To affinity and beyond: simulating germinal center B cell receptor sequence maturation

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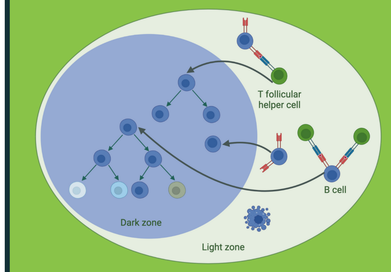
Background

In order to develop a robust immune response to incoming antigen, vertebrate germinal centers (GCs) act as sites of enzyme-driven somatic B cell mutation, specifically at antibody-encoding regions. B cells that are successful at binding antigen tend to proliferate most, and can outcompete less successful lineages. T cells in the GC produce signals for this proliferation, and B cells compete for this help based on the amount of antigen they can capture. Novel data sets, including sequence data from GCs that have been "replayed" from the same monoclonal starting conditions and deep mutational scans of the B cell receptor (BCR), have expanded knowledge of GC evolution, especially at the sequence level.

Introduction

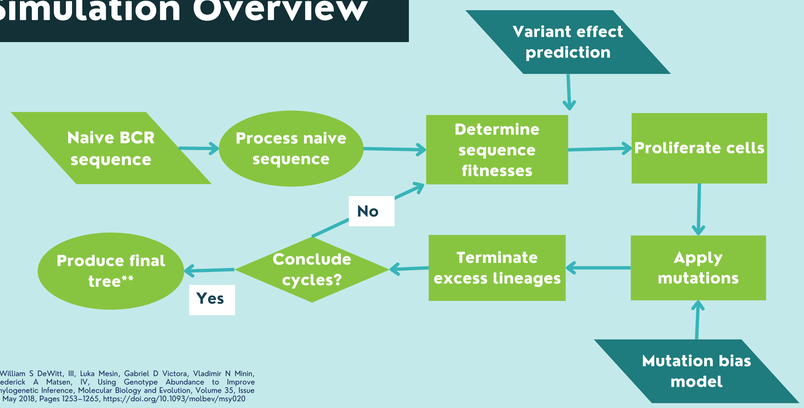


Cycles of B cells through the light zone and dark zone facilitate BCR evolution and expansion of fit lineages. This work simulates cyclic selection, proliferation, and mutation of BCR sequences.

Objectives

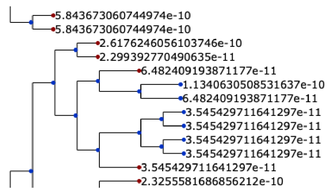
- Test T cell help hypothesis: **does competition for T cell help drive evolution in the GC?**
- Does the molecular phenotype produce a **deterministic fitness advantage?**
- **Is the BCR DNA sequence an accurate and precise indicator** of this fitness advantage?

Simulation Overview

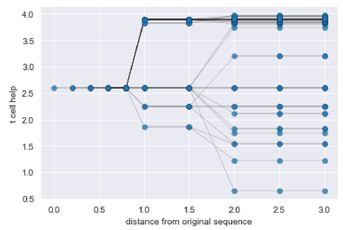


Analysis

- Simulations inferring fitness from sequence **may be able to reproduce GC composition**
  - Stochasticity in selection model is necessary to allow sublineage replacement
  - Substitutions at preferred sites produce a more significant decrease in affinity to antigen than random substitution
  - Both "clonal bursts" of strong affinity maturation and gradual maturation appear
- **Significant diversity remains in real and simulated GCs**
  - Variation in distribution of T cell help and mutations contribute to diversity



Over simulation cycles, affinity to antigen (shown on cropped tree tips) generally improved.

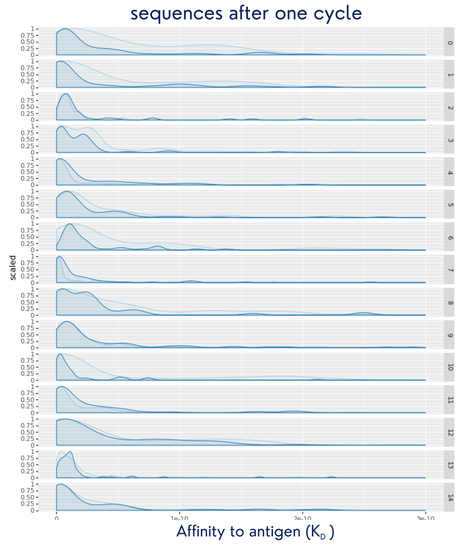


Under a less stochastic model, T cell help generally remains the same for a lineage after the first two dark zone/light zone cycles.

Results

Multiple models of selection, proliferation, and mutation were tested and compared to observed sequences derived from replay experiments. Both simulation from the same naive sequence as these experiments as well as simulation by extension of one cycle were used to compare these data.

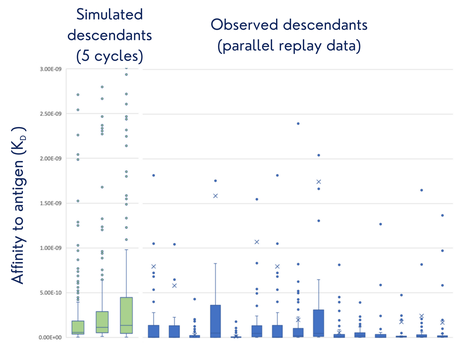
Estimated antigen affinity in descendant BCR sequences after one cycle



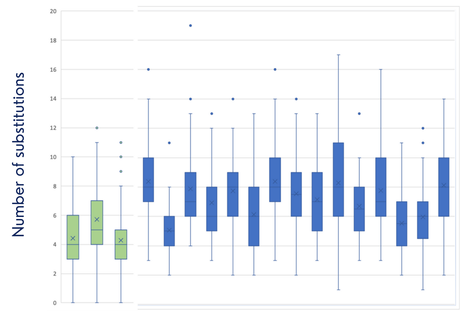
Simulation parameters:
- Maximum T cell help: 5
- T cell help/B cell: 1/2
- Antigen concentration: 10^-10 M
- Minimum antigen bound: 20%
- Mutation model: hotspot-aware

category
observed
simulated_descendants

Over repeated single-cycle extensions of diverse sets of observed data, the distribution of K_D values generally decreased with an 82% average decrease.



Distribution of predicted affinity values at 20 days post-immunization are within the same range as simulated descendant affinity after 5 dark zone/light zone ycles.



Observed descendant cells have a higher median number of somatic mutations than simulated cells.

Conclusions

Including novel data from deep mutational scans and explicitly modeling T cell help based on B cell receptor sequence allows simulation that captures some key characteristics of sequence evolution over time. However, this simulation does not currently capture all aspects of this sequence distribution, and future work aims to more closely reproduce other benchmarks.

Future Work

Next steps:
- Infer tree shape and compare to models of observed tree shape
- Fine-tune parameters for more exact match to observed data
- Integrate with other models of germinal center dynamics

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