Cell-cycle dependent DNA repair and replication unifies patterns of chromosome instability

Bingxin Lu, Samuel Winnall, William Cross, and Chris P. Barnes
b.lu@surrey.ac.uk, christopher.barnes@ucl.ac.uk

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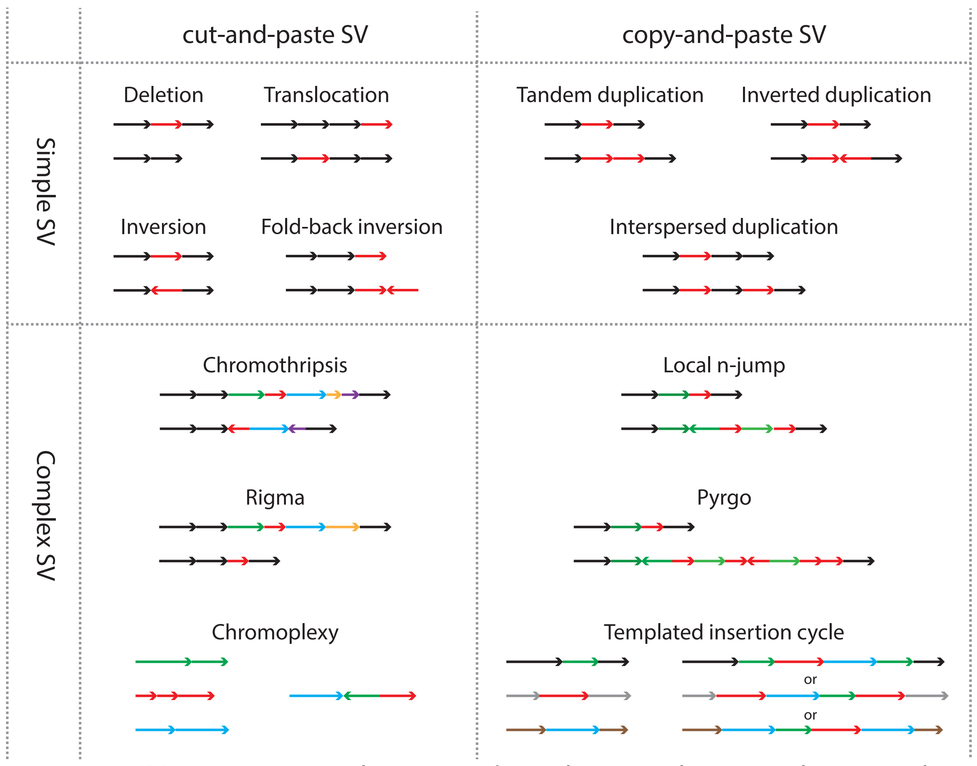
Introduction

- Chromosomal instability (CIN) is widely present in human tumours [1].
- CIN often leads to structural or numerical chromosomal aberrations.
- CIN plays an important role in cancer evolution.
- Somatic structural variants (SVs) are large genomic rearrangements.
- Many studies have analysed and catalogued the patterns of SVs [2, 3].

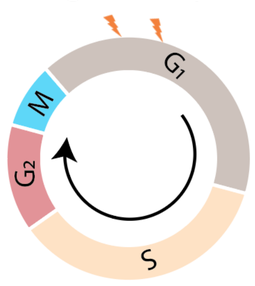


How erroneous DNA repair mechanisms directly contribute to the complex SVs observed in cancer genomes remains unclear [4, 5].

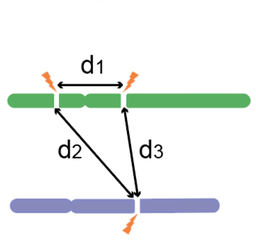
We develop a quantitative cell-cycle model for the generation of a wide spectrum of SV patterns caused by CIN at the whole genome level, incorporating DNA damage along with erroneous repair and replication processes.

Method

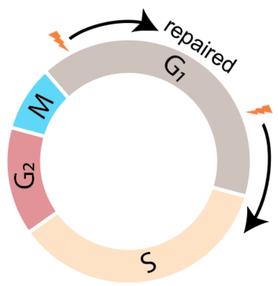
We simulate cell divisions with a stochastic birth-death branching process and introduce random double strand breaks which are repaired via non-homologous end joining or unrepaired, accounting for cell cycle stage.



