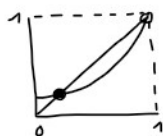Turnover

$$0 \xrightarrow{p_0} x \qquad 0 \xrightarrow{p_1} 0 \qquad 0 \xrightarrow{p_2} 00$$

$$q = p_0 + p_1 q + p_2 q^2 \qquad p_1 = 1 - p_0 - p_2$$

$$\boxed{q = \min\left(1, \frac{p_0}{p_2}\right)}$$
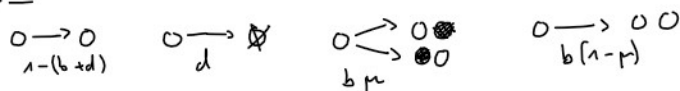

Two branching processes:

clones

$$0 \xrightarrow{d} \varnothing \qquad 0 \overset{b}{\underset{}{\longrightarrow}} \begin{smallmatrix} 0 \\ 0 \end{smallmatrix}$$

$$q = d\,\delta t + (1-(b+d)\,\delta t)\,q + b\,\delta t\,q^2 \quad \Longleftrightarrow \quad q = \frac{d}{b+d} + \frac{b}{b+d}q^2$$

$$\Longleftrightarrow \quad (q-1)\left(q - \frac{d}{b}\right) = 0 \qquad q = \min\left(1, \frac{d}{b}\right)$$
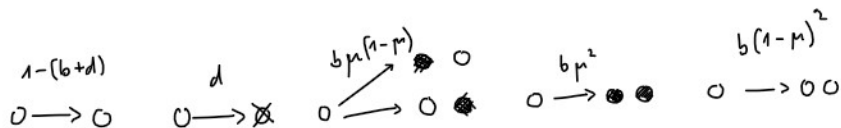
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haplotypes

$$0 \xrightarrow[1-(b+d)]{} 0 \qquad 0 \xrightarrow{d} \varnothing \qquad 0 \overset{}{\underset{b\mu}{\longrightarrow}} \begin{smallmatrix} 0 \bullet \\ \bullet 0 \end{smallmatrix} \qquad 0 \xrightarrow{b(1-\mu)} 0\,0$$

$$q = d\,\delta t + [1-(b+d)\,\delta t]\,q + b\mu\,\delta t\,q + b(1-\mu)\,\delta t\,q^2$$

$$\Updownarrow$$

$$\boxed{q = \frac{d}{b(1-\mu)}} \quad \longleftarrow \quad q = \frac{d}{b+d} + \frac{b\mu}{b+d}q + \frac{b(1-\mu)}{b+d}q^2$$

$$0 \xrightarrow{1-(b+d)} 0 \qquad 0 \xrightarrow{d} \varnothing \qquad 0 \overset{b\mu(1-\mu)}{\nearrow} \begin{smallmatrix} \bullet \; 0 \\ 0 \bullet \end{smallmatrix} \qquad 0 \xrightarrow{b\mu^2} \bullet\bullet \qquad 0 \xrightarrow{b(1-\mu)^2} 00$$

$$q = \frac{d + b\mu^2}{b+d} + \frac{2b\mu(1-\mu)}{b+d}q + \frac{b(1-\mu)^2}{b+d}q^2$$

$$\boxed{q = \frac{d + b\mu^2}{b(1-\mu)^2}} \qquad d_s = b(1-\mu)^2 - b\mu^2 = b - 2b\mu = \underline{b(1-2\mu)}$$

here 2μ is the mutation rate per division
μ is the —"— per division per cell

Johannus' calculations:

haplotype $\qquad t = \dfrac{q}{1-q} \dfrac{r}{(1-p)^2} + \dfrac{r}{1-q}$
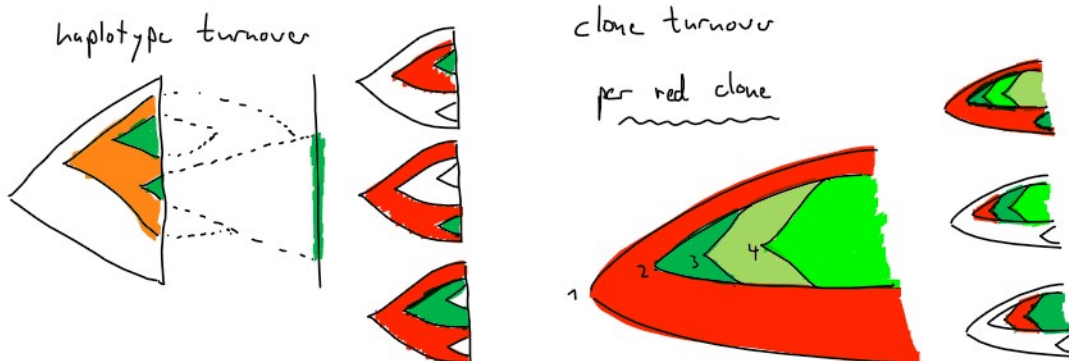
clone $\qquad t = \dfrac{q}{2 \log(N_{cutoff})}$
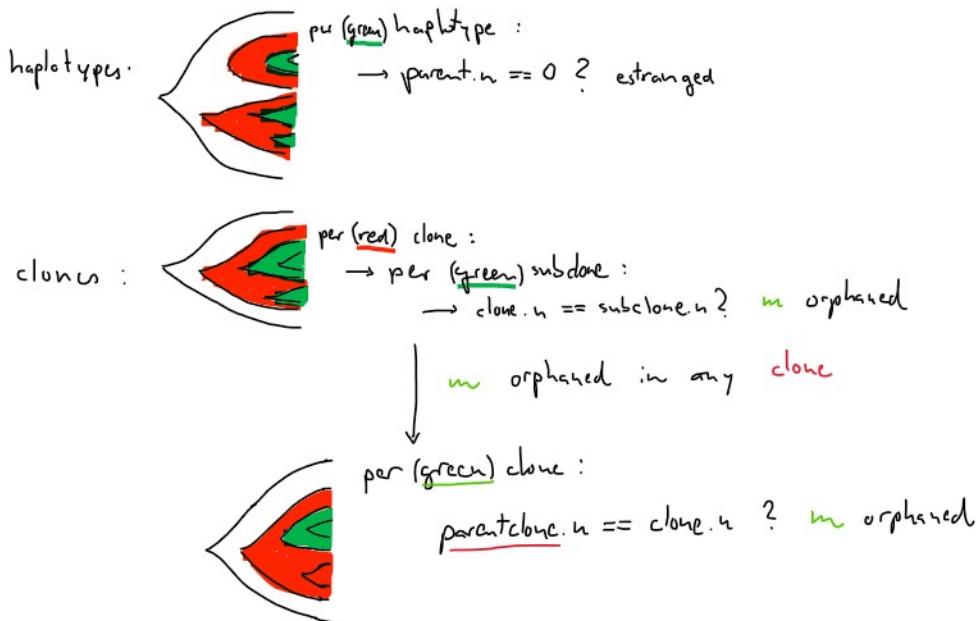
a mutation we insert the rates (2) into the turnover (15) and take the limit $\gamma \to a - b$ which gives
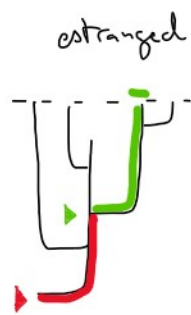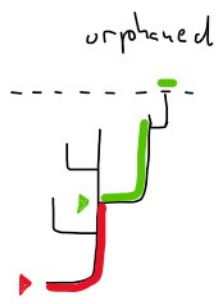
$$W_d = \frac{b/a}{2(a-b)T}(1 - e^{-2(a-b)T}) . \qquad (16)$$

For the turnover of the haplotypes we insert the rates (4) into the turnover (15) and obtain

$$W_h = \frac{\mu(b + \mu^2)}{(1-\mu)^2(a - b - a\mu)} \frac{1 - e^{-2(a-b-a\mu)T}}{1 - e^{-2a\mu T}} . \qquad (17)$$

Algorithms

haplotypes.

per (green) haplotype :
→ parent.n == 0 ? estranged

clones :

per (red) clone :
→ per (green) subclone :
→ clone.n == subclone.n ? ⟶ orphaned

⟶ orphaned in any clone

per (green) clone :
parentclone.n == clone.n ? ⟶ orphaned

haplotype turnover

clone turnover

per red clone

orphaned   estranged

"tree-less" turnover

Per - green m-clone

$\lceil$ filter (¬iszero(htype.n) , tumor) $\rfloor$

{ trunc , ... }

{ trunc , m , m_{clonal} , ... }
$\underbrace{\qquad\qquad\qquad\qquad}_{trunc}$

the m-clone might
have been <u>swept</u> by
additional mutations
m_{clonal}
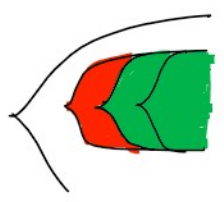
first idea :

per (green) m-clone

$clone[trunc\backslash^m].n == clone[m].n$? orphaned
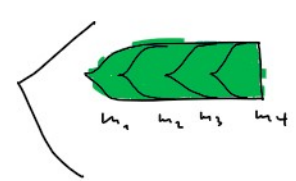
alg : m_1, m_2, m_3, m_4 orphaned

real : $\quad\; m_2, m_3, m_4$ orphaned

<u>Note</u> :   — m_1 not orphaned but indistinguishable from m_2, m_3, m_4

— m_1, m_2, m_3 not estranged but extinct
  m_4 estranged or extinct

— actual frequency n irrelevant
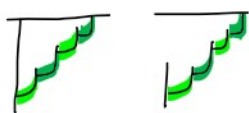
haplotypes $\longrightarrow$ clones $\longrightarrow$ truncs

