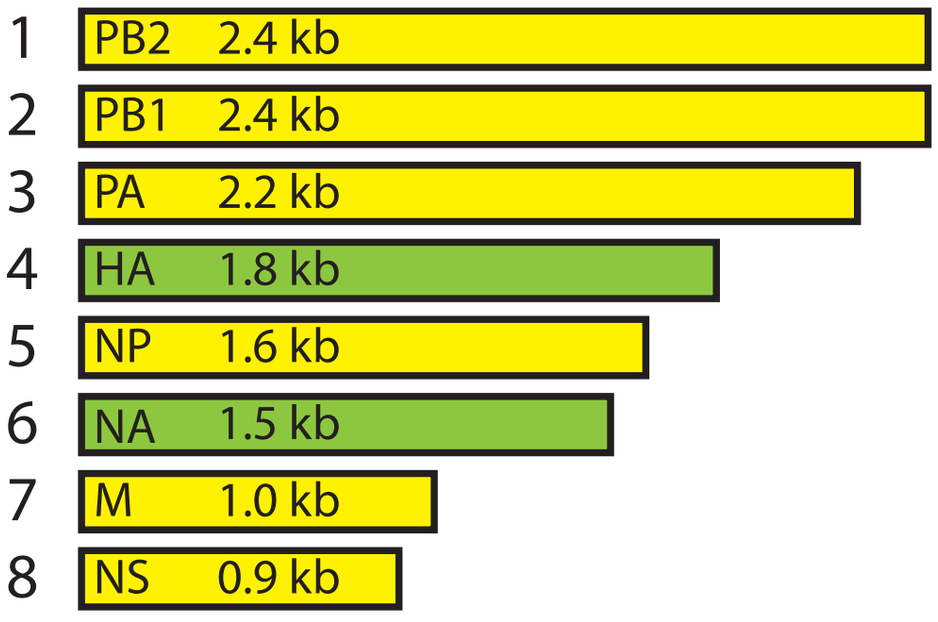
Reassortment Primes Influenza for Host Group Switches

Eric J. Ma

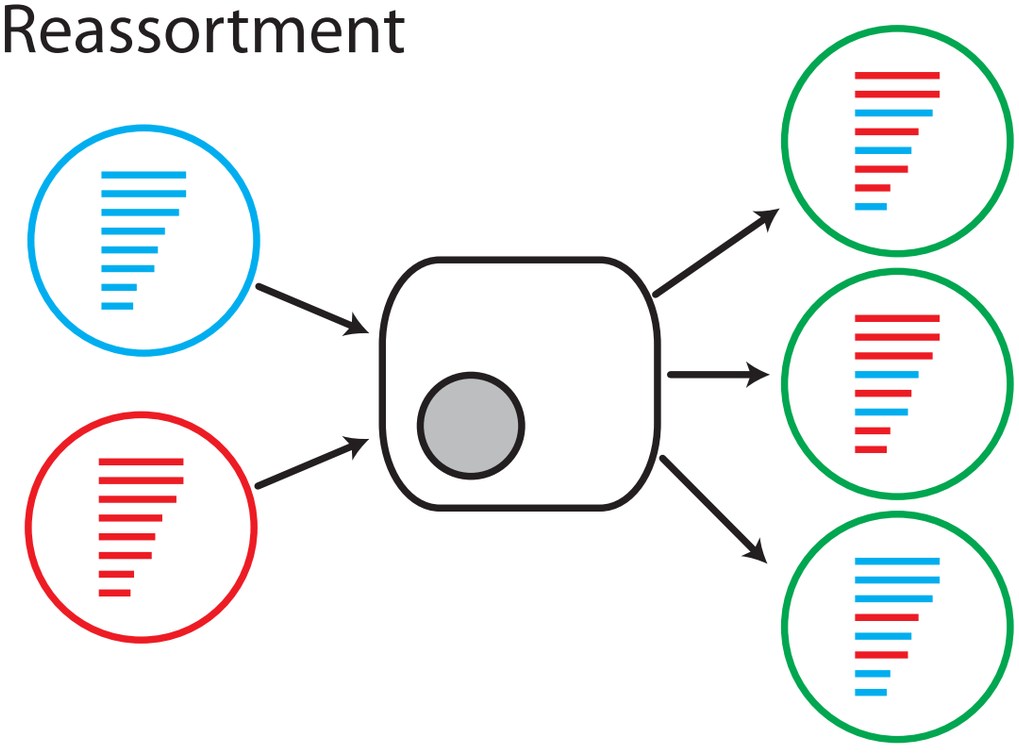
CSB Student Seminar 2015

Reassortment

(a) Influenza Genome Structure

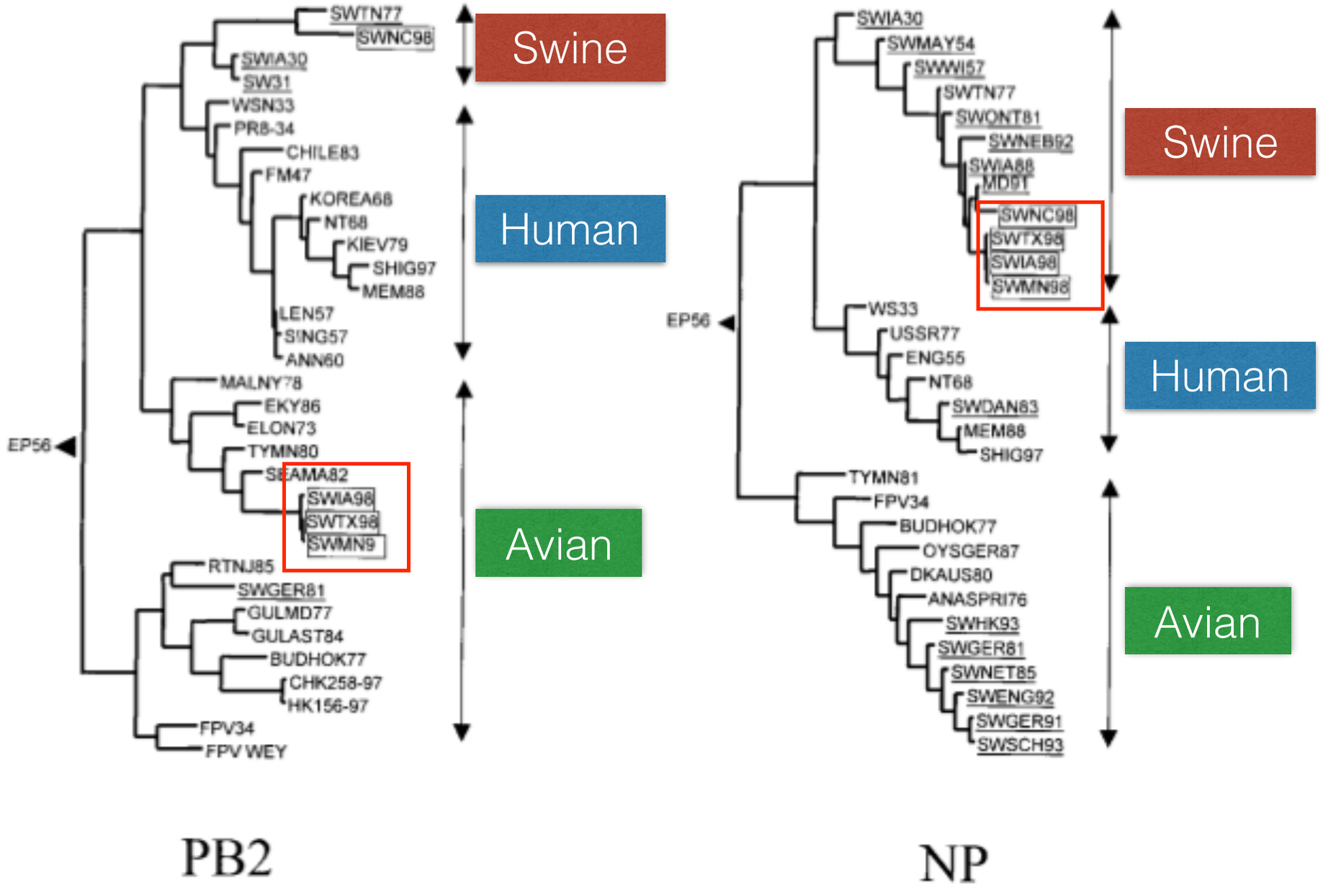


(b) Reassortment



All pandemic viruses since 1980 have been reassortants.

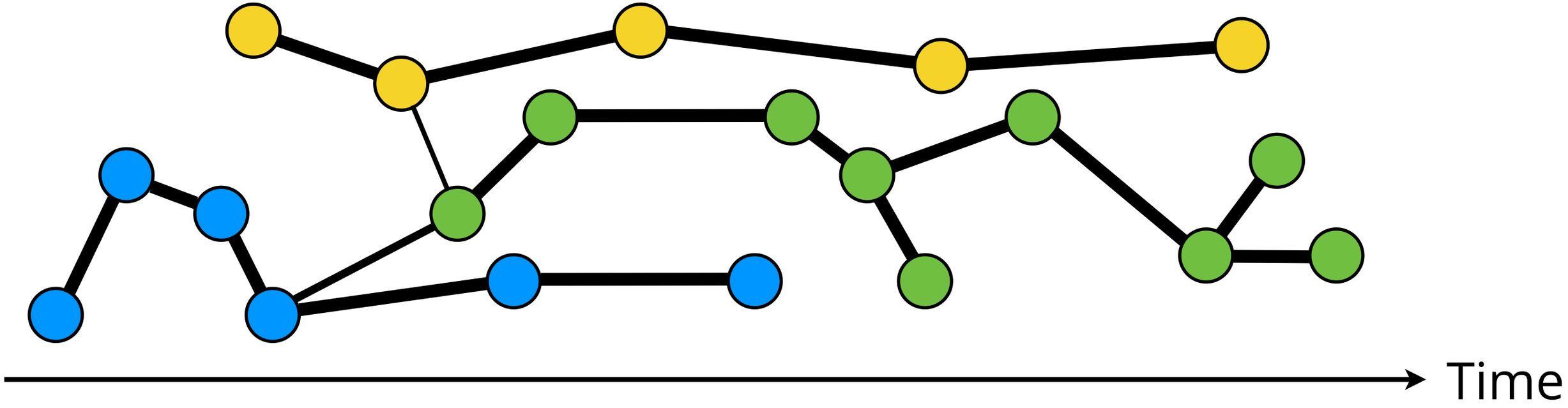
Reassortment: “Discordant Similarity”



Zhou, N. N. et al. Genetic reassortment of avian, swine, and human influenza A viruses in American pigs. J. Virol. 73, 8851–8856 (1999).

