Using tree sequences for pop gen inference

Tree sequences are efficient, easy to deal with, and potentially very informative for inference of demographic events. By using spatial relationships (eg RF distance) along the sequence as predictive features we may be able to better infer demographic events even when using inferred trees.

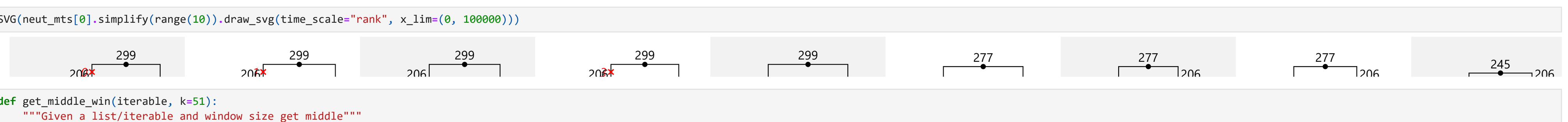
```python
import msprime
from IPython.display import SVG
from dendropy.calculate.treecompare import symmetric_difference
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
from tqdm import tqdm
from ete3 import Tree
import tsinfer
from sklearn.model_selection import train_test_split
from sklearn.ensemble import RandomForestClassifier
from sklearn.metrics import f1_score, roc_auc_score, confusion_matrix
```

Running replicates https://tskit.dev/msprime/docs/stable/replication.html#sec-randomness-replication

```python
#Simulate 200 reps
L=1e6
N= 10000
n_reps = 100

#Neut
neut_reps = msprime.sim_ancestry(
    1000,
    recombination_rate=1e-8,
    sequence_length=L,
    ploidy=1,
    population_size=N,
    num_replicates=n_reps)

neut_mts = [msprime.sim_mutations(ts, rate=1e-8) for ts in neut_reps]

for idx, ts in enumerate(neut_mts):
    ts.dump(f"treeseqs/neut/{idx}.trees")

print("Done with neuts")

#Hard sweep
sweep_model = msprime.SweepGenicSelection(
    position=L / 2,  # beneficial mutation location: middle of chrom
    start_frequency=1.0 / (2 * N), # starting frequency of the sweeping mutation
    end_frequency=0.99, # final frequency of the mutation (incomplete sweep)
    s=0.25, # selection coefficient of the beneficial mutation
    dt=1e-6, # nevermind this!
)

sweep_reps = msprime.sim_ancestry(
    1000,
    model=[sweep_model, msprime.StandardCoalescent()],
    population_size=N,
    recombination_rate=1e-8,
    sequence_length=L,
    ploidy=1,
    num_replicates=n_reps
)

sweep_mts = [msprime.sim_mutations(ts, rate=1e-8) for ts in sweep_reps]

for idx, ts in enumerate(sweep_mts):
    ts.dump(f"treeseqs/sweep/{idx}.trees")

print("Done with sweeps")
```

```
Done with neuts
Done with sweeps
```

```python
SVG(neut_mts[0].simplify(range(10)).draw_svg(time_scale="rank", x_lim=(0, 100000)))
```




```python
def get_middle_win(iterable, k=51):
    """Given a list/iterable and window size get middle"""
    center_idx = int(len(iterable)/2)
    half_win = int(k/2)

    return [iterable[i] for i in range(center_idx - half_win, center_idx + half_win)]
```

```python
def calc_ts_rf(ts):
    """
    Iterate through a tree sequence
        convert to newick
        convert to ETE object
        calculate pairwise RF dists
    """
    trees = [tree.as_newick() for tree in ts.trees()]
    etes = [Tree(tree) for tree in get_middle_win(trees)]
    rfs = []
    for idx in range(len(etes)-1):
        rfs.append(etes[idx].robinson_foulds(etes[idx+1])[0])

    return rfs
```

```python
#Read in trees to ete3 through newick conversion, calc RFs while in memory, move on to next
neut_reps_rfs = []
sweep_reps_rfs = []
for neut_rep, sweep_rep in tqdm(zip(neut_mts, sweep_mts), total=len(neut_mts)):
    neut_reps_rfs.append(calc_ts_rf(neut_rep))
    sweep_reps_rfs.append(calc_ts_rf(sweep_rep))
```

```
100%|██████████| 100/100 [18:33<00:00, 11.13s/it]
```

