TreeFix-VP: Phylogenetic Error-Correction for Viral Transmission Network Inference

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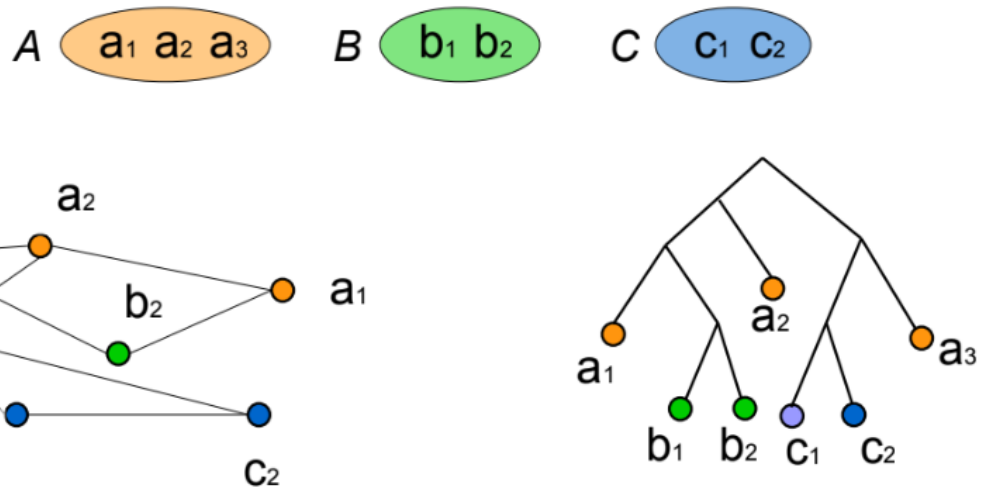
Viral Transmission Inference

Problem

Reconstruct transmission of disease

Given: *Viral sequences from infected hosts*

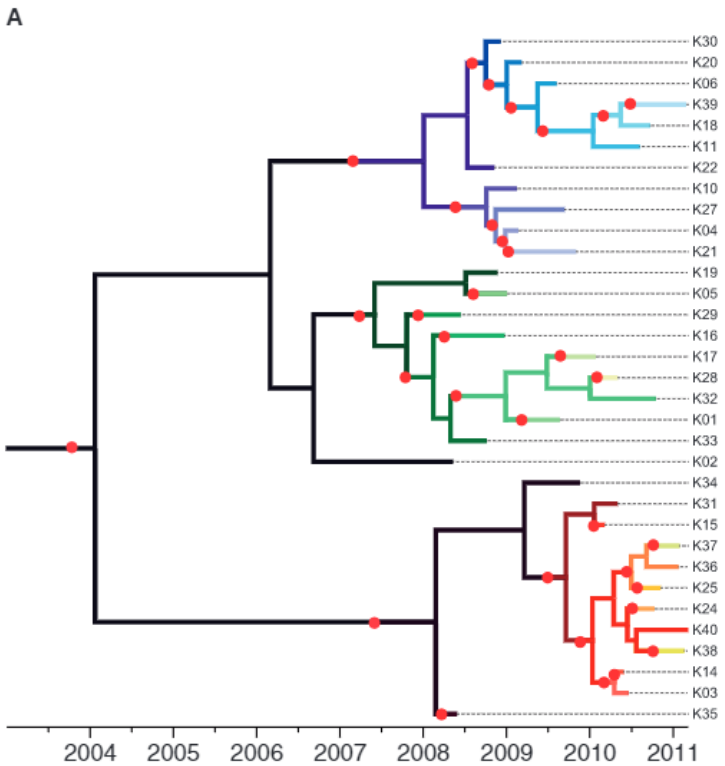
Goal: *Network $G(V, E)$ where V is the set of infected hosts, and each edge in E represents a transmission of the disease*



Bansal 2017

Phylogeny-Based Transmission Network Inference

- Label internal nodes of viral sequence phylogeny with hosts
- Didelot et. al 2014, Hall et. al 2015, Klinkengerg et al. 2017



Didelot et. al 2014

Improved Phylogenetic Inference

Goals:

- Improve downstream transmission inference
- Improve scalability by reducing the need for MCMC or coestimation of phylogeny

Approach: Error correction for reconstruction of highly accurate viral phylogenies

Improved Phylogenetic Inference

Problem

Reconstruct viral phylogeny

Given: *Viral sequences from infected hosts*

Goal: *Tree T representing evolutionary history of the virus, where leaves are labeled with infected hosts*

TreeFix-DTL

Improved gene tree error correction in the presence of horizontal gene transfer

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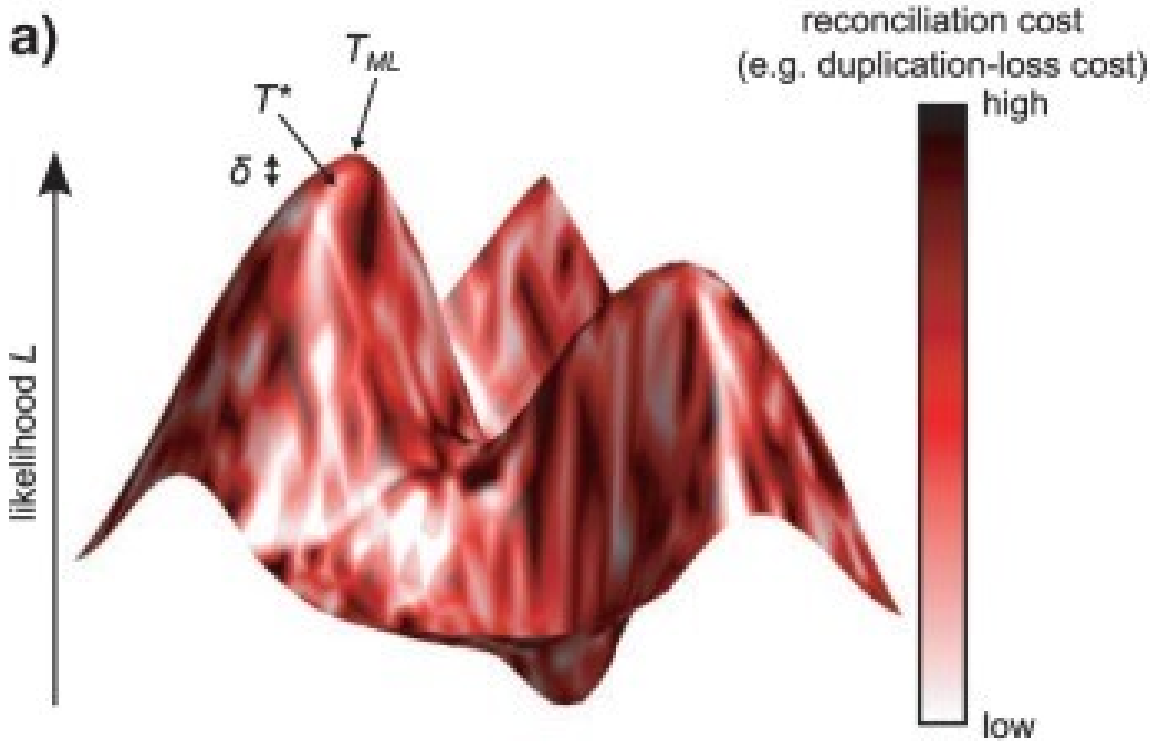
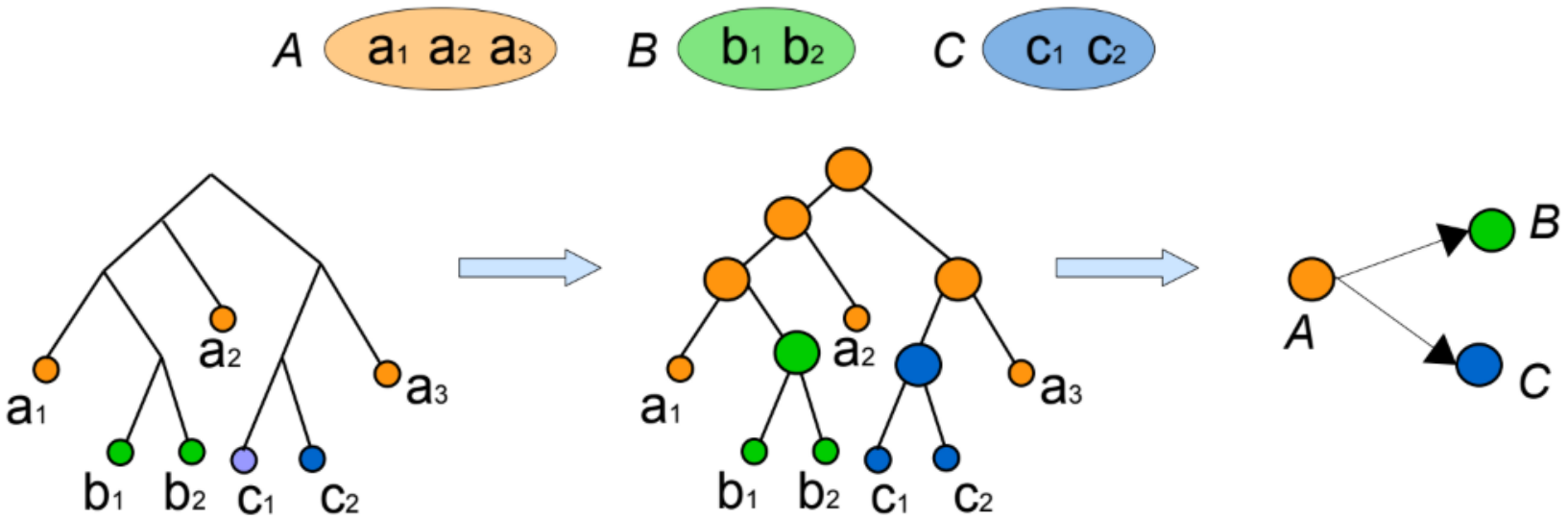
Search in Maximum Likelihood Neighborhood