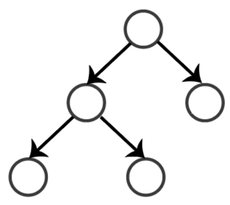
DSBs formation in G1
Genome replication in S
Cytokinesis in M



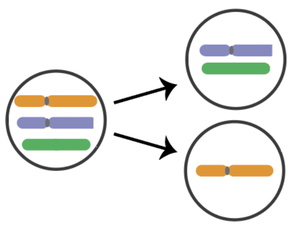
DSBs rejoin in a distance dependent manner



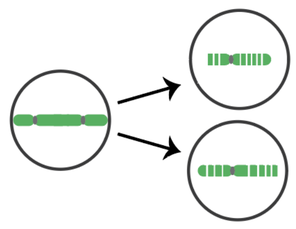
A proportion of DSBs may remain unrepaired and pass through checkpoints



Cell division within a branching process model



DNA segregation depends on number of centromeres



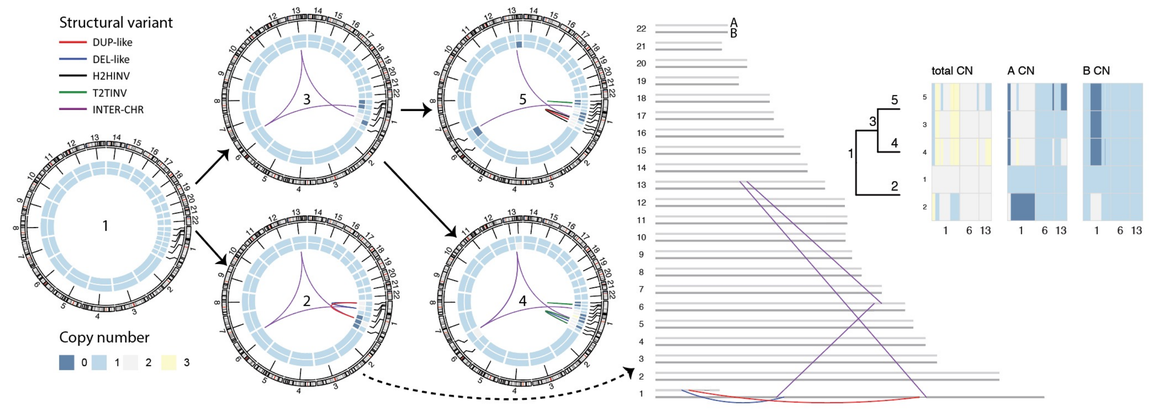
Multiple centromeres may result in breakage and fragmentation

To capture the complexity of SVs in a complete diploid human genome, we use an interval adjacency graph representation, where each node is a breakpoint, and each edge is an adjacency between two breakpoints.

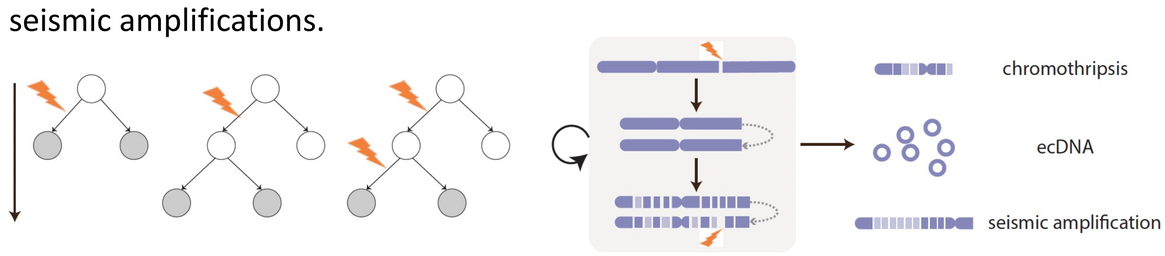
To gain insight into the formation and evolution of rearranged genomes, we developed a simulation-based inference approach using approximate Bayesian computation (ABC).

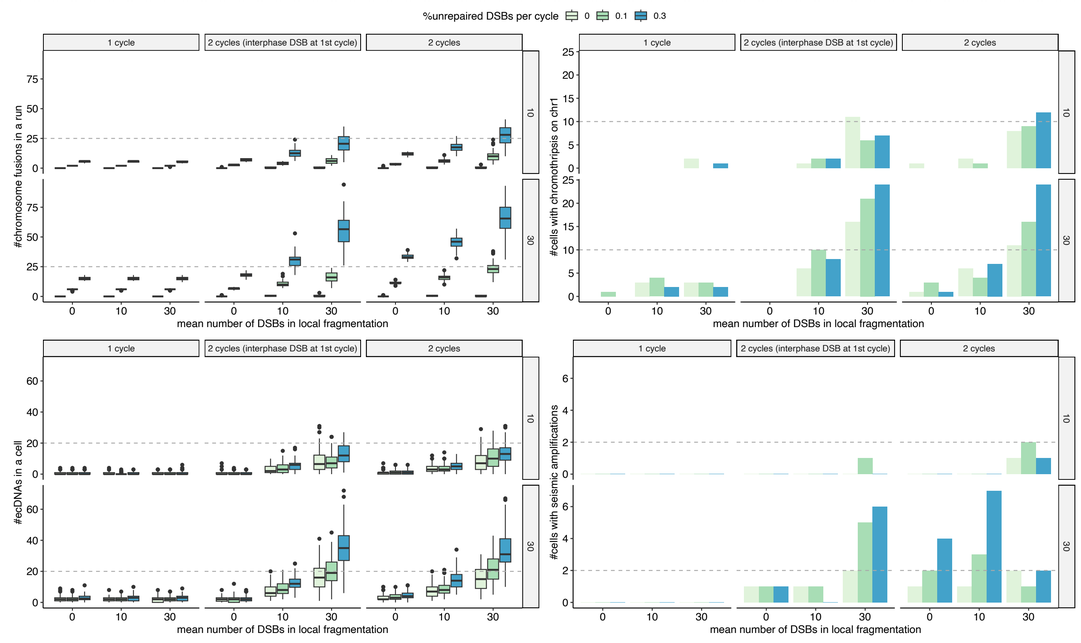
Results

The simulations enable the stepwise visualization of SV accumulation and quantification of SV patterns.

