THE UNIVERSITY OF
MELBOURNE

FACULTY OF
VETERINARY &
AGRICULTURAL
SCIENCES

Evaluation of Foot and Mouth Disease Outbreak Transmission Models

Simon Firestone, Mark Stevenson
Asia-Pacific Centre for Animal Health, The University of Melbourne

OIE Collaborating Centre for Diagnostic Test Validation Science in the Asia-Pacific Region

Yoko Hayama, Takehisa Yamamoto, Toshiyuki Tsutsui
National Institute of Animal Health, NARO, Japan

Richard Bradhurst
Centre of Excellence for Biosecurity Risk Analysis,
The University of Melbourne

The University of Melbourne,

OIE Collaborating Centre
Diagnostic Test Validation Science

simon.firestone@unimelb.edu.au

Vet Epi @ Melbourne: http://fvas.unimelb.edu.au/veam

“Essentially, all models are wrong, but some are useful.”

George E. P. Box,
Professor of Statistics at the University of Wisconsin.

Outline

Introduction

- FMD transmission network modelling & validation

AIM: To evaluate fitness for purpose of models that infer **who infected whom** using epidemiologic & genomic data

Methods & Results

- Outbreak simulation in a free country (AU)
- Modelling outputs

Discussion and Conclusions

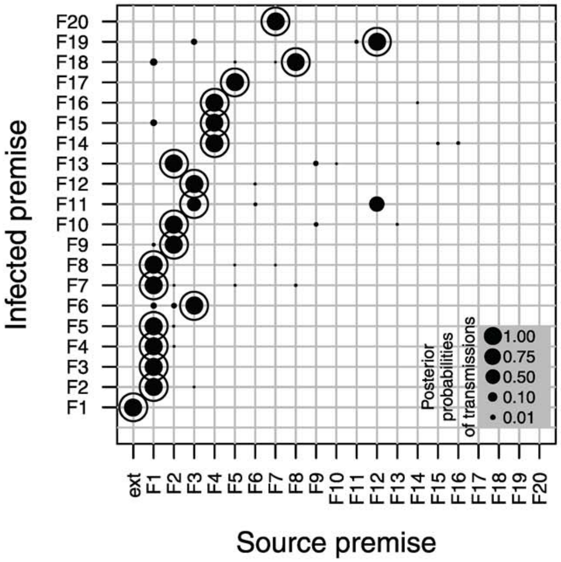
Introdution: Models run

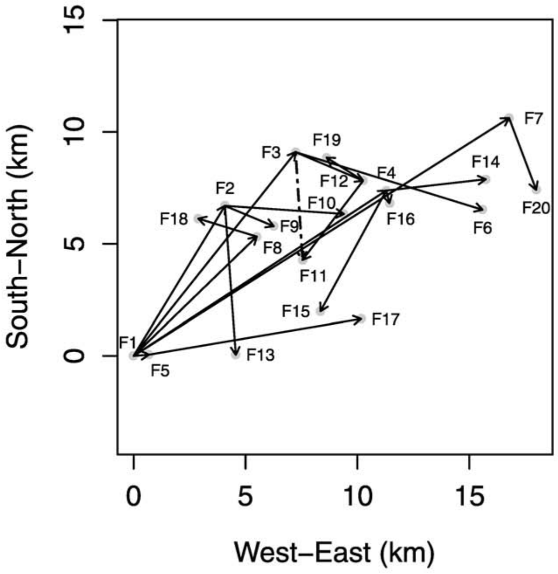
Frequentist

- Cottam (trees ranked by epi likelihood)
- Cottam + spatial kernel + tracing data

Bayesian

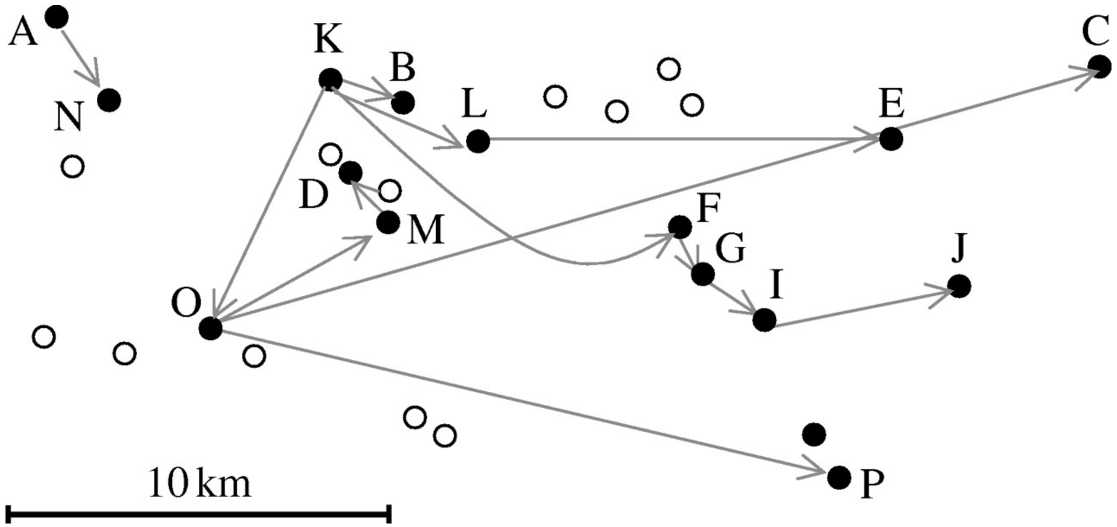
- Lau (full inference of everything!)
- SCoTTi (BEAST) - incl within host model
- Phybreak (partial inference)
- Outbreaker & Outbreaker 2 (partial)
- *BeastLier, Sampled ancestors* (BEAST)
- *TransPhyloR*



