Palimpsest: an R package for studying mutational and structural variant signatures along clonal evolution in cancer

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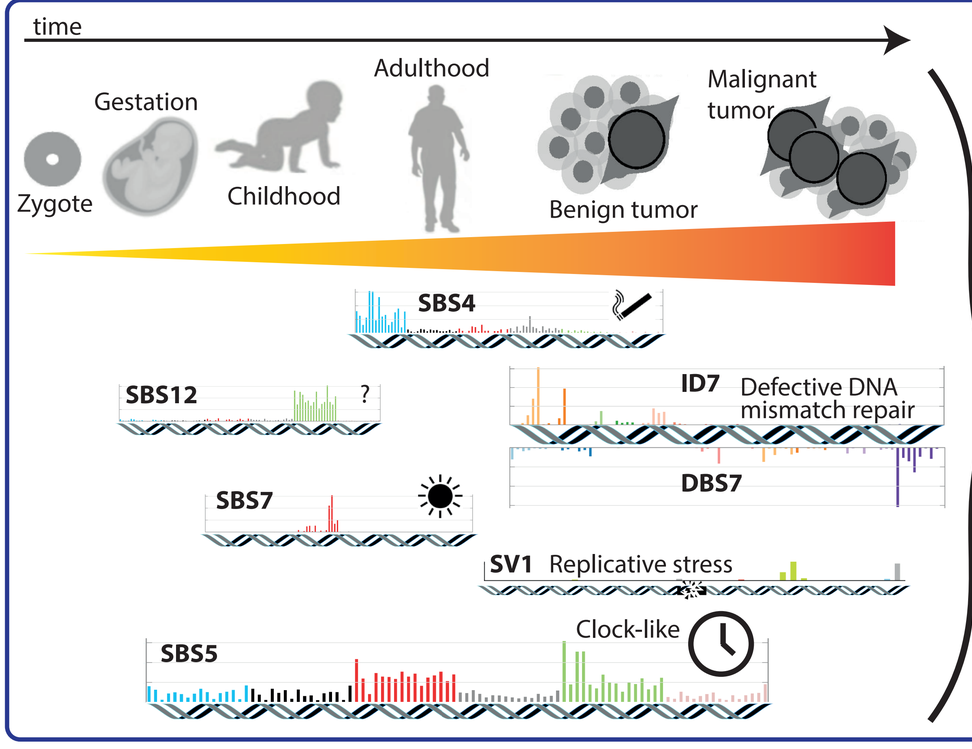
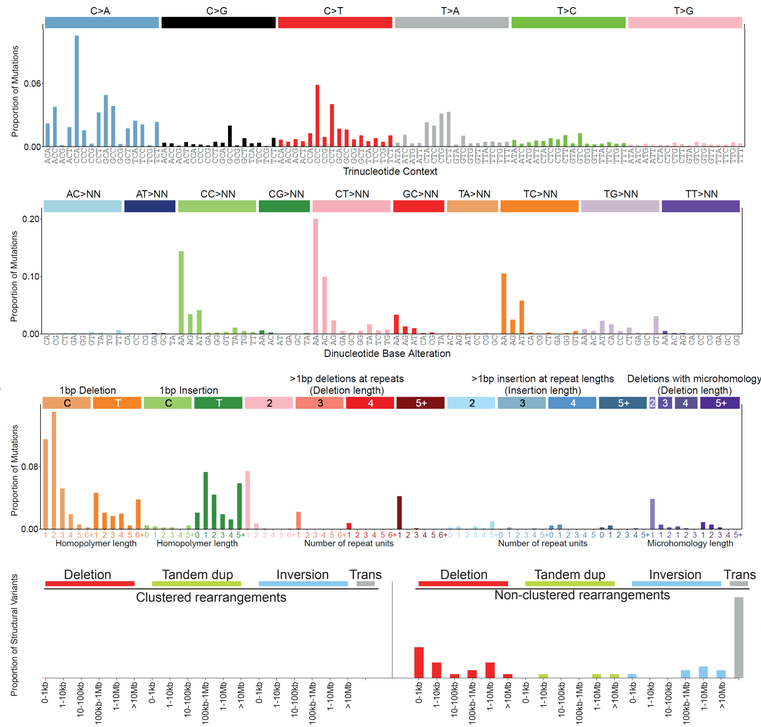
Cancer genomes are altered by various **mutational processes** and, like palimpsests, bear the signatures of these different processes.
Mutational signature analysis is a powerful approach to **decipher the origin of somatic mutations in cancer** [1].
The **Palimpsest R package** [2] allows to **integrate mutational signature and clonality analyses** in order to reconstruct the **natural history of a tumor**.