Method

Viral Isolate



Numbers

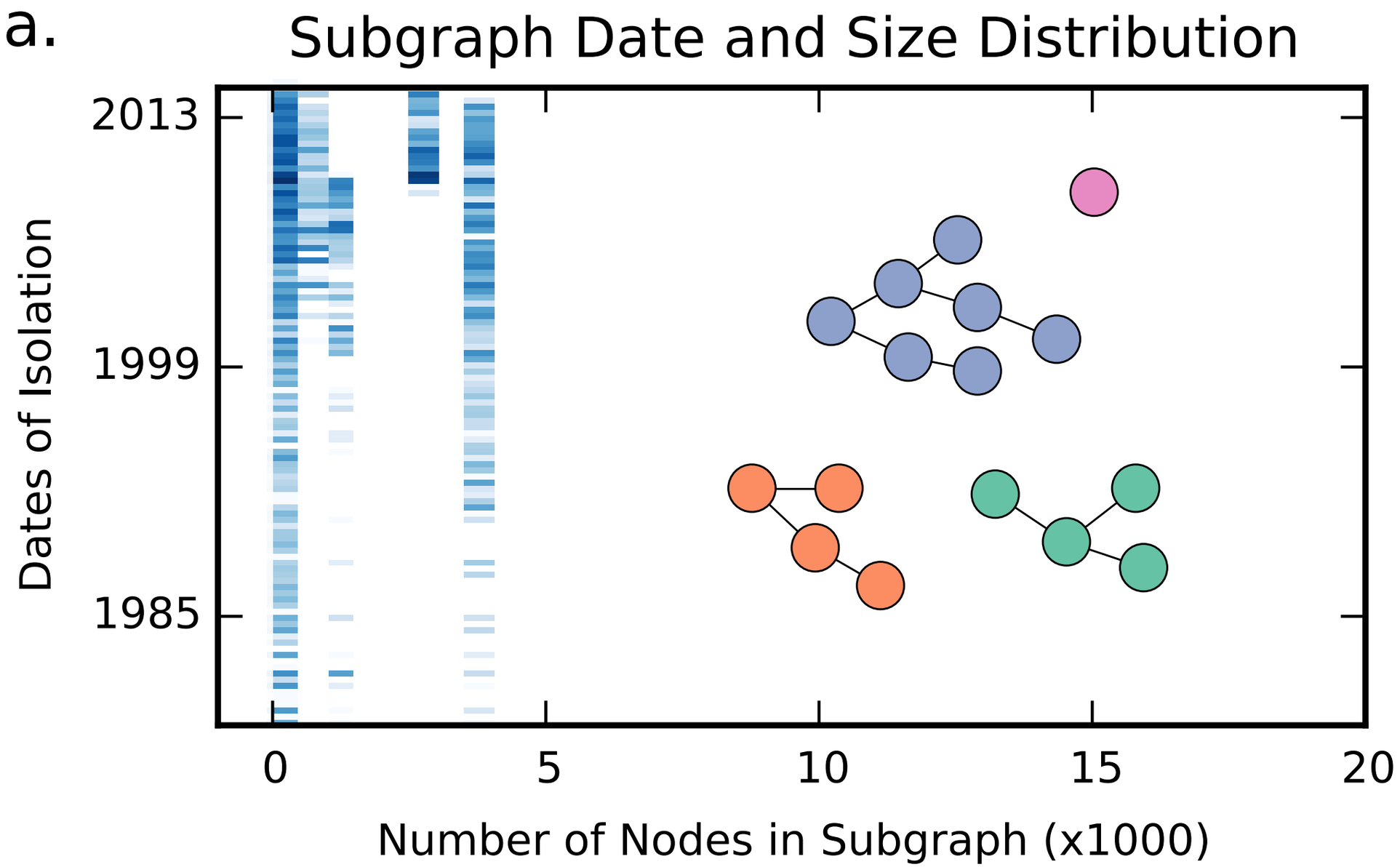
16,656 Number of isolates in dataset

133,248 Number of sequences

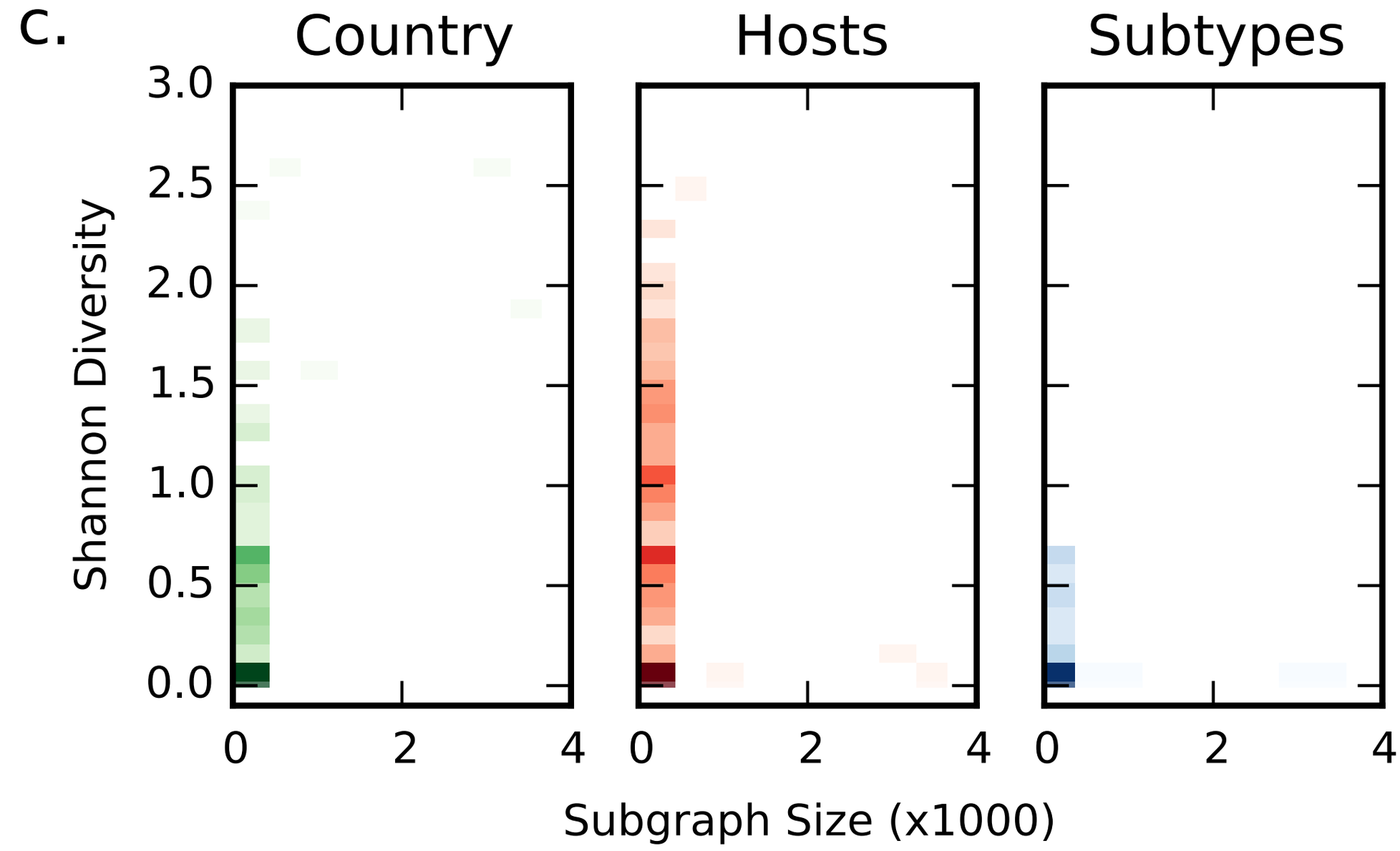
1980-2014 Date range of sequences

All data were sourced from the
Influenza Research Database

Reassortment joins influenza isolates in a global network of gene exchange

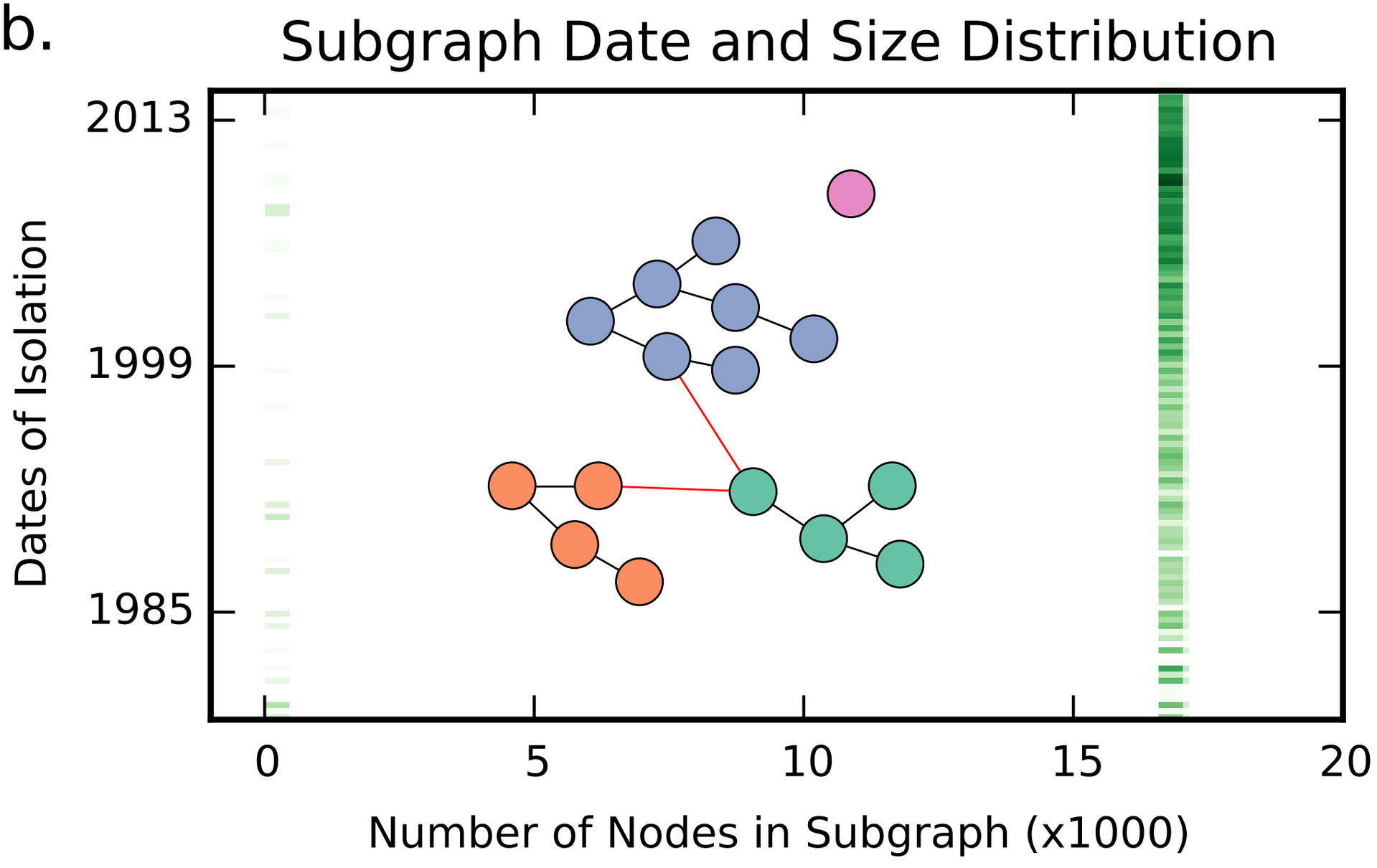


Reassortment joins influenza isolates in a global network of gene exchange