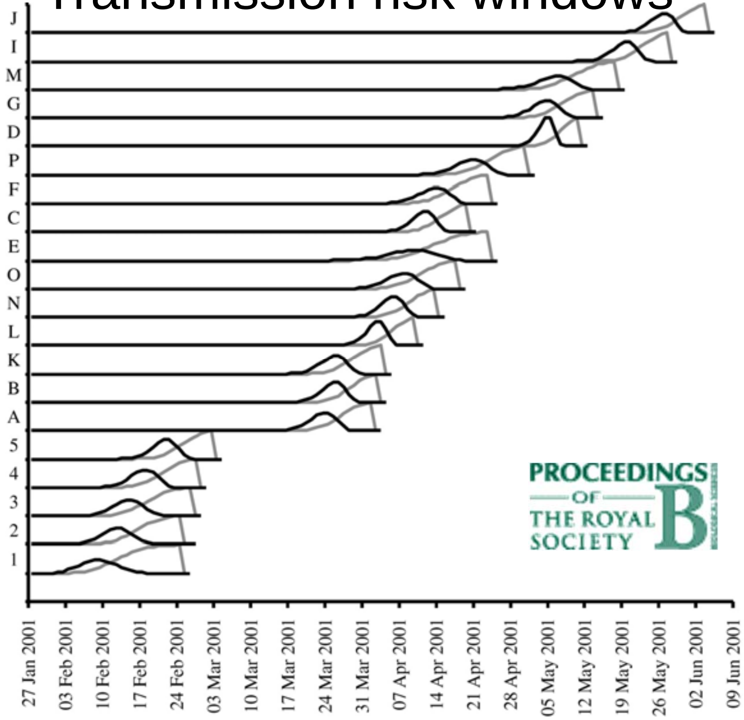


Integrating Genetic and Epidemiological Data to Determine Transmission Pathways of FMD UK 01 (Cottam et al, 2008a)

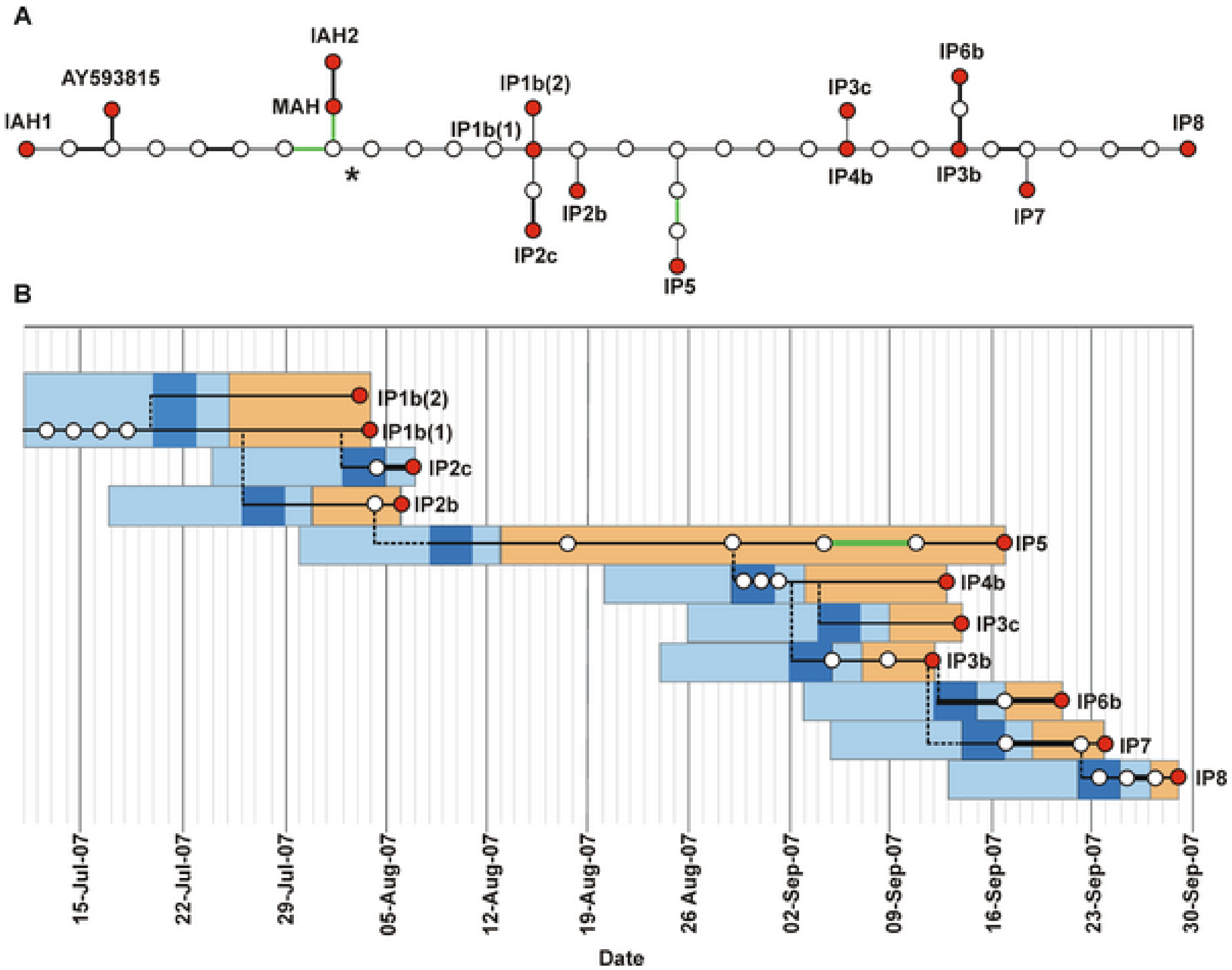
- frequentist approach, ‘epi’ likelihood functions for:
  - farm *i* was infectious at time, *t*
  - farm *i* infected farm *j*
- Rank all possible genomic networks (MRCA/TCS) by ‘epi’ likelihood score



