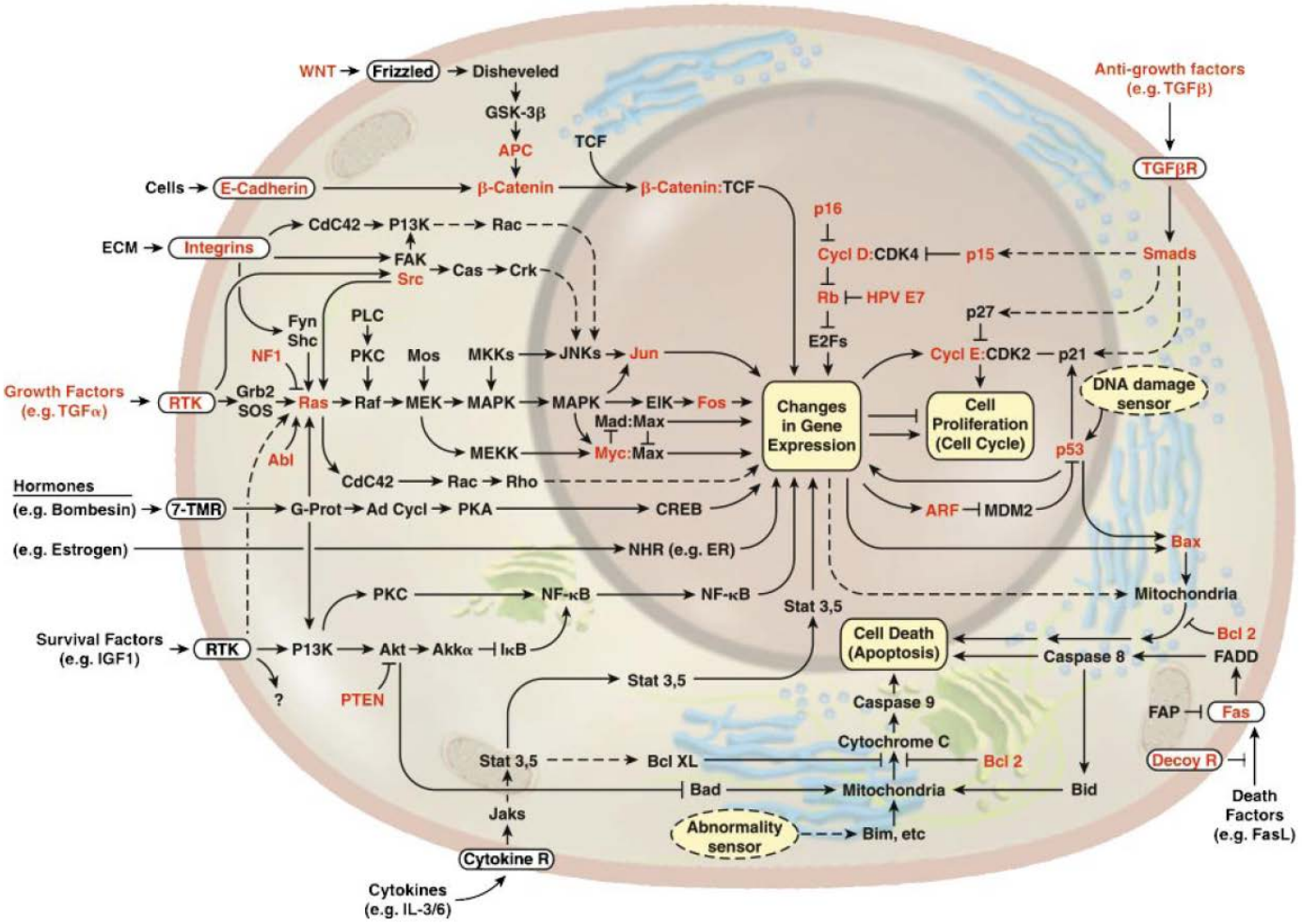
Outline

- Somatic evolution of cancer
- Oncogenes
- Tumor suppressor genes
- Genetic instability
- Dynamics of cancer initiation

Cancer is an evolutionary process

- For multicellular organisms to evolve from unicellular organisms, the major innovation was *cooperation* among many individual cells.
- Multicellular organisms maintain an elaborate control network of signaling pathways to maintain cooperative behavior and regular functionality.
- Cancer is a breakdown of cellular cooperation.
- The somatic (affecting non-germ cells) evolution of cancer is the uncontrolled, selfish replication of cells.
- These cells give rise to *tumors*, lesions formed by abnormal cell growth.

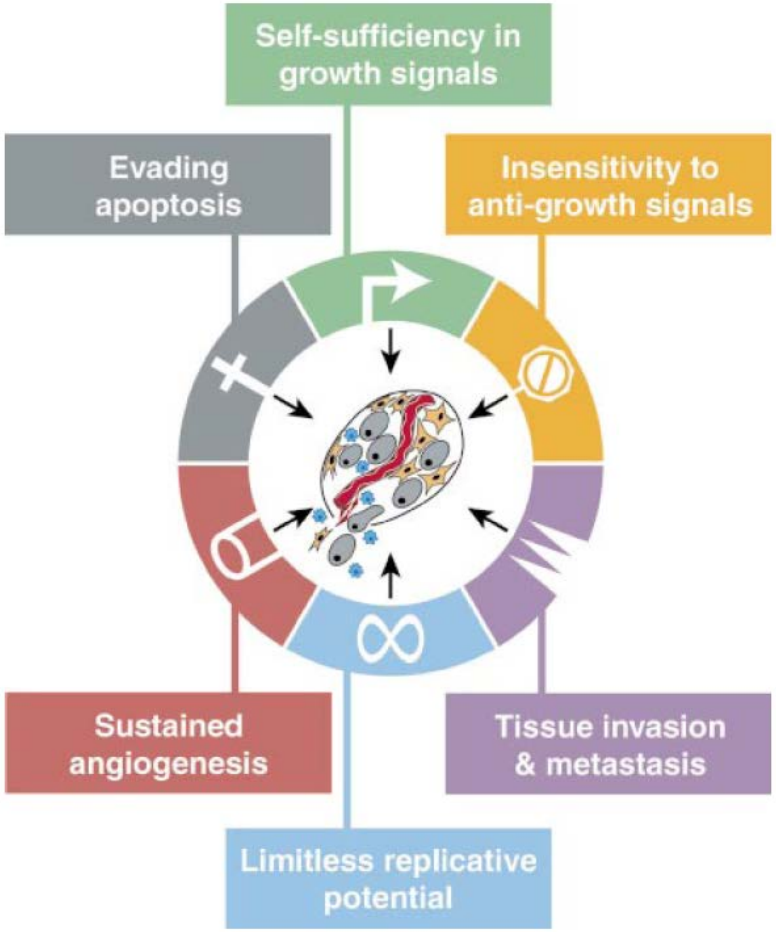
Snapshot of cell signaling pathways



cancer-associated genes

The hallmarks of cancer

- The cellular signaling network controls several properties whose breakdown is key to the development of cancer:
  - integrity of the genome
  - timely and correct cell division
  - monitoring of cell status and initiation of programmed cell death (apoptosis) if necessary.
  - cell motility



Cancer is a genetic disease

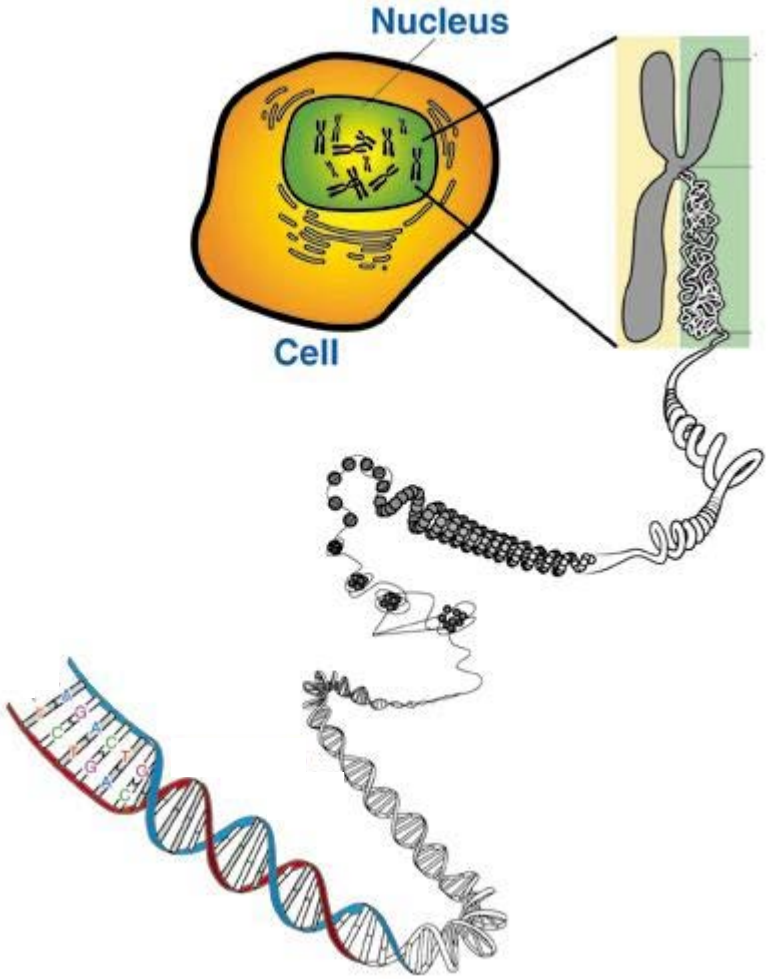
- Cancer progression is characterized by the accumulation of mutations in genes that participate in maintaining cellular cooperation.

- A relatively large fraction of mutations will increase the somatic fitness of cells, because their effect is to inactivate signaling pathways.