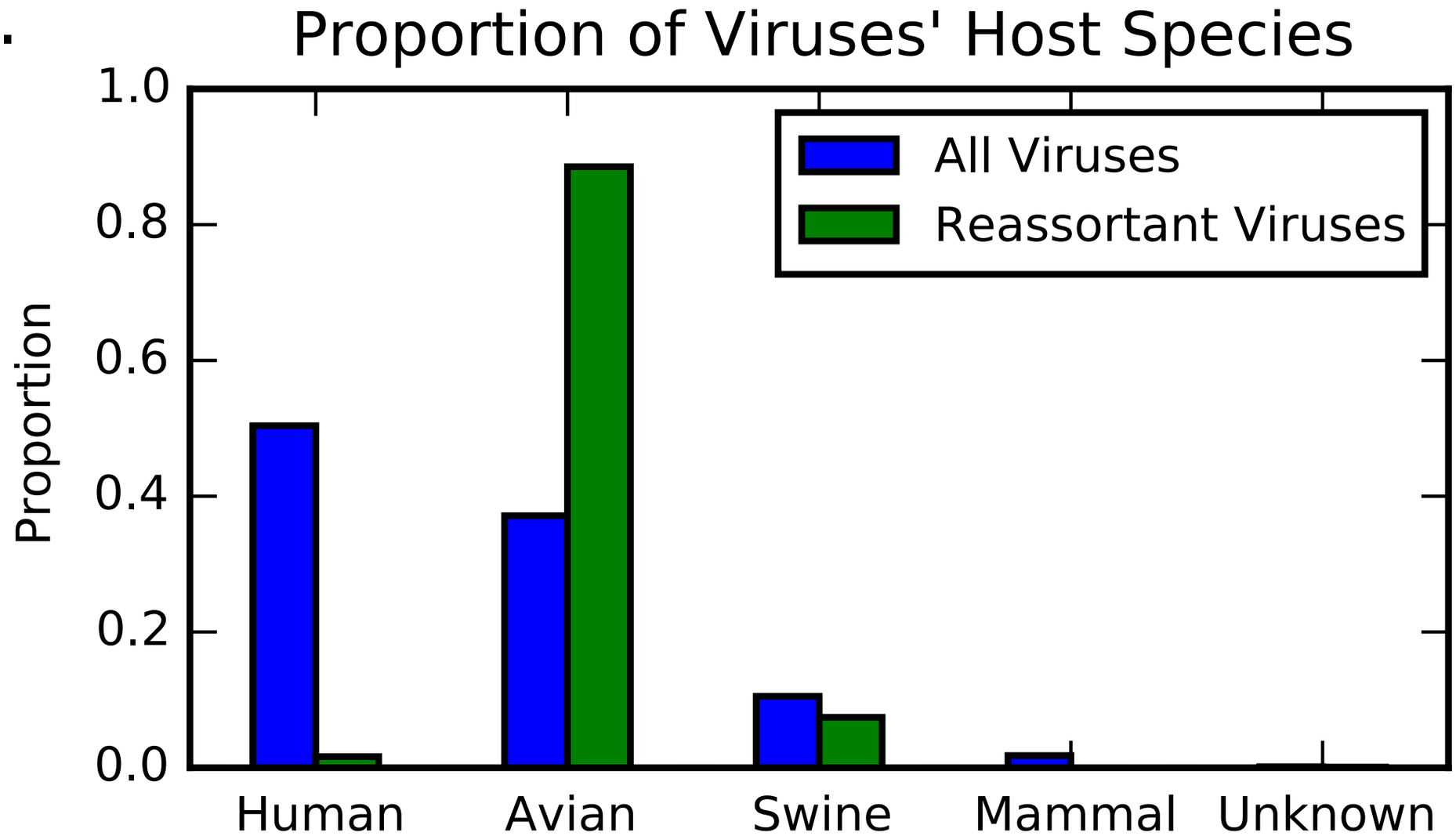
Reassortment joins influenza isolates in a global network of gene exchange

b.



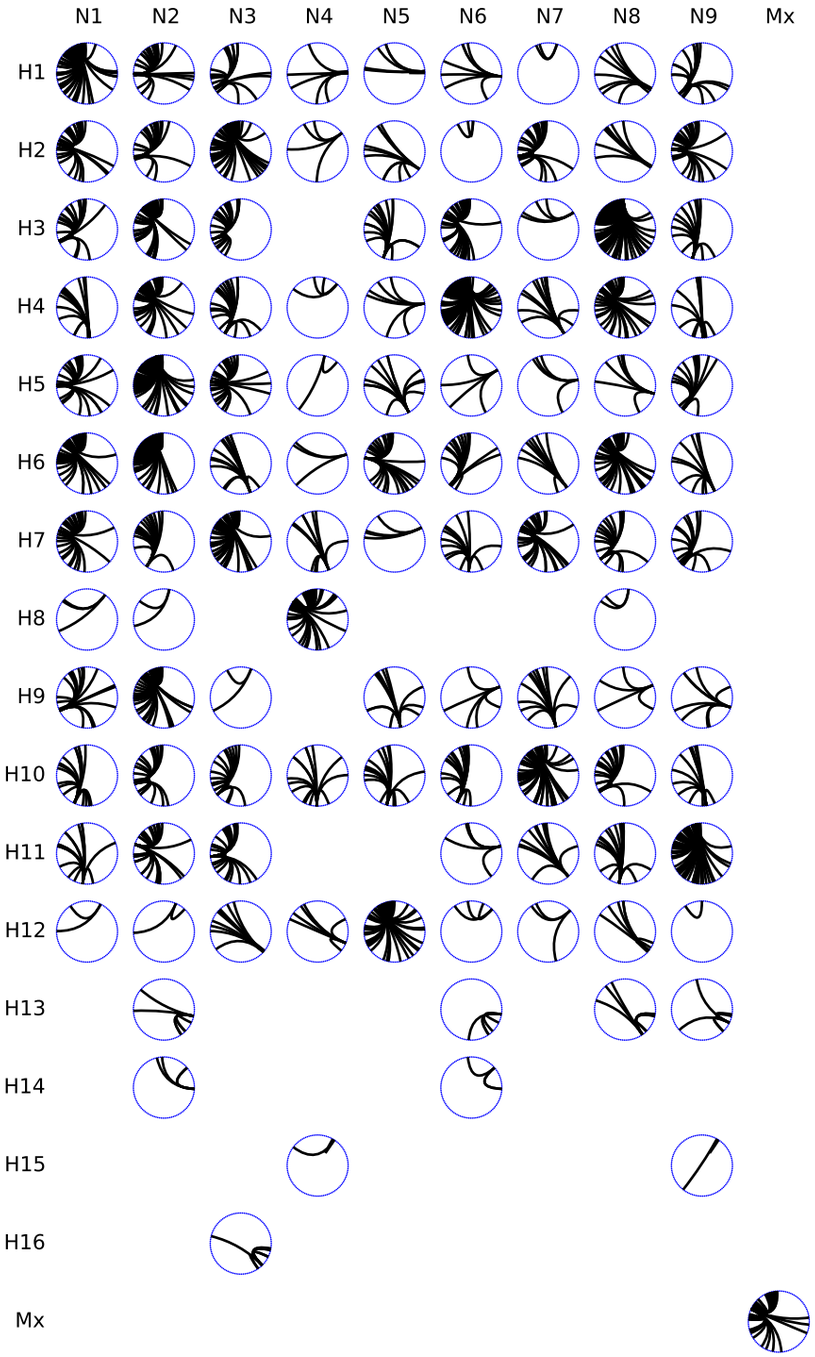
Reassortment joins influenza isolates in a global network of gene exchange

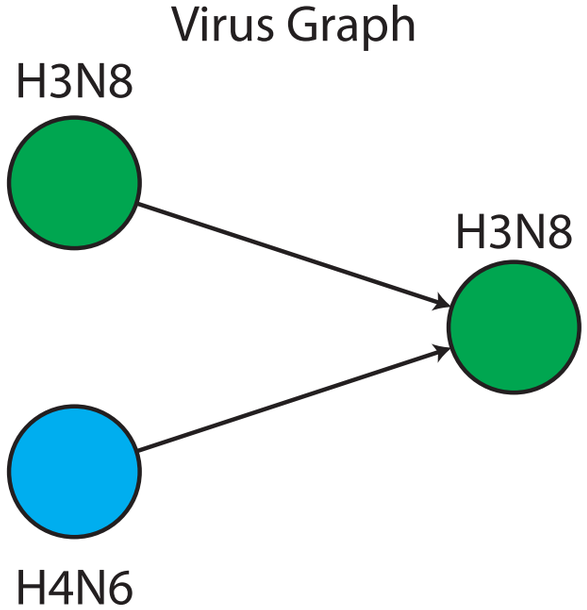
d.

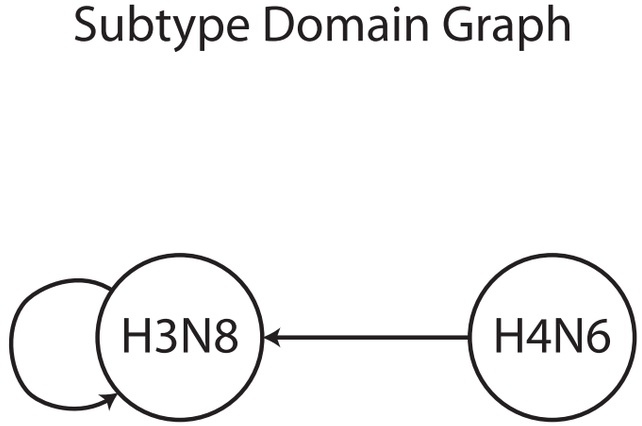


Hub subtypes are defined by broad host ranges and wide geographic dispersal

a.