Transmission risk windows



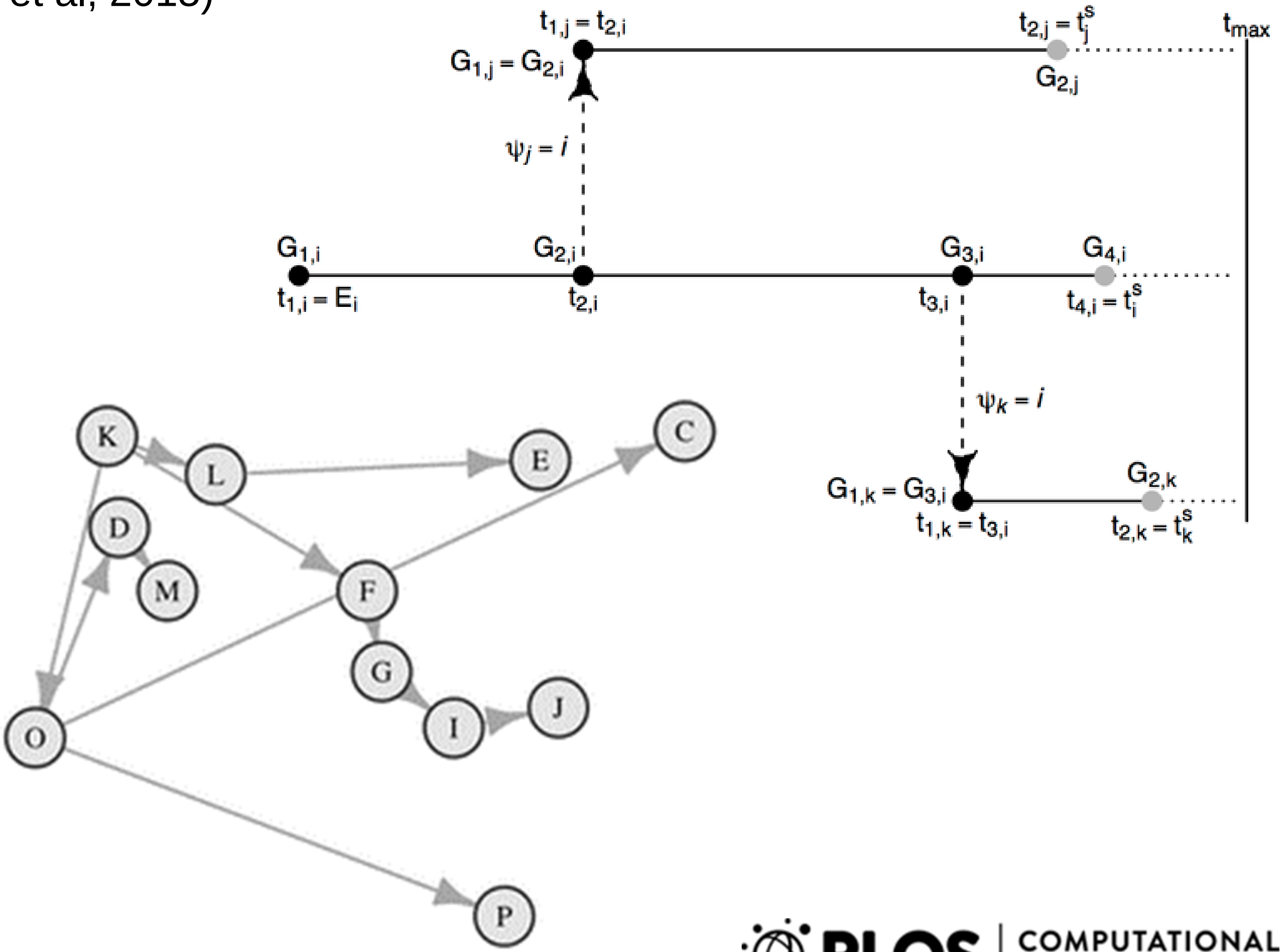
Transmission Pathways of Foot-and-Mouth Disease Virus in the United Kingdom in 2007 (Cottam et al 2008b)



http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1000050

PLOS | PATHOGENS

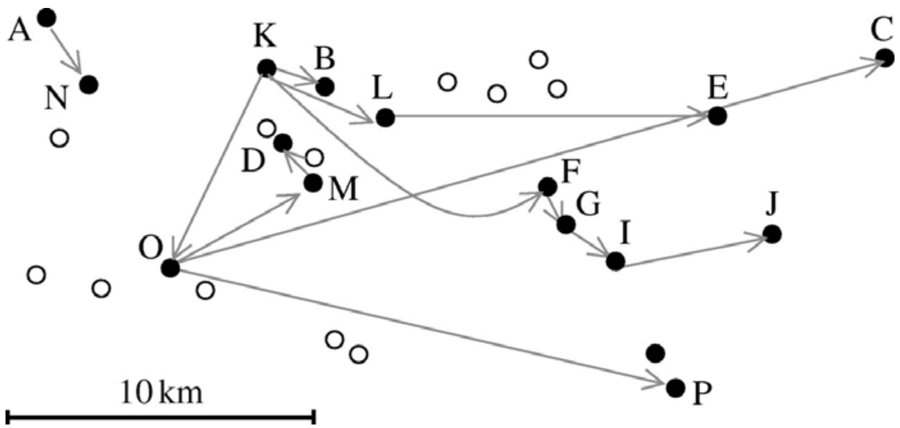
A Systematic Bayesian Integration of Epidemiological and Genetic Data
(Lau et al, 2015)



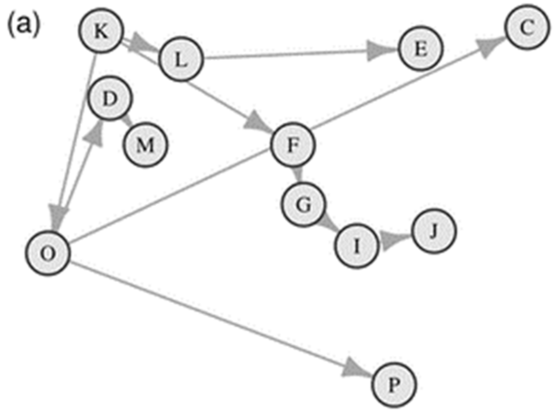
http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1004633

