Capturing Within-Host HIV-1 Evolution Dynamics Using Simulation Methods

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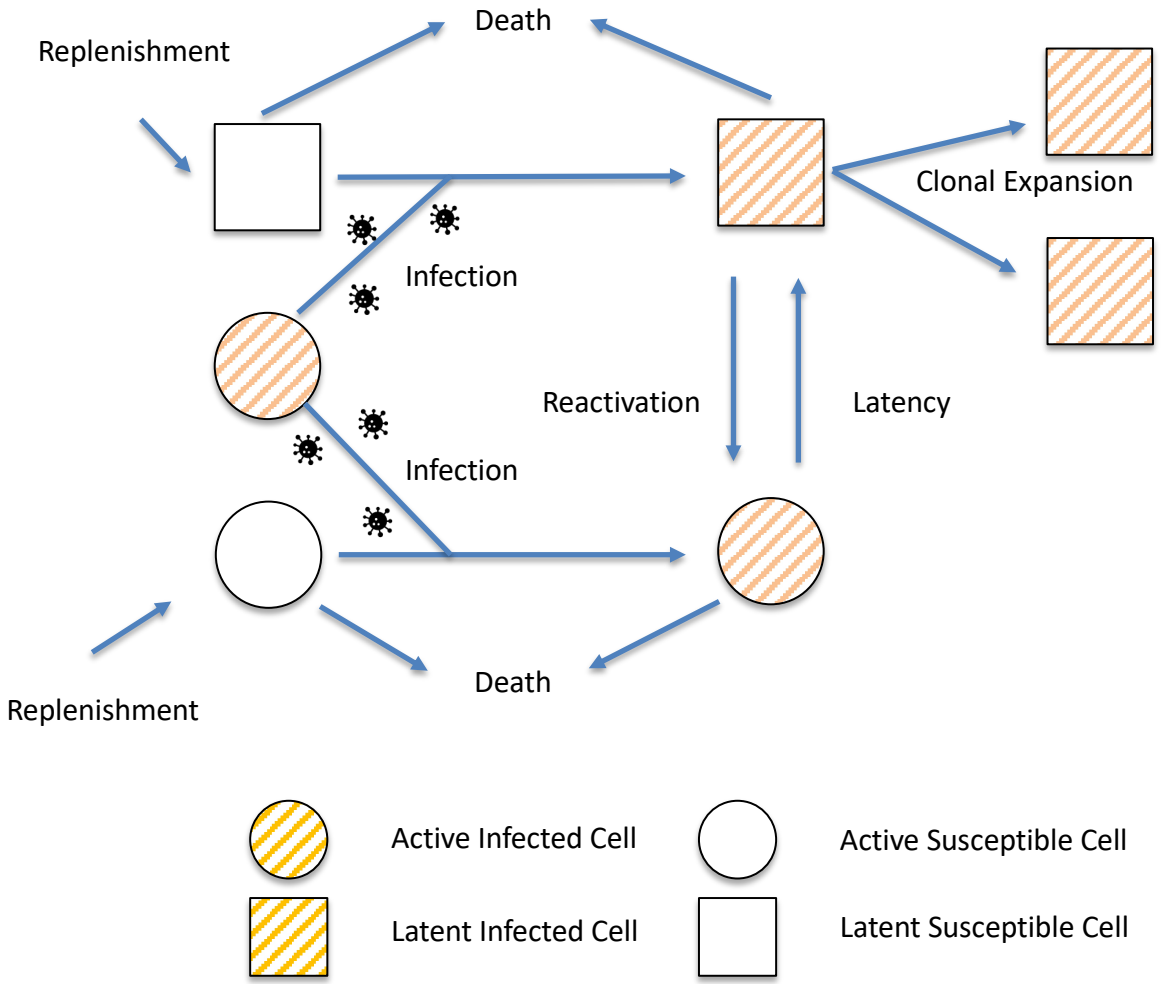
Introduction

- Latent reservoir remains an area of active research, an HIV cure necessarily addresses the latent reservoir
- Studying the latent reservoir *in vivo* is expensive and difficult due to its relatively small size and the timescale involved
- Simulating the dynamics of the latent reservoir can provide deep insights into the interactions at play that cannot be easily captured through *in vivo* studies
- Clonality describes how many identical sequences there are in the latent reservoir – it is evidence of proliferation through clonal expansion
- Current measures of clonality uses a proportionality statistic that has not been evaluated for efficacy