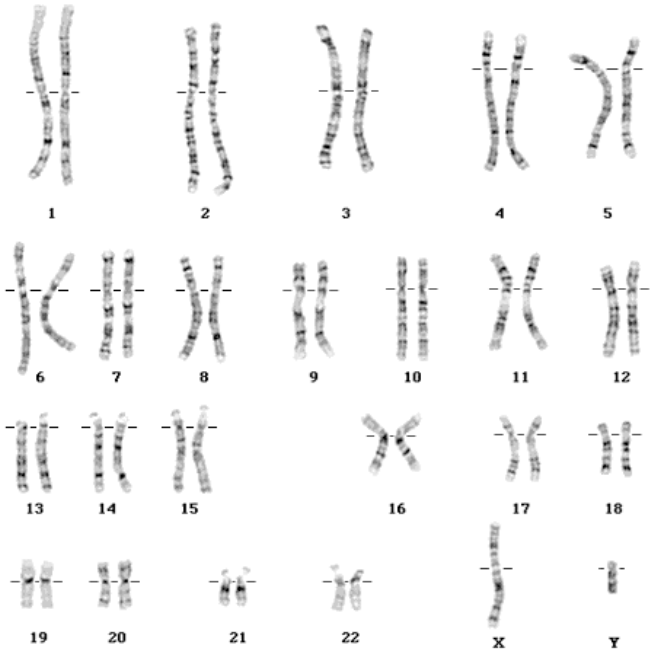
- Thus, cancer is the *evolution of defection*.

Genetic alterations in cancer cells

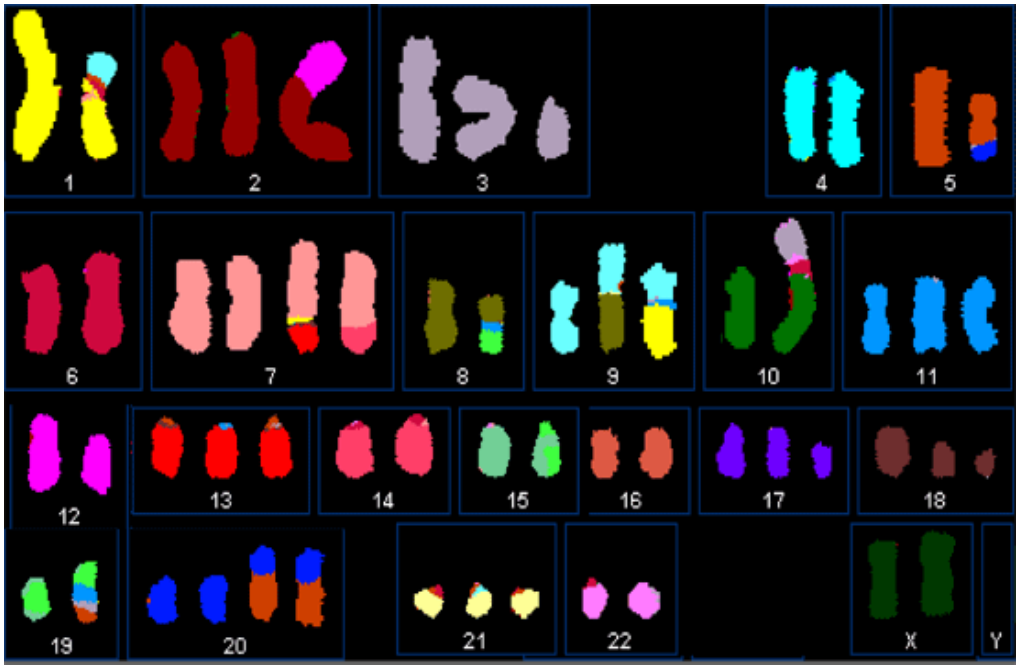
- We will use the term “mutation” to denote any type of genetic alteration, including
  - point mutations
  - insertions
  - deletions
  - chromosome rearrangements
  - mitotic recombination
  - loss or gain of whole chromosome arms



Most cancer cells are *aneuploid*



normal karyotype

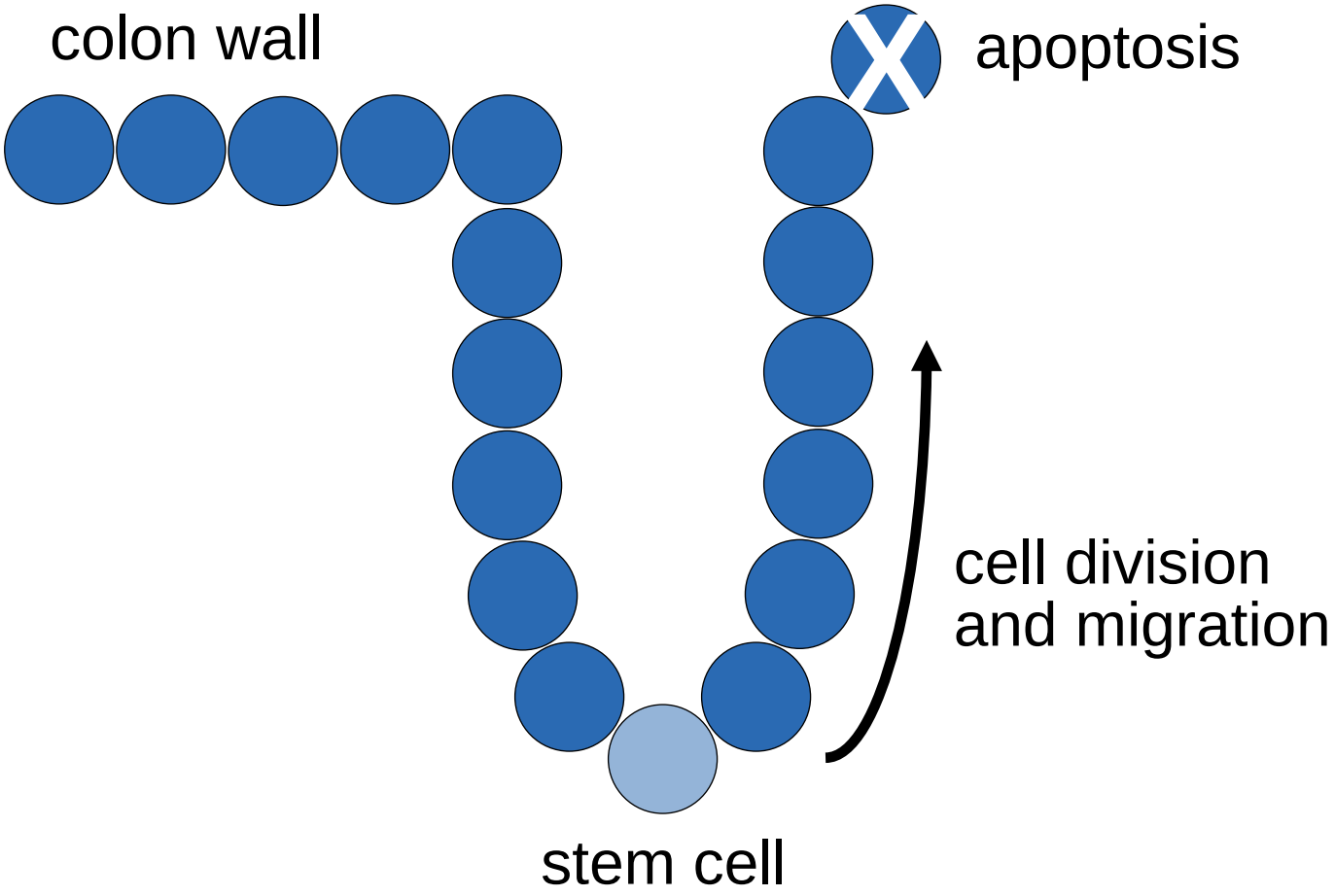


karyotype of a colon cancer cell

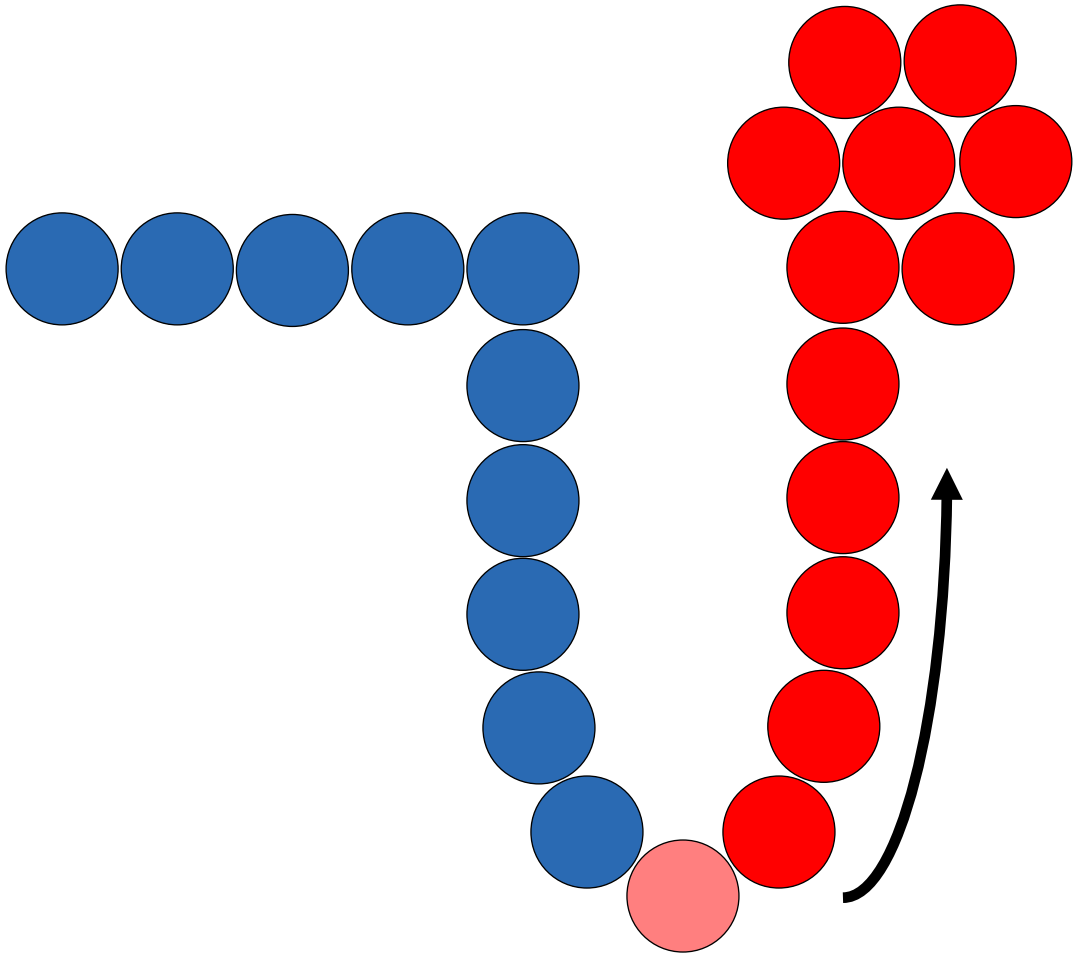
Example: colon cancer

- The epithelial layer of the colon has a very high cellular turnover.
- Therefore, these dividing cells are at high risk of being hit by mutations.
- The geometry of the tissue architecture reduces this risk.