PLOS | COMPUTATIONAL BIOLOGY

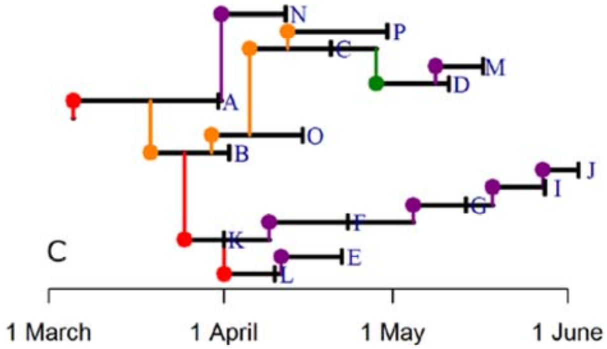
Cottam et al, 2008a



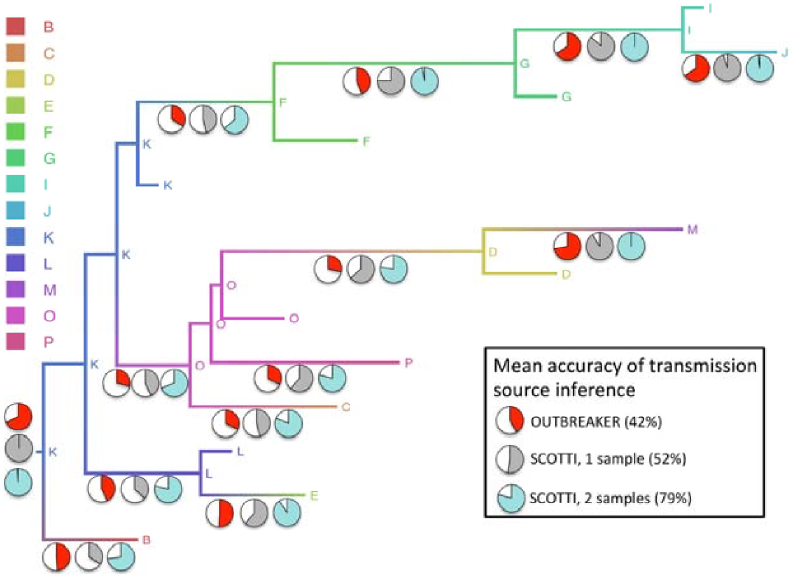
Lau et al, 2015



Klinkenberg et al, 2016 (Phybreak)



De Maio et al, 2016
(SCoTTi v Outbreaker)

