Estimating historical tumor growth dynamics from bulk DNA-seq data with clock-like mutational signatures and variant allele frequencies

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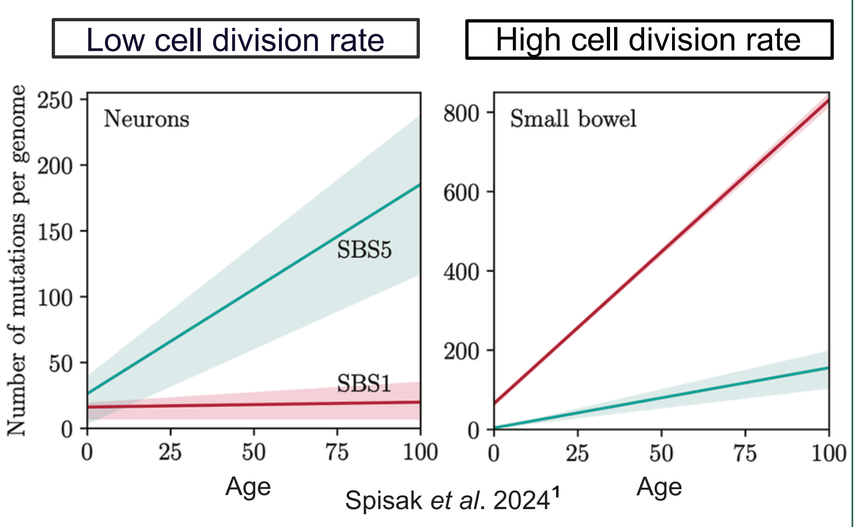
Can we infer tumor growth dynamics from clock-like mutational signatures?

Spisak et al. found clock-like mutational signatures accruing at roughly constant rates according to the number of cell divisions (SBS1) and the passage of time (SBS5).[1]

We can use the intensity of SBS1 and SBS5 at different stages in tumor development to estimate the number of cell divisions per unit time (i.e., the tumor growth rate).



Spisak *et al.* 2024[1]

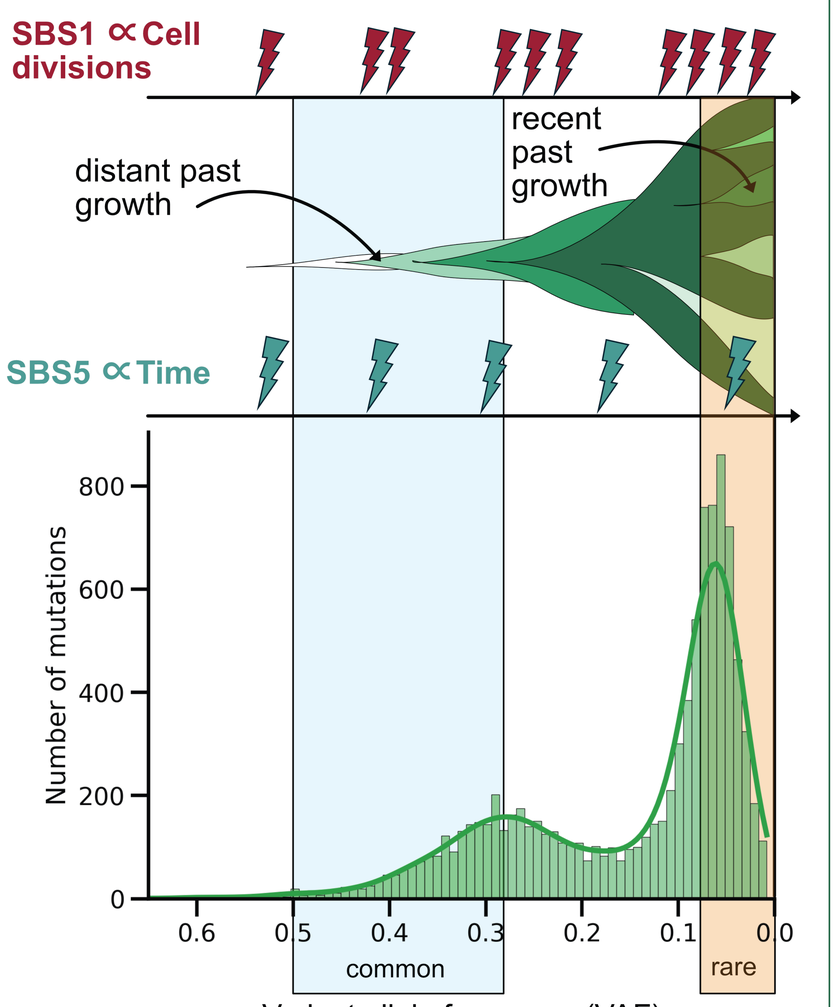
Approximating tumor developmental stages with variant allele frequencies

Variant allele frequency (VAF): how many mutations are present at a given frequency in a tumor.