The colon is organized into 10^7 crypts. Each crypt consists of 1,000 to 4,000 cells.

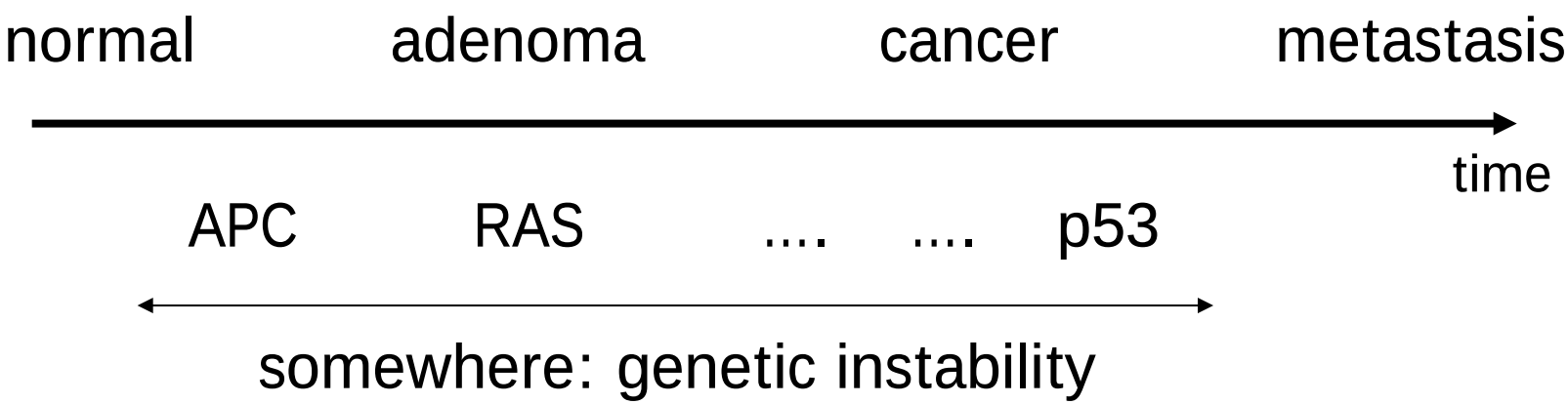


Colon cancer arises in a crypt



polyp
(~1mm^3, ~10^6 cells)

Colon cancer susceptibility genes



- APC is mutated in 95% of colon cancer cases.
- APC and p53 are examples of *tumor suppressor genes*.
- RAS and BRAF are examples of *oncogenes*.
- *Genetic instability genes* are responsible for DNA copying fidelity. Their mutation results in elevated mutation rates.

Oncogenes

- Oncogenes increase fitness if one allele is mutated or inappropriately expressed. They are activated by:

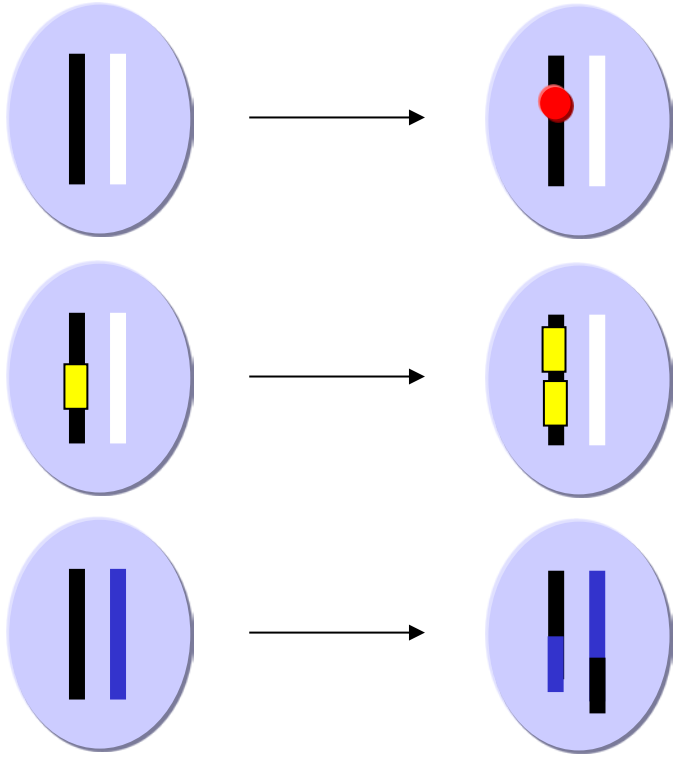
1. a specific point mutation

or

2. a gene amplification

or

3. chromosomal fusion



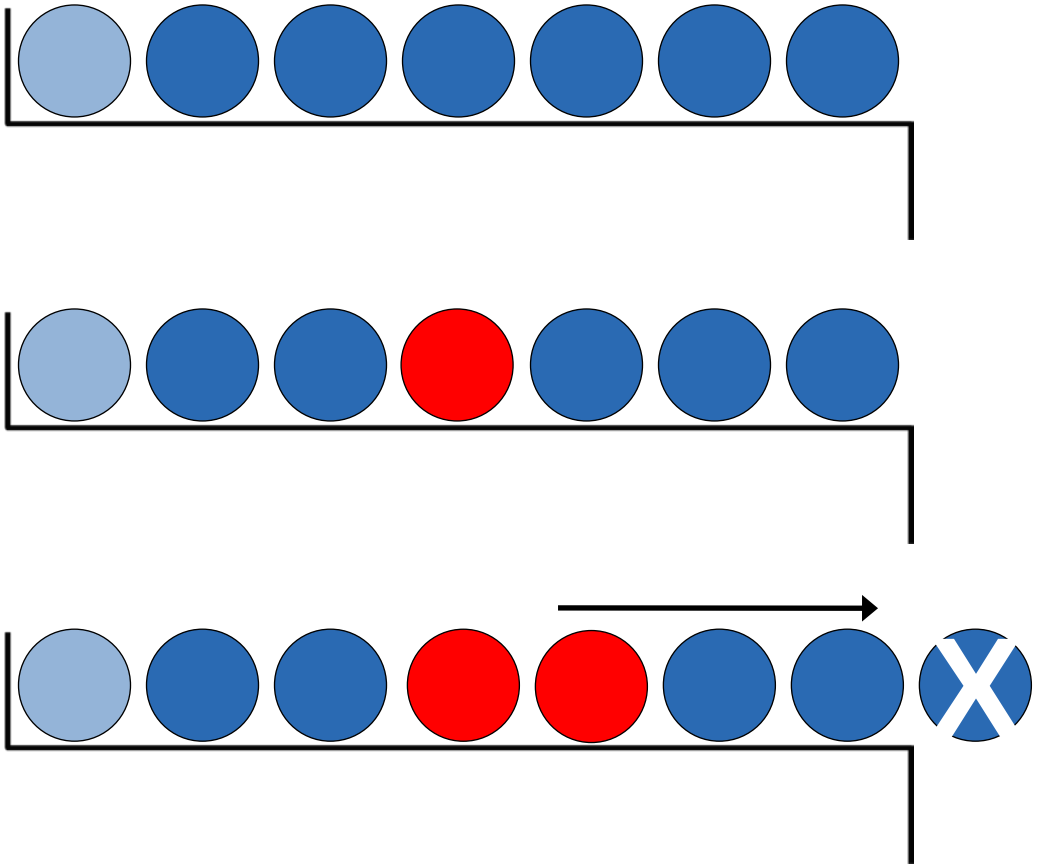
Fixation of oncogene mutations

- We consider the Moran process in a (small) compartment of initially normal cells with effective population size N.
  - Mutants arise with probability u and have relative fitness r (r > 1 advantageous, r = 1 neutral, r < 1 deleterious).
  - The fixation probability is $\rho = x_1 = (1 - 1/r)/(1 - 1/r^N)$.
- The probability that a mutant has been fixed by time t is

$$P(t) = 1 - e^{-Nu\rho t}$$

- P(t) is increasing in N if r > 1, and decreasing in N if r < 1.
- Large compartments accelerate the accumulation of advantageous mutations, small compartments slow it down.
- Most tissues with high cell turnover are organized in many small compartments.