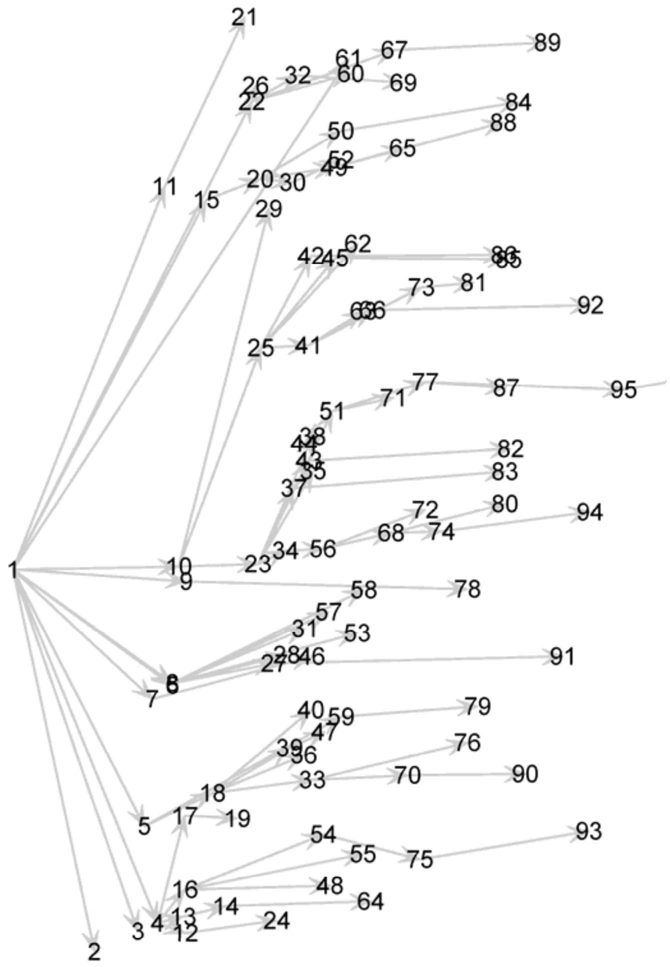


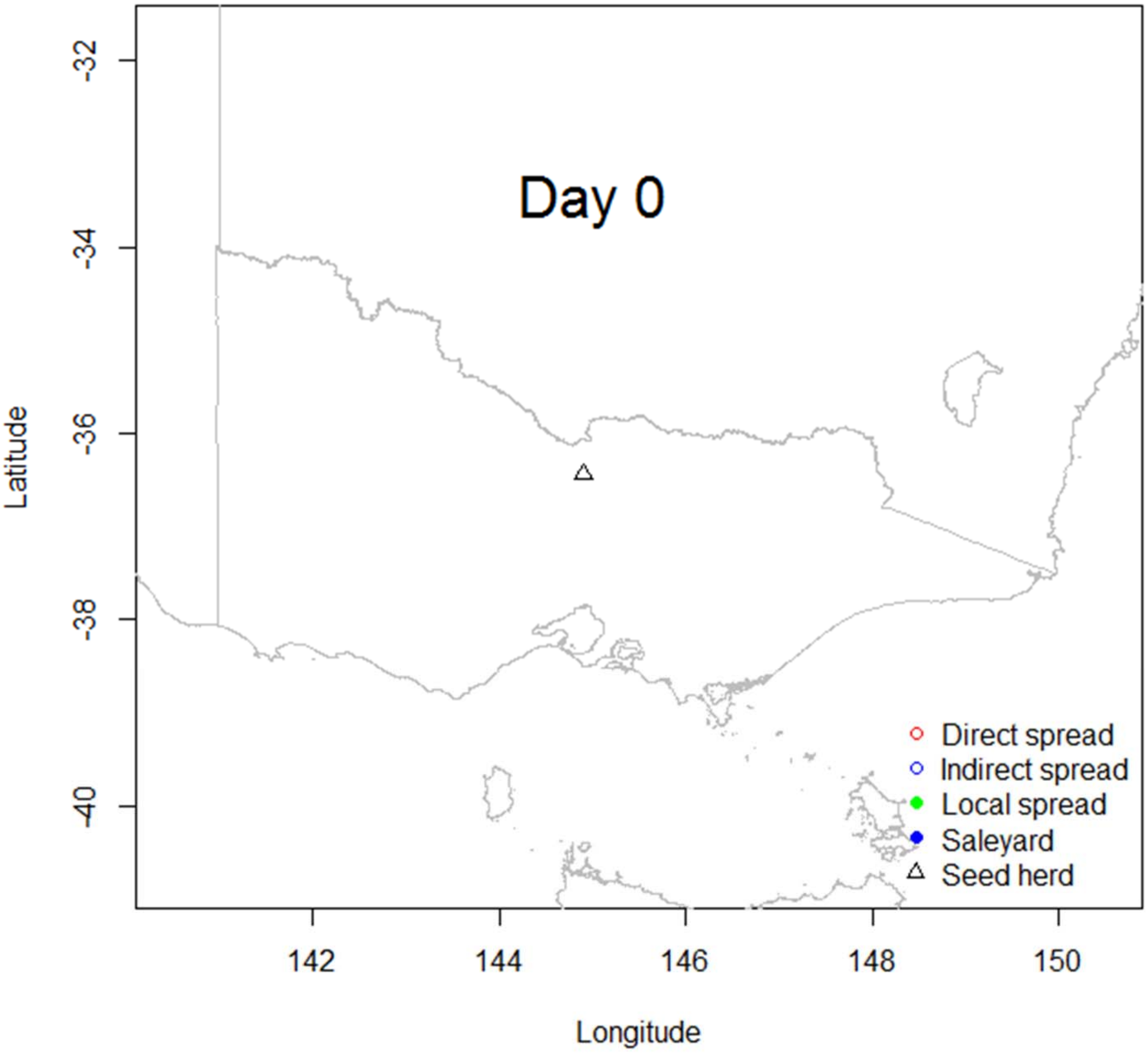
Simulated with model considerably different to both SCOTTI and Outbreaker

Methods: Outbreak simulations

Australian Animal Disease Spread (AADIS) hybrid model

(Bradhurst et al, 2015)





Methods: Genomic data simulations

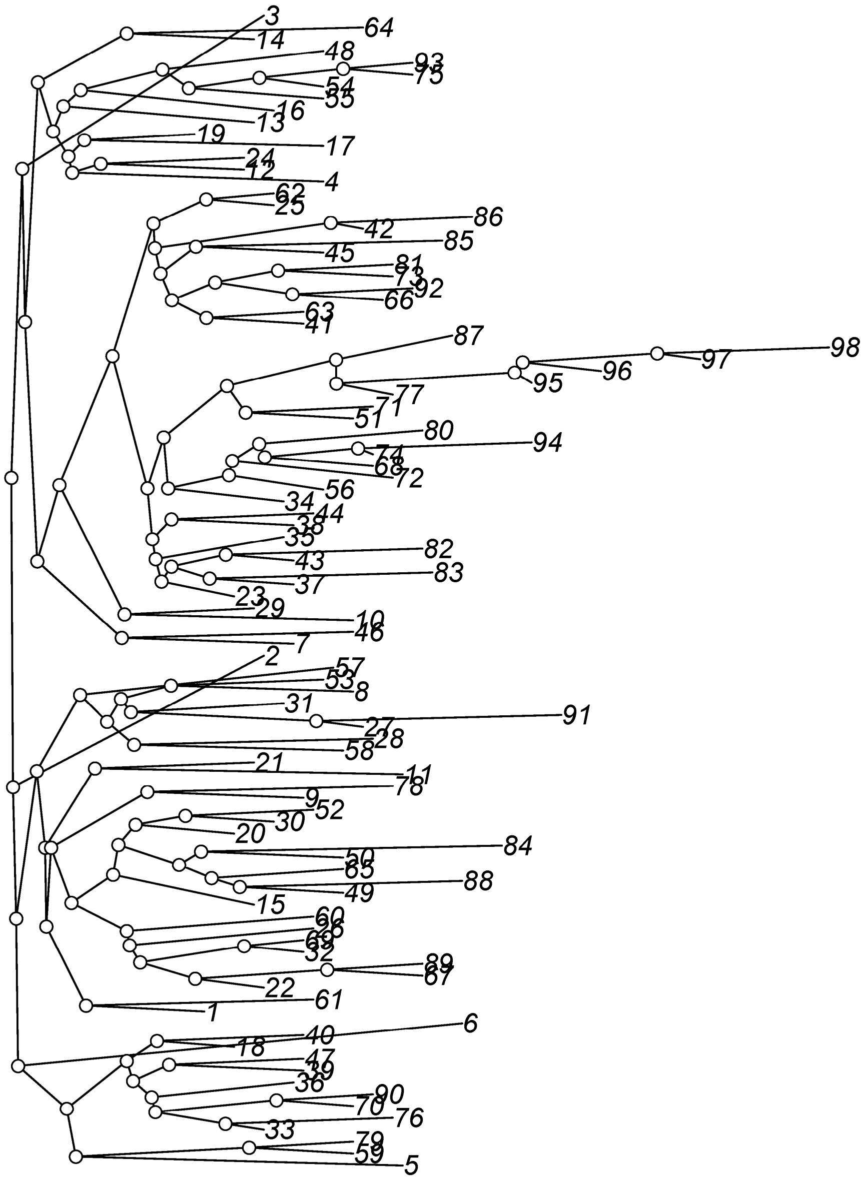
Phylogenies simulated: with VirusTreeSimulator