Bansal and Wu et. al 2014

Multiple Sequences per Host



Bansal 2017

TreeFix-VP

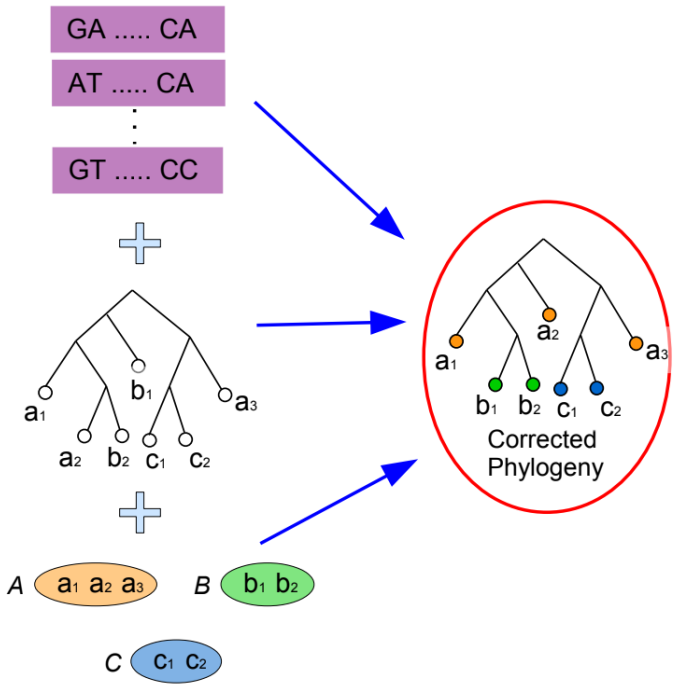
Computational method for error correction of viral sequence phylogenies

- Accurate reconstruction of phylogenies
- Increased accuracy of outbreak and transmission inference
- Scalable analysis

TreeFix-VP

Input: Maximum likelihood phylogeny, multiple sequence alignment, sequence-host mapping

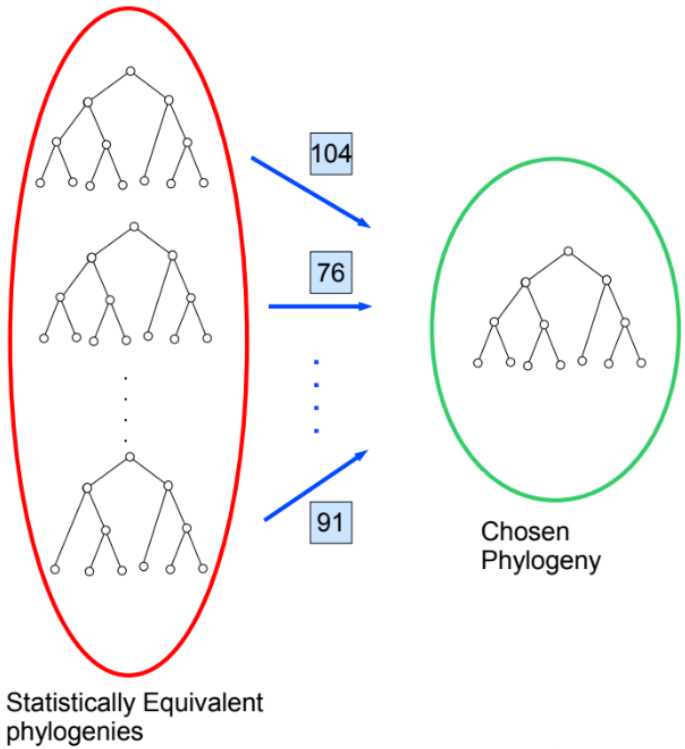
Output: Error-corrected viral phylogeny



Bansal 2017

TreeFix-VP

Approach: Use host information to select the best tree that is still well supported by sequence data.

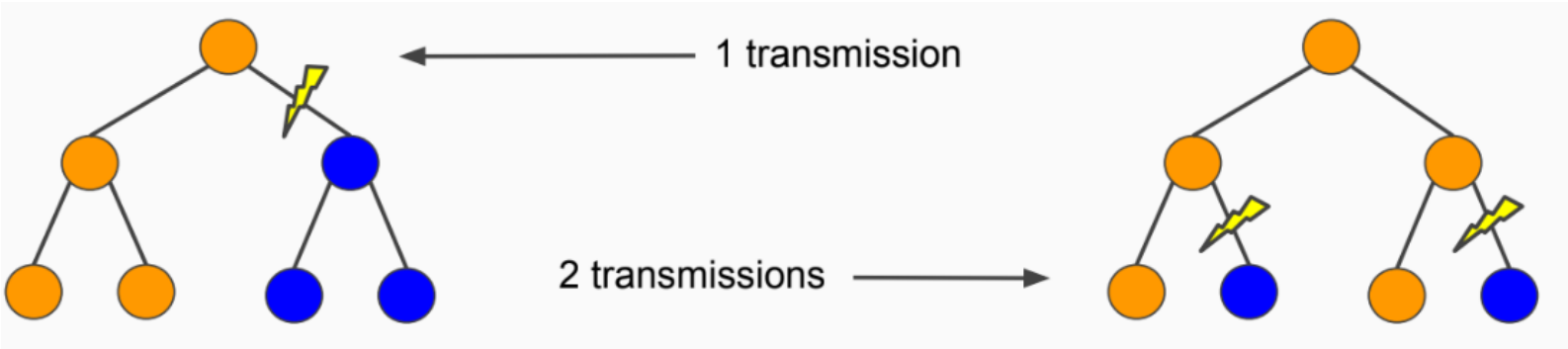


Bansal 2017

Tree Score

Question: How to determine the "best" tree?

1. Label leaves with associated hosts.
2. Use Fitch's algorithm for the small parsimony problem to calculate the minimum number of required transmissions.
   - For a tree on n leaves and k hosts, complexity $O(nk)$
   - Biologically meaningful: edges with different hosts represent transmission (direct or indirect)

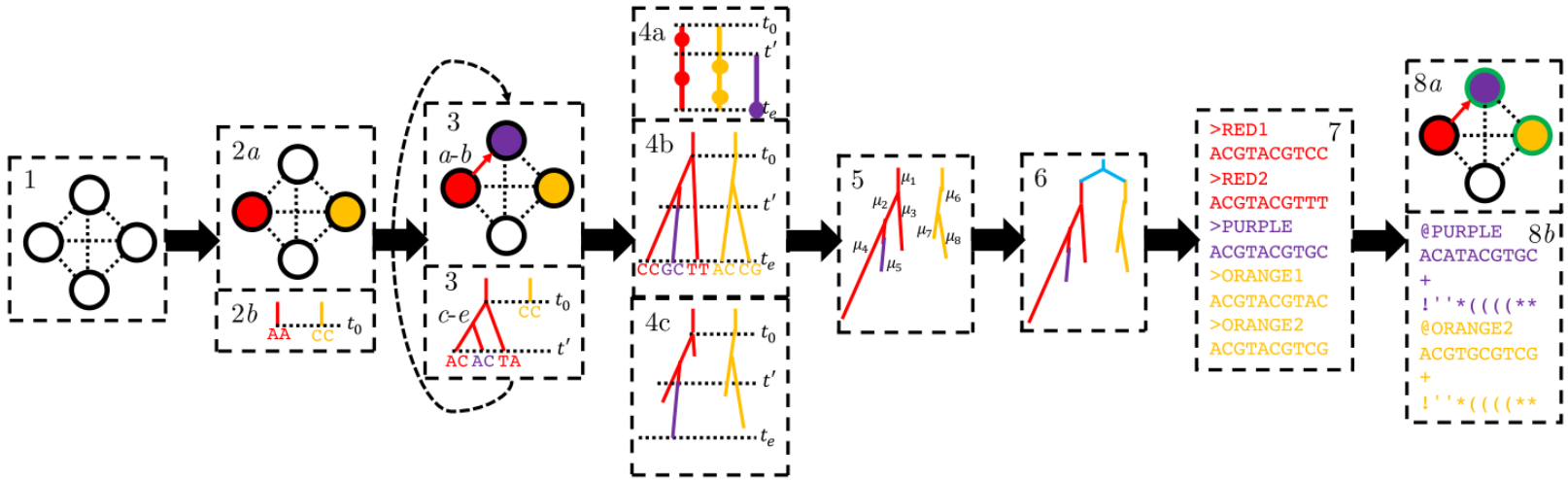


Outbreak Data

Dataset:

- 142 intra-host HCV populations from 33 outbreaks (provided by CDC)
- Outbreaks contain from 2 to 19 samples, and
- A few dozen to a few hundred sequences
- True transmission history known for 14 of the outbreaks