m-clone trunc
$[-, m, m_c]$

← sweep
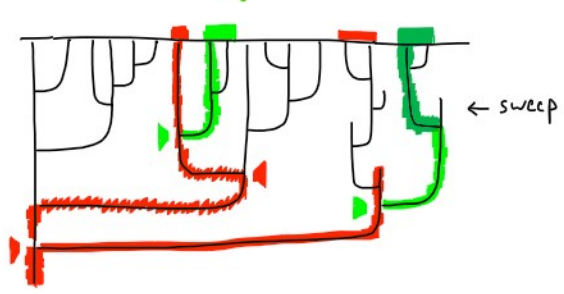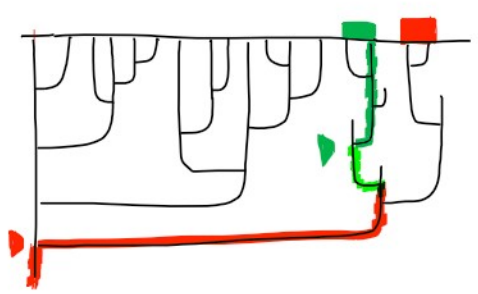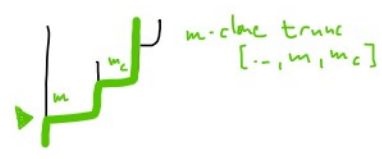
[for haplotypes only the leaves are green and red]

$trunc[m] = \bigcap clone = \{ m | m \in h \; \forall h \in clone \}$

haplotypes

(por (green) m clone
  haplotype [trunc\m] in tumor ?)

 all estranged _or_ extinct ⟶ extinct haplotypes cannot be (uniquely) identified !

- last m in this motif is estranged if trunc in htypes !
- if motif has length $\underline{1}$ trunc$^{\setminus m}$ must be in htypes too !
- exclude typeones ie. $|trunc| == 1$

$m_1 \ m_2 \ m_3 \ m_4$

algorithm

$trunc \ [.. , m_1, m_2, m_3, m_4]$

$truncp = filter \ (issubtype, trunc)$

$t = |truncp|$

$(issubtype(m_i, trunc) = truncs[m_i] == trunc)$

	is estranged	isgreen
$t > 1$	$\dfrac{(trunc \ in \ htypes)}{t}$	$\dfrac{(trunc \ in \ htypes)}{t}$
$length(trunc) == 1$	$0.$	$0.$
$t == 1$	$(trunc \ in \ htypes)$ $\&\&$ $(trunc \setminus truncp \ in \ htypes)$	$(trunc \ in \ htypes)$

clones

- first in motif never orphaned (exclude typeone)
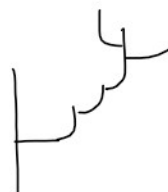 all others are always orphaned

per green clone
  $truncp = filter \ (issubtype, trunc)$
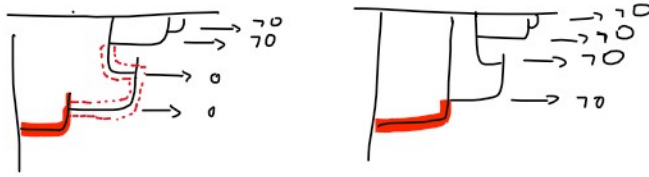
  $t = |truncp|$

  $isorphaned \ [m] = t^{-1}/t$

  $isgreen \ [m] = truncp == trunc \ ? \ \dfrac{t-1}{t} \ : \ 1$
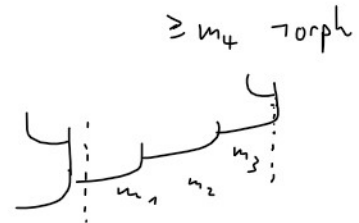
  ↳ ≙ motif has typeone

Per red m-clone

→ should recover "per green clone" if mutations are reported as orphaned instead of counted

- On trunc of m-clone all mutations upstream of m are orphaned
- beyond trunc no mutation is orphaned

→ count mean upstream-trunc and "foliage" size

per red clone

$$\ell = \#\text{twigs} = |(\bigcup_{m\text{-clone}}) \cap \text{trunc}|$$

$$\text{filter} \cdot (\text{issubclone}, \text{trunc})$$

$$t = |\text{trunc}|$$

$$\text{isorphaned} = \frac{1}{t} \sum_{n=0}^{t-1} n = \frac{t-1}{2}$$

$$\text{isgreen} = \frac{1}{t} \sum_{n=0}^{t-1} \ell + n = \ell + \frac{t-1}{2}$$