Sequences simulated: along phylogenies with Seq-Gen

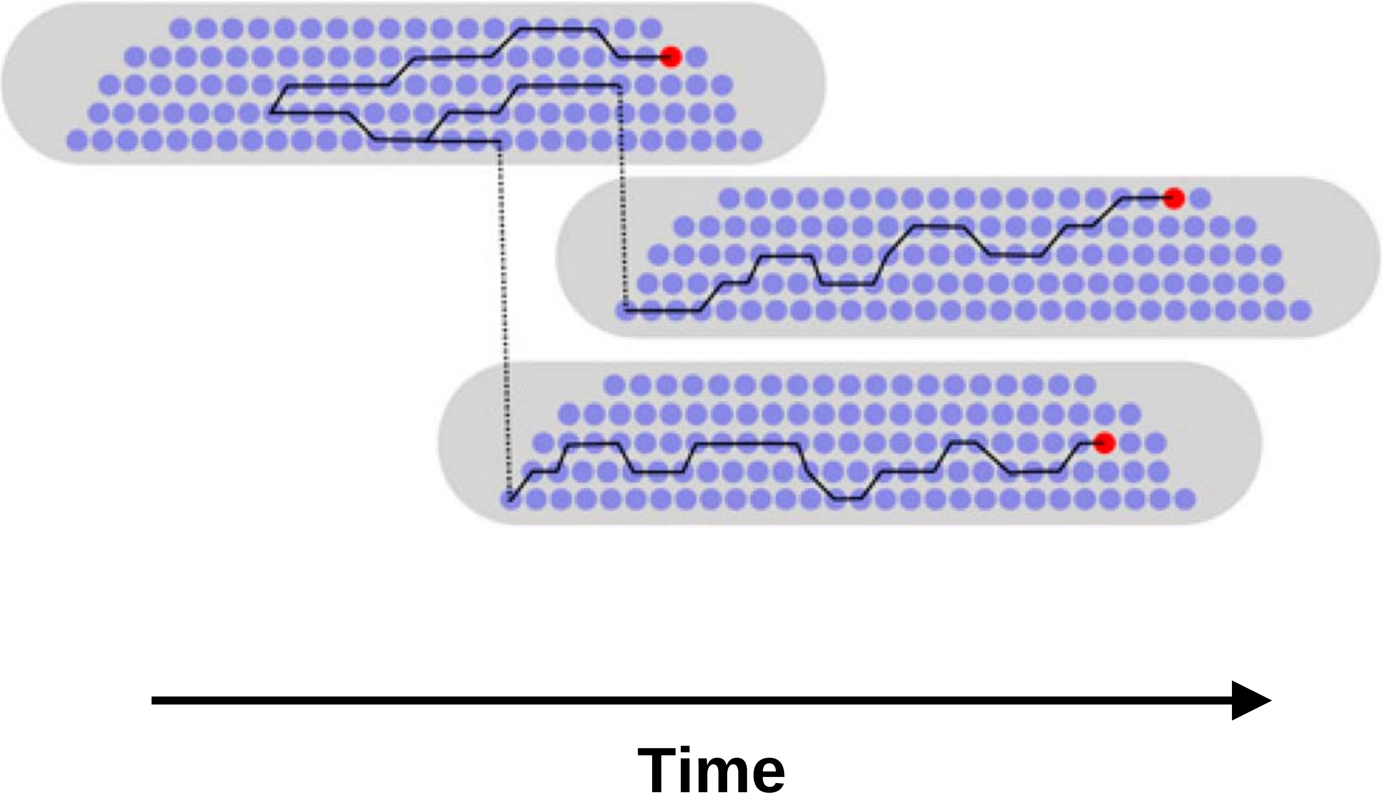
Kimura 2-parameter model (K80)

mutation rate (2.076 × 10^{-5} changes per site per day) and TS/TV (7.61) based on FMD UK 2001

(Cottam et al., 2006, 2008; Juleff et al., 2013)