FAVITES (FrAmework for VIral Transmission and Evolution Simulation



Moshiri et al. 2018

Simulation Model

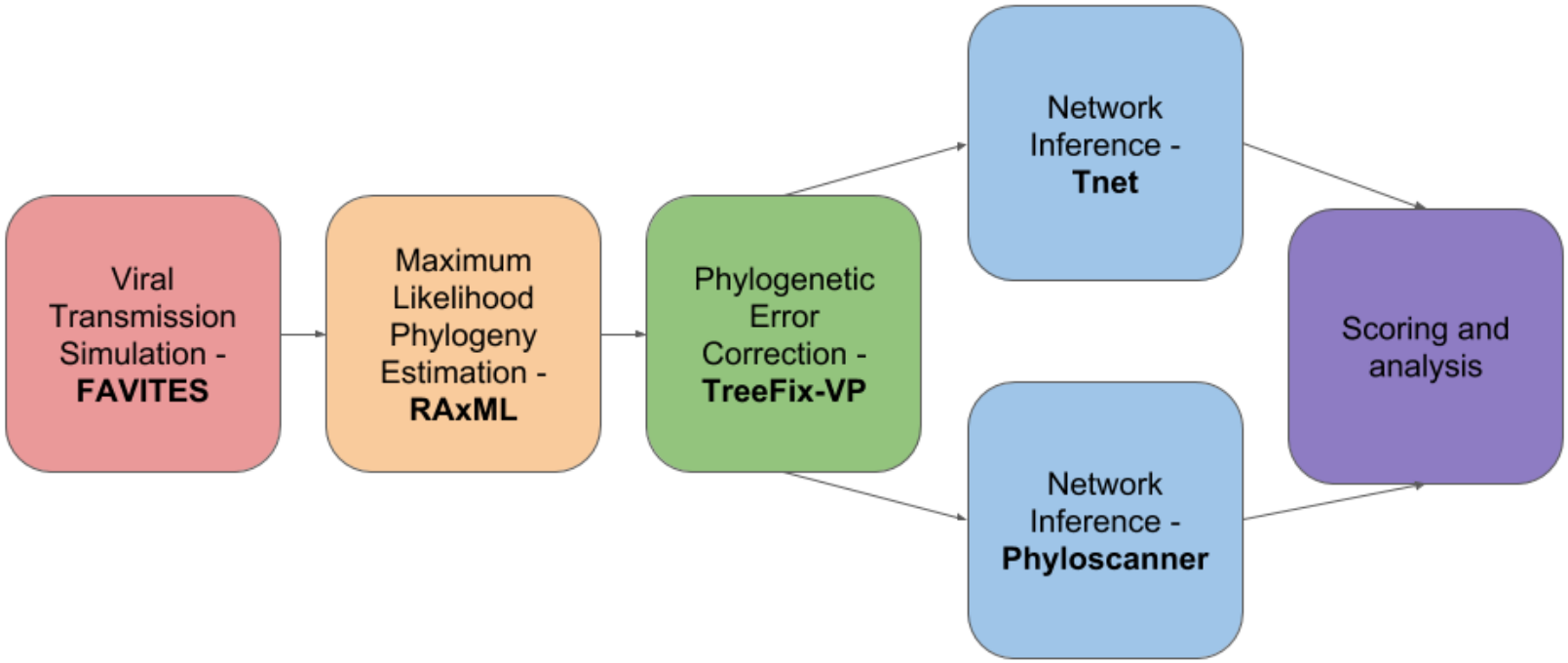
- Barabasi-Albert model for contact network generation
  - 1000 nodes
- Models of transmission
  - Used SEIR and SIR models
  - Transmission parameters chosen to evenly space transmissions
- Coalescent model with logistic growth rate for phylogeny generation
  - Coalescent parameters chosen to give even branch lengths
- GTR+Γ model of sequence evolution
  - Nucleotide frequencies and transmission rates estimated from real outbreak data

Simulation Model

Varied Parameters:

- Sequence Length
- Viruses per Host
- Mutation Rate

Analysis Pipeline

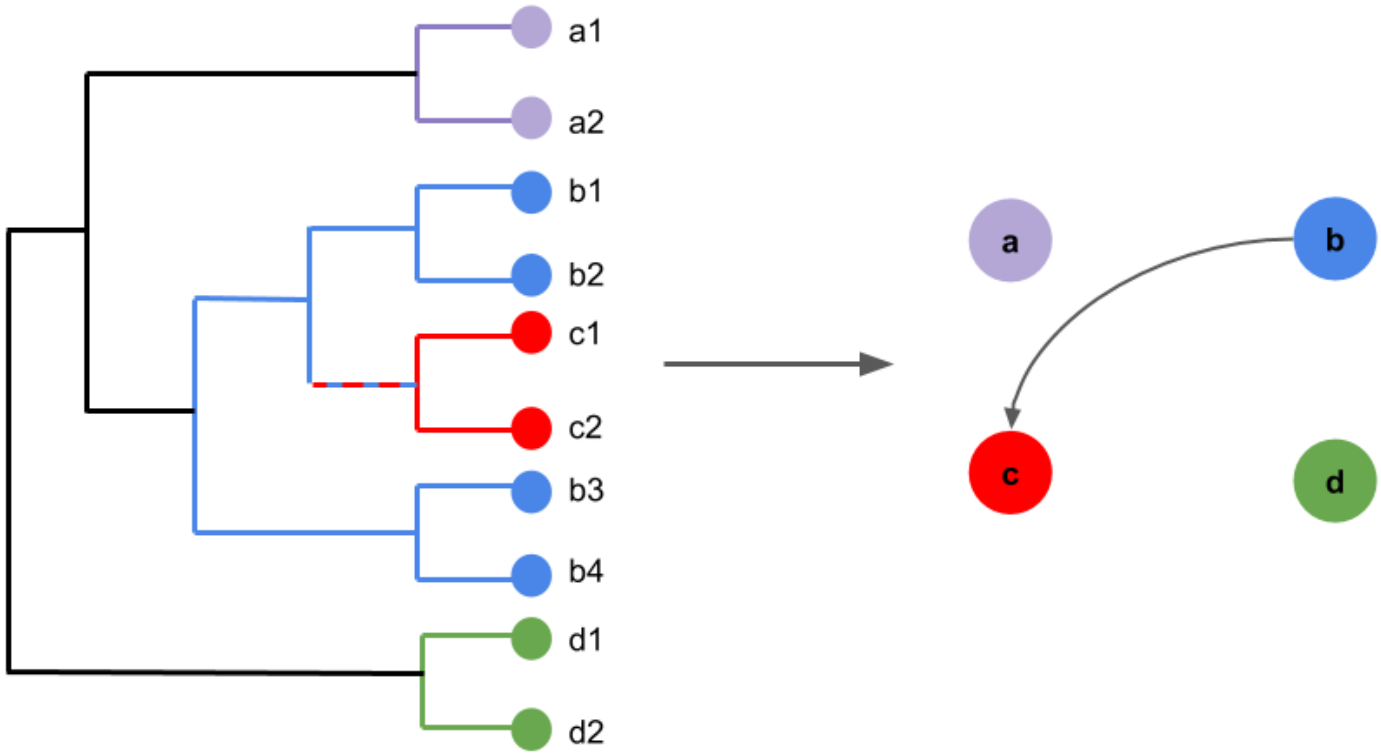


Analysis Pipeline

- **RAxML:** 25 bootstraps, GTRGAMMA model, rooted phylogeny
- **TreeFix-VP:** Run for 5000 iterations
- **Tnet:** Uses Sankoff's algorithm to label internal nodes of phylogeny and infer transmission edges
- **Phyloscanner:** Wymant and Hall et al. 2017
  - Also uses parsimony
  - Leaves some internal nodes unlabeled

