

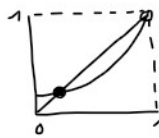
Turnover

Extinction

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

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

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



Two branching processes:

clones $0 \xrightarrow{d} \times \quad 0 \xrightarrow{b} 0$

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

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

haplotypes

$$0 \xrightarrow{1-(b+d)} 0 \quad 0 \xrightarrow{d} \times \quad 0 \xrightarrow{b\mu} 0 \quad 0 \xrightarrow{b(1-\mu)} 00$$

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

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

vs.

$$1-(b+d) \quad d \quad b\mu(1-\mu) \quad b\mu^2 \quad b(1-\mu)^2$$

$$0 \rightarrow 0 \quad 0 \rightarrow \times \quad 0 \rightarrow 0 \quad 0 \rightarrow 00 \quad 0 \rightarrow 00$$

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

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

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

Johannes' calculations:

haplotype $t = \frac{q}{1-q} \frac{r}{(1-p)^2} + \frac{r}{1-q}$

clone $t = \frac{q}{2 \log(N_{\text{cutoff}})}$

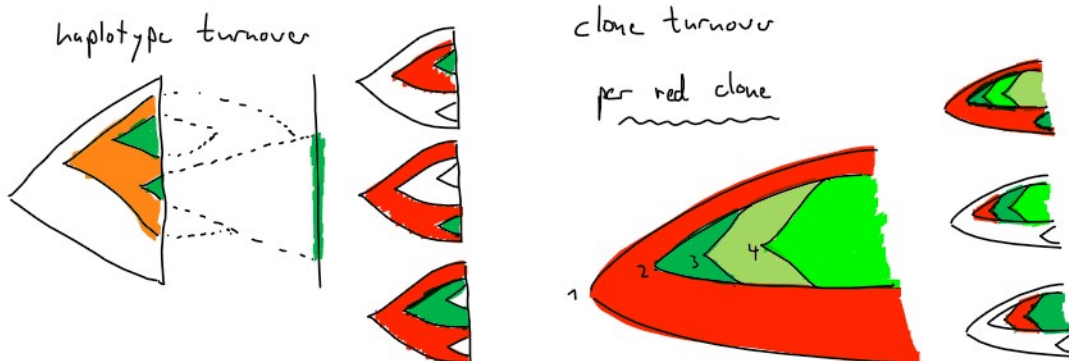
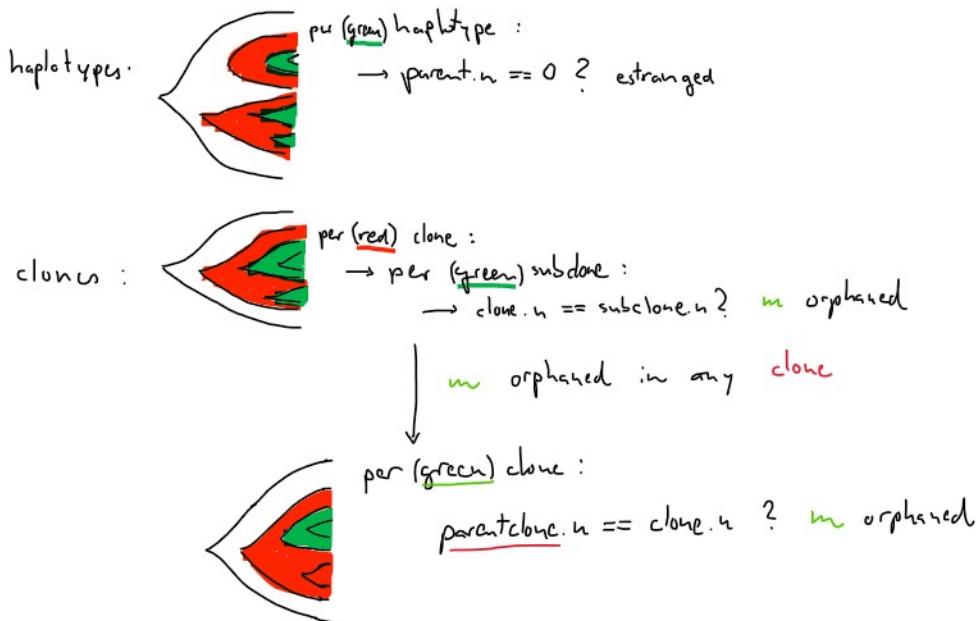
a mutation we insert the rates (2) into the turnover (15) and take the limit $\gamma \rightarrow a - b$ which gives

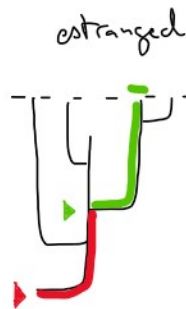
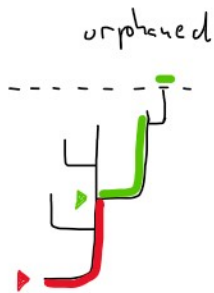
$$W_d = \frac{b/a}{2(a-b)T} (1 - e^{-2(a-b)T}) \quad (16)$$

