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# Population genetics of Cancer

2/23/2016

4. Cancer: oncogenes & tumor suppressors

Phenotypes:

divide without control

evade programmed cell death

invade other tissues

etc

Mutations

p53

kRas

etc

oncogenes  
& tumor suppressors

Mutations:

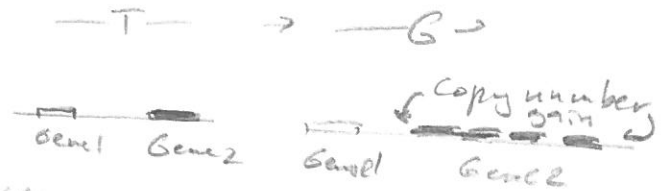
- single nucleotide

- chromosomal rearrangements

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:  $\mu$

For single nucleotide:

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

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

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

2. Model of drivers & passengers

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

drivers  $T_d = [\text{number of driver genes}] \times [\# \text{ of relevant Bps}]$

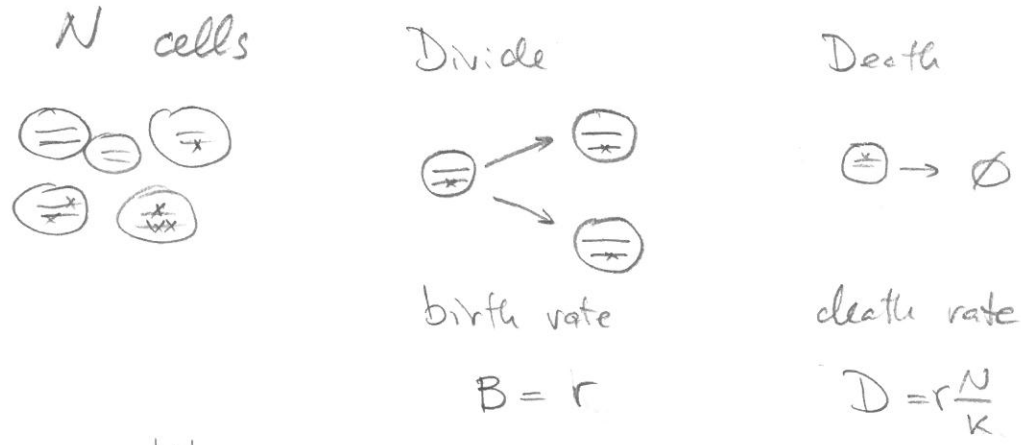
$\sim 100 \times [10-50] \approx 5000$

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

$$M_d = \mu \cdot T_d$$

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

• Population dynamics model

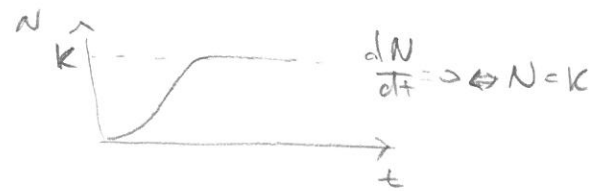


$$\frac{dN}{dt} = N \left(1 - \frac{N}{K}\right) \cdot r$$

P.F. Verhulst  
1840 prediction of 1940 population

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

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



• Birth & death rates are affected by mutations

• Effects of mutations

$S_d$  = effect of a driver ;  $S_d > 0$   $S_d \sim 1$   
 $S_p$  = effect of a passenger — Non neutral passengers  
 $S_p \ll 1$