Analysis Pipeline

Phyloscanner - Conservative estimation of transmissions



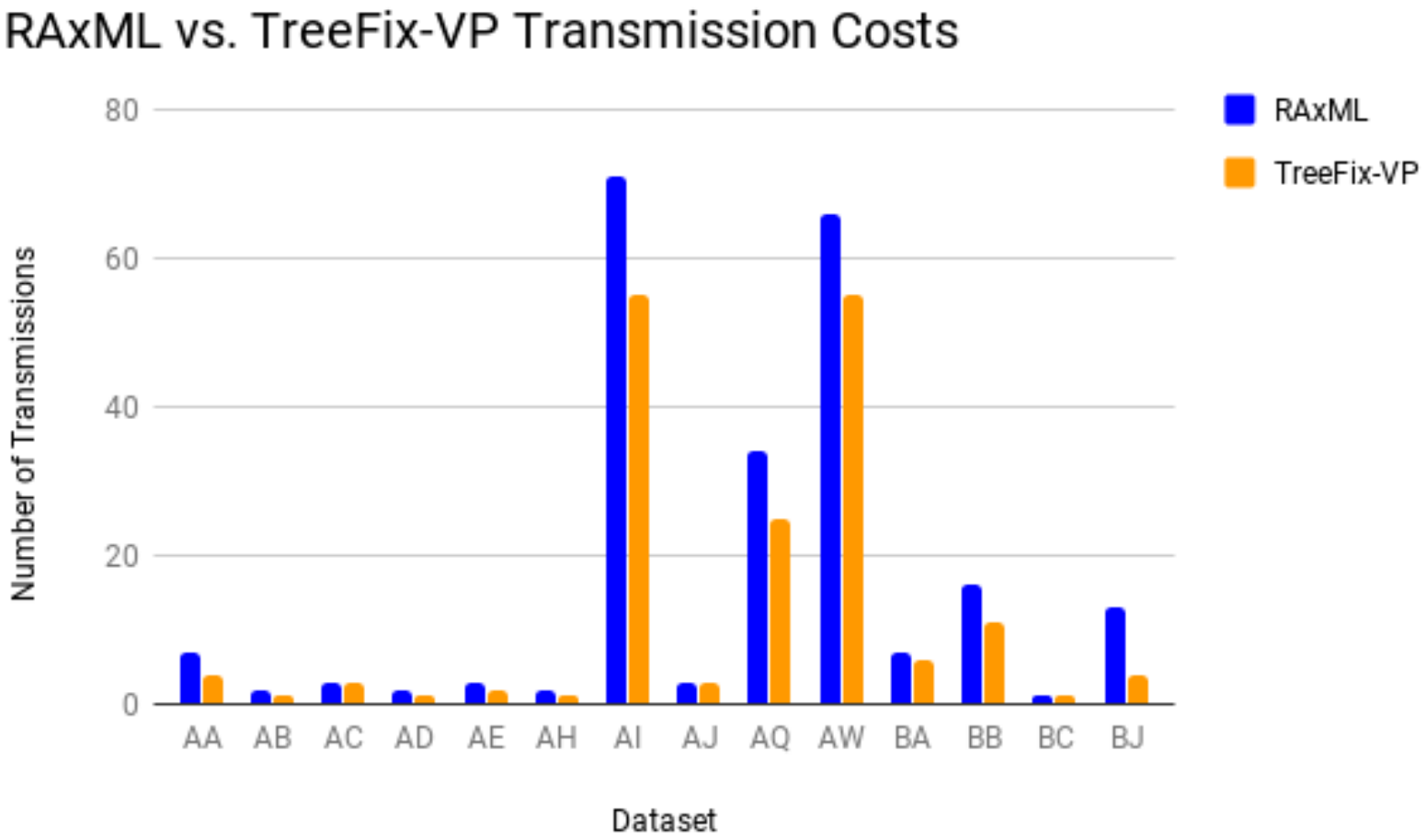


Figure: Outbreak Transmission Cost

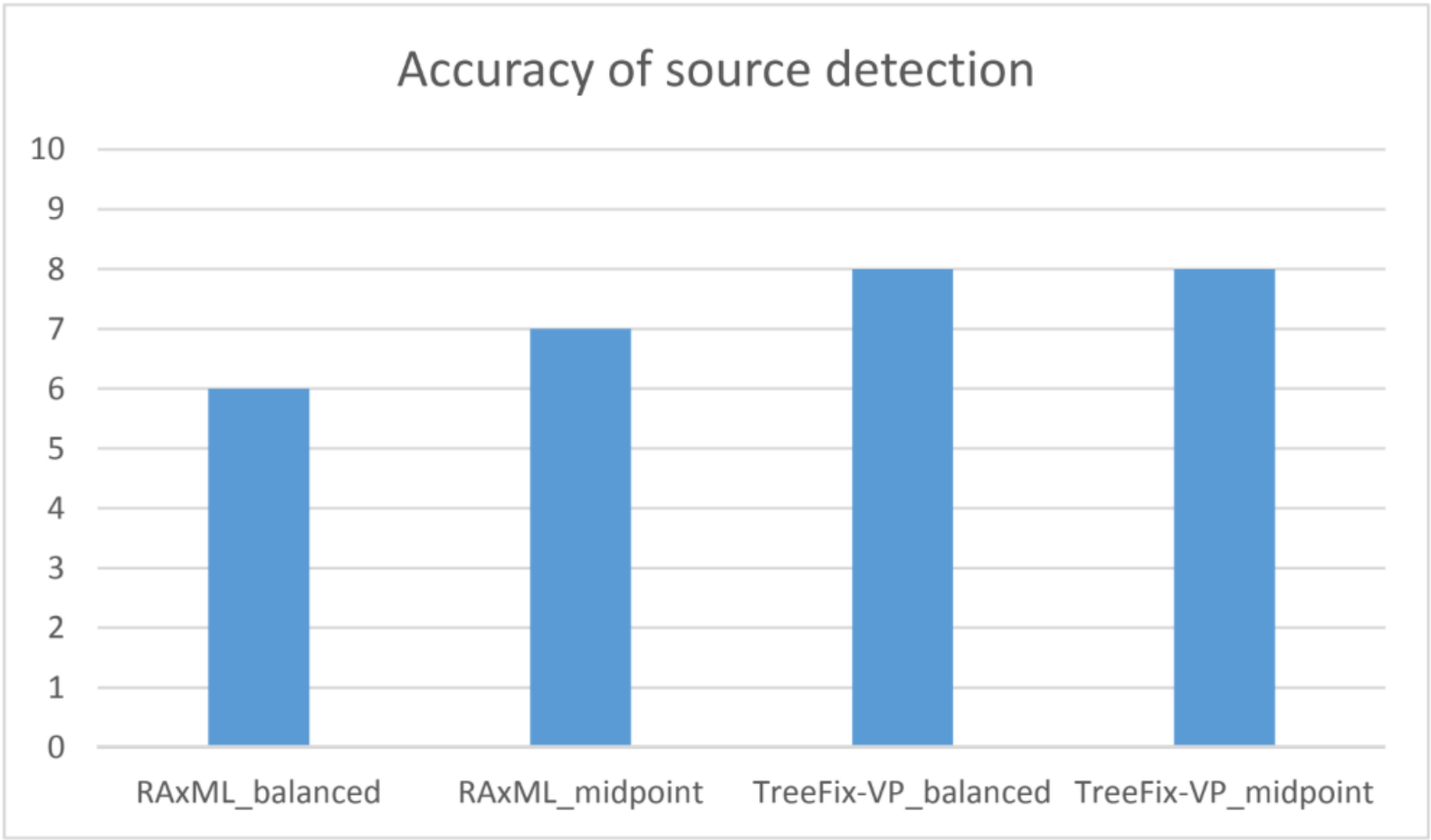


Figure: Outbreak Source Detection

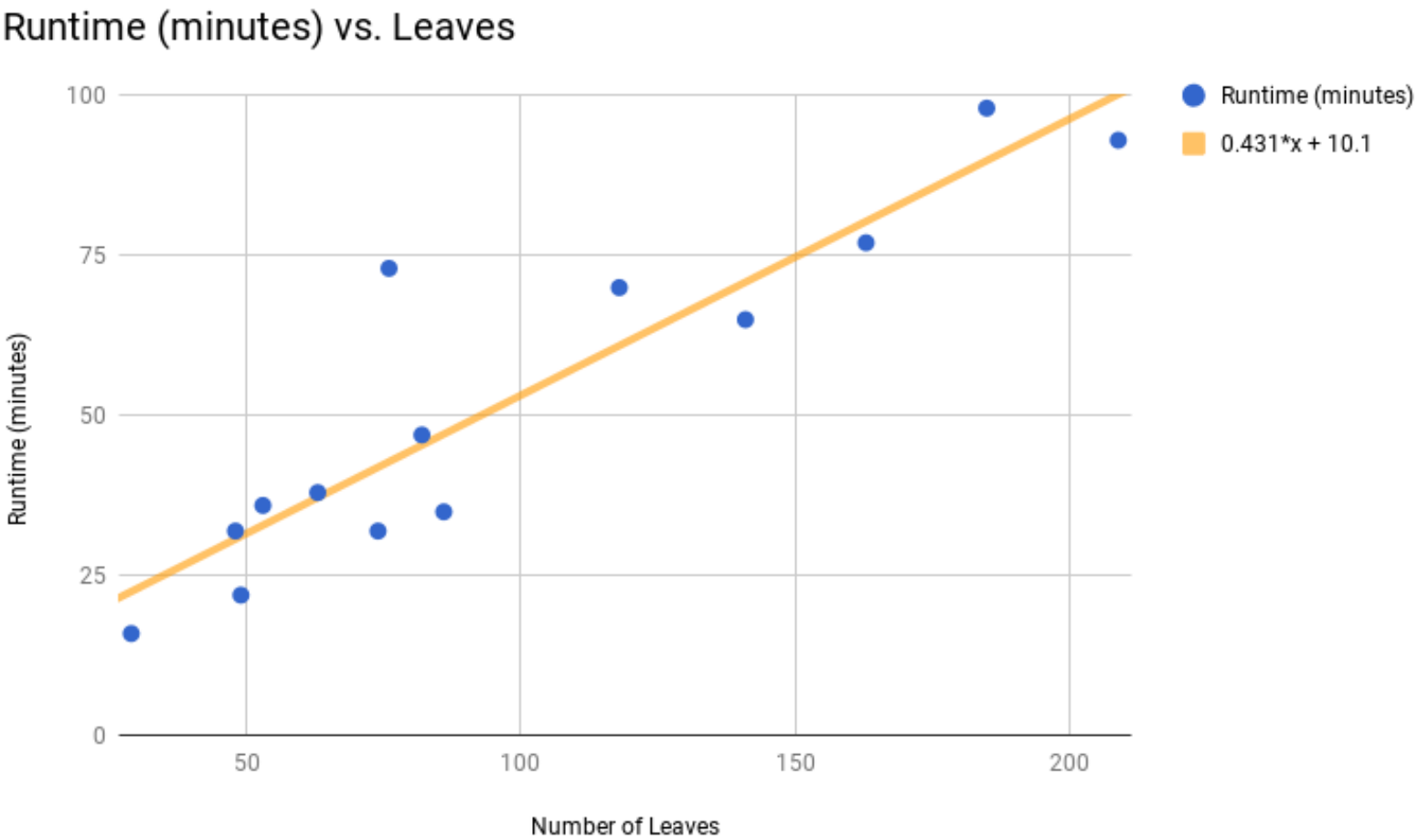


Figure: Outbreak Runtime

Simulation Parameters

Baseline

- SEIR model of transmission
- **Sequence Length:** 1000
- **Viruses per Host:** 10
- **Mutation Rate:** 0.25