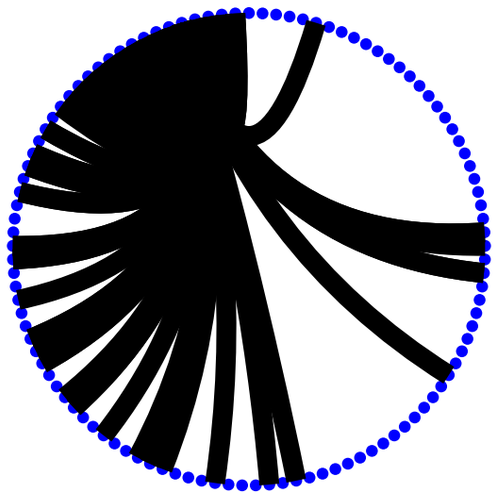
a.

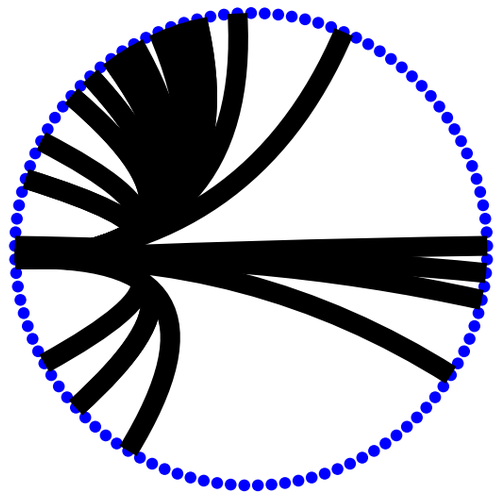
increasing
subtype
connectivity

N1

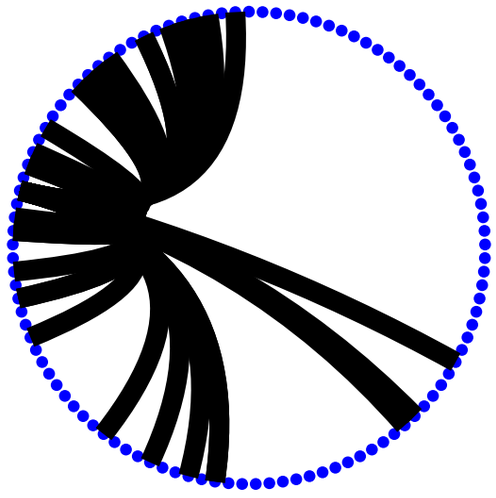
N2

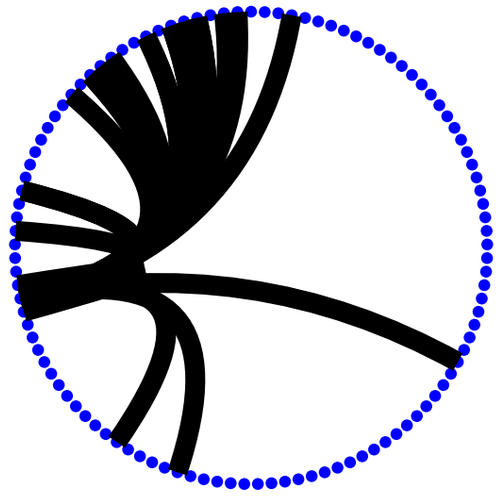
H1



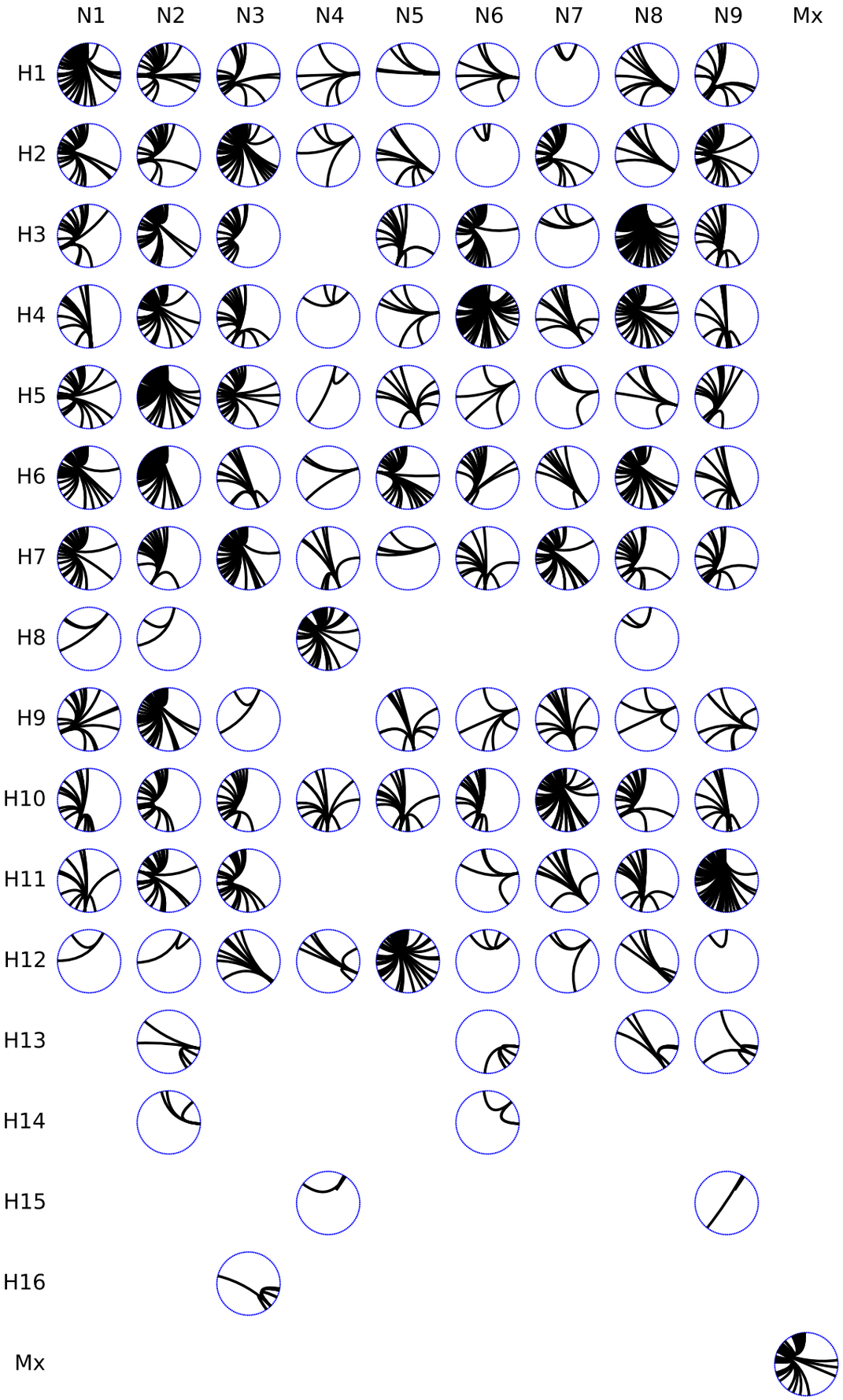


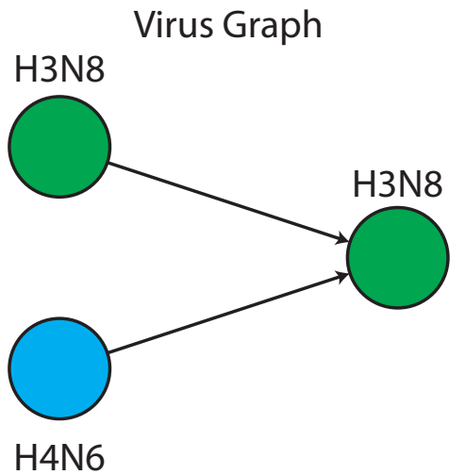
H2

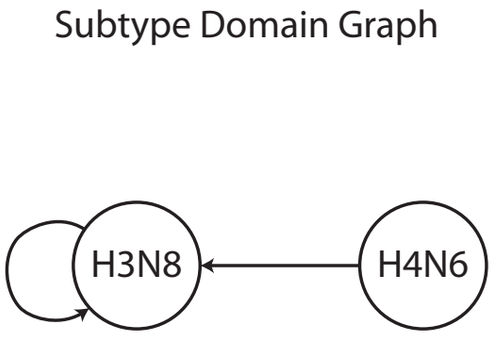


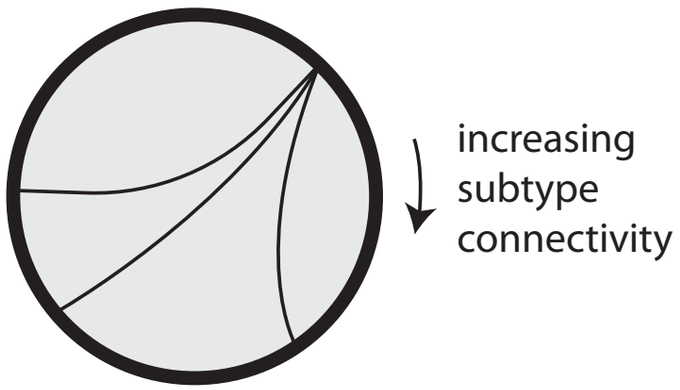


a.