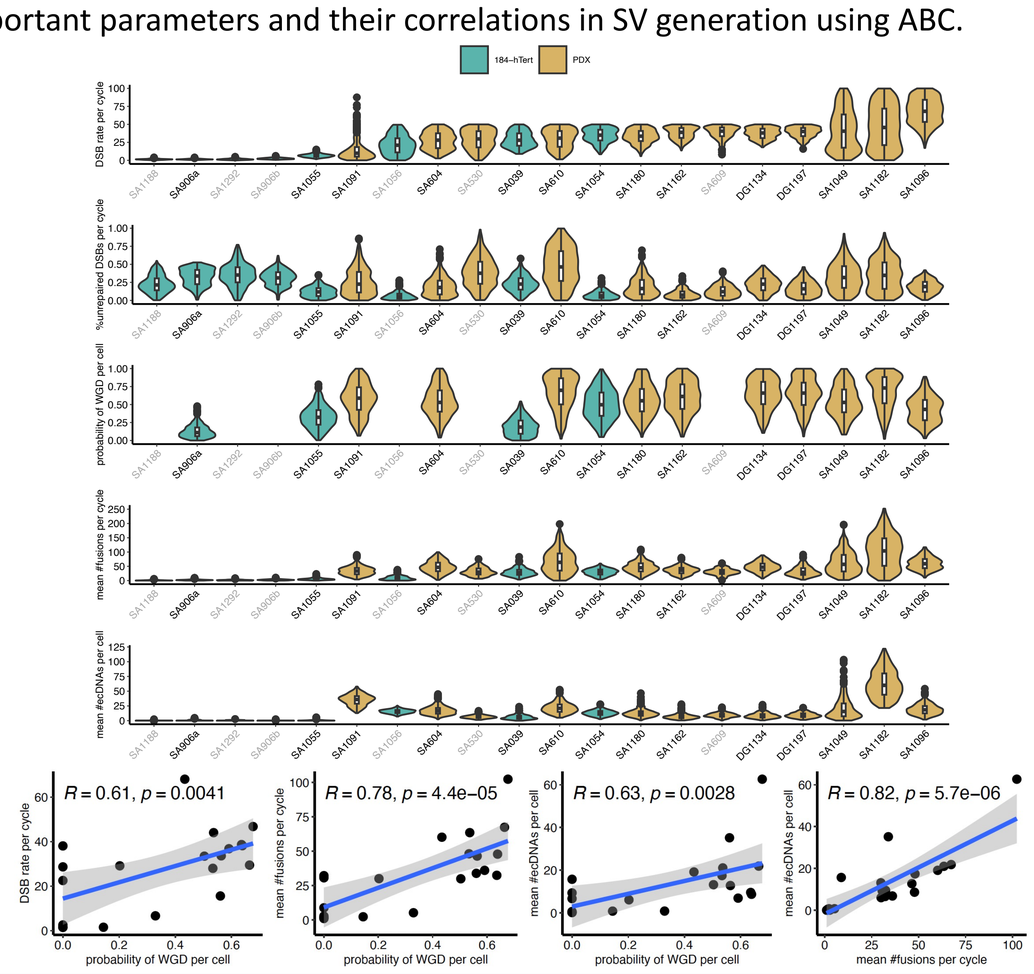


Chromothripsis-like patterns are generated in one or two cell cycles, along with breakage-fusion-bridges (BFBs), extrachromosomal circular DNAs (ecDNAs), and seismic amplifications.





Given single-cell whole-genome sequencing data [6], the model allows to infer important parameters and their correlations in SV generation using ABC.



Conclusion

Our quantitative model

- unifies disparate genomic patterns resulting from CIN,
- provides a null mutational model for SV generation,
- reveals new insights into the impact of CIN on tumour evolution.

Reference

[1] Watkins et al., Nature (2020) 587: 126–132.
[2] Li et al., Nature (2020) 578: 112–121.
[3] Hadi et al., Cell (2020) 183: 197–210.
[4] Dahiya et al., Seminars in Cell & Developmental Biology (2022) 123: 100–109.
[5] Zhang and Pellman, Annual Review of Cancer Biology (2022) 6: 245–268.
[6] Funnell et al., Nature (2022) 612: 106–115.