Higher frequency mutations (common)
→ earlier in tumor development

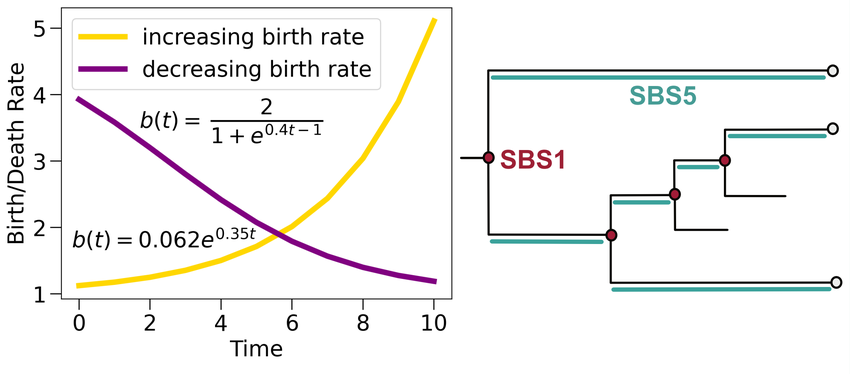
Lower frequency mutations (rare)
→ later in tumor development

SBS1/SBS5 relative intensity at different mutational frequencies may reveal changing tumor growth rates through time.



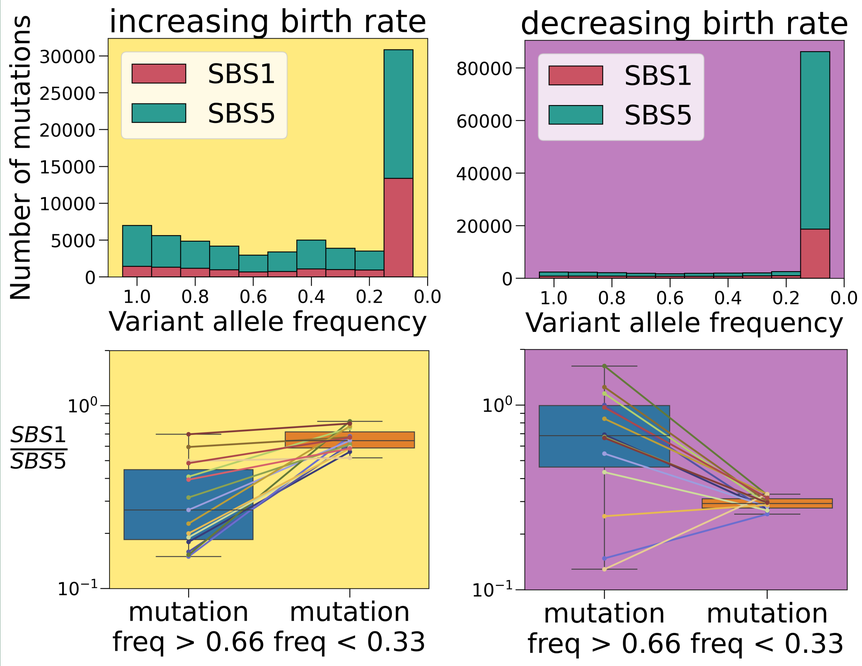
Validating expected SBS1/5 activities at different VAFs in growth simulations

We simulated birth-death processes in which birth rate increased or decreased over time. Cells accrued SBS5 mutations at a constant rate through time, and SBS1 mutations only at cell divisions.



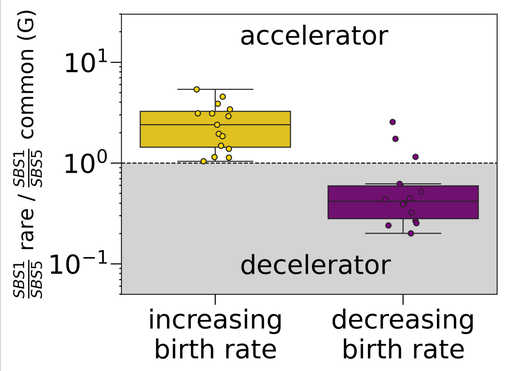
In tumors with *increasing* birth rate, rare (i.e., recent) mutations enriched for SBS1 activity (∝cell divisions) relative to common (i.e., early) mutations.

In tumors with *decreasing* birth rate, rare mutations depleted for SBS1 activity relative to common mutations.