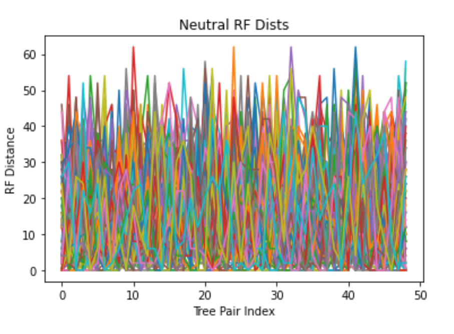
If we pull some metrics about the resulting distributions it's pretty clear that spatially-resolved RF distances are drastically different in the pattern we'd also expect from pi under sweep conditions

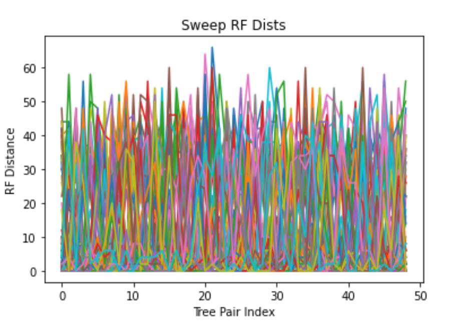
```python
#RF Dist Stats
neut_arr = np.array(neut_reps_rfs)
sweep_arr = np.array(sweep_reps_rfs)

np.savetxt("neut_data.tsv", neut_arr, delimiter="\t")
np.savetxt("sweep_data.tsv", sweep_arr, delimiter="\t")

print(neut_arr.shape)

neut_df = pd.DataFrame(neut_arr.T)
sweep_df = pd.DataFrame(sweep_arr.T)

print("Neutral")
print(neut_df.describe())

print("\nSweep")
print(sweep_df.describe())
```

```
(100, 49)
Neutral
               0          1          2          3          4          5   \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean   13.469388  14.979592  13.918367  14.571429  15.755102  11.346939
std    12.184522  12.616936  13.904191  13.121230  13.623709  10.672299
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     4.000000   6.000000   2.000000   4.000000   4.000000   2.000000
50%     8.000000  12.000000   8.000000  14.000000  14.000000   8.000000
75%    20.000000  22.000000  22.000000  20.000000  26.000000  20.000000
max    46.000000  46.000000  50.000000  54.000000  54.000000  30.000000

               6          7          8          9   ...         90         91  \
count  49.000000  49.000000  49.000000  49.000000  ...  49.000000  49.000000
mean   16.489796  15.836735  13.836735  13.714286  ...  11.836735  13.632653
std    13.301194  13.752798  12.870099  13.063945  ...  11.253420  13.854443
min     0.000000   0.000000   0.000000   0.000000  ...   0.000000   0.000000
25%     4.000000   6.000000   4.000000   2.000000  ...   4.000000   2.000000
50%    14.000000  14.000000  10.000000  10.000000  ...   8.000000  10.000000
75%    28.000000  24.000000  20.000000  22.000000  ...  18.000000  18.000000
max    48.000000  48.000000  56.000000  56.000000  ...  36.000000  50.000000

               92         93         94         95         96         97  \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean   11.551020  11.591837  14.530612  14.040816  14.000000  12.530612
std    11.742127  12.062197  13.624583  12.861375  13.753787  13.636810
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     2.000000   2.000000   4.000000   4.000000   2.000000   2.000000
50%     6.000000   8.000000  10.000000  10.000000  10.000000   8.000000
75%    18.000000  20.000000  22.000000  24.000000  22.000000  20.000000
max    46.000000  46.000000  48.000000  42.000000  48.000000  48.000000

               98         99
count  49.000000  49.000000
mean   17.918367  15.591837
std    16.360314  12.496530
min     0.000000   0.000000
25%     2.000000   2.000000
50%    18.000000  16.000000
75%    28.000000  24.000000
max    56.000000  44.000000

[8 rows x 100 columns]

Sweep
               0          1          2          3          4          5   \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean    8.448980   7.959184  13.673469   7.591837   9.673469   7.387755
std    15.385411  14.127336  18.020113  12.144818  15.483039  12.063748
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
50%     2.000000   2.000000   4.000000   2.000000   2.000000   2.000000
75%     6.000000   6.000000  26.000000   6.000000   8.000000   8.000000
max    66.000000  54.000000  52.000000  42.000000  54.000000  46.000000

               6          7          8          9   ...         90         91  \
count  49.000000  49.000000  49.000000  49.000000  ...  49.000000  49.000000
mean    8.530612  11.428571  11.142857  11.714286  ...  10.122449  12.285714
std    14.444004  15.481171  15.827192  15.816658  ...  13.130170  15.953056
min     0.000000   0.000000   0.000000   0.000000  ...   0.000000   0.000000
25%     0.000000   2.000000   0.000000   0.000000  ...   2.000000   0.000000
50%     2.000000   4.000000   2.000000   2.000000  ...   4.000000   4.000000
75%     8.000000  18.000000  28.000000  26.000000  ...  24.000000  22.000000
max    48.000000  58.000000  48.000000  54.000000  ...  42.000000  56.000000

               92         93         94         95         96         97  \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean   11.714286  12.326531  11.551020  10.775510  15.142857   7.469388
std    17.559423  15.375017  15.865399  13.328018  17.185265  11.970627
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     0.000000   2.000000   0.000000   0.000000   2.000000   0.000000
50%     4.000000   4.000000   2.000000   4.000000   4.000000   0.000000
75%    16.000000  24.000000  22.000000  20.000000  30.000000  16.000000
max    58.000000  60.000000  52.000000  46.000000  58.000000  48.000000

               98         99
count  49.000000  49.000000
mean   10.734694   9.918367
std    15.086936  13.777755
min     0.000000   0.000000
25%     0.000000   0.000000
50%     2.000000   4.000000
75%    18.000000  10.000000
max    50.000000  44.000000

[8 rows x 100 columns]
```

```python
#Plot location-based RF
neut_df.plot(title="Neutral RF Dists", ylabel="RF Distance", xlabel="Tree Pair Index", legend=None)
sweep_df.plot(title="Sweep RF Dists", ylabel="RF Distance", xlabel="Tree Pair Index", legend=None)
```

```
<AxesSubplot:title={'center':'Sweep RF Dists'}, xlabel='Tree Pair Index', ylabel='RF Distance'>
```





