1. Cancer: oncogenes & tumor suppressors

**Phenotypes:**
- Divides without control
- Evasion of programmed cell death
- Invades other tissues

**Mutations:**
- Single nucleotide
- Chromosomal rearrangements

**Oncogenes:** one copy mutated, usually activation

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

- Cancer needs high rate of mutations: μ
  - For single nucleotide:
    - Normal per cell division: \( μ = 10^{-11} \) [bp]
    - Cancer: \( μ = 10^{-8} - 10^{-7} \) [bp per cell division]

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

2. Model of drivers & passengers

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

\[
\text{Drivers } T_d = \text{[number of driver genes]} \times \text{[# of relevant bps]} \times 100 \times [10^{-50}] \approx 25000
\]

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

\[
M_d = μ \times T_d
\]
Rate of new passengers $m_p = T_p \cdot \mu$ (will estimate $T_p$ later)

- Population dynamics model

\[ \frac{dN}{dt} = N(1 - \frac{N}{K}) \cdot r \]

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

\[ \frac{dN}{dt} = N(1 - \frac{N}{K}) \]

- Birth and death rates are affected by mutations

P.F. Verhulst
1840 prediction of 1940 population

Effects of mutations

- $S_d$ = effect of a driver; $S_d > 0$ [\( S_d = 1 \)]
- $S_p$ = effect of a passenger — Non-neutral passengers
  \[ |S_p| \ll 1 \]

\[ (1 + S_d)^{n_d} \text{ — independent effects of mutations} \]

\[ (1 - S_p)^{n_p} \]

Rationalized $(1 + s)$ - fitness $n$ prob to survive

\[ \frac{1}{(1 + S_p)^{n_p}} = \left( \frac{1 + S_p - S_p}{1 + S_p} \right)^{n_p} = (1 - \frac{S_p}{1 + S_p})^{n_p} = (1 - S_p)^{n_p} \]

\[ B = \frac{(1 + S_d)^{n_d}}{(1 + S_p)^{n_p}} \]

\[ D = \frac{N}{K} \]
Drivers \( T_d, S_d \); Estimates: \( T_p = [\text{\# of expressed genes}] \times [\text{sites per gene}] \)
\[
\approx 10^3 - 10^7 \times 10^3 = 10^6 - 10^7
\]
\( T_d = [\text{\# of cancer causing}] \times [\text{\# of sites}] \)
\[
\approx [10^3 \times (10^7 - 10^2)] \approx 10^3 - 10^7
\]

\( S_d > S_p \)
\( T_d < T_p \)

- **Dynamics**

\[
\frac{dN}{dt} = V = V_d - V_p
\]

Passengers

\( V_p = \frac{\text{rate of passenger accumulation}}{\text{\# of passengers}} \)

\[
\Delta N = N_{n+p} - N_n
\]

\[
\frac{(1 + S_d)^{n_d}}{(1 + S_p)^{n_p}} = \frac{N_{n+p}}{K} \cdot \frac{(1 + S_d)^{n_d}}{(1 + S_p)^{n_p} + 1} = \frac{N_{n+p}}{K}
\]

\[
N_{n+p+1} = N_{n+p} (1 + S_p)
\]

\[
\Delta N = N S_p
\]

\[
\Pi(y) = 1 - e^{-2Ns_0} = \frac{2Ns_0}{Ns} = y
\]

\[
V_p = N \mu T_p \frac{1}{N} \quad N S_p = \mu T_p N S_p
\]
Drivers

\[ V_d = N \cdot M \cdot T_d \cdot \Pi_i \left( \frac{1}{N} \right) \Delta N \quad s \leq 1 \therefore N \gg 1 \]

\[ T_i(y) = \frac{1 - e^{-2Ns_y}}{1 - e^{-2Ns_y}} \quad \text{for haploid} \]

\[ y = \frac{1}{N} \quad 1 - e^{-y} \approx y \]

\[ N \gg N_s y \Rightarrow \]

\[ V_d = N \cdot M \cdot T_d \cdot S_d \cdot N \cdot S_d \]

\[ \Delta N = N_{nd+1} - N_{nd} = N_{nd} \cdot S_d \]

\[ \frac{(1 + S_d) n+1}{(1 + S_d) n} = \frac{N_{nd+1}}{N_{nd}} = \frac{N_{nd} \cdot (1 + S_d)}{N_{nd}} \]

\[ V = N^2 \cdot M \cdot T_d \cdot S_d^2 - N \cdot M \cdot T_p \cdot S_p \]

\[ V \rightarrow N \quad N_0 \]

\[ N_0 \cdot T_d \cdot S_d^2 = T_p \cdot S_p \]

\[ N_0 = \frac{T_p \cdot S_p}{T_d \cdot S_d^2} \]

\[ \Rightarrow \text{Critical population size} \]

\[ \text{lesion} \rightarrow \text{regress} \]

\[ \text{large} \rightarrow \text{progress} \]

\[ N_0 \approx \frac{10^7 \cdot 10^{-3}}{10^3 \cdot 10^{-2}} = 10^3 \quad \text{cells} \]

\[ \approx 30 \text{ cells in diameter (2D)} \]

\[ \phi \text{ of a cell } = 30 \mu m \]

\[ \text{diameter of lesion } \approx 1000 \mu m \sim 1 \text{ mm} \]

\[ \text{Clinical cutoff } \sim 5 - 10 \text{ mm} \]