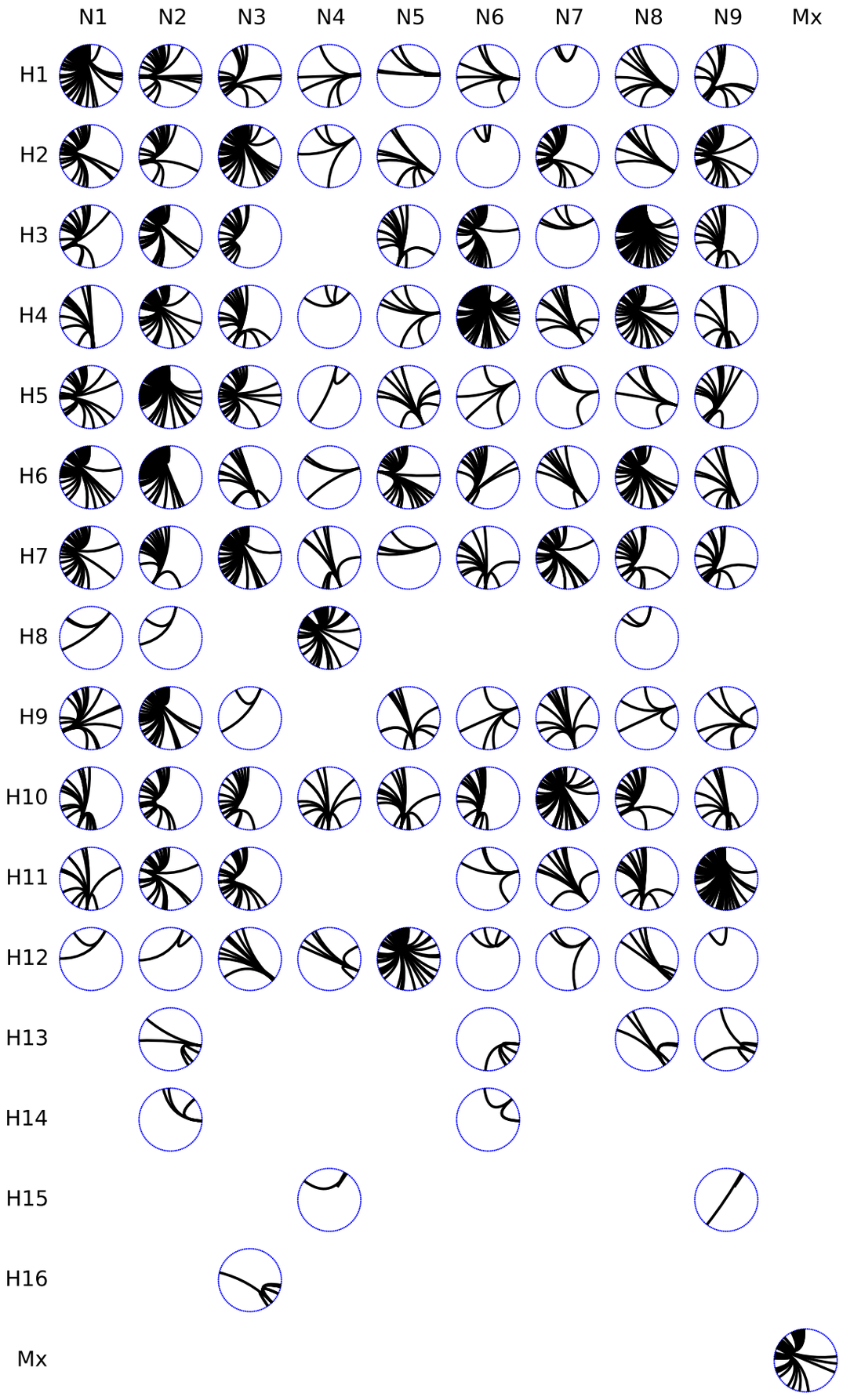

N1
N2
N3
N4
N5
N6
N7
N8
N9
Mx
H1
H2
H3
H4
H5
H6
H7
H8
H9
H10
H11
H12
H13
H14
H15
H16
Mx


Virus Graph
H3N8
H3N8
H4N6


Subtype Domain Graph
H3N8
H4N6


increasing
subtype
connectivity

a.


N1
N2
N3
N4
N5
N6
N7
N8
N9
Mx
H1
H2
H3
H4
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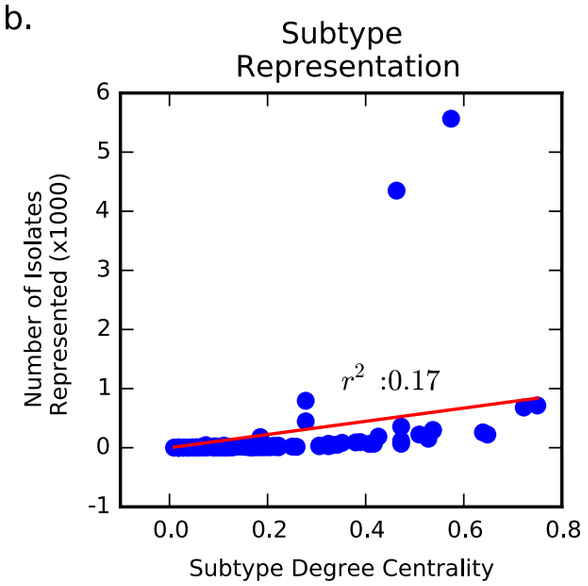
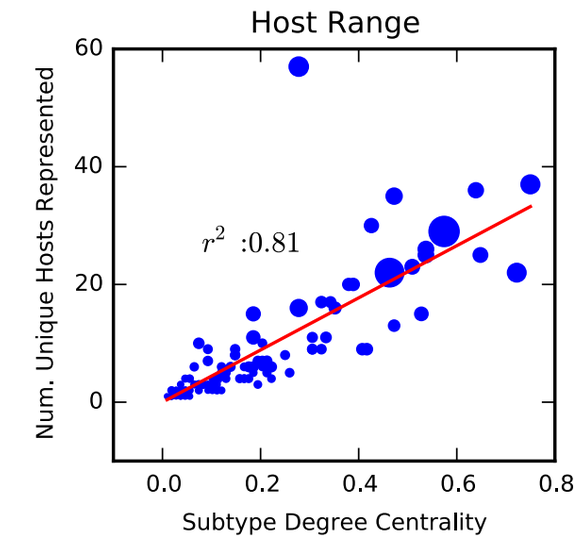
H6
H7
H8
H9
H10
H11
H12
H13
H14
H15
H16
Mx

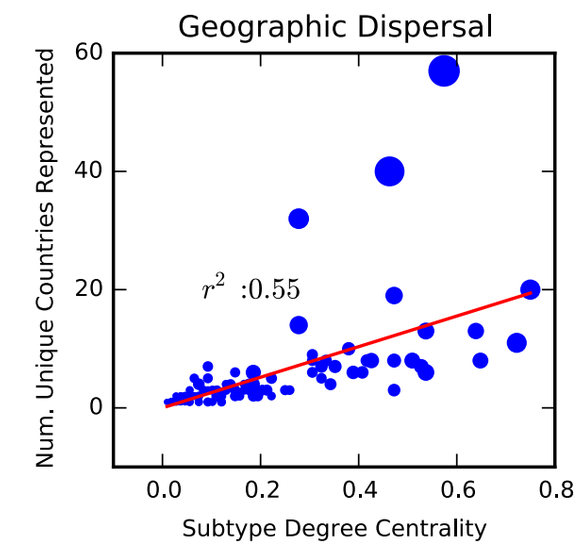
b.


Subtype Representation
Number of Isolates Represented (x1000)
r^2 :0.17
Subtype Degree Centrality

c.

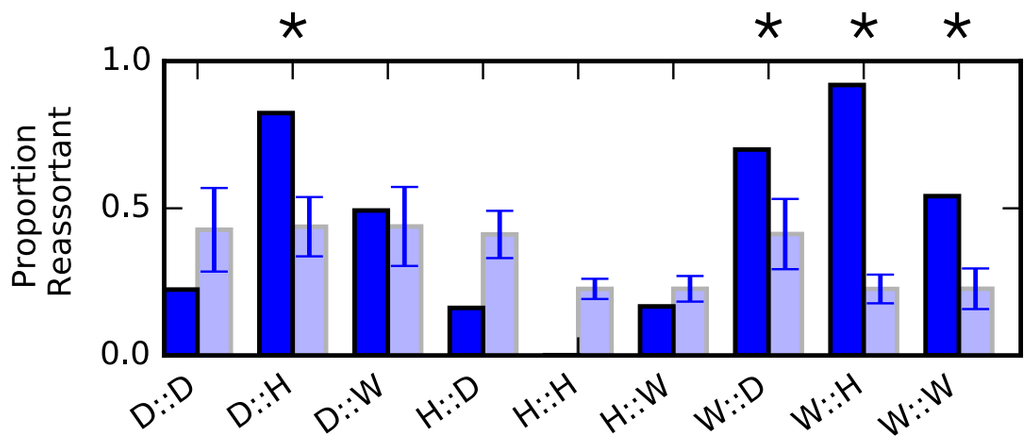

Host Range
Num. Unique Hosts Represented
r^2 :0.81
Subtype Degree Centrality

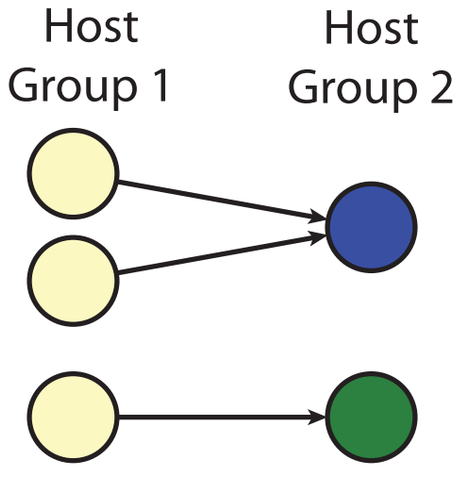
d.


Geographic Dispersal
Num. Unique Countries Represented
r^2 :0.55
Subtype Degree Centrality

Reassortment primes host group switches

a.





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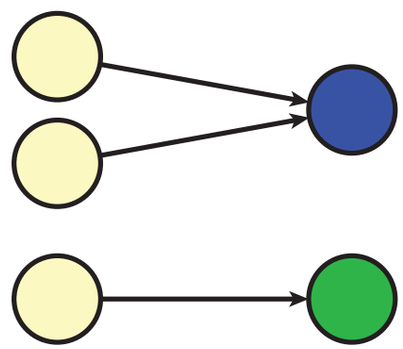
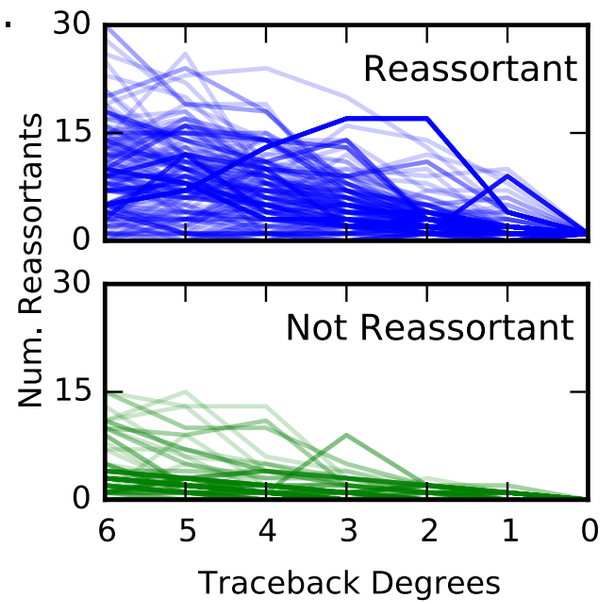
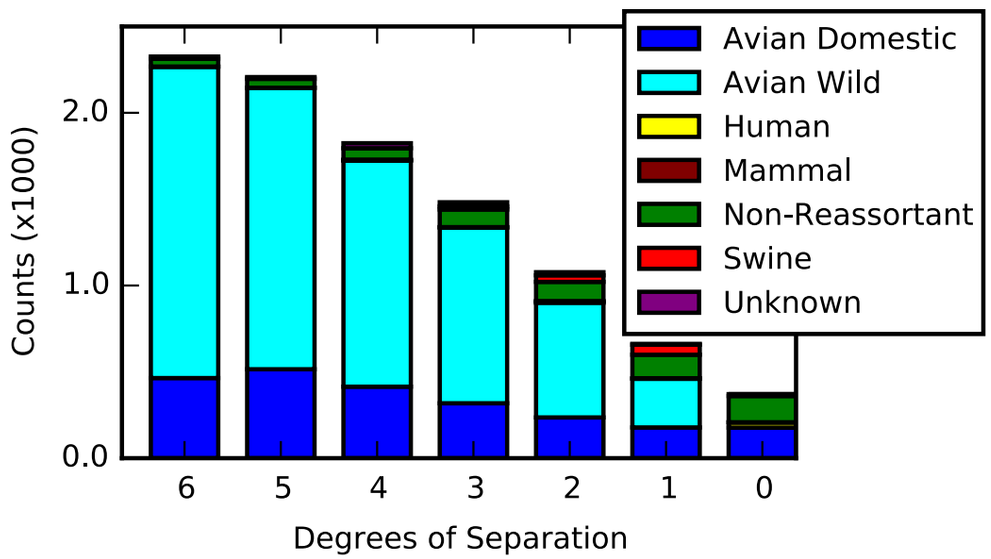


c.