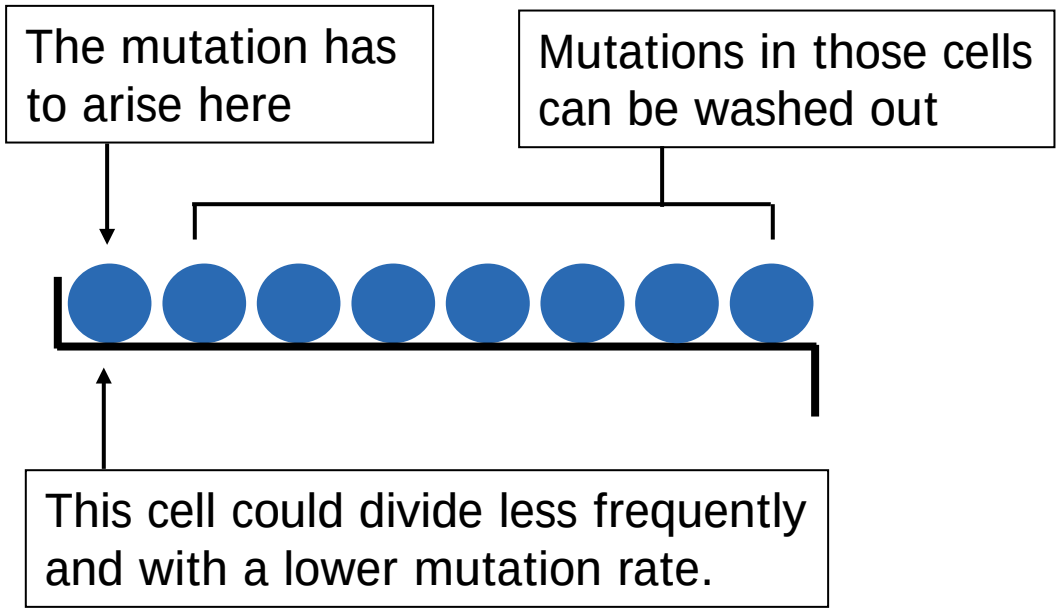
The linear process of cancer



The linear process delays advantageous mutations

- A mutant with relative fitness difference r has fixation probability $\rho = 1/N$, because only a mutation in the left most stem cell leads to fixation; all other mutants are “washed out”.
- The probability that the mutant has taken over by time t is $P(t) = 1 - e^{-ut}$ and independent of r.
- In contrast to well-mixed populations, where advantageous mutations accumulate faster, all types of mutations (advantageous, neutral, or deleterious) have the same fixation probability in the linear process.

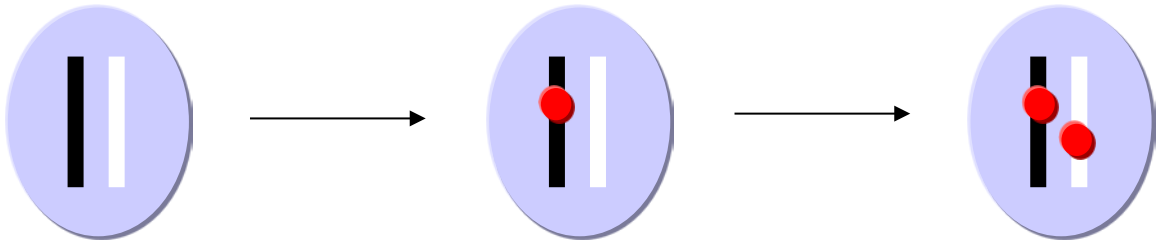
Linear design reduces the mutational load



The perfect design to protect against mutations in tumor suppressor genes and oncogenes, but vulnerable to genetic instability.

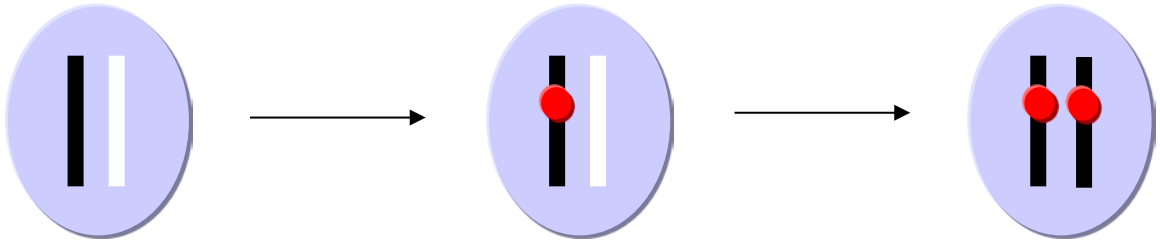
Tumor suppressor genes (TSGs)

- Somatic mutations in TSGs are recessive: inactivation of one allele is (nearly) neutral, while inactivating the second allele confers a fitness advantage. TSGs are inactivated by
  1. two point mutations



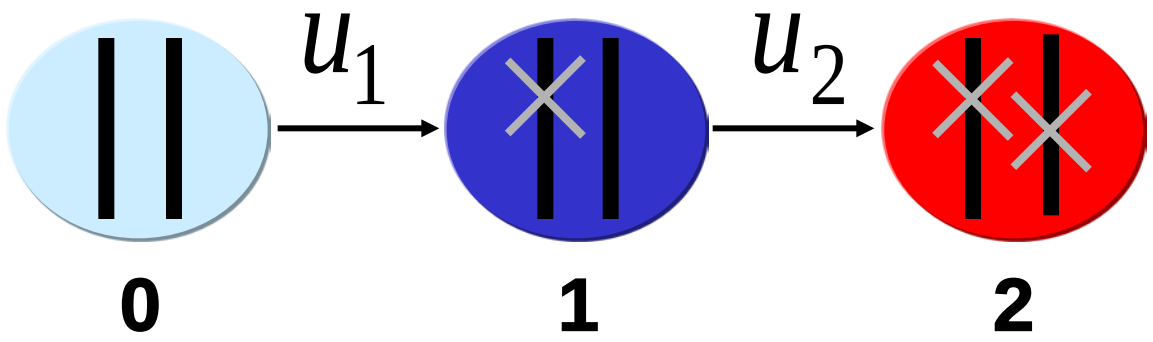
or

  2. one point mutation followed by loss of heterozygosity (LOH).



Dynamics of TSG inactivation

- We consider a TSG, A, and write
  - $A^{+/+}$, or “type 0”, if both alleles are unmutated (wild type)
  - $A^{+/-}$, or “type 1”, if one allele is mutated
  - $A^{-/-}$, or “type 2”, if both alleles are mutated



- In a population of size N, what is the probability that at least one cell has been hit by two mutations by time t?

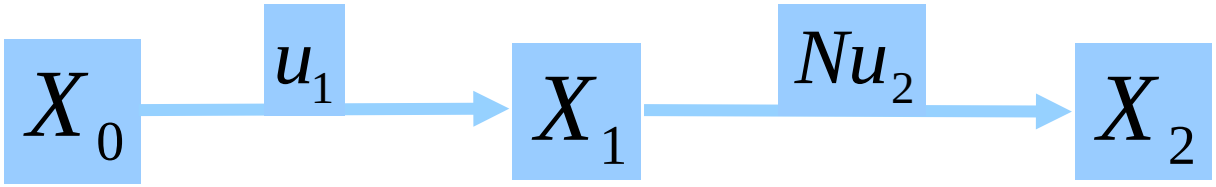
Small population size

- The average fixation time of the first mutation is $1/\rho$ = N in the Moran process.
- The average waiting time for the second mutation (in any cell) is $1/(Nu_2)$.
- So, type 1 cells reach fixation before a type 2 cell arises, if

$$N \ll 1/(Nu_2) \quad \Longleftrightarrow \quad N \ll 1/\sqrt{u_2}$$

- In this case, the dynamics can be described by the probabilities $X_i(t)$ of being in the three states i = 0, 1, 2.
  - State 0: all cells are of type 0
  - State 1: all cells are of type 1
  - State 2: at least one cell is of type 2

Three-state ODE model



$$\dot{X}_0 = -u_1 X_0$$
$$\dot{X}_1 = u_1 X_0 - N u_2 X_1$$
$$\dot{X}_2 = N u_2 X_1$$

- Initially, X(0) = (1, 0, 0). For $t \to \infty$, X(t) $\to$ (0, 0, 1).
- Solution:

$$P(t) = X_2(t) = 1 - \frac{N u_2 e^{-u_1 t} - u_1 e^{-N u_2 t}}{N u_2 - u_1}$$

Two hits in small populations

Three time scales

- For short times, $t \ll 1/(Nu_2)$, $P(t) \approx N\, u_1\, u_2\, t^2 / 2$, i.e., there are two rate limiting events (Knudson's two-hit theory).
- For long times, $1/(Nu_2) < t < 1/u_1$, $P(t) \approx 1 - \exp(-u_2\, t)$, i.e., only the first hit is rate limiting.
- For very long times (beyond human life time), $t \gg 1/u_1$, there are no rate limiting events.

- The number of rate limiting events is defined as the slope of $\log P(t)$ plotted versus $\log t$.
- It depends on the time scale.

Intermediate population size

- The average waiting time for a type 1 cell is $1/(Nu_1)$, which is long (i.e., > 1), if $N < 1/u_1$.
- A type 2 cell is generated before fixation of the type 1 lineage, if $N > 1 / (u_2)^{1/2}$.
- Thus, type 1 is "*tunneled*" in the intermediate regime

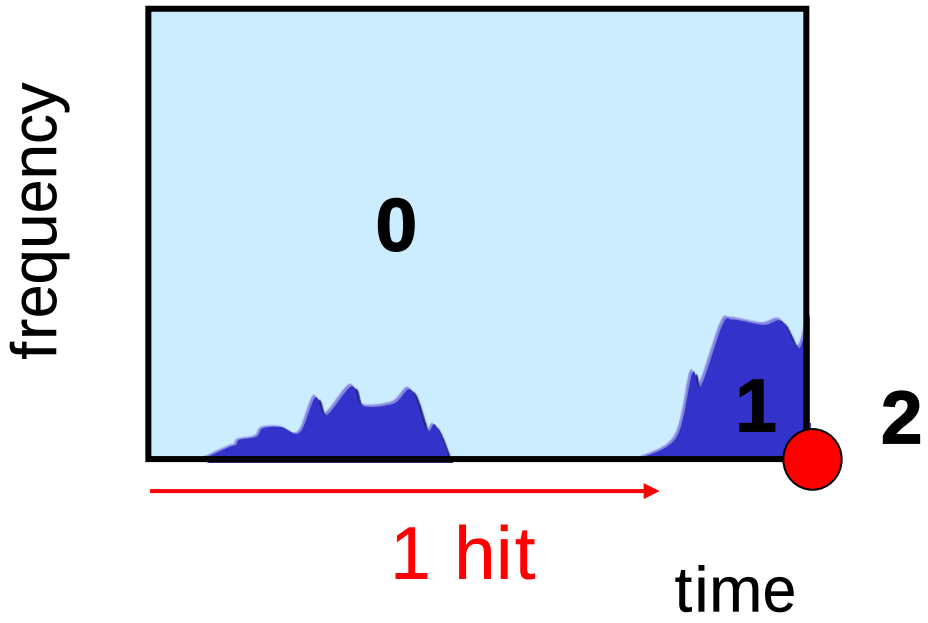
$$1/\sqrt{u_2} \ll N \ll 1/u_1$$

- In this parameter region, the probability that at least one cell with two hits has arisen before time t is

