Population genetics of Cancer

4. Cancer: oncogenes & tumor suppressors

Phenotypes:

- divide without control
- evade programmed cell death
- invade other tissues
- etc

Mutations:

- p53
- kRas
- etc

} oncogenes and tumor suppressors

Mutations:

- Single nucleotide
- Chromosomal rearrangements

—T— → —G→

Gene1 Gene2 Gene1 Gene2 (copy number gain)

Oncogenes: one copy mutated, usually activation

Tumor suppressors: both copies need to be affected usually one mutated & one lost

} drivers

- Cancer needs high rate of mutations: μ

For single nucleotide:

normal per cell division: $\mu \sim 10^{-10} - 10^{-11}$ / bp per cell division

cancer $\mu \sim 10^{-8} - 10^{-9}$

- But: the rest of the genome can be affected by large # of mutations (passengers)

2. Model of drivers & passengers

- T - mutation target (B_p) - # of loci in the genome where a mutation can lead to a particular phenotype

drivers T_d = [number of driver genes] x [# of relevant bps]

$\sim 100 * [10-50] \approx 5000$

Rate of new driver mutations: (collectively oncogenes & tumor suppressors)

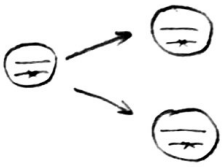
$M_d = \mu \cdot T_d$

(2) Rate of new passangers $\mu_p = T_p \mu$ (will estimate T_p later)

- Population dynamics model

N cells

Divide



Death

birth rate $B = r$

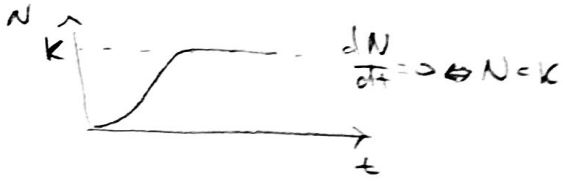
death rate $D = r\frac{N}{K}$

$$\frac{dN}{dt} = N\left(1 - \frac{N}{K}\right) \cdot r$$

P.F. Verhulst 1840 prediction of 1940 population

let's choose time units such that $r = 1$

$$\frac{dN}{dt} = N\left(1 - \frac{N}{K}\right) \quad ;$$



- Birth & death rates are affected by mutations

- Effects of mutations

S_d - effect of a driver ; $S_d > 0$ $\boxed{S_d \sim 1}$

S_p - effect of a passenger — Non neutral passengers $\boxed{|S_p| << 1}$

$(1+S_d)^{n_d}$ - independent effects of mutations

Rational. $(1+s)$ - fitness ~ prob to survive

$(1-S_p)^{n_p}$

A_1	A_2
1	$1+s$

$$\frac{1}{(1+S_p)^{n_p}} = \left(\frac{1+S_p-S_p}{1+S_p}\right)^{n_p} = \left(1 - \frac{S_p}{1+S_p}\right)^{n_p} \simeq (1-S_p)^{n_p}$$

$$B = \frac{(1+S_d)^{n_d}}{(1+S_p)^{n_p}} \quad ; \quad D = \frac{N}{K}$$

③ Drivers T_d, S_d ; Estimates: $T_p \simeq$ [# of expressed genes] × [sites per gene]

Passengers T_p, S_p

$\simeq 10^3 - 10^4 \cdot 10^3 \simeq 10^6 - 10^7$

$S_d \gg S_p$

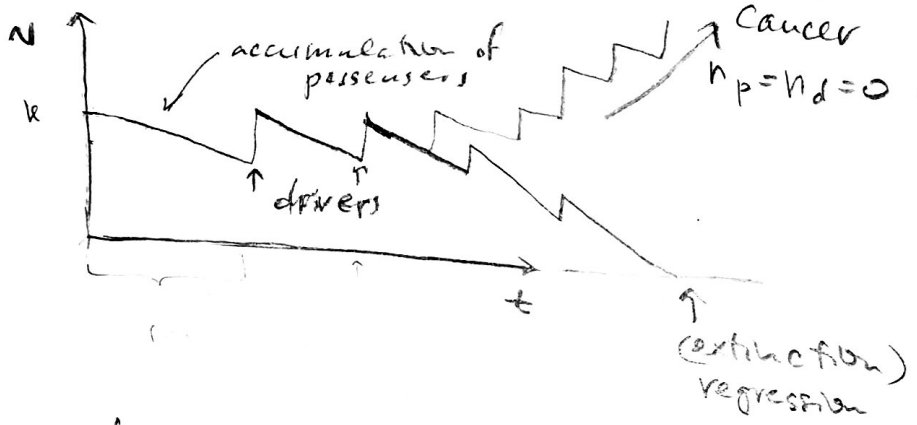
$T_d \ll T_p$

$T_d \simeq$ [# of cancer causing genes] × [# of hits]

$\simeq [10^2] \cdot [10^1 - 10^2]$

$\simeq 10^3 - 10^4$

- Dynamics



$$\frac{dN}{dt} \equiv V = V_d - V_p$$

Passengers

$V_p = \{$ rate of passenger accumulation $\} \cdot \Delta N$

$\Delta N = N_{n_p+1} - N_{n_p}$; $\frac{(1+S_d)^{n_d}}{(1+S_p)^{n_p}} = \frac{N_{n_p}}{K}$; $\frac{(1+S_d)^{n_d}}{(1+S_p)^{n_p+1}} = \frac{N_{n_p+1}}{K}$

$\{$ rate of accumulation $\}$

$= N \cdot \mu \cdot T_p \ \Pi_1(1/N)$

$N_{n_p+1} = N_{n_p}(1+S_p)$

$\Delta N = N S_p$

$$\Pi(y) = \frac{1 - e^{-2Ns y}}{1 - e^{-2Ns}} \underset{Ns \ll 1}{\simeq} \frac{2Nsy}{2Ns} = y$$

$$V_p = N \mu T_p \tfrac{1}{N} \cdot N S_p = \mu T_p N S_p$$

④ Drivers

$V_d = N \cdot \mu T_d \cdot \Pi_1(1/N) \Delta N \quad s \leq 1 \; ; \; N \gg 1$

$$\Pi(y) = \frac{1 - e^{-2Nsy}}{1 - e^{2Ns}} \quad \underline{\underline{\text{for haploid } 2N \to N}} \quad \frac{1 - e^{-Nsy}}{1 - e^{-Ns}} \quad \underline{\underline{y = 1/N}} \quad 1 - e^{-s} \approx s$$

$V_d = N \mu T_d \cdot s_d \cdot N \cdot s_d$

$\Delta N = N_{n_{d+1}} - N_{n_d} = N_{n_d} \cdot s_d$

$V = N^2 \mu T_d s_d^2 - N \mu T_p \cdot s_p$

$$\frac{(1+s_d)^{n_{d+1}}}{(1+s_p)^{n_p}} = \frac{N_{n_{d+1}}}{K} = \frac{N_{n_d} \cdot (1+s_d)}{K}$$

$N_0 T_d s_d^2 = T_p s_p$

$$N_0 = \frac{T_p s_p}{T_d s_d^2}$$

⇒ Critical population size

lesions → regress

large → progress

$$N_0 \sim \frac{10^7 \cdot 10^{-3}}{10^3 \cdot 10^{-2}} = 10^3 \text{ cells}$$

~30 cells in diameter (20)

Ø of a cell ≃ 30 μm

diameter of lesion ~ 1000 μm ~ 1 mm

Clinical cutoff ≃ 5-10 mm