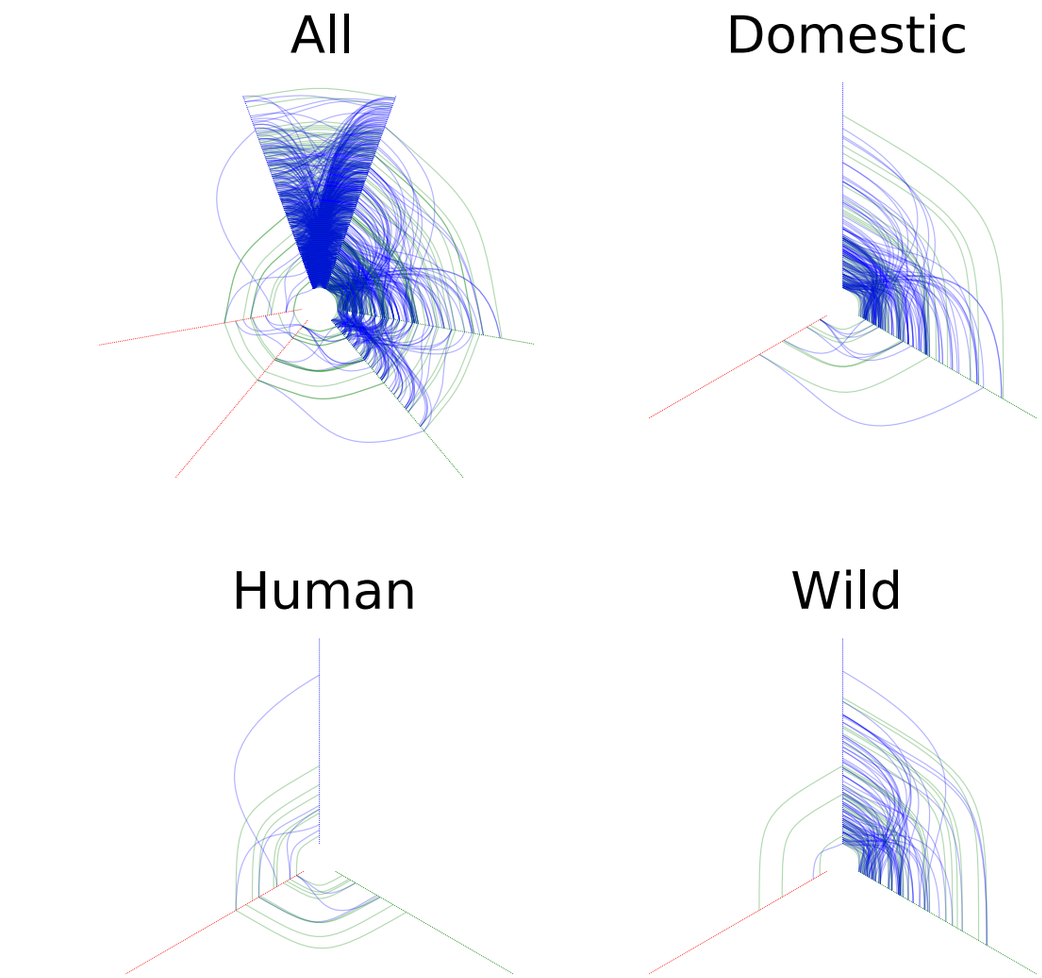


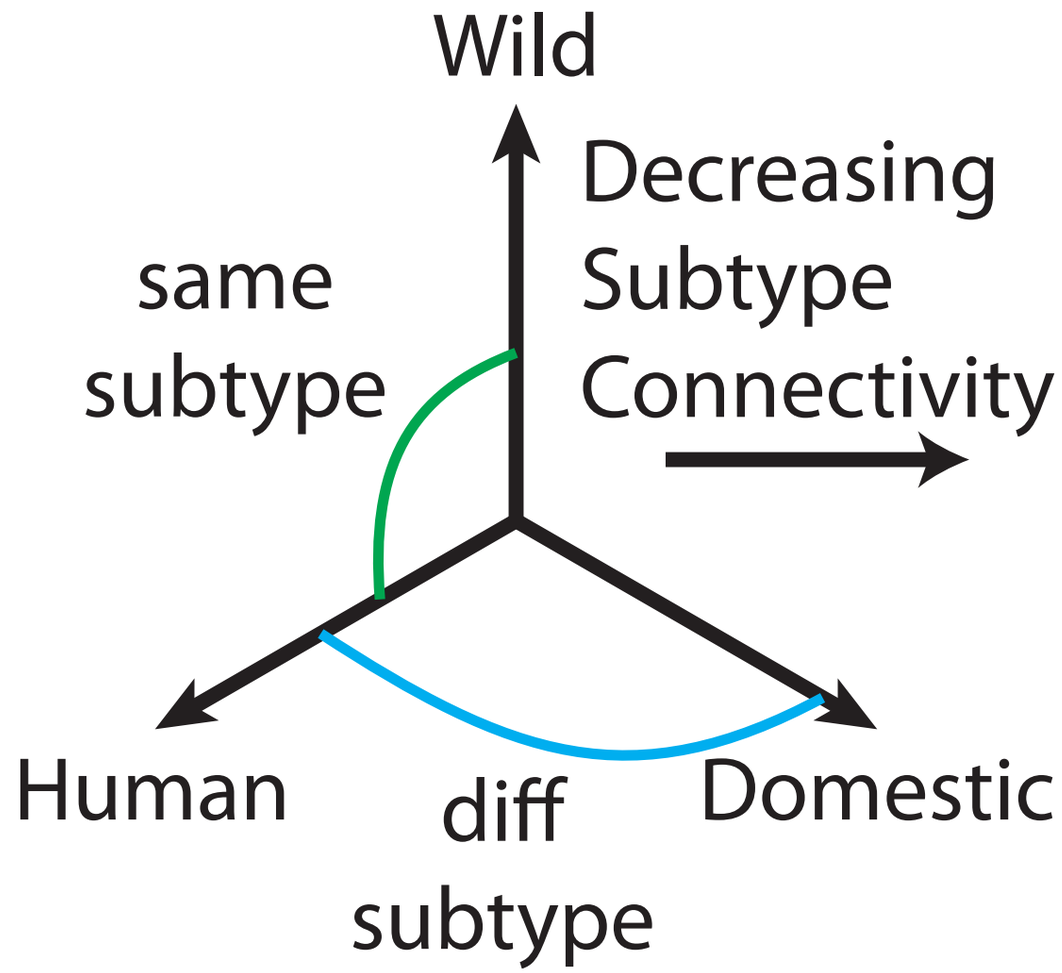
d.



Host groups structure subtype interactions

a.