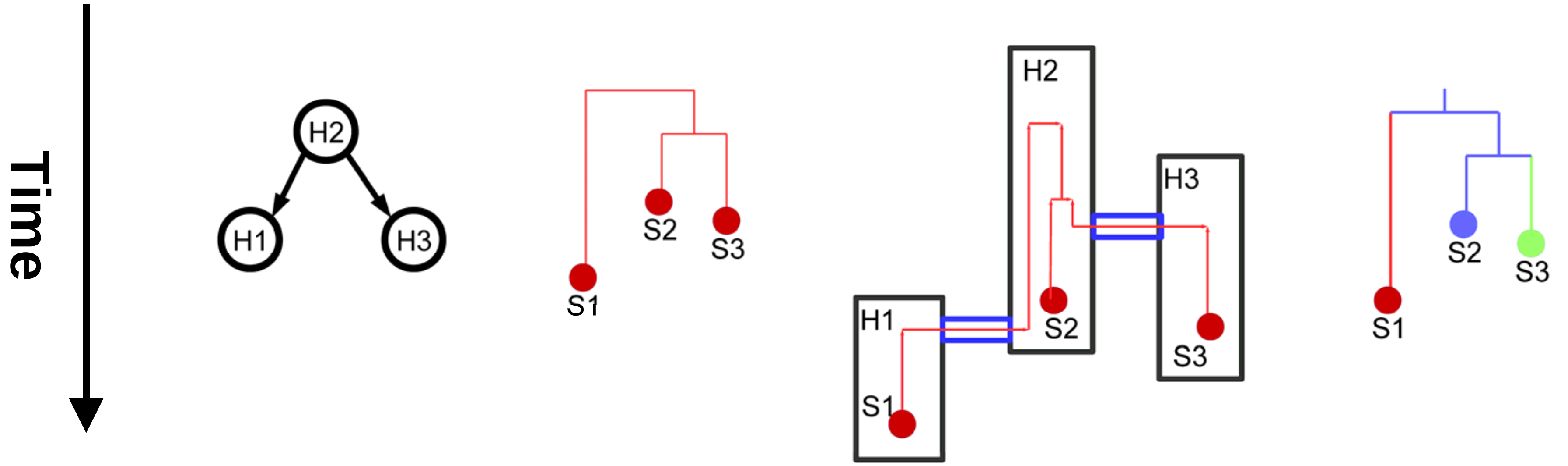


Methods: Inference issues



Ypma, et al (2013) Genetics

Methods: Inference issues



Transmission (“beanbag”) tree

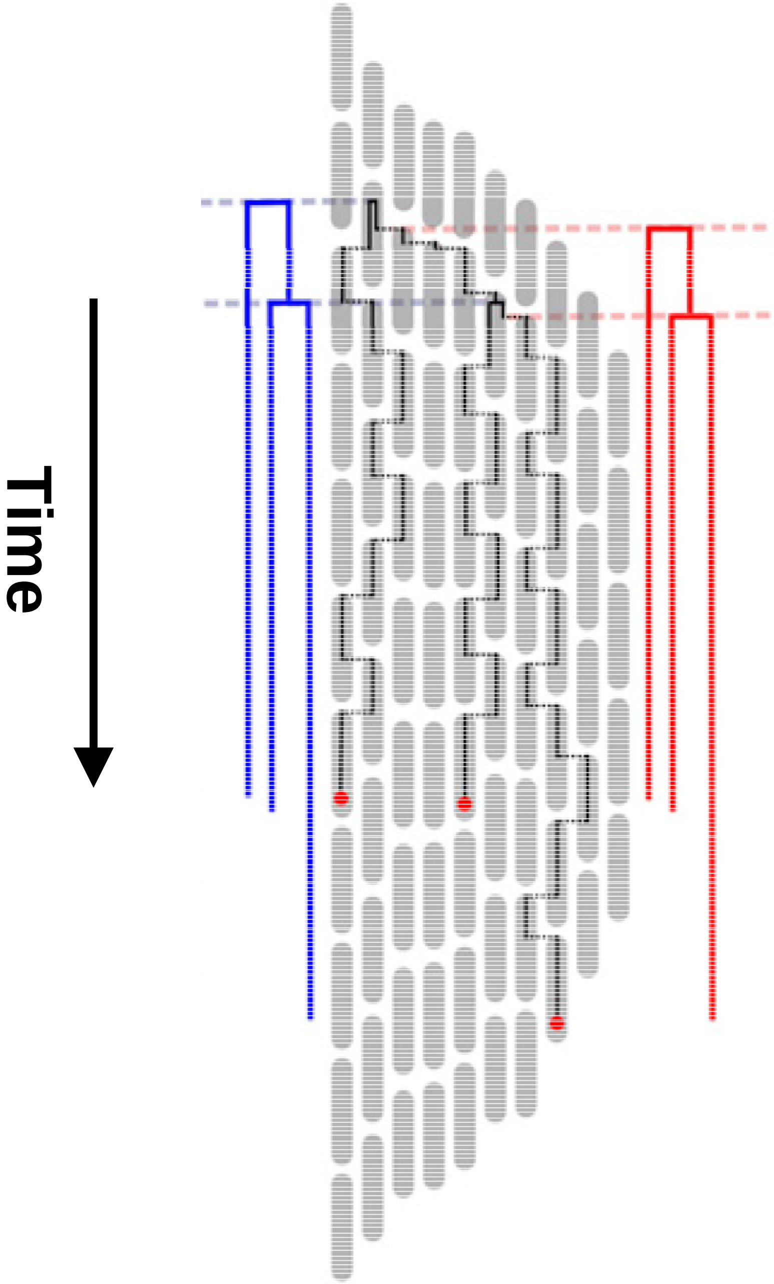
Phylogenetic tree

Nested transmission & phylogenetic tree

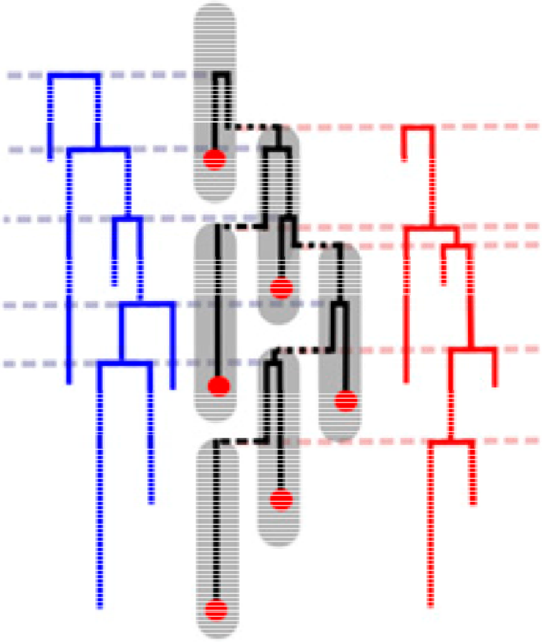