Now we create and train an RF model to use this as a predictive feature

```python
#Split train/test
data = np.concatenate([neut_arr, sweep_arr], axis=0)
labs = np.concatenate([len(neut_arr)*[0], len(sweep_arr)*[1]])

x_train, x_test, y_train, y_test = train_test_split(data, labs, stratify=labs)
```

```
(150,)
```

```python
#RF model
clf = RandomForestClassifier()
clf.fit(x_train, y_train)

pred = clf.predict_proba(x_test)

roc_auc = roc_auc_score(y_test, pred[:,1])
print(f"ROC AUC: {roc_auc}")

confmat = confusion_matrix(y_test, np.argmax(pred, axis=1))
print("Confusion matrix")
print(confmat)
```

```
ROC AUC: 0.9639999999999999
Confusion matrix
[[22  3]
 [ 2 23]]
```

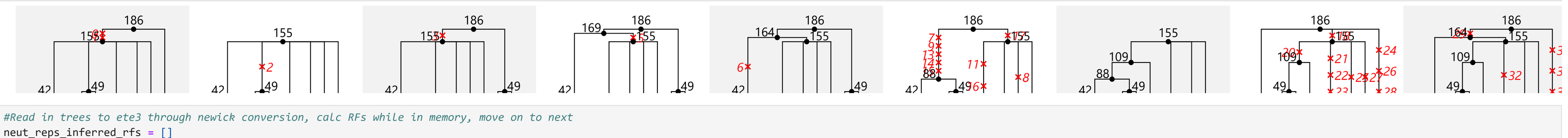
Now do the entire thing again but with inferred trees