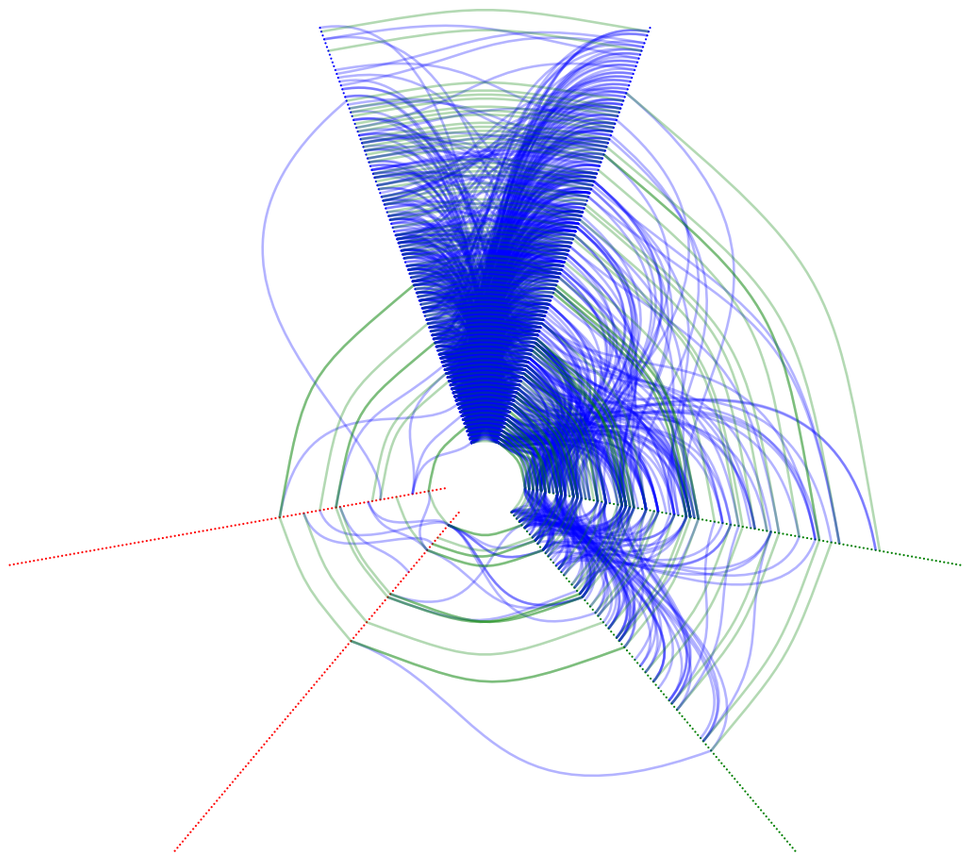




Host groups structure subtype interactions

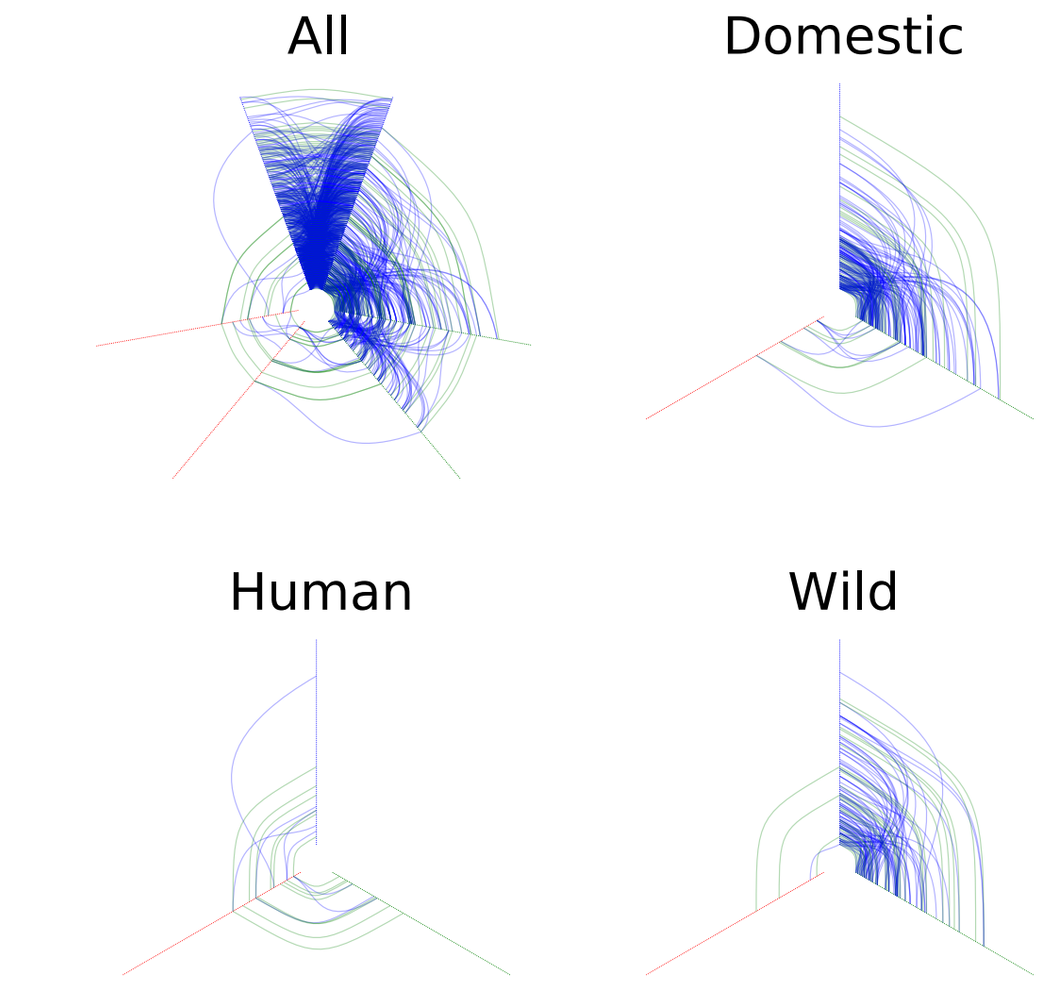
a.

All



Host groups structure subtype interactions

a.



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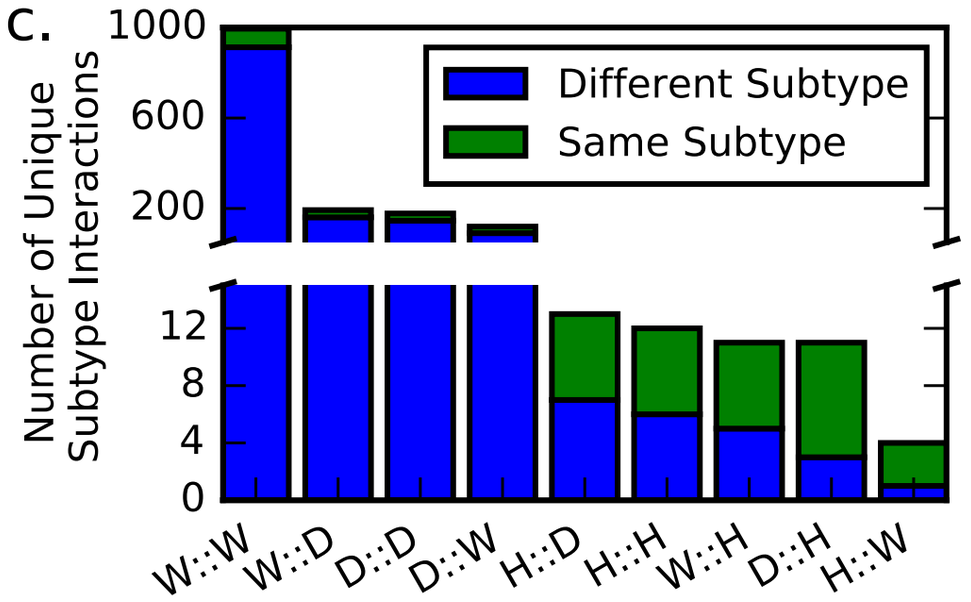

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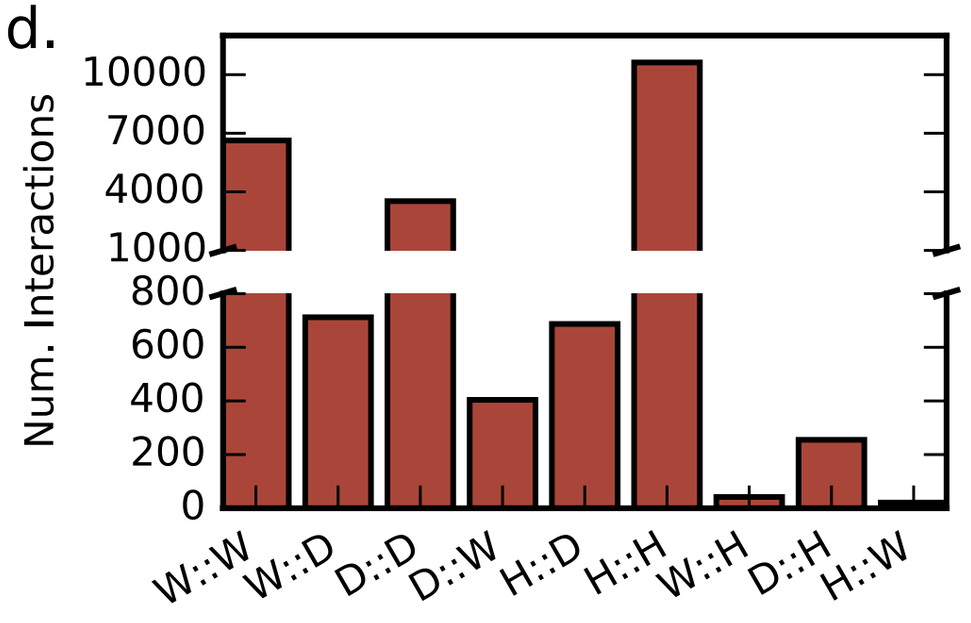


What have we learned?

- Reassortment is prevalent in birds, *9 times as much as in other animals.*

- Numerous reassortment events precede host switches — priming mechanism?

- Reassortment is over-represented at interfaces that we care about.

- Highly reassorting subtypes are found in humans.

- The ecological interfaces are probably where we can best do *pre-emptive surveillance*.

Pre-emptive surveillance

- Prevailing paradigm:
  - outbreak —> sample —> continuously monitor
- Proposed paradigm:
  - hypothesis-driven sampling: **test interfaces identified**
  - co-sample interacting species and co-circulating subtypes, **sample sink before source**
  - test **phylogenetic susceptibility**

Can we apply this elsewhere?

- Absolutely! :) This requires:
  - Time-stamped, full genomic sequences.
  - Defined genomic partitions: CDS, chromosome
  - *Metadata*

Reproducibility Endeavors

- Entire analysis in Python, completely reproducible
- Used Free-Licensed Open-Source Software (FLOSS)

- Code will be on Github at time of publication.

Acknowledgments

RUNSTADLER LABORATORY

Nichola Hill
Islam Hussein

Kyle Yuan
Justin Zabilansky

Jonathan Runstadler (MIT)
Mark Bathe (MIT)
JP Onnela (HSPH)