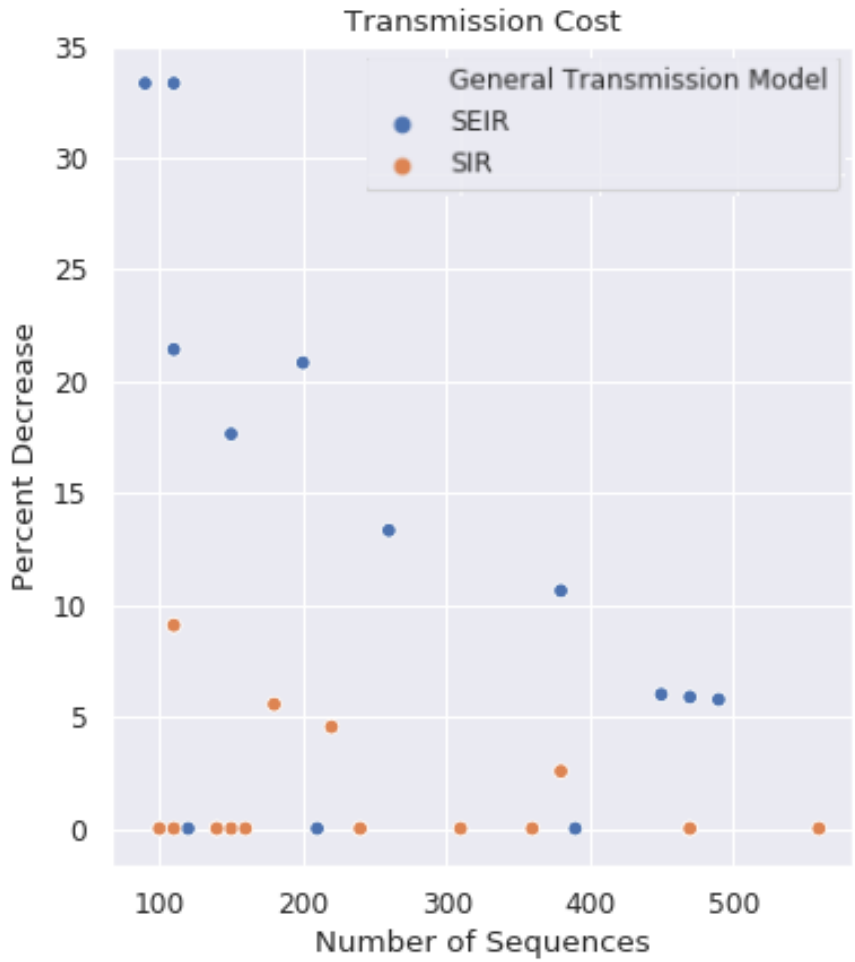


Figure: Error Corrected Transmission Cost

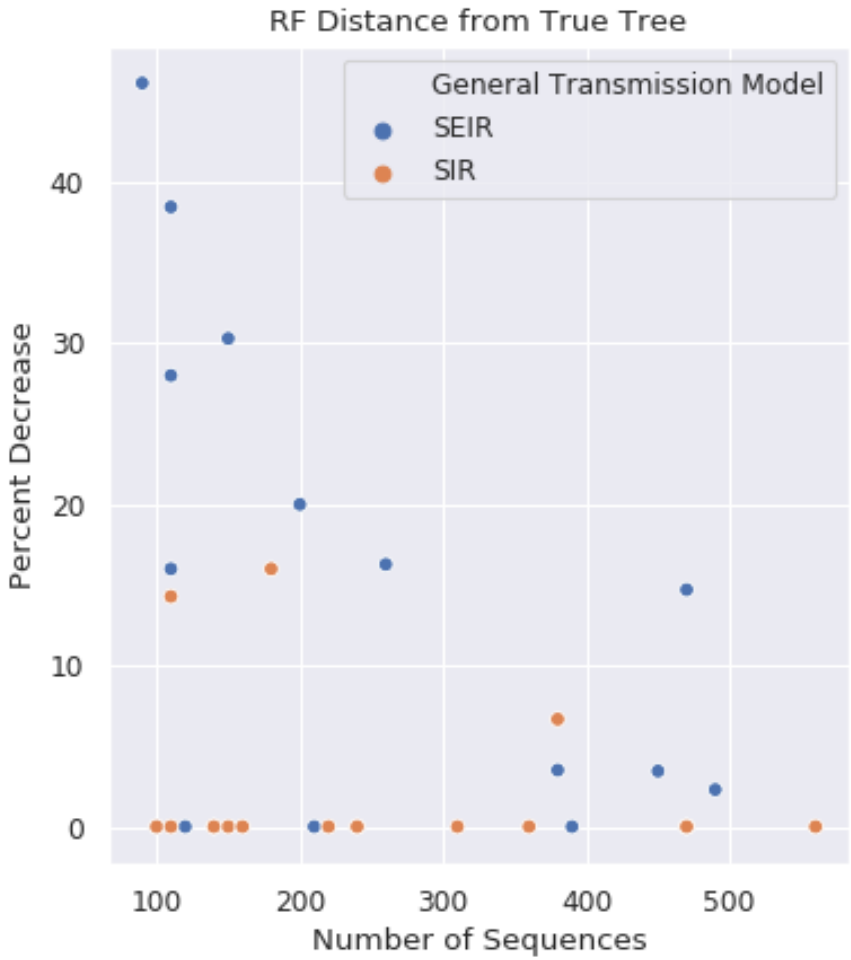


Figure: Error Corrected Robinson-Foulds Distance

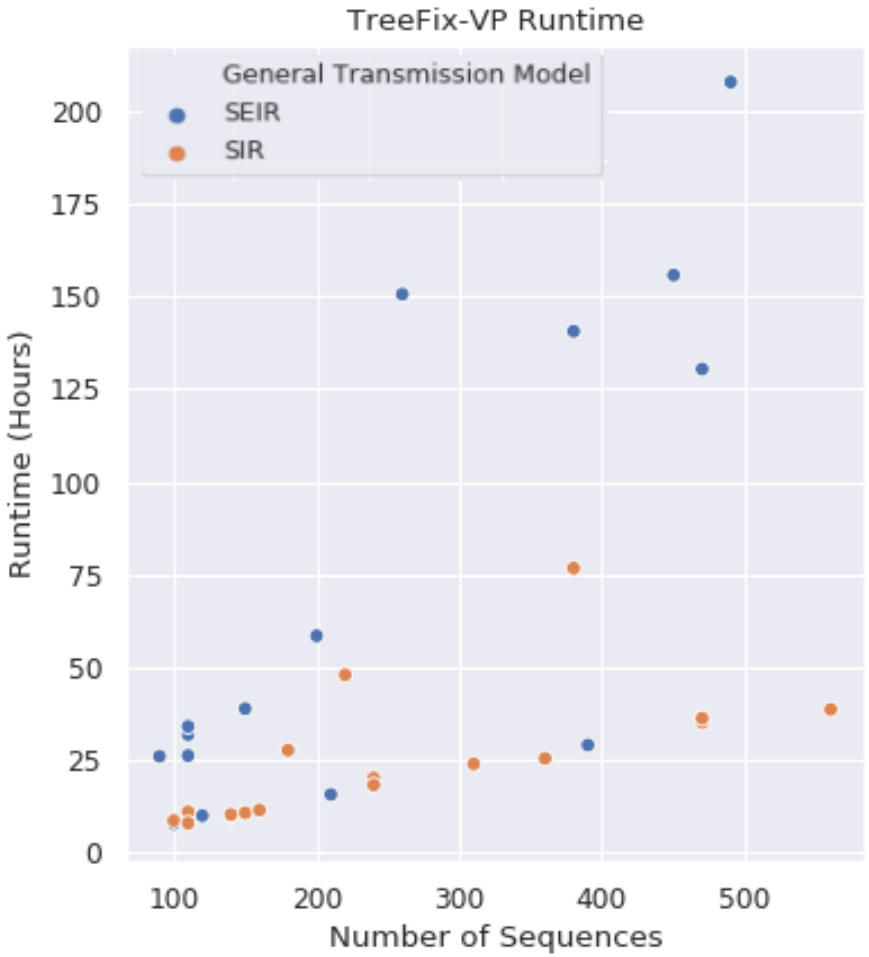


Figure: TreeFix-VP Runtime

Figure: All Runs

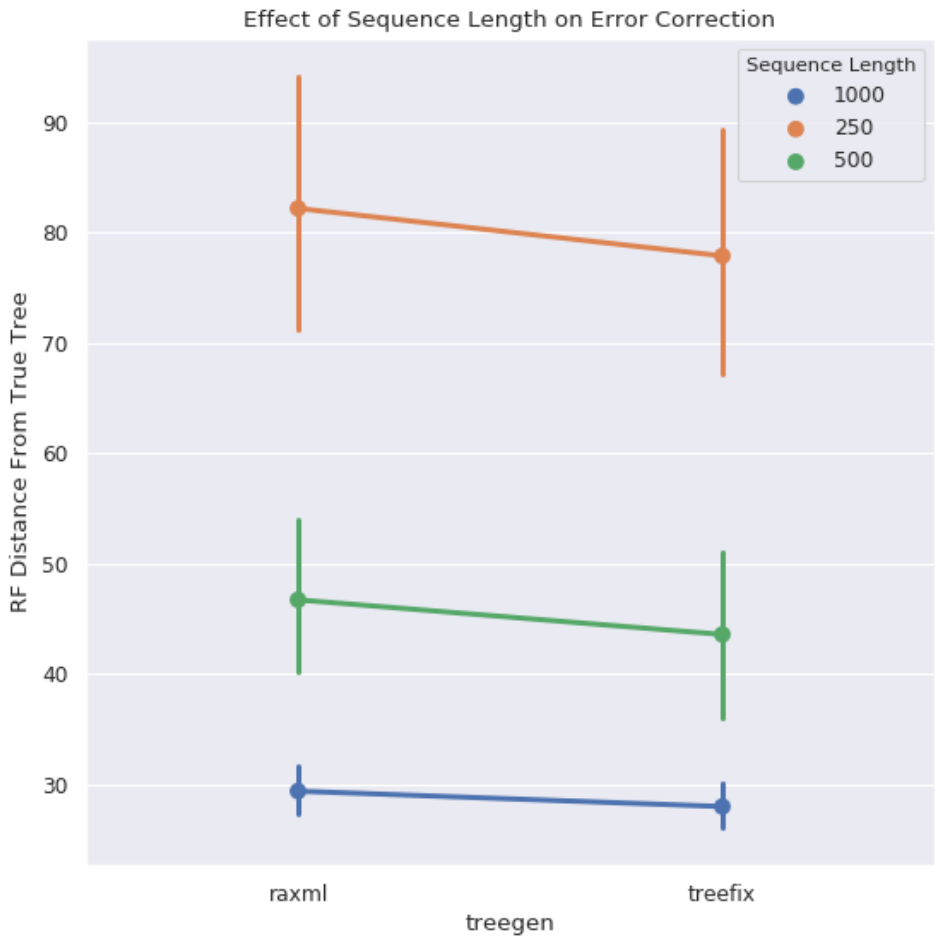


Figure: Varied Sequence Length

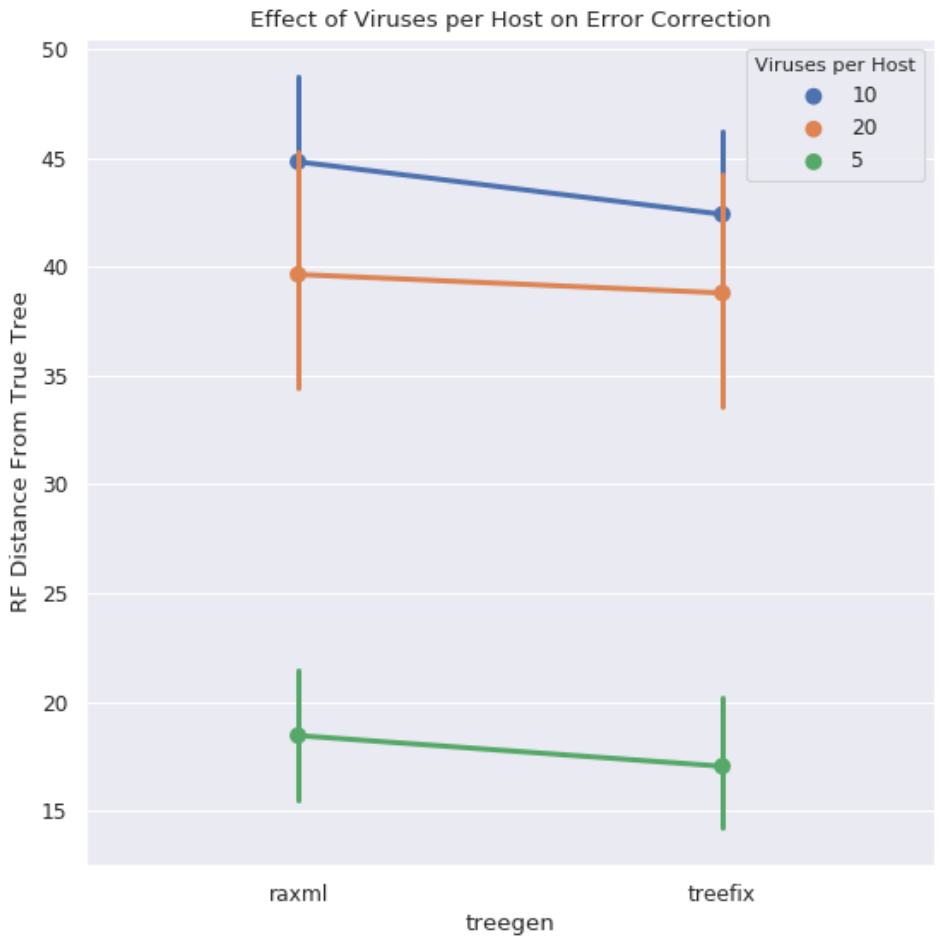