We can capture increasing or decreasing growth rate patterns with a summary statistic:

$$G = \frac{SBS1_{rare}/SBS5_{rare}}{SBS1_{common}/SBS5_{common}}$$

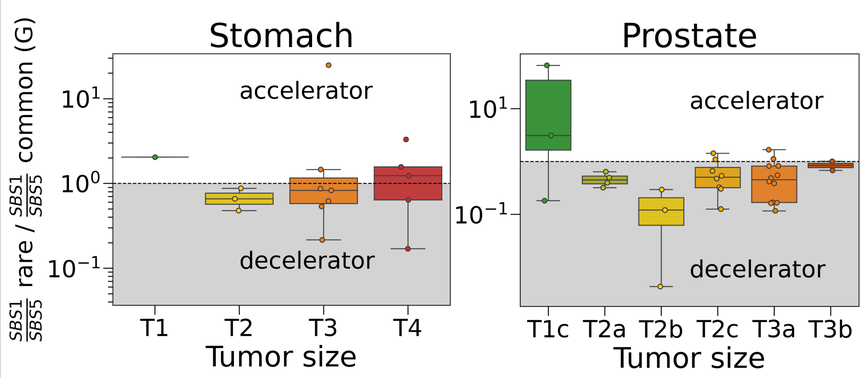


G captures true growth dynamics in simulated tumors:

- tumors with increasing birth rate: accelerators (G>1)
- tumors with decreasing birth rate: decelerators (G<1).

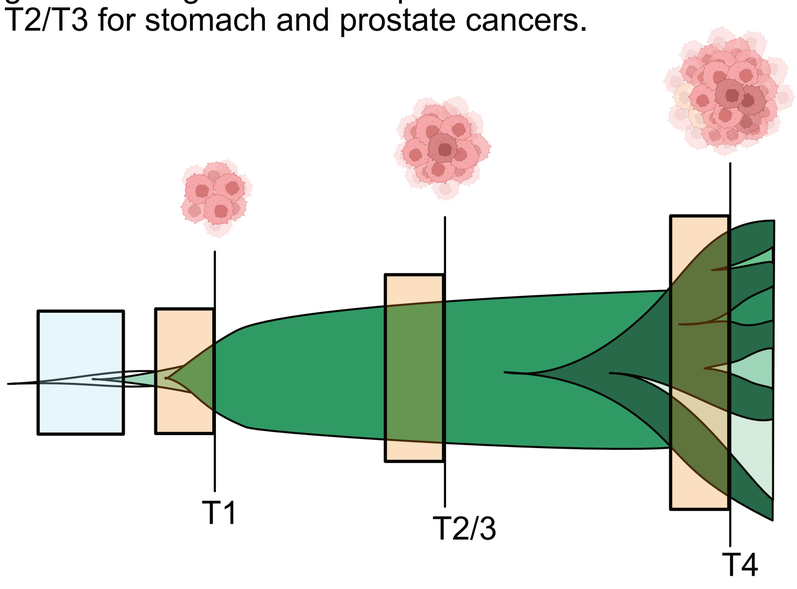
Inferred period of slower growth in stomach and prostate cancer development

We applied this approach to measure growth dynamics in primary stomach (n=16) and prostate (n=32) tumors from ICGC[2]. We partitioned mutations from each sample by their frequencies and used SigProfilerAssignment[3] to fit SBS signatures separately for the 1/3rd most common and rare mutations.



Surprisingly, many tumors showed slower growth rates among more recent divisions (G<1), especially in intermediate-sized tumors (T2&T3). Consistent size-dependent effects across stomach and prostate cancers: smallest (T1) and largest (T4) tumors showed the strongest signals of recent growth (G≥1).

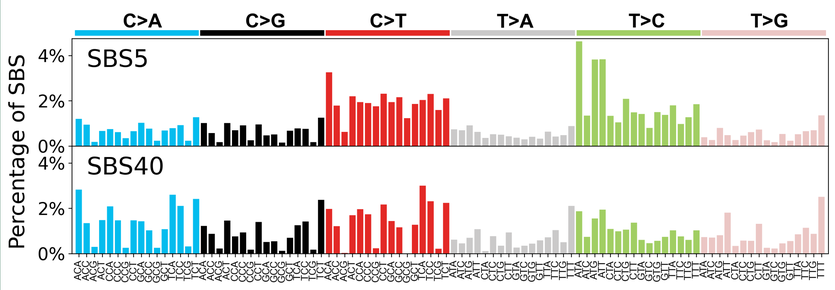
This pattern could be consistent with a period of slower growth during tumor development observed at size T2/T3 for stomach and prostate cancers.