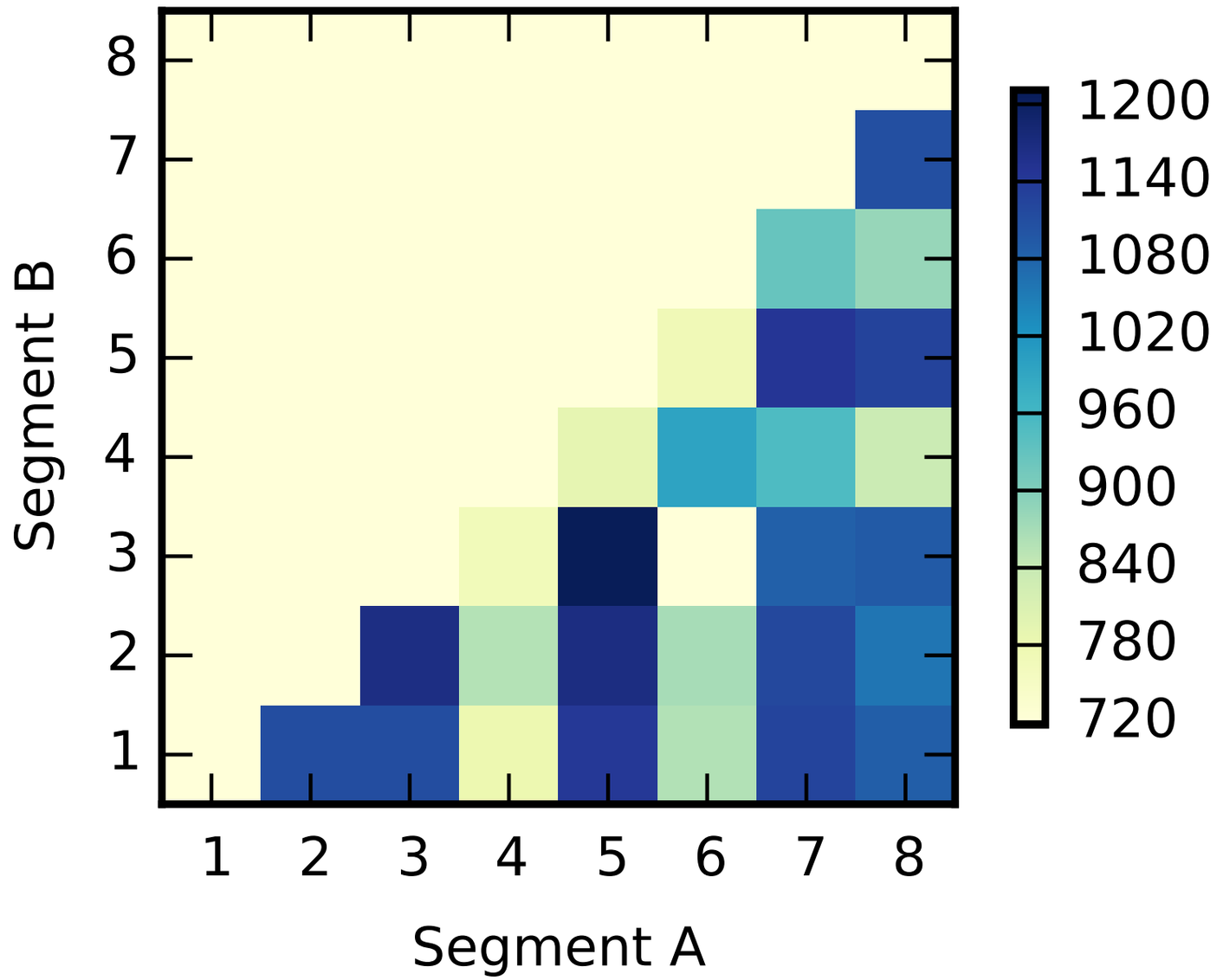
MIT BE BIOLOGICAL ENGINEERING

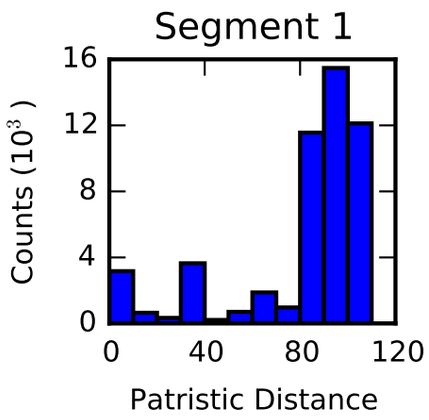
MIT CEHS

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

The Division of Comparative Medicine
MIT - DCM Building 16, Room 825
77 Massachusetts Avenue
Cambridge, MA 02139

Co-assortment Frequencies

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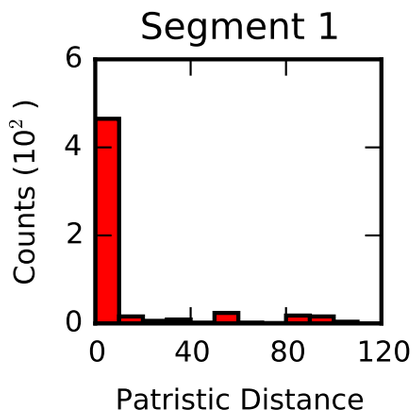
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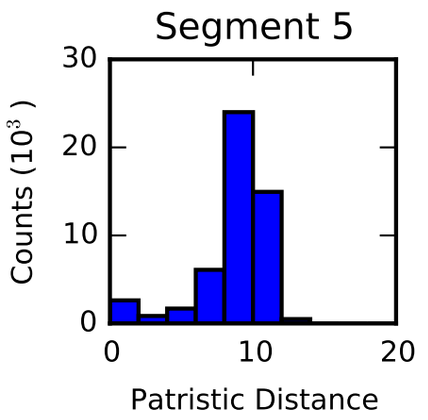
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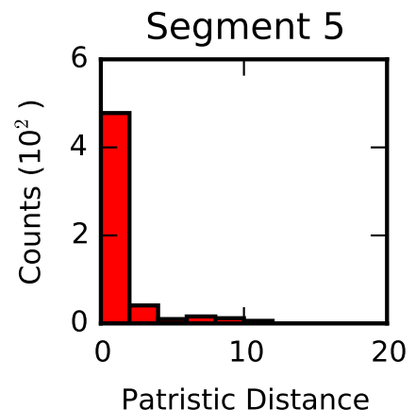
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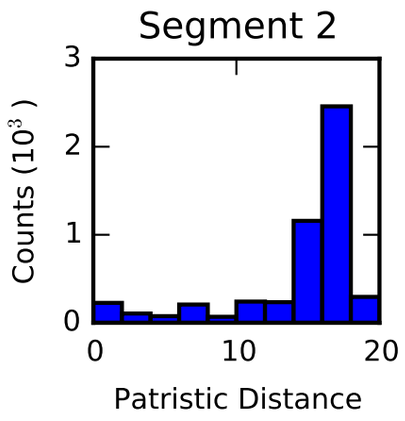
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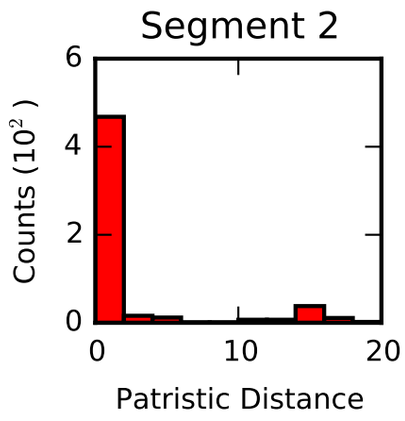
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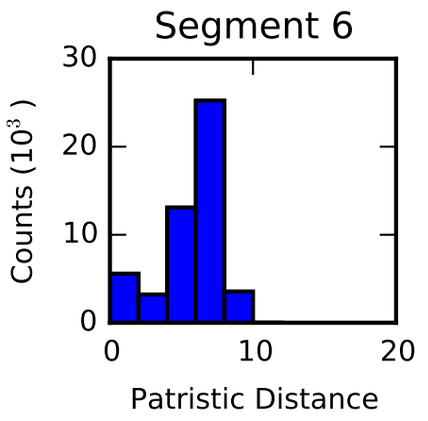
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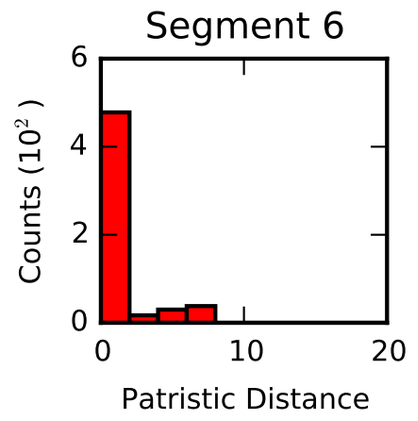
Segment 6
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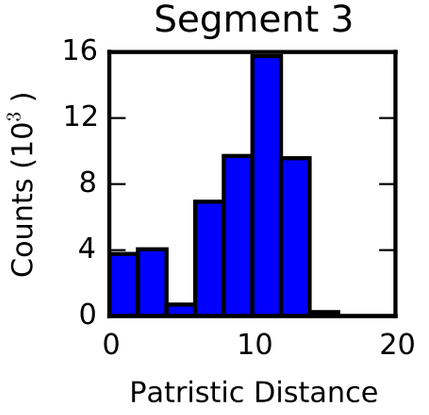
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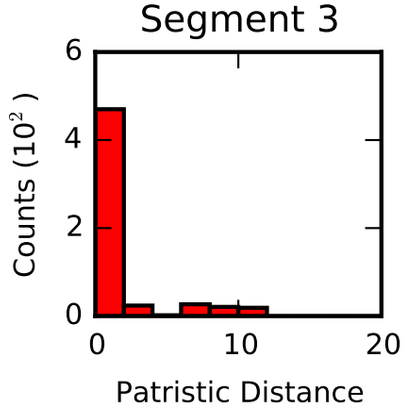
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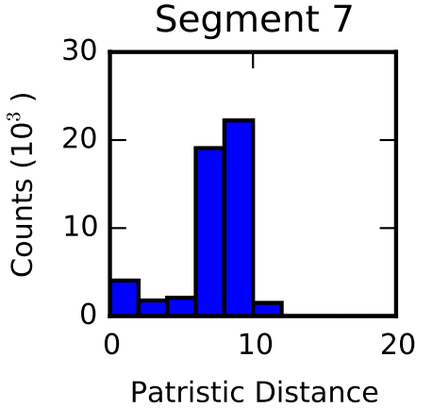
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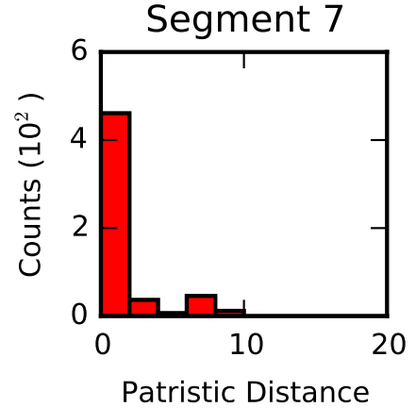
Segment 7
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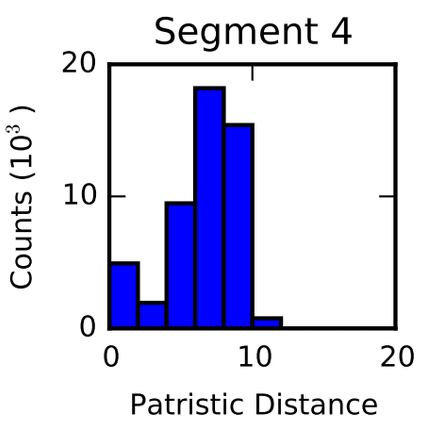
Patristic Distance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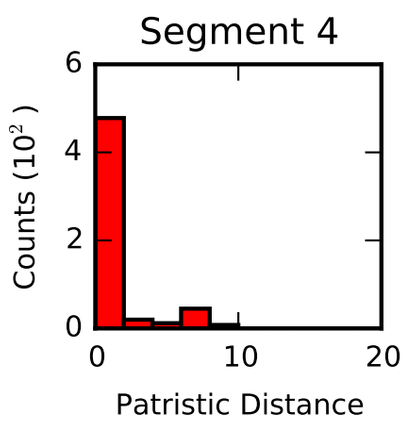
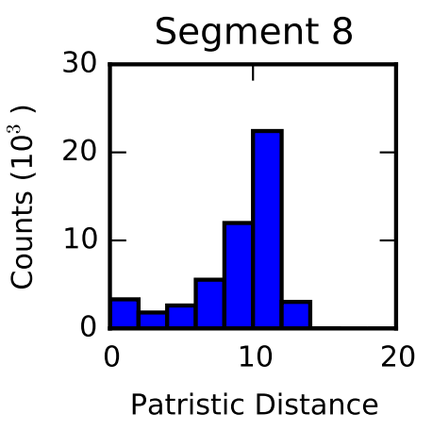
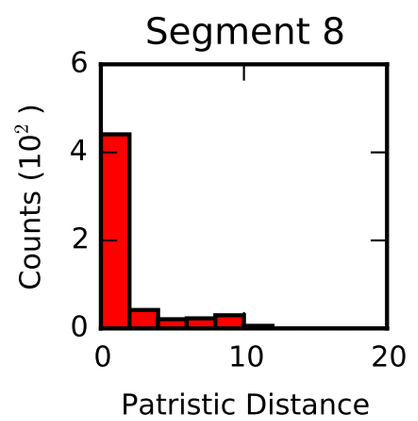

Segment 4
Counts (10^2)
Patristic Distance


Segment 8
Counts (10^3)
Patristic Distance


Segment 8
Counts (10^2)
Patristic Distance