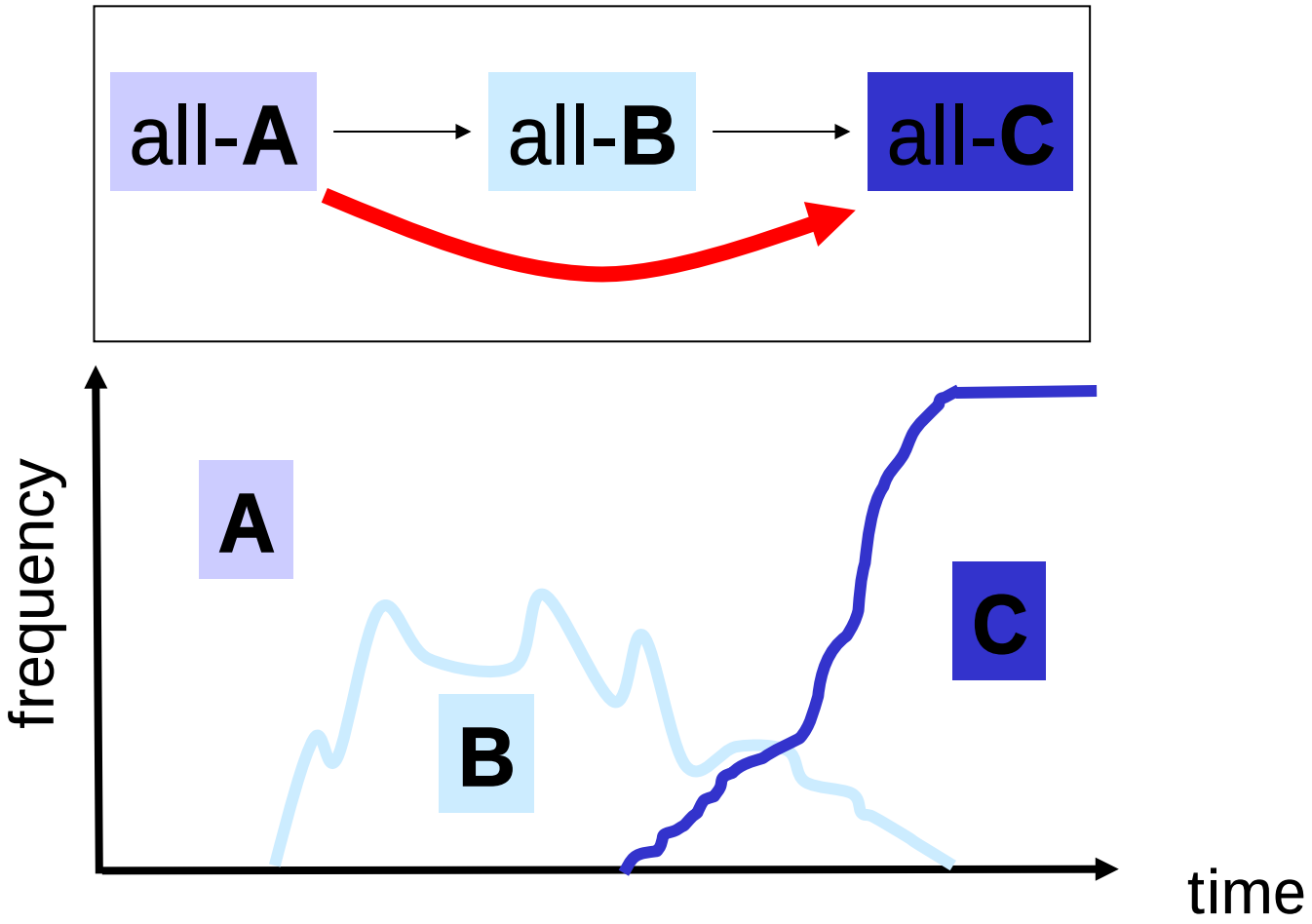
$$P(t) = 1 - e^{-Nu_1\sqrt{u_2}t}$$

(Komarova et al. 2003, Iwasa et al. 2005).

One hit in intermediate populations



Tunneling



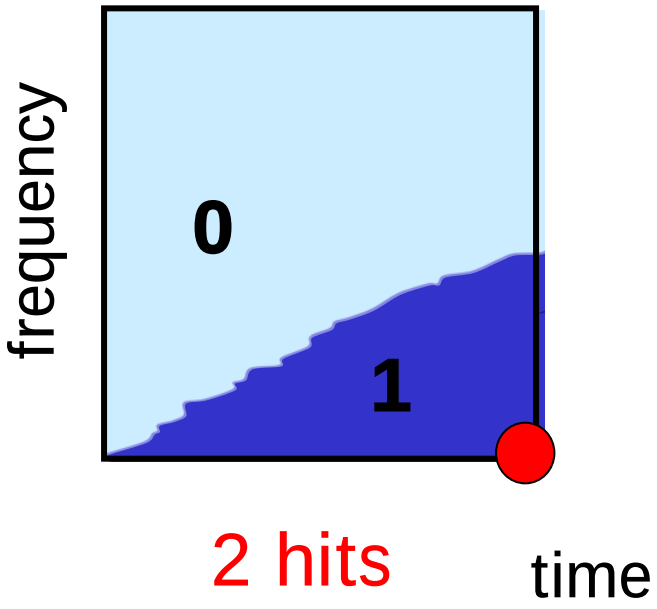
Large population size

- If $N \gg 1/u_1$ then type 1 cells are generated immediately and they grow according to $x_1(t) = N u_1 t$.
- The probability of producing a type 2 mutant during type 1 growth is

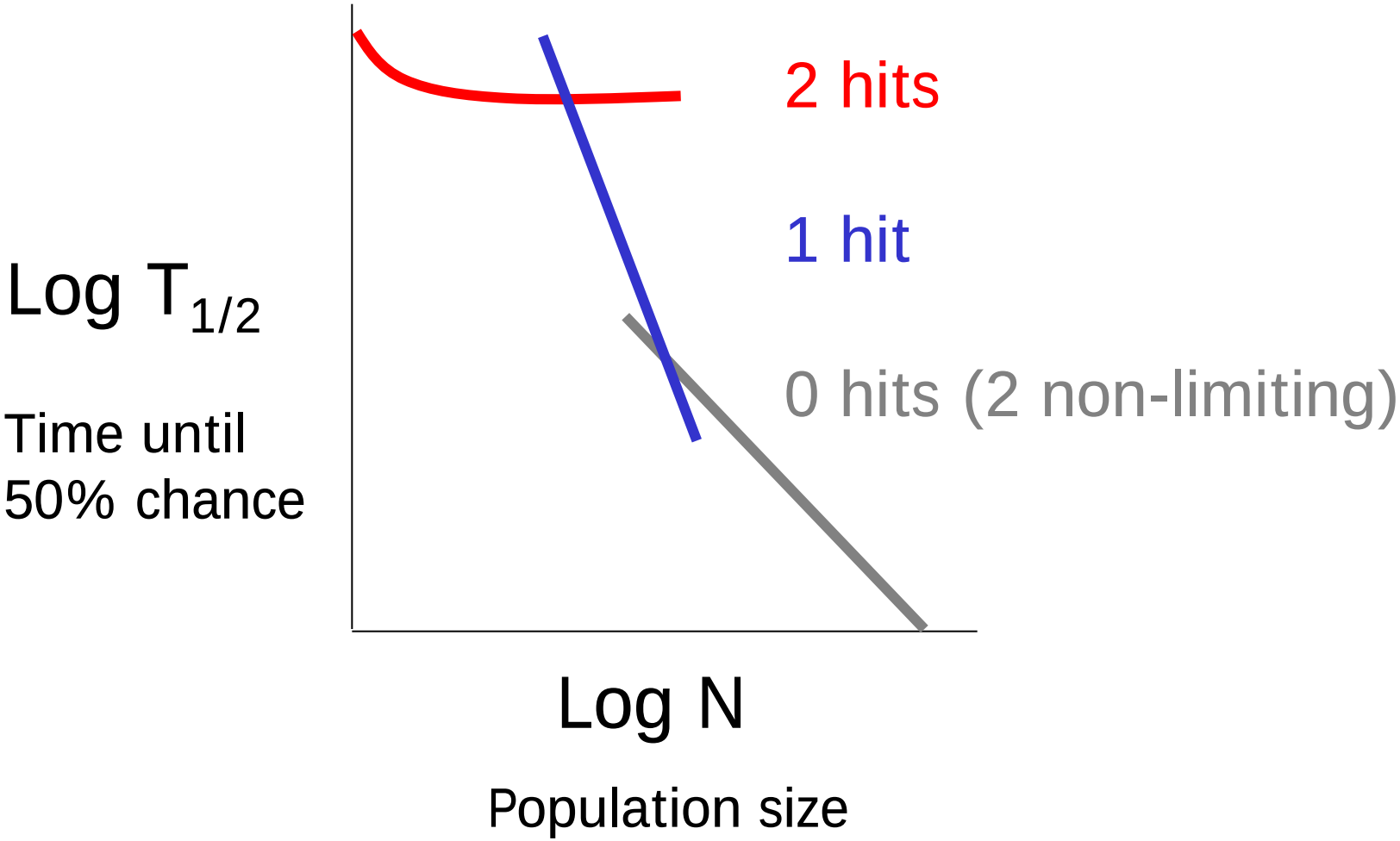
$$P(t) = 1 - \exp\left\{-u_2 \int_0^t x_1(t)dt\right\}$$

$$= 1 - \exp\left(-\frac{1}{2} N u_1 u_2 t^2\right)$$

Two hits in large populations (not rate limiting)