Much harder problem to solve because now information in the tree sequence is bottlenecked by ability to infer

```python
neut_inferred_ts = []
sweep_inferred_ts = []

for idx, (neut_rep, sweep_rep) in tqdm(enumerate(zip(neut_mts, sweep_mts)), total=len(neut_mts)):
    neut_samp = tsinfer.SampleData.from_tree_sequence(
        neut_rep,
        path=f"samples/neut/{idx}.samples",
        num_flush_threads=2)

    neut_inferred_ts.append(tsinfer.infer(neut_samp))

    sweep_samp = tsinfer.SampleData.from_tree_sequence(
        sweep_rep,
        path=f"samples/sweep/{idx}.samples",
        num_flush_threads=2)

    sweep_inferred_ts.append(tsinfer.infer(sweep_samp))
```

```
100%|██████████| 100/100 [16:18<00:00,  9.78s/it]
```

```python
SVG(neut_inferred_ts[0].simplify(range(10)).draw_svg(time_scale="rank", x_lim=(0, 100000)))
```




```python
#Read in trees to ete3 through newick conversion, calc RFs while in memory, move on to next
neut_reps_inferred_rfs = []
sweep_reps_inferred_rfs = []
for neut_rep, sweep_rep in tqdm(zip(neut_inferred_ts, sweep_inferred_ts), total=len(neut_mts)):
    neut_reps_inferred_rfs.append(calc_ts_rf(neut_rep))
    sweep_reps_inferred_rfs.append(calc_ts_rf(sweep_rep))
```

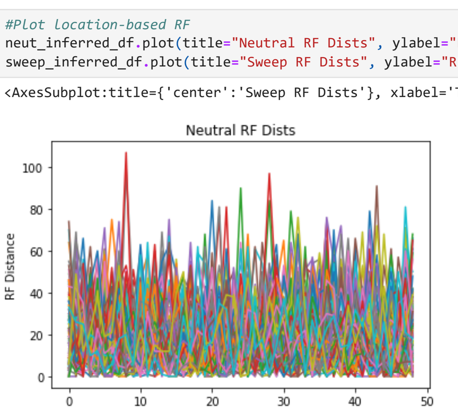
```
100%|██████████| 100/100 [17:13<00:00, 10.33s/it]
```