Cancer genomes bear the signatures of different mutational processes





Single base substitution
SBS

Double base substitution
DBS

Small insertions and deletions
ID

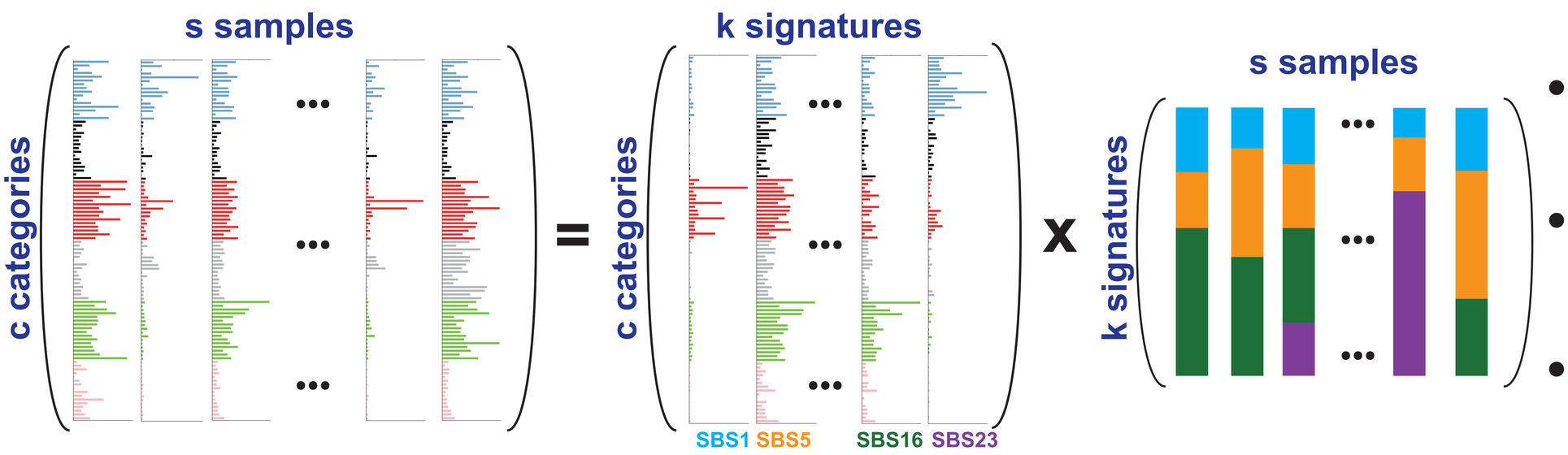
Structural variants
SV

Somatic alterations are **classified into categories** [3,4] according to:
- **Type** (T>A, Inversion, Deletion ...)
- **Context** (trinucleotide, repeats ...)
- **Size** (for ID and RS)
- **...**

Identification of **recurrent patterns** reveals the **signatures of each mutational processes**

These can occur **from the zygote through adulthood**, and also **throughout the lifespan of the tumor**

Palimpsest package: extracting signatures of known and new mutational processes



Mutation catalog = Processes × Exposures

- Blind source separation with **NMF** (non-negative matrix factorization)
- Can be applied to any type of somatic alteration (**SBS**, **DBS**, **ID** or **SV**)
- *De novo* extracted signatures can be **compared to Cosmic** signatures with cosine similarities

Processes
- ***De novo* extraction of novel signatures**
- **Already known signatures (Cosmic database)**

NMF: finding the solution to

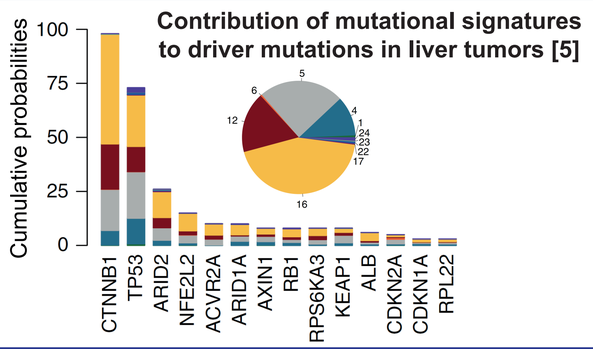
$$\min_{P \in M_{R^+}^{(c,k)}, E \in M_{R^+}^{(k,s)}} \|M - P \times E\|_F$$

Assigning the causal process of each alteration

For each variant in each sample:

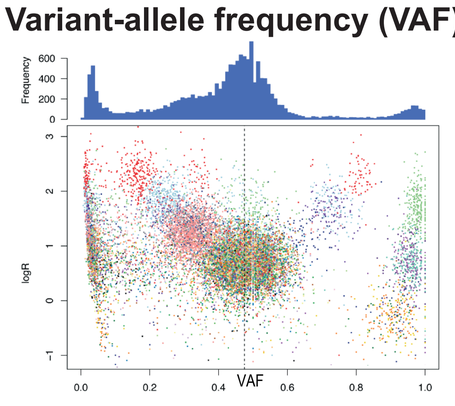
- probability that it was due to each identified signatures
- assign the most likely signature