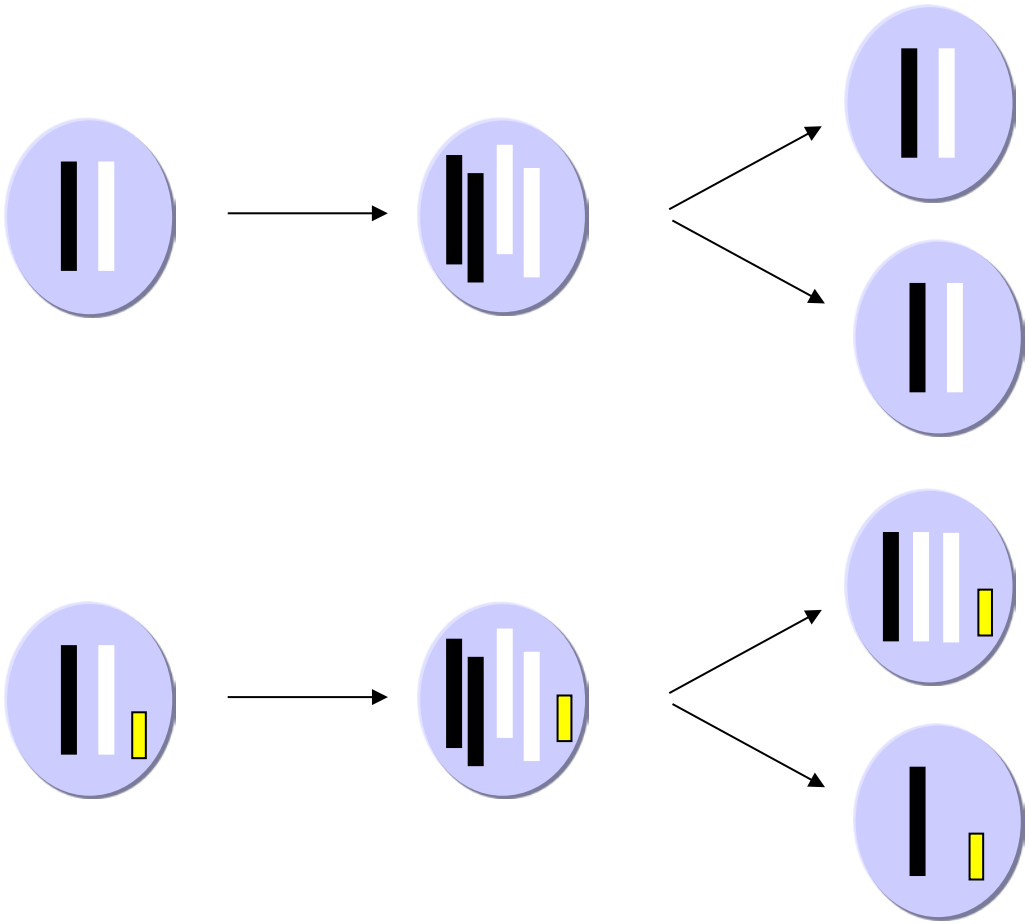
Summary: three dynamic laws for TSG inactivation



Genetic instability

- Microsatellite instability (MIN)
  - caused by mutations in mismatch repair genes
  - increases the point mutation rate by a factor of up to 1,000
  - 15% of colon cancers have it
- Chromosomal instability (CIN)
  - increased rate of gaining or losing whole chromosomes or large parts of it
  - increases the rate of losing a chromosome by a factor of 10,000
  - 85% of colon cancers have it

Chromosomal instability



normal cell division

aneuploidy

Three classes of CIN genes

Onco CIN genes

Class I CIN genes trigger CIN if one allele is mutated or lost.
Example: MAD2

Class II CIN genes trigger CIN if one allele is mutated in a dominant negative fashion.
Example: hBUB1

Class III CIN genes trigger CIN if both alleles are mutated.
Example: BRCA2

CIN suppressor genes

Early adenomas have allelic imbalances

32 adenomas; size 1-3mm

Allelic imbalance:

1p ... 10%

5q ... 55% (location of APC)