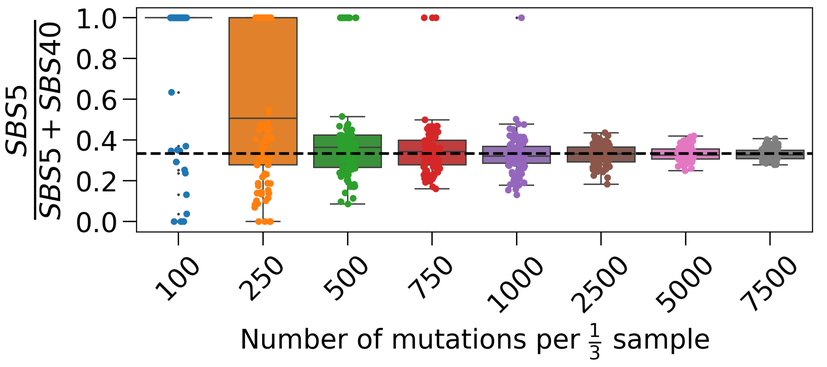
Ongoing challenges with SBS1 & SBS5 mutational signatures inference

Mutational signatures with flat profiles can be confounded with SBS5

SBS5 has a relatively flat signature profile, making it difficult for signature inference tools to distinguish it from other similarly flat signatures, e.g. SBS40.

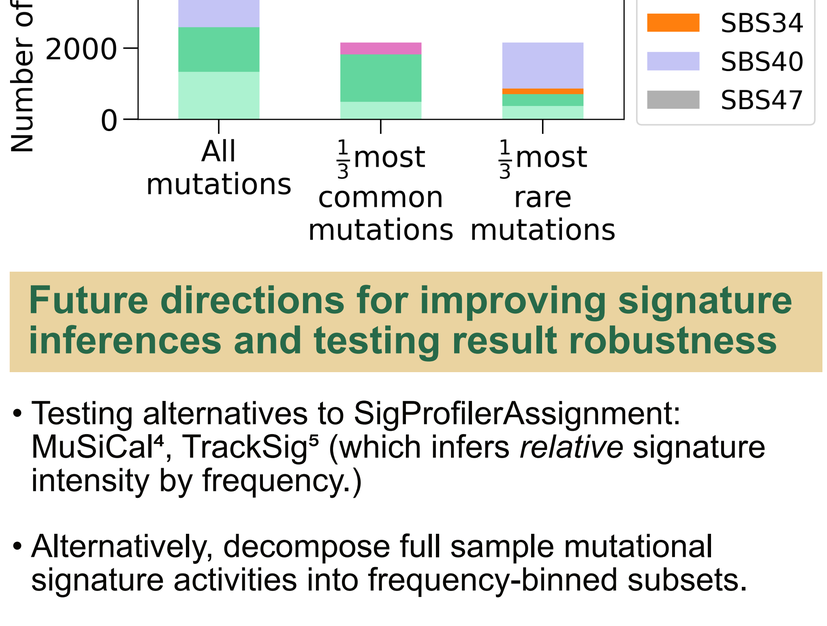


We tested SigProfilerAssignment's ability to factorize SBS5 and SBS40 correctly using simulations, and found ~2500 mutations were necessary. This limits the cancer types on which we can compute G.



Signature activities inferred separately from rare and common mutations are often inconsistent with the full sample

Inference on data subsets sometimes identifies mutational signatures absent in full sample, and sometimes infers more absolute signature activity in a subsample than the full sample.



Future directions for improving signature inferences and testing result robustness

- Testing alternatives to SigProfilerAssignment: MuSiCal[4], TrackSig[5] (which infers *relative* signature intensity by frequency.)
- Alternatively, decompose full sample mutational signature activities into frequency-binned subsets.

Conclusions

- Ratio of clock-like signatures that track either cell division or time can reveal changing growth dynamics in simulated tumors over time.
- Application to stomach and prostate WGS data suggests tumor growth rates are not constantly increasing as tumors grow. Results may point to a period of decelerated growth at intermediate tumor sizes (T2/T3), in which tumors have reached carrying capacity or are waiting for additional growth drivers.
- Challenges remain to ensure that SBS1/SBS5 activity estimation is robust enough for this type of inference.

References

1. Spisak, Natanael, et al. PLoS biology 22.6 (2024)
2. Zhang, Junjun, et al. Nature biotechnology 37.4 (2019)
3. Díaz-Gay, Marcos, et al. Bioinformatics 39.12 (2023)
4. Jin, Hu, et al. Nature Genetics 56.3 (2024)
5. Rubanova, Yulia, et al. Nature communications 11.1 (2020)