Figure: Varied Number of Viruses per Host

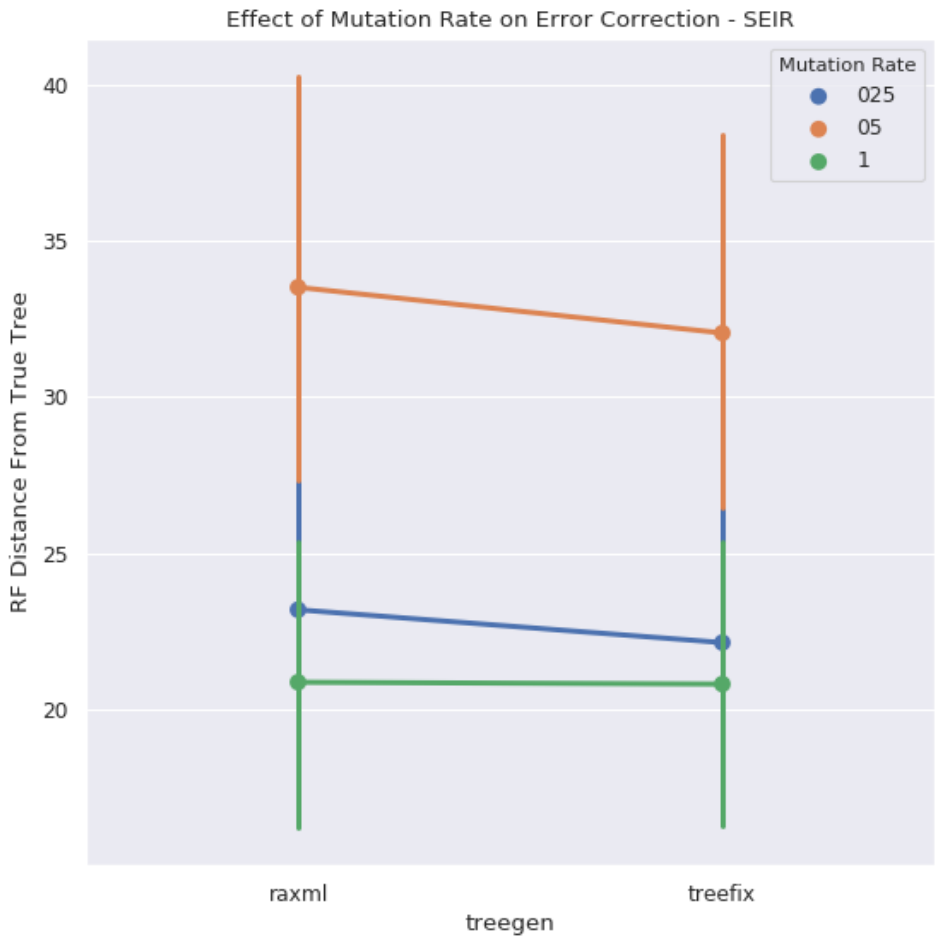


Figure: Varied Mutation Rate - SEIR

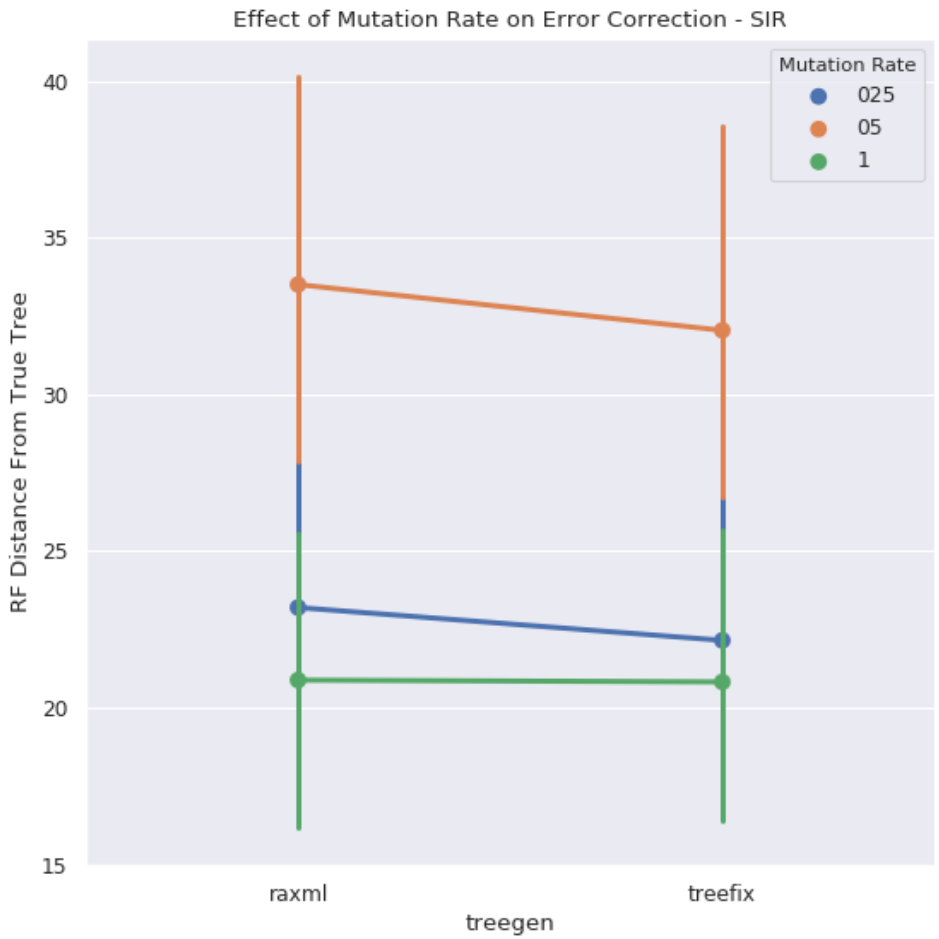


Figure: Varied Mutation Rate - SIR

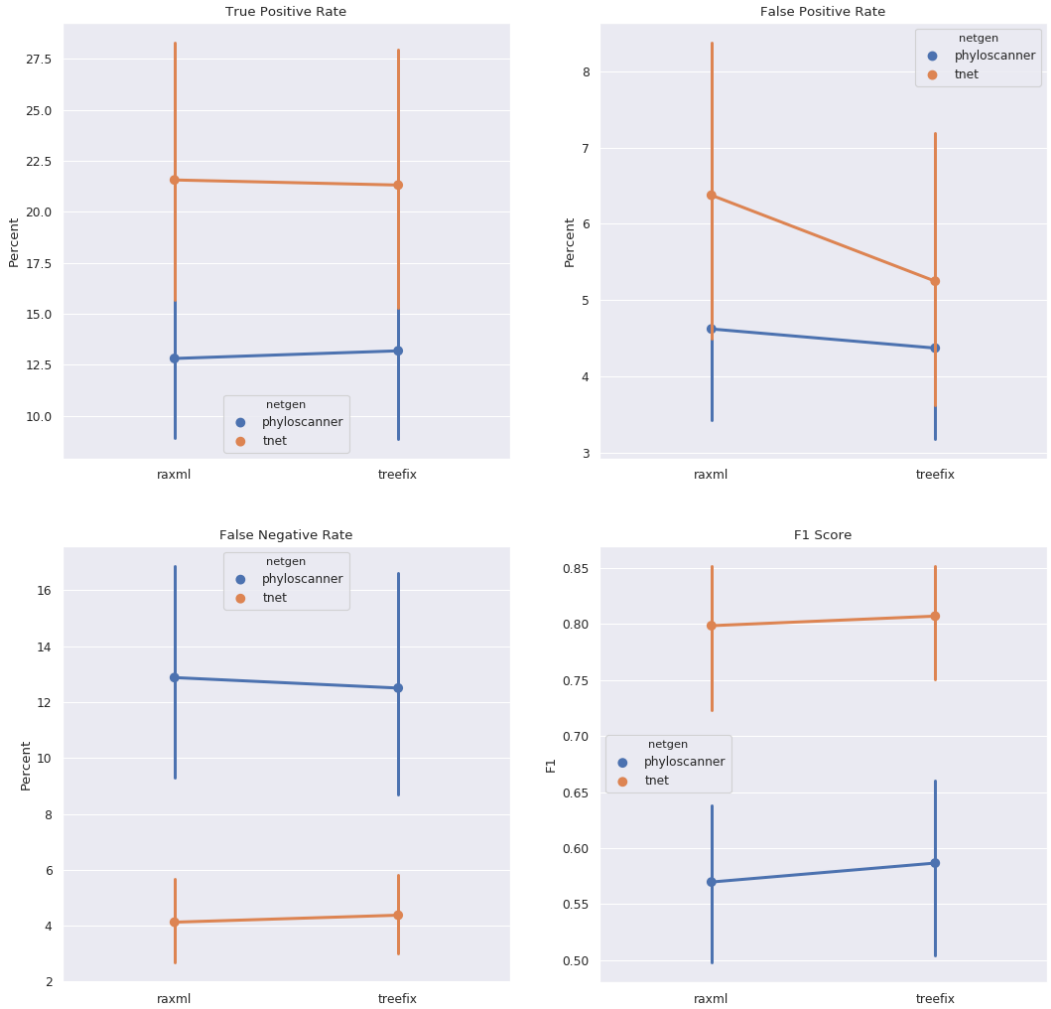


Figure: SEIR Transmission Model

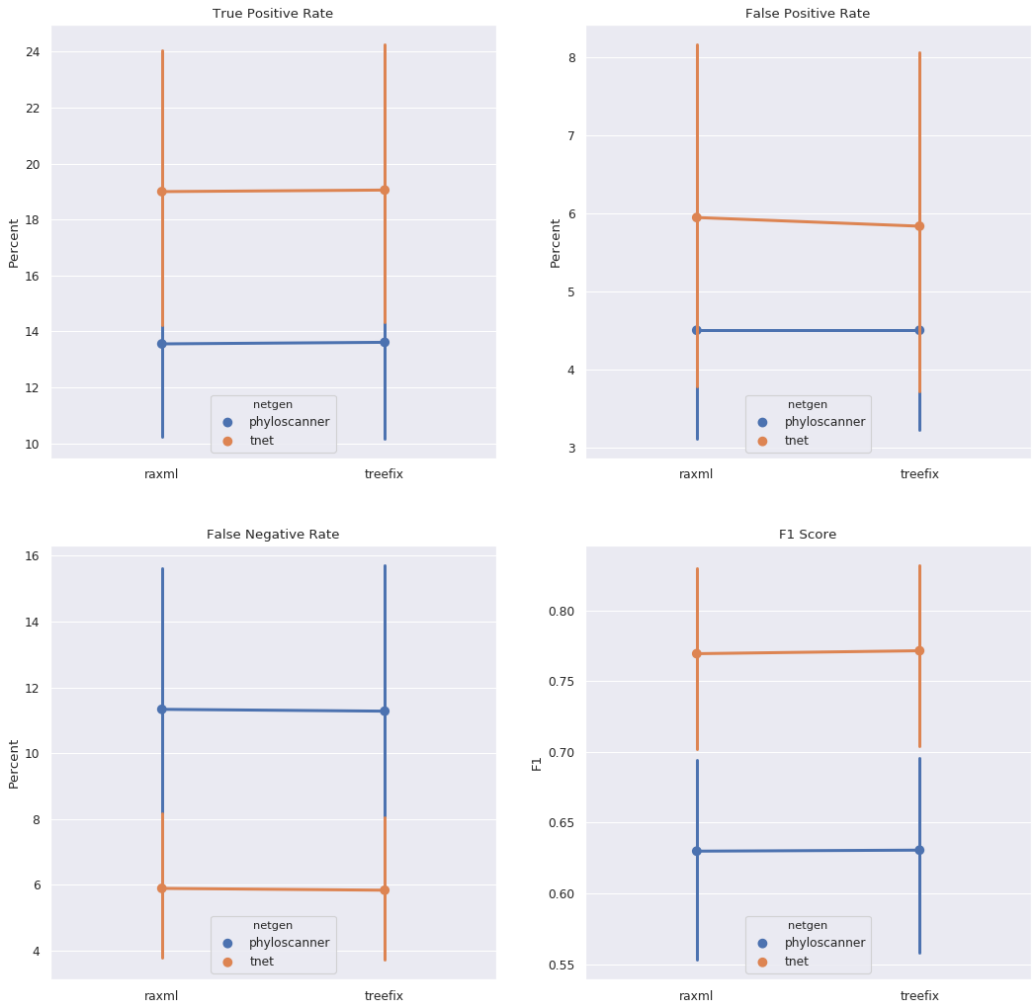


Figure: SIR Transmission Model