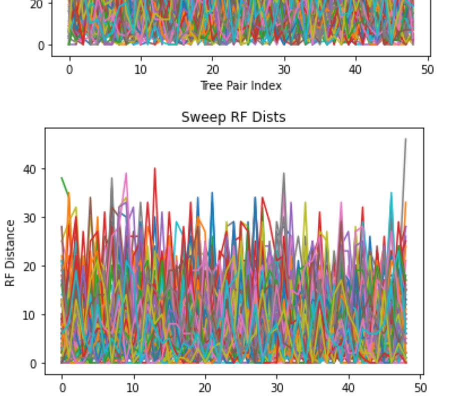
```python
#RF Dist Stats
neut_inferred_arr = np.array(neut_reps_inferred_rfs)
sweep_inferred_arr = np.array(sweep_reps_inferred_rfs)

np.savetxt("neut_inferred_data.tsv", neut_arr, delimiter="\t")
np.savetxt("sweep_inferred_data.tsv", sweep_arr, delimiter="\t")

neut_inferred_df = pd.DataFrame(neut_inferred_arr.T)
sweep_inferred_df = pd.DataFrame(sweep_inferred_arr.T)

print("Neutral")
print(neut_inferred_df.describe())

print("\nSweep")
print(sweep_inferred_df.describe())
```

```
(100, 49)
Neutral
               0          1          2          3          4          5   \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean   17.612245  17.224490  20.142857  15.224490  17.755102  17.061224
std    14.934323  13.855302  17.926935  15.724537  12.341547  15.615708
min     1.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     6.000000   6.000000   6.000000   3.000000   9.000000   5.000000
50%    16.000000  15.000000  14.000000  13.000000  16.000000  16.000000
75%    25.000000  25.000000  32.000000  22.000000  24.000000  24.000000
max    62.000000  52.000000  79.000000  81.000000  52.000000  91.000000

               6          7          8          9   ...         90         91  \
count  49.000000  49.000000  49.000000  49.000000  ...  49.000000  49.000000
mean   15.673469  20.346939  20.632653  17.877551  ...  19.979592  14.693878
std    13.357875  14.154727  16.802398  12.137464  ...  13.876674  10.801628
min     0.000000   0.000000   0.000000   0.000000  ...   0.000000   0.000000
25%     3.000000  10.000000   8.000000  11.000000  ...  10.000000   8.000000
50%    14.000000  19.000000  19.000000  17.000000  ...  16.000000  12.000000
75%    21.000000  29.000000  28.000000  25.000000  ...  27.000000  20.000000
max    60.000000  69.000000  71.000000  56.000000  ...  60.000000  45.000000

               92         93         94         95         96         97  \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean   14.448980  17.306122  19.428571  16.877551  16.979592  18.469388
std    11.462005  14.544764  14.386046  15.520997  12.938138  15.891693
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     6.000000   7.000000   9.000000   6.000000   7.000000   5.000000
50%    12.000000  14.000000  17.000000  13.000000  13.000000  18.000000
75%    23.000000  23.000000  28.000000  25.000000  25.000000  27.000000
max    41.000000  63.000000  57.000000  74.000000  52.000000  65.000000

               98         99
count  49.000000  49.000000
mean   22.857143  20.081633
std    17.716518  16.165597
min     0.000000   0.000000
25%    12.000000   9.000000
50%    20.000000  18.000000
75%    34.000000  29.000000
max    76.000000  62.000000

[8 rows x 100 columns]

Sweep
               0          1          2          3          4          5   \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean    5.061224   8.755102   8.081633   6.673469   7.734694   6.959184
std     5.963109   6.514505   9.641137   7.425709   5.769083   6.515875
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     0.000000   4.000000   1.000000   2.000000   4.000000   2.000000
50%     4.000000   7.000000   5.000000   4.000000   6.000000   5.000000
75%     7.000000  12.000000  13.000000   9.000000  10.000000   9.000000
max    26.000000  25.000000  38.000000  40.000000  22.000000  23.000000

               6          7          8          9   ...         90         91  \
count  49.000000  49.000000  49.000000  49.000000  ...  49.000000  49.000000
mean    5.591837   9.979592   6.734694   5.673469  ...   4.775510   5.918367
std     5.837802   7.741904   7.108608   5.643535  ...   5.152933   5.901401
min     0.000000   0.000000   0.000000   0.000000  ...   0.000000   0.000000
25%     2.000000   5.000000   0.000000   2.000000  ...   0.000000   1.000000
50%     4.000000   9.000000   4.000000   4.000000  ...   4.000000   3.000000
75%     7.000000  13.000000  11.000000   8.000000  ...   6.000000  10.000000
max    21.000000  30.000000  26.000000  23.000000  ...  19.000000  21.000000

               92         93         94         95         96         97  \
count  49.000000  49.000000  49.000000  49.000000  49.000000  49.000000
mean    9.000000   5.163265   8.081633   9.081633   8.448980   9.102041
std     7.071068   6.472206   8.918232   6.396082   7.257356   6.973894
min     0.000000   0.000000   0.000000   0.000000   0.000000   0.000000
25%     3.000000   1.000000   3.000000   4.000000   2.000000   4.000000
50%     8.000000   3.000000   5.000000   8.000000   7.000000   8.000000
75%    14.000000   7.000000  10.000000  14.000000  13.000000  14.000000
max    24.000000  26.000000  33.000000  23.000000  27.000000  29.000000

               98         99
count  49.000000  49.000000
mean    6.795918   6.693878
std     6.528717   5.870846
min     0.000000   0.000000
25%     1.000000   2.000000
50%     5.000000   6.000000
75%    11.000000   8.000000
max    25.000000  23.000000

[8 rows x 100 columns]
```

```python
#Plot location-based RF
neut_inferred_df.plot(title="Neutral RF Dists", ylabel="RF Distance", xlabel="Tree Pair Index", legend=None)
sweep_inferred_df.plot(title="Sweep RF Dists", ylabel="RF Distance", xlabel="Tree Pair Index", legend=None)
```

```
<AxesSubplot:title={'center':'Sweep RF Dists'}, xlabel='Tree Pair Index', ylabel='RF Distance'>
```





Now we create and train an RF model to use this as a predictive feature

```python
#Split train/test
data = np.concatenate([neut_inferred_arr, sweep_inferred_arr], axis=0)
labs = np.concatenate([len(neut_inferred_arr)*[0], len(sweep_inferred_arr)*[1]])

x_train, x_test, y_train, y_test = train_test_split(data, labs, stratify=labs)
```

```python
#RF model
clf_inf = RandomForestClassifier()
clf_inf.fit(x_train, y_train)

pred = clf_inf.predict_proba(x_test)

roc_auc = roc_auc_score(y_test, pred[:,1])
print(f"Inferred ROC AUC: {roc_auc}")

confmat = confusion_matrix(y_test, np.argmax(pred, axis=1))
print("Inferred Confusion matrix")
print(confmat)
```

```
Inferred ROC AUC: 1.0
Inferred Confusion matrix
[[24  1]
 [ 0 25]]
```