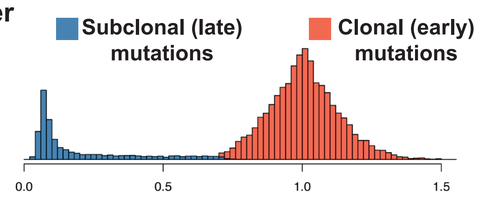
Drivers ⟷ Etiologies



Clonal architecture of tumors - single sample

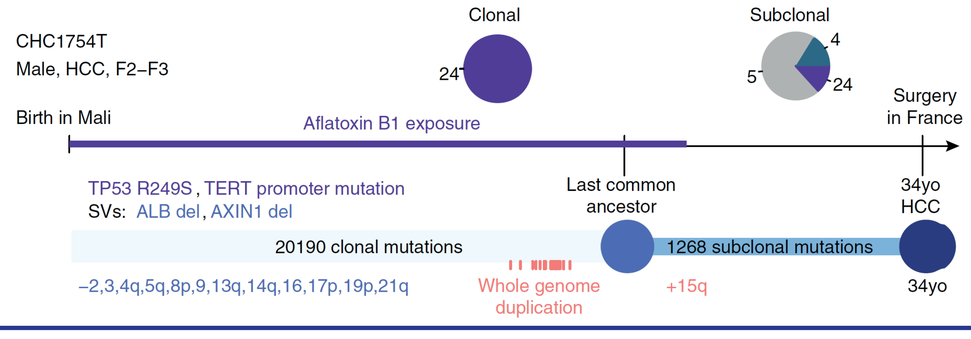
Variant-allele frequency (VAF) → **Cancer Cell Fraction (CCF)**
+ Tumor purity
+ Copy-number





$$CCF = VAF \times \frac{\rho N_t + (1-\rho) N_n}{\rho n_{chr}}$$

Comparison of mutational processes between clonal and subclonal mutations:



[5]

Clonal architecture of tumors - multiple samples

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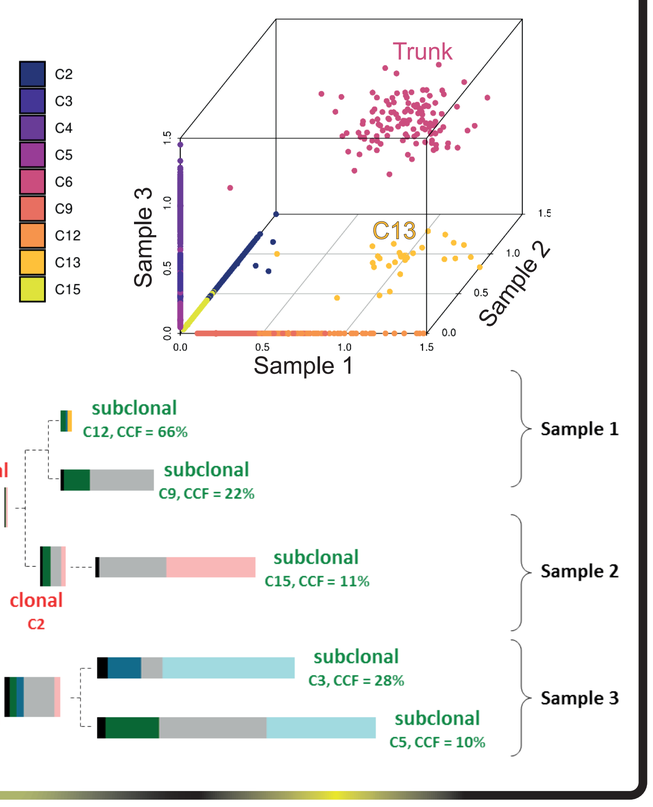
For each mutation, compute the CCF in each sample

Bayesian Dirichlet process to identify clusters of CCF

Reconstruct the evolutionary tree of the tumor

Analyze mutational signatures in each branch



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Our GitHub

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https://github.com/FunGeST/Palimpsest

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[1] Alexandrov *et al*, Nature 2013. PMID: 23945592
[2] Shinde *et al*, Bioinformatics 2018. PMID: 29771315
[3] Bayard *et al*, Nature Communications 2018. PMID: 30531861
[4] Alexandrov *et al*, Preprint 2018. bioRxiv 322859
[5] Letouzé*, Shinde* *et al*, Nature Communications 2017. PMID: 29101368