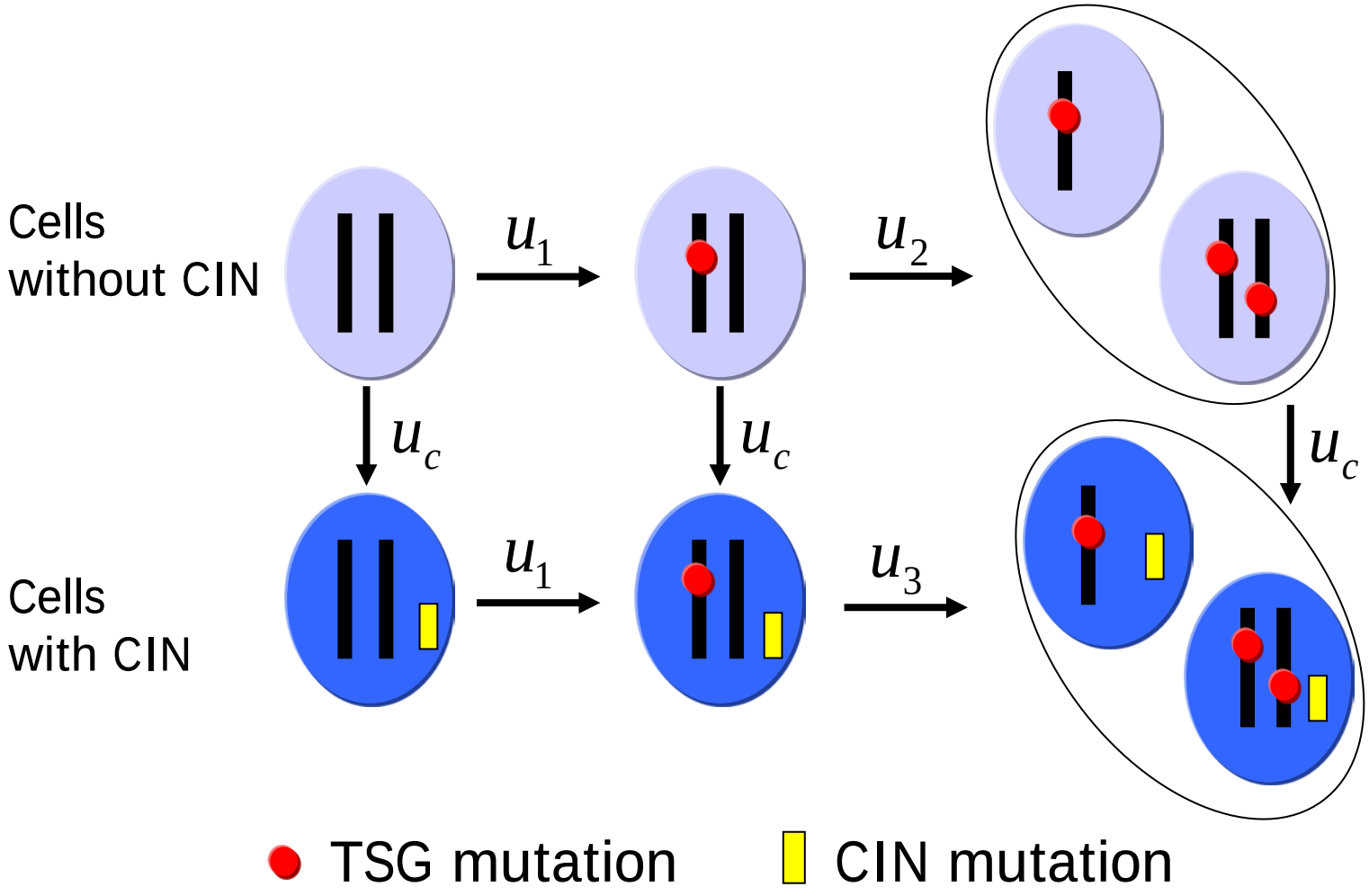
8p ... 19%

15q ... 28%

18q ... 28%

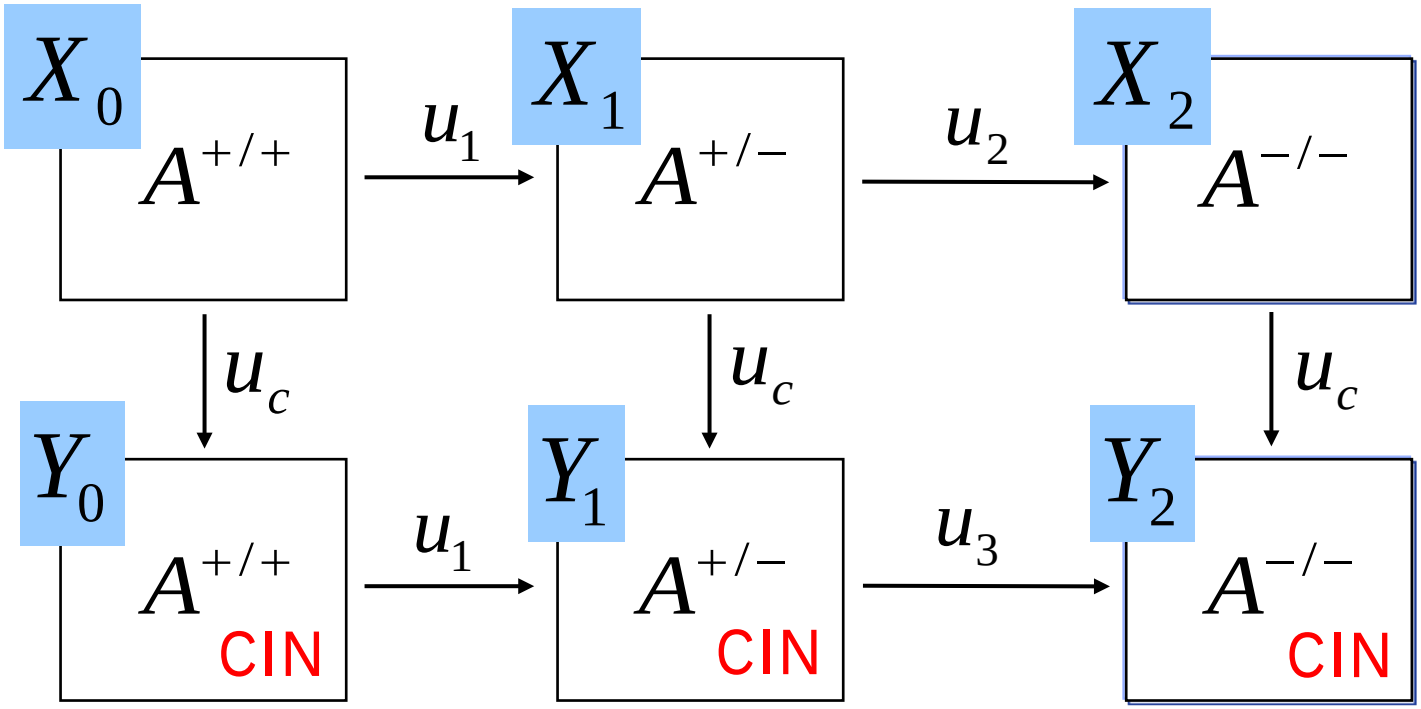
any one of these 5 ... 90%

TSG inactivation with and without CIN



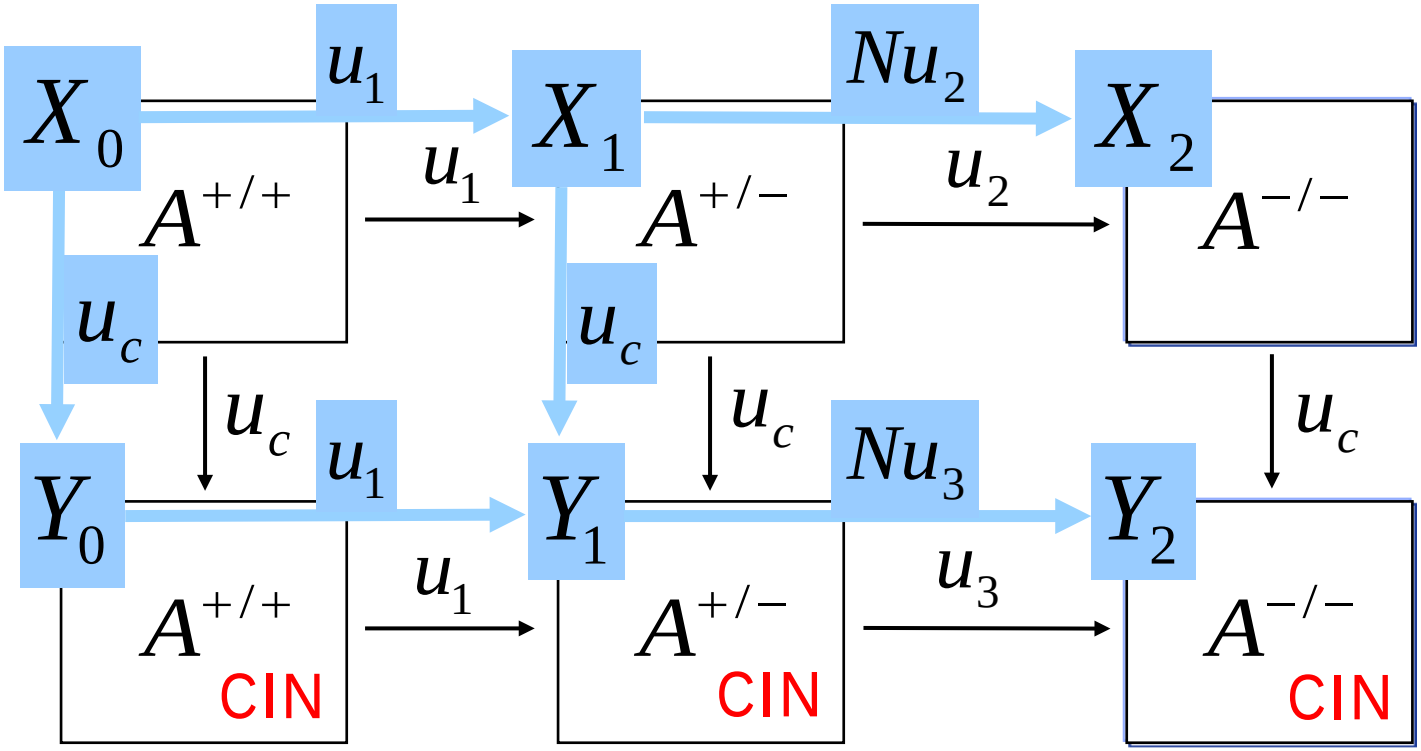
Homogeneous states approximation

- For small compartments, $N \ll 1/u_1, 1/u_2, 1/u_c$, we consider the corresponding homogeneous states.



Neutral CIN

- We assume that CIN and $A^{+/-}$ are neutral ($\rho = 1/N$), and that $A^{-/-}$ will be fixed immediately ($\rho = 1$).
- The state probabilities are related by the rates of evolution:



Neutral CIN

- The ODE system of state probabilities (with $X_0(0) = 1$)

$$\dot{X}_0 = -(u_1 + u_c)X_0 \quad \dot{X}_1 = u_1 X_0 - (u_c + N u_2)X_1 \quad \dot{X}_2 = N u_2 X_1$$

$$\dot{Y}_0 = u_c X_0 - u_1 Y_0 \quad \dot{Y}_1 = u_c X_1 + u_1 Y_0 - N u_3 Y_1 \quad \dot{Y}_2 = N u_3 Y_1$$

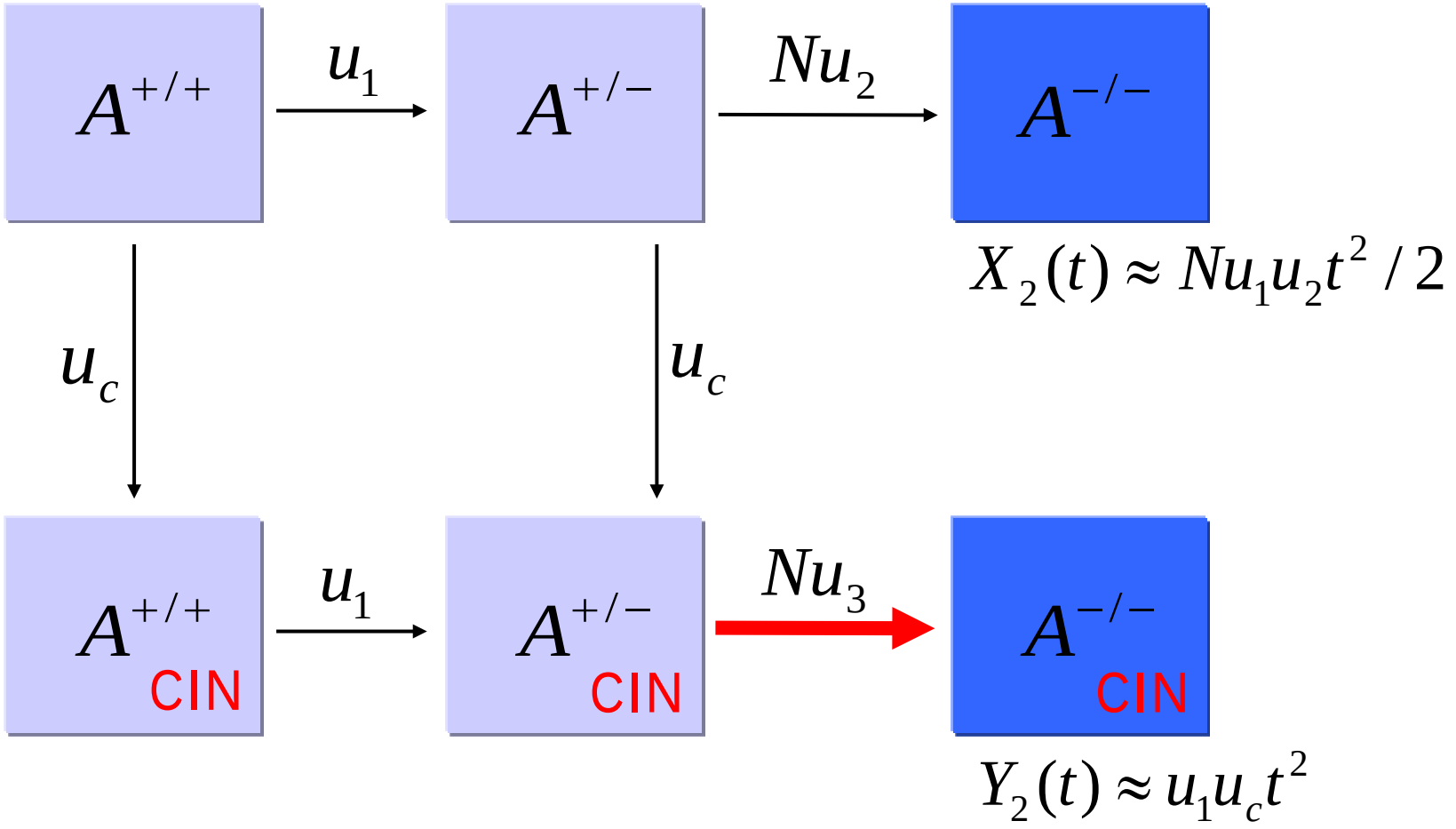
  has, on the relevant time scale, the approximate solution

$$X_0(t) \approx 1 \quad X_1(t) \approx u_1 t \quad X_2(t) \approx N u_1 u_2 t^2/2$$