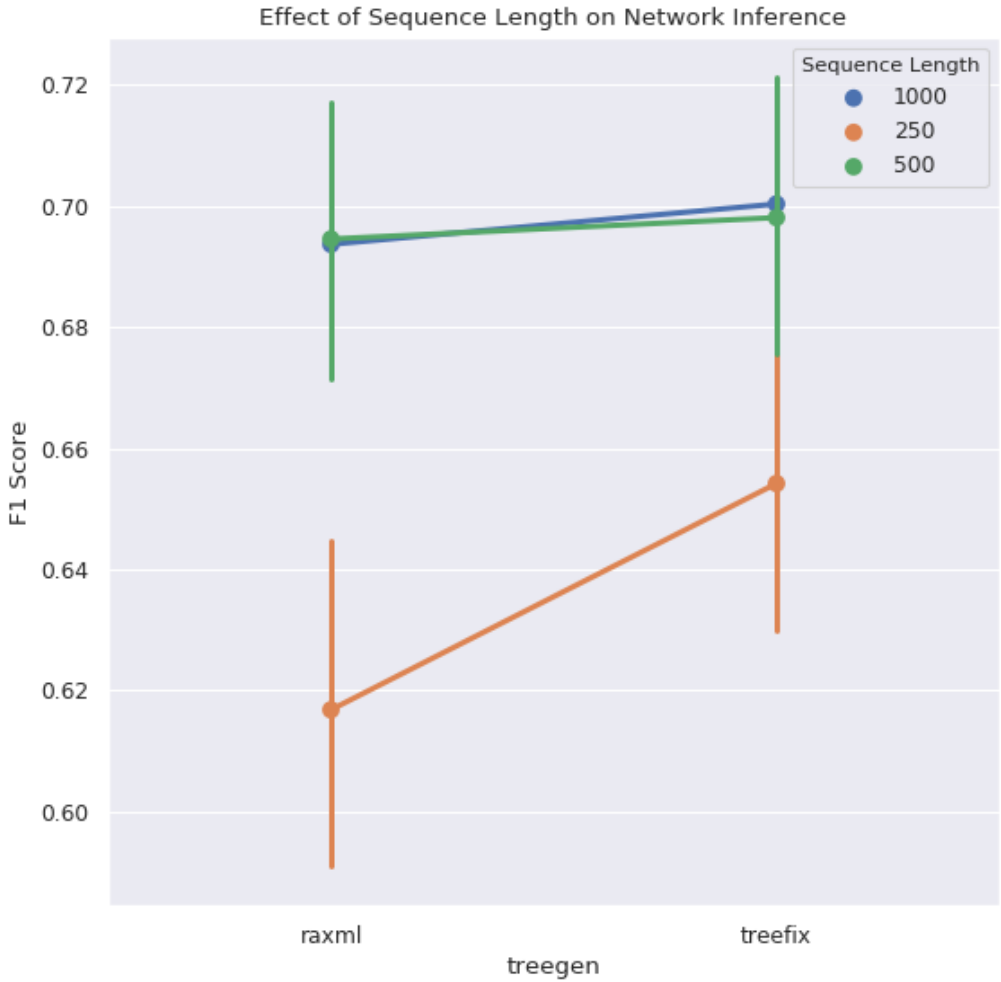


Figure: Varied Sequence Length

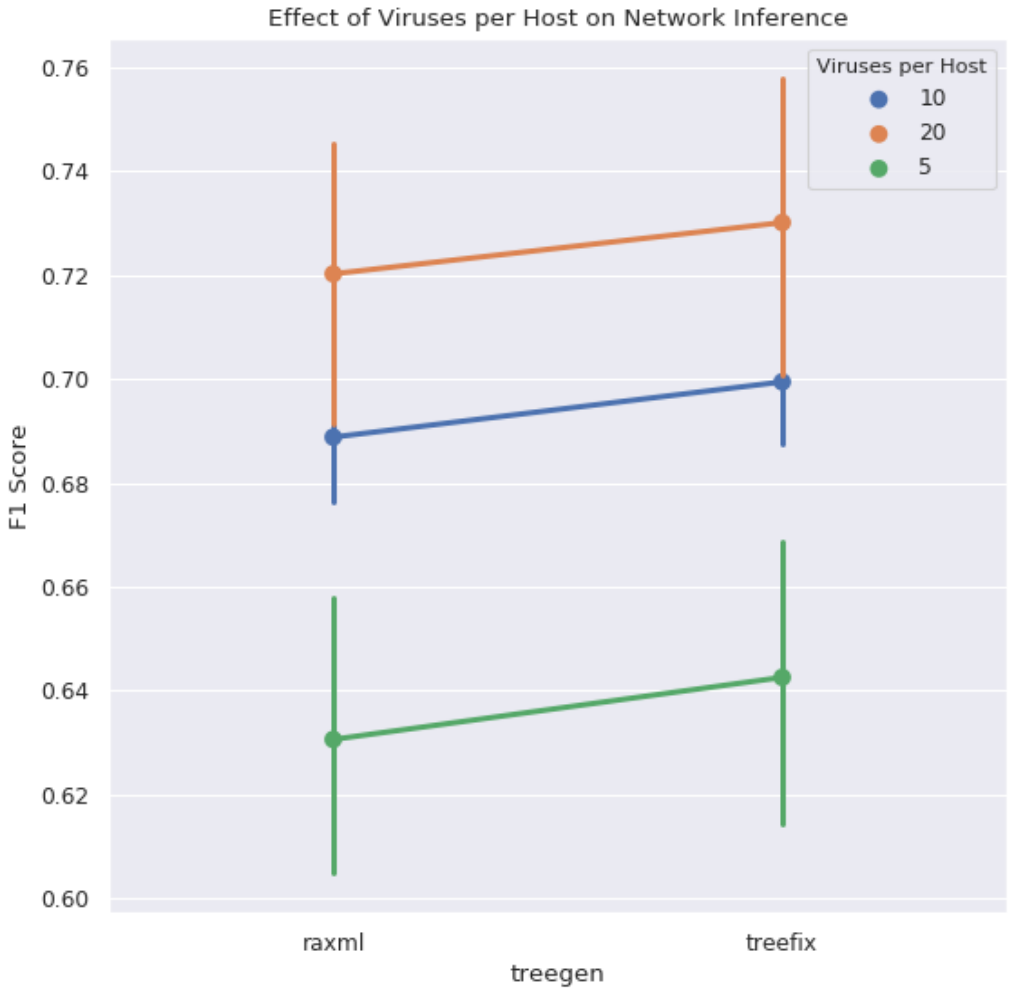


Figure: Varied Number of Viruses per Host

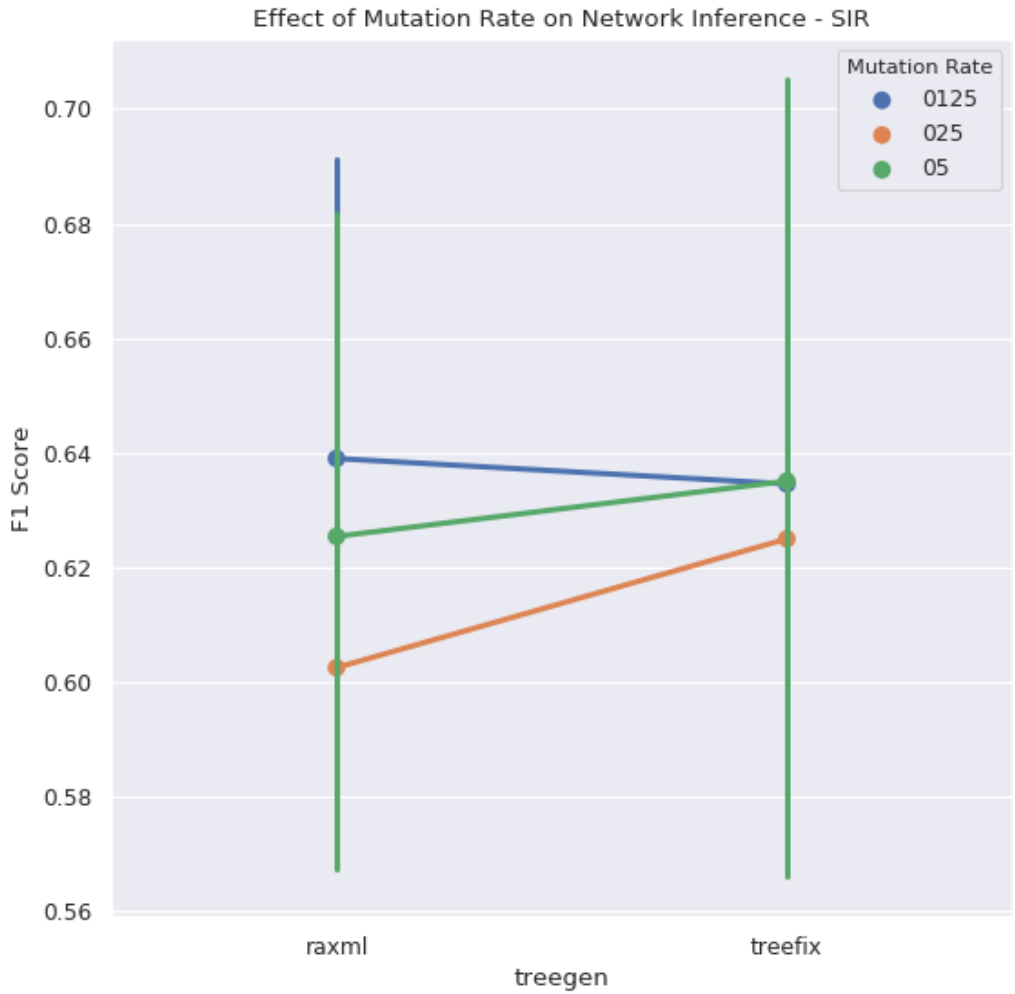


Figure: Varied Mutation Rate - SEIR

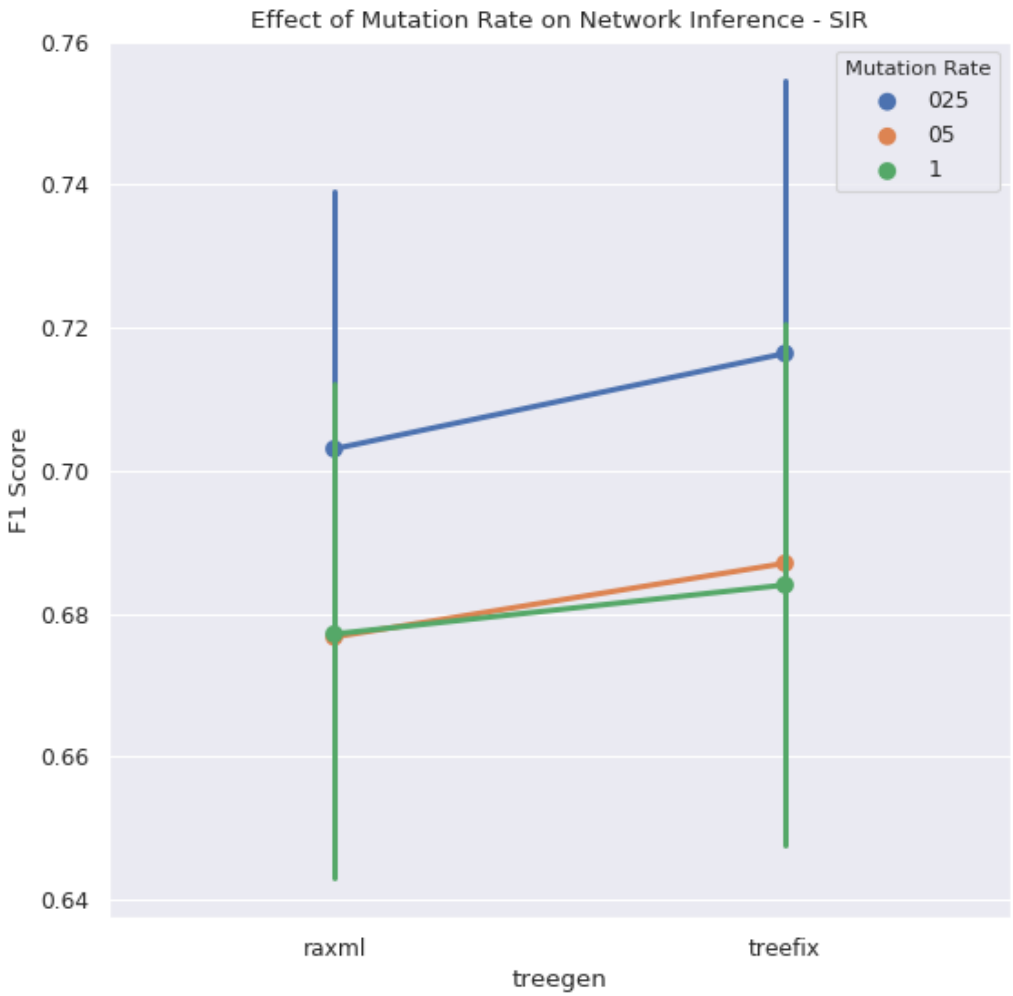


Figure: Varied Mutation Rate - SIR

Future Work

1. Evaluate performance of TreeFix-VP compared to MCMC methods using a single sequence