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

$$(1 - S_p)^{n_p}$$

Rational.  $(1 + s)$  — fitness  $\sim$  prob to survive

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

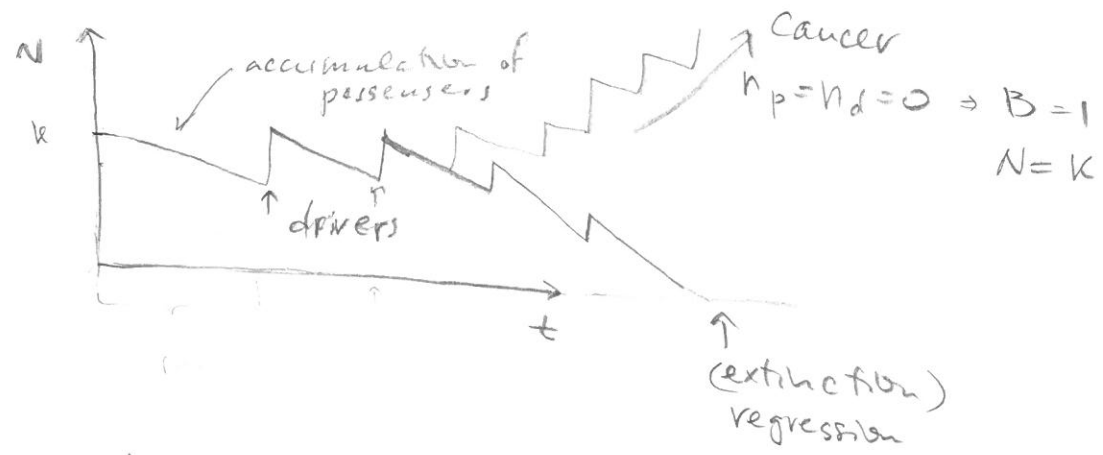
$$B = \frac{(1 + S_d)^{n_d}}{(1 + S_p)^{n_p}} ; D = \frac{N}{K}$$

3) Drivers  $T_d, S_d$ ; Estimates:  $T_p \approx [\# \text{ of expressed genes}] \times [\text{sites per gene}]$   
 Passengers  $T_p, S_p$   $\approx 10^3 - 10^4 \cdot 10^3 \approx 10^6 - 10^7$

$S_d \gg S_p$   
 $T_d \ll T_p$

$T_d = [\# \text{ of cancer causing genes}] \times [\# \text{ of sites}]$   
 $\approx [10^2] \times [10^1 - 10^2]$   
 $\approx 10^3 - 10^4$

• Dynamics



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

Passengers  $V_p = \{ \text{rate of passenger accumulation} \} \times \Delta N$

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

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

$N_{n_{p+1}} = N_{n_p} (1+S_p)$   
 $\Delta N = N S_p$

$\Pi(y) = \frac{1 - e^{-2Ns_y}}{1 - e^{-2Ns}} \approx \frac{2Ns_y}{2Ns} = y$

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

#### ④ Drivers

$$V_d = N \cdot \mu T_d \cdot \Pi_1 \left( \frac{1}{N} \right) \Delta N \quad S \leq 1; N \gg 1$$

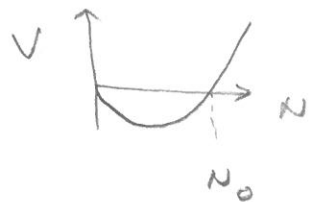
$$\Pi_1(y) = \frac{1 - e^{-2Ny}}{1 - e^{-2Ns}} \quad \text{for haploid} \quad \frac{2N \rightarrow N}{1 - e^{-Ns}} \quad \frac{y=1/N}{1 - e^{-s}} \approx s$$

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

$$\Delta N = N_{nd+1} - N_{nd} = N_{nd} S_d$$

$$V = N^2 \mu T_d S_d^2 - N \mu T_p S_p$$

$$\frac{(1+S_d)^{N_{nd+1}}}{(1+S_p)^{N_{nd}}} = \frac{N_{nd+1}}{N_{nd}} = \frac{N_{nd} (1+S_d)}{N_{nd}}$$



$$N_0 \mu T_d S_d^2 = \mu T_p S_p$$

$$N_0 = \frac{T_p S_p}{T_d S_d^2}$$

⇒ 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)

∅ of a cell ≈ 30 μm

diameter of lesion ~ 1000 μm ~ 1 mm

Clinical cutoff ≈ 5-10 mm