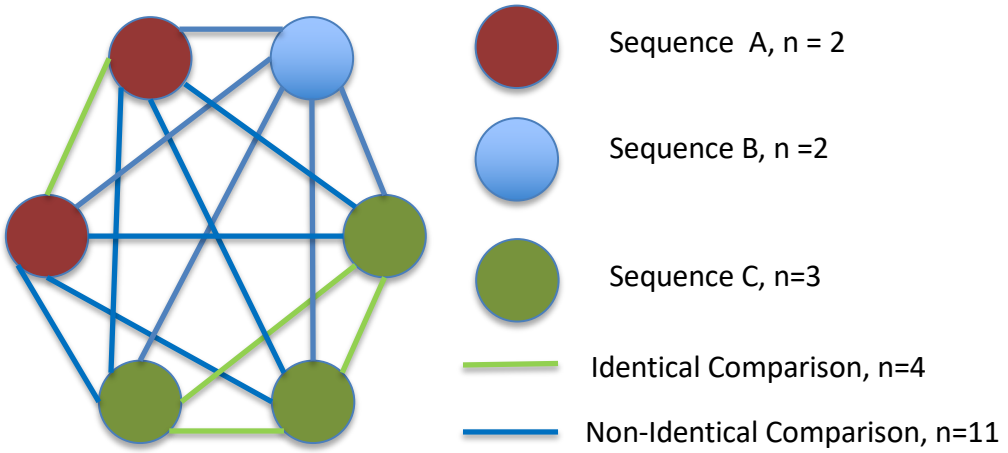
Defining the Simulation model

- Simulation of within-host dynamics and evolution conducted in R using *twt* package (github.com/poonlab/twt)
- Gillespie method to sample discrete events over reverse time
- Model dynamics controlled by 13 parameters
  - e.g. starting size, transmission & transition rates
- INDELible used to simulation sequence evolution on output trees from *twt*



Proportional, GINI and Pairwise Clonality Scores

- Proportional clonality score – the proportion of sequences in a sample that have at least one other identical sequence is the gold standard for calculating clonality
- Gini coefficient has been used as a summary statistic to quantify viral population diversity [2,3]
- Proportional clonality score and Gini Coefficient scores were unresponsive to changes in drivers of clonal expansion
- We propose the pairwise clonality score, calculated as the proportion of total pairwise comparisons that are identical



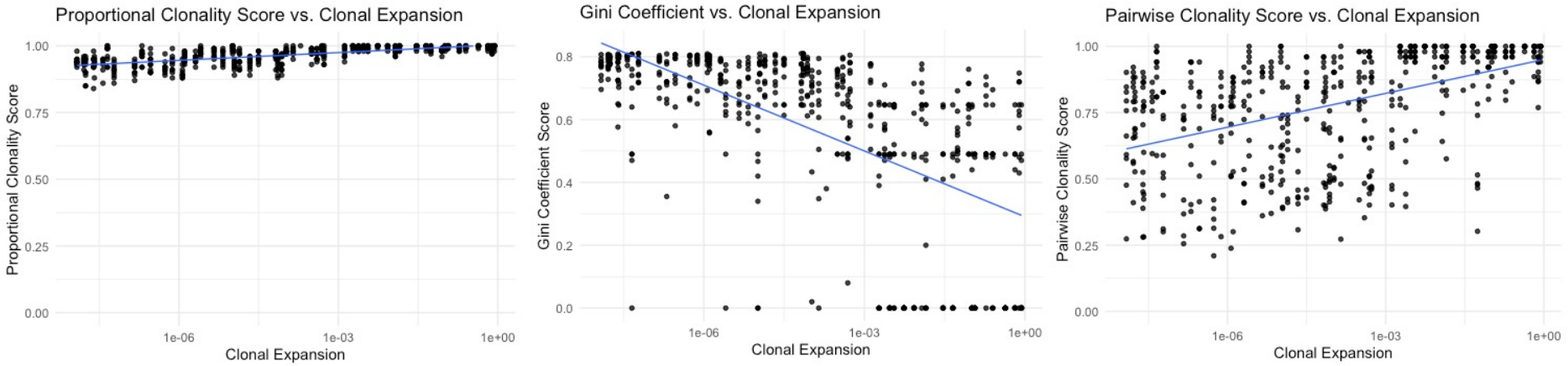
In above example:

Proportional Clonality = Identical / non-identical
= 5/6
= 0.8333

Gini Coefficient = 0.222

Pairwise Clonality = 4/15
= 0.267

High clonality scores found despite of increased clonal expansion



- GINI Coefficient is a flawed measure. GINI coefficient generally has an inverse relationship with diversity. However populations where all sequences are identical, Gini Coefficient is zero. Within-host HIV populations are regularly completely identical [4].
- Pairwise clonality significantly associated with increases in drivers of clonal expansion ($p < 0.005$)
- Pairwise clonality captures information about the population structure & has useful statistical properties.
  - Pairwise comparisons are independent comparisons – good for statistical tests

Conclusions

- Current measures of clonality (proportional clonality & GINI coefficient) are not associated with clonal expansion
- Clonality is not a definite sign of clonal expansion, especially when studying a viral population that contains early integrations
- Pairwise Clonality score captures population structure and responds to drivers of clonal expansion in various simulated scenarios

References

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