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

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

Algorithms





"tree-less" turnover

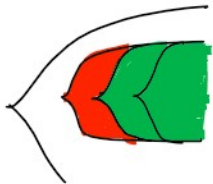
Per - green m-clone

$\lceil \text{filter}(\neg \text{iszero}(h_{type}.n), \text{tumor}) \rceil$

$\{ \text{trunc}, \dots \}$

$\{ \text{trunc}, m, m_{\text{clonal}}, \dots \}$
trunc

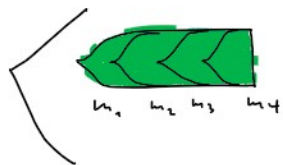
the m-clone might have been swept by additional mutations m_{clonal}



first idea:

per (green) m-clone

$\text{clone}[\text{trunc} \setminus m].n == \text{clone}[m].n$? orphaned



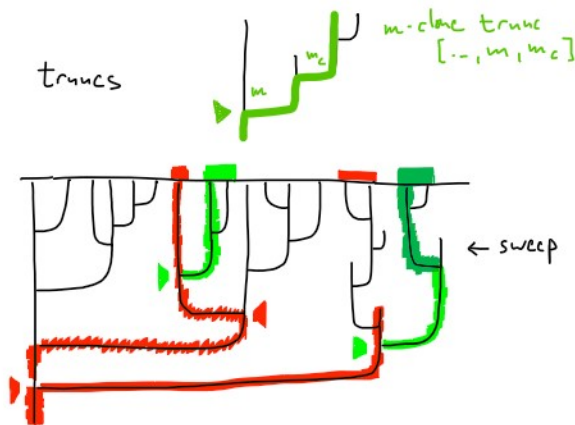
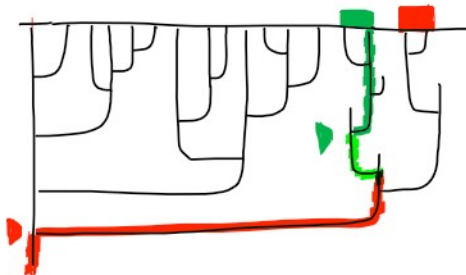
alg: m_1, m_2, m_3, m_4 orphaned

real: m_2, m_3, m_4 orphaned

Note:

- 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 is irrelevant

haplotypes \rightarrow clones \rightarrow trunks



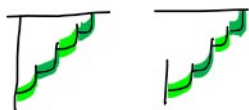
[for haplotypes only the leaves are green and red]

$\text{trunc}[m] = \bigcap \text{clone} = \{ m \mid m \in h \forall h \in \text{clone} \}$

haplotypes

Note \longrightarrow this is an issue for haplotypes too

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



all estranged or extinct \longrightarrow

extinct haplotypes cannot be (uniquely) identified!

- last m in this motif is estranged if trunc in htypes!



- if motif has length 1 trunc m must be in htypes too!
- exclude typeones i.e. $|\text{trunc}| == 1$

algorithm

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

truncp = filter (issubtype, trunc)

$t = |\text{truncp}|$

$(\text{issubtype}(m_i, \text{trunc}) = \text{truncs}[m_i] == \text{trunc})$

$t > 1$

is estranged
 $\frac{(\text{trunc in htypes})}{t}$

is green
 $\frac{(\text{trunc in htypes})}{t}$

$\text{length}(\text{trunc}) == 1$

0.

0.

$t == 1$

$\frac{(\text{trunc in htypes})}{\&\&}$
 $(\text{trunc truncp in htypes})$

(trunc in htypes)

Note:

The following definition is equivalent!

- consider all haplotypes
- a haplotype is estranged if there is no haplotype with exactly one mutation less

clones

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

per green clone

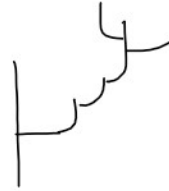
$$trunc = \text{filter}(\text{issubtype}, trunc)$$

$$t = |trunc|$$

$$\text{is orphaned}[m] = \frac{t-1}{t}$$

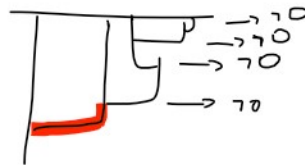
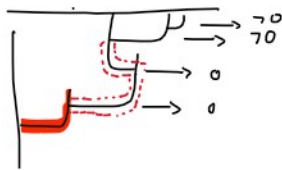
$$\text{is green}[m] = trunc == trunc ? \frac{t-1}{t} : 1$$

$\hookrightarrow \hat{=} \text{ motif has type one}$



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

→ can't mean upstream-trunc and "foliage" size

$\geq m_4 \rightarrow \text{orph}$



per red clone

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

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

$$t = |trunc|$$

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

$$\text{is green} = \frac{1}{t} \sum_{n=0}^{t-1} l+n = l + \frac{t-1}{2}$$