2. Evaluate effect of using multiple sequences per host on network inference
3. Evaluate performance of TreeFix-VP when some hosts are unsampled

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Questions?

Supplementary Figures - Branch Length Distribution

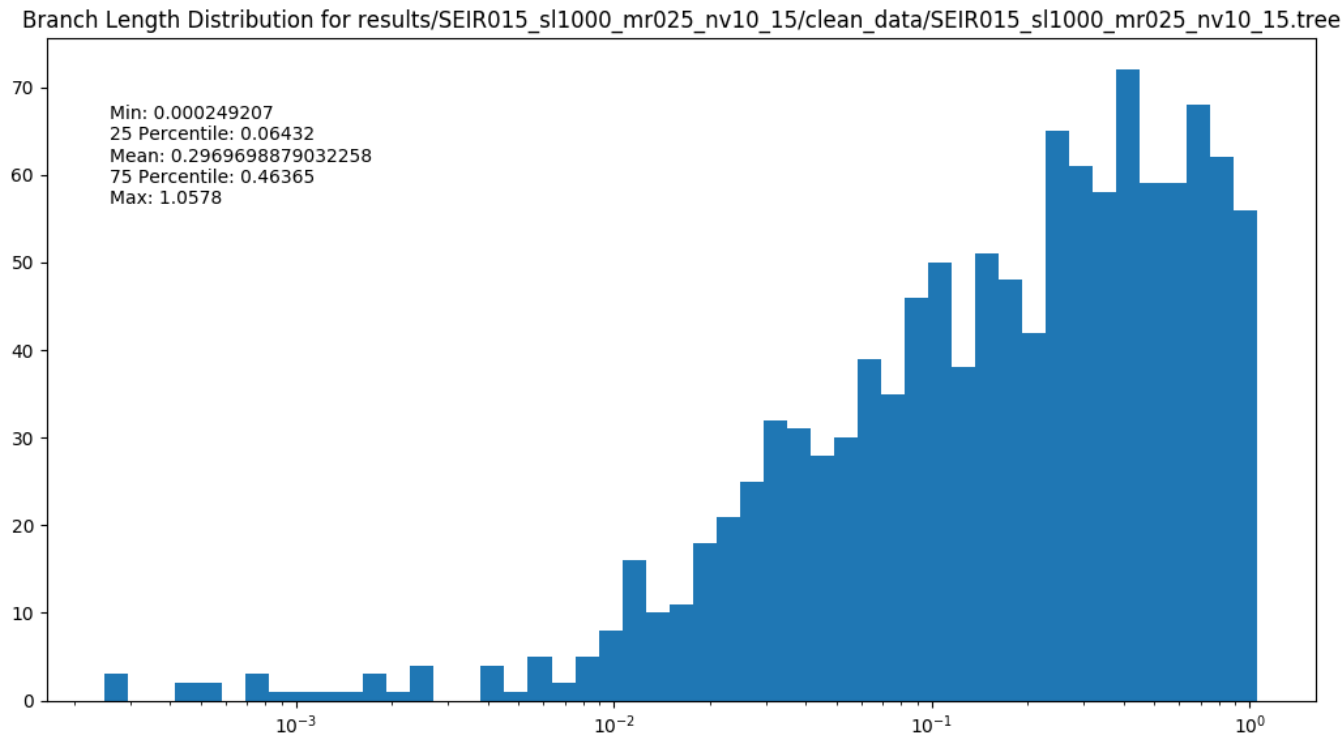

Figure: Sample Distribution of Branch Lengths