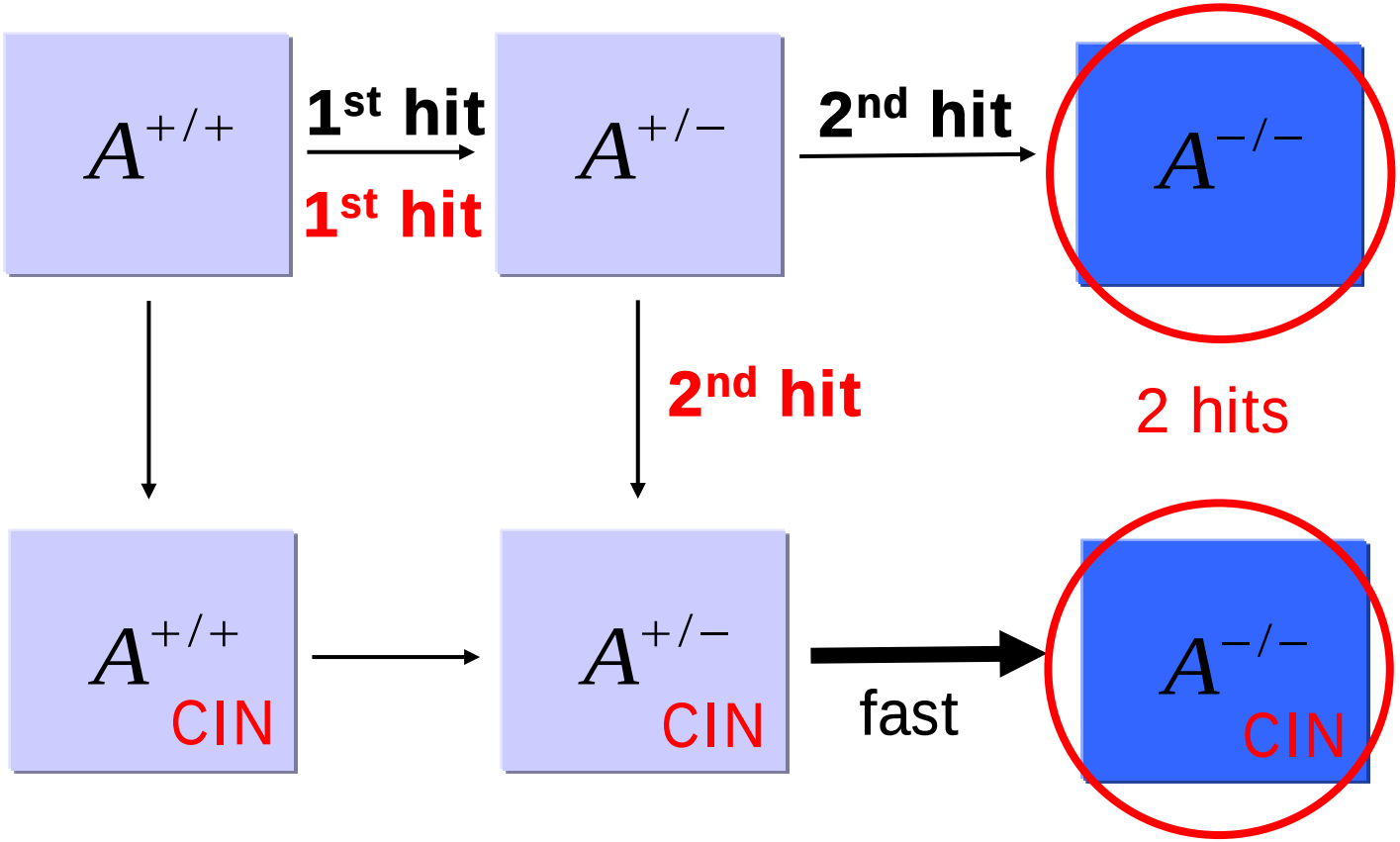
$$Y_0(t) \approx u_c t \quad Y_1(t) \approx u_1 u_c t^2 \quad Y_2(t) \approx u_1 u_c t^2$$

- $Y_1 \approx Y_2$, because $u_3 \approx 10^{-2}$ and $N u_3 t \gg 1$. This step is not rate limiting: the waiting time for LOH in CIN cells is negligible compared to the other events.

Cancer initiation with neutral CIN



Two possibilities for Knudson's two hit hypothesis



Costly CIN in small compartments

- If CIN cells have fitness r < 1, their fixation probability in the Moran process is $\rho = (1 - 1/r)/(1 - 1/r^N)$ and the non-CIN-to-CIN transition rate is $N\rho u_c$.
- On the relevant time scale, we find approximately

$$X_0(t) \approx 1 \qquad X_1(t) \approx u_1 t \qquad X_2(t) \approx N u_1 u_2 t^2/2$$

$$Y_0(t) \approx N\rho u_c t \quad Y_1(t) \approx N\rho u_1 u_c t^2 \quad Y_2(t) \approx N\rho u_1 u_c t^2$$

Costly CIN in large compartments

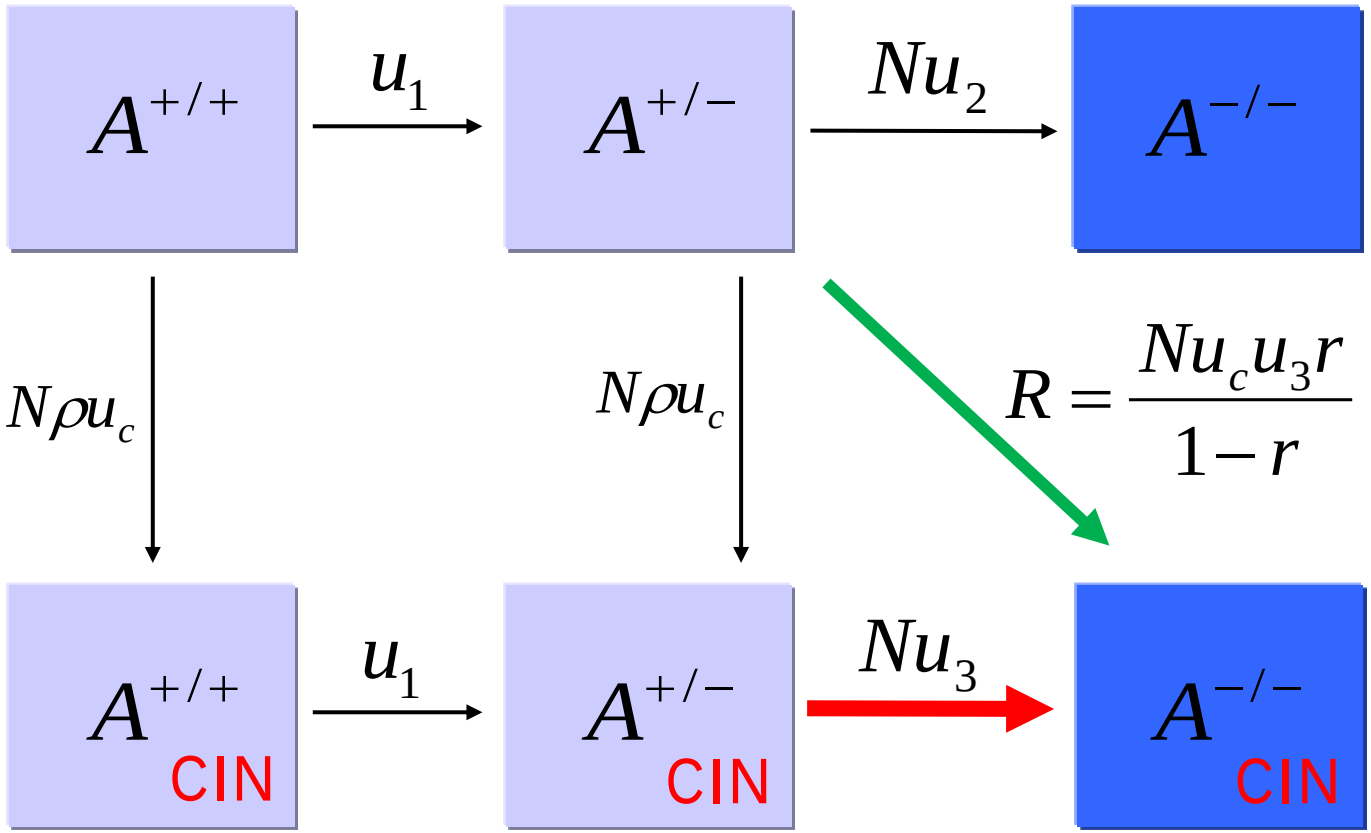
- For large N and r < 1, the product Nρ becomes vanishingly small, such that the intermediate CIN types $A^{+/+}$*CIN* and $A^{+/-}$*CIN* will not reach fixation.
- $A^{+/-}$*CIN* cells are produced at rate Nu_c and they remain near a mutation-selection balance with average abundance $Nu_c/(1 - r)$. They produce $A^{-/-}$*CIN* cells at rate ru_3.
- Thus, the population tunnels from X_1 to Y_2 at rate
  $R = (Nu_c ru_3)/(1 - r)$
- On the relevant time scale, we obtain approximately

$$X_0(t) \approx 1 \quad X_1(t) \approx u_1 t \quad X_2(t) \approx N u_1 u_2 t^2/2$$

$$Y_0(t) \approx 0 \quad Y_1(t) \approx 0 \quad Y_2(t) \approx R u_1 t^2/2$$

Iwasa et al., Genetics 2004

Tunneling is important for costly CIN and large N



Summary

- Cancer is an evolutionary process.
- The rate of activating oncogenes and inactivating TSGs depends on population size, mutation rates, and fitness.
- Tissue architecture can affect the rate of evolution of cancer. The linear process delays cancer initiation.
- In small, intermediate, and large populations, a TSG is eliminated in 2, 1, and 0, rate-limiting steps, respectively.
- CIN can precede inactivation of (the second allele of) a TSG, accelerating subsequent steps.

References

- Iwasa Y, Michor F, Nowak MA. Stochastic tunnels in evolutionary dynamics. Genetics 166: 1571–1579, 2004.