Annotated phylogenetic (“Maypole”) tree

Adapted from De Moaio, et al (2016) PLoS Comp Biol

Sparse sampling



Dense sampling

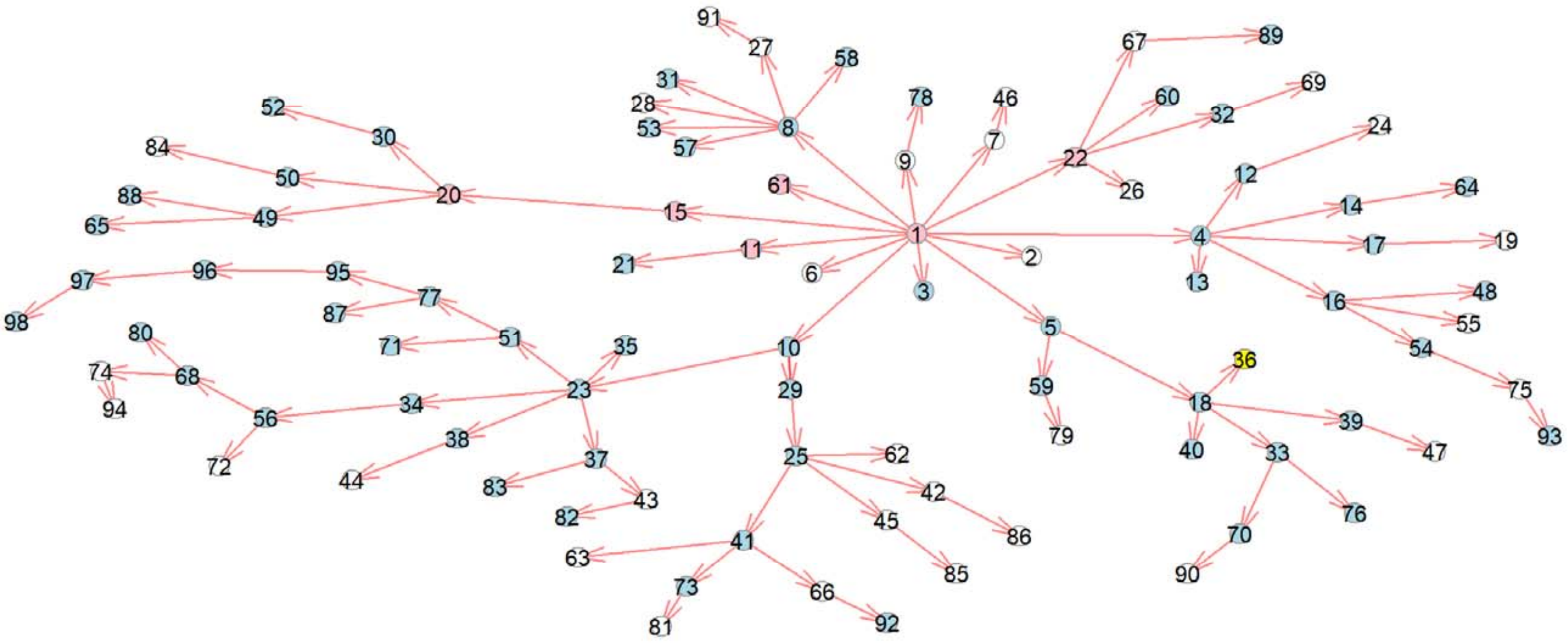


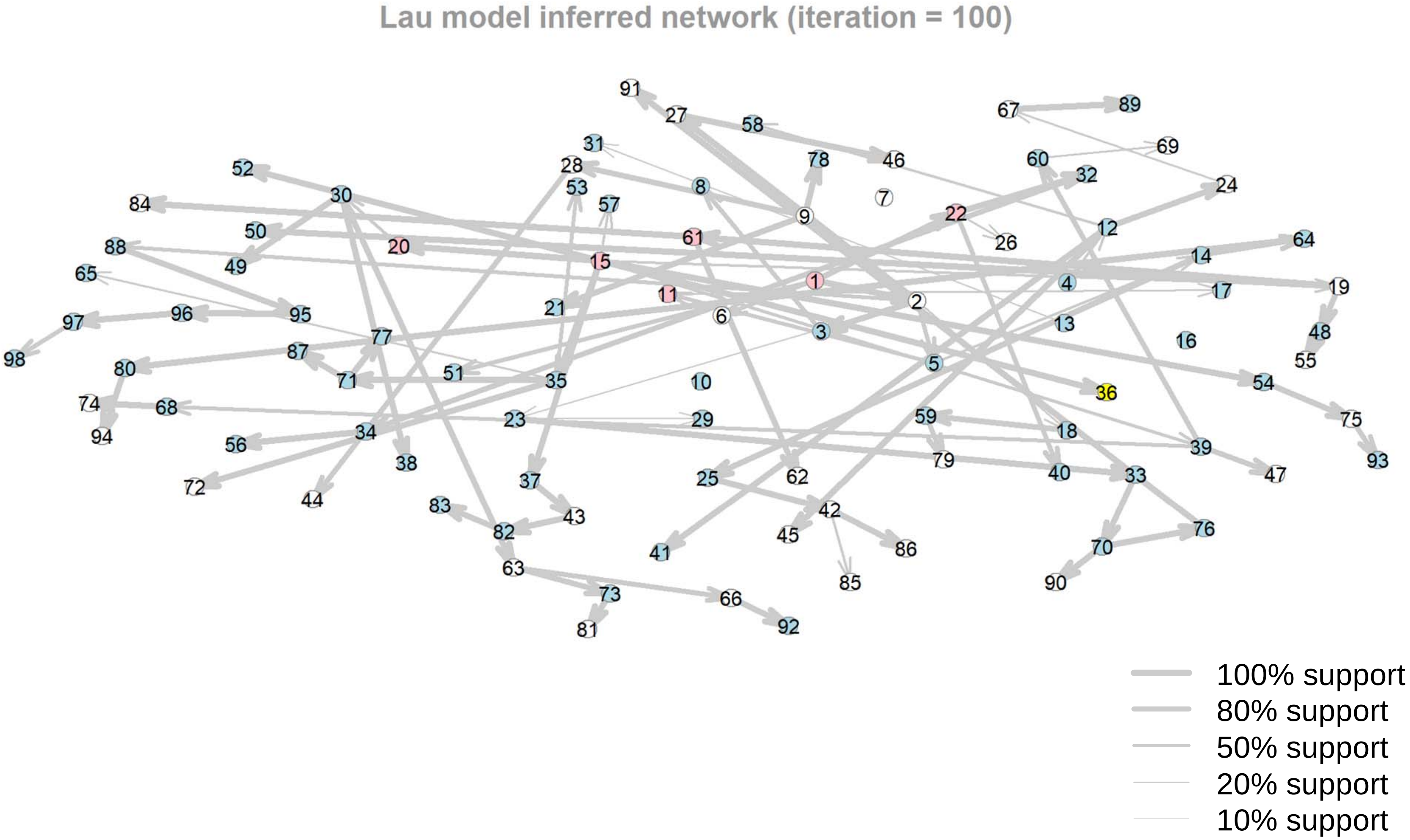
phylogenetic tree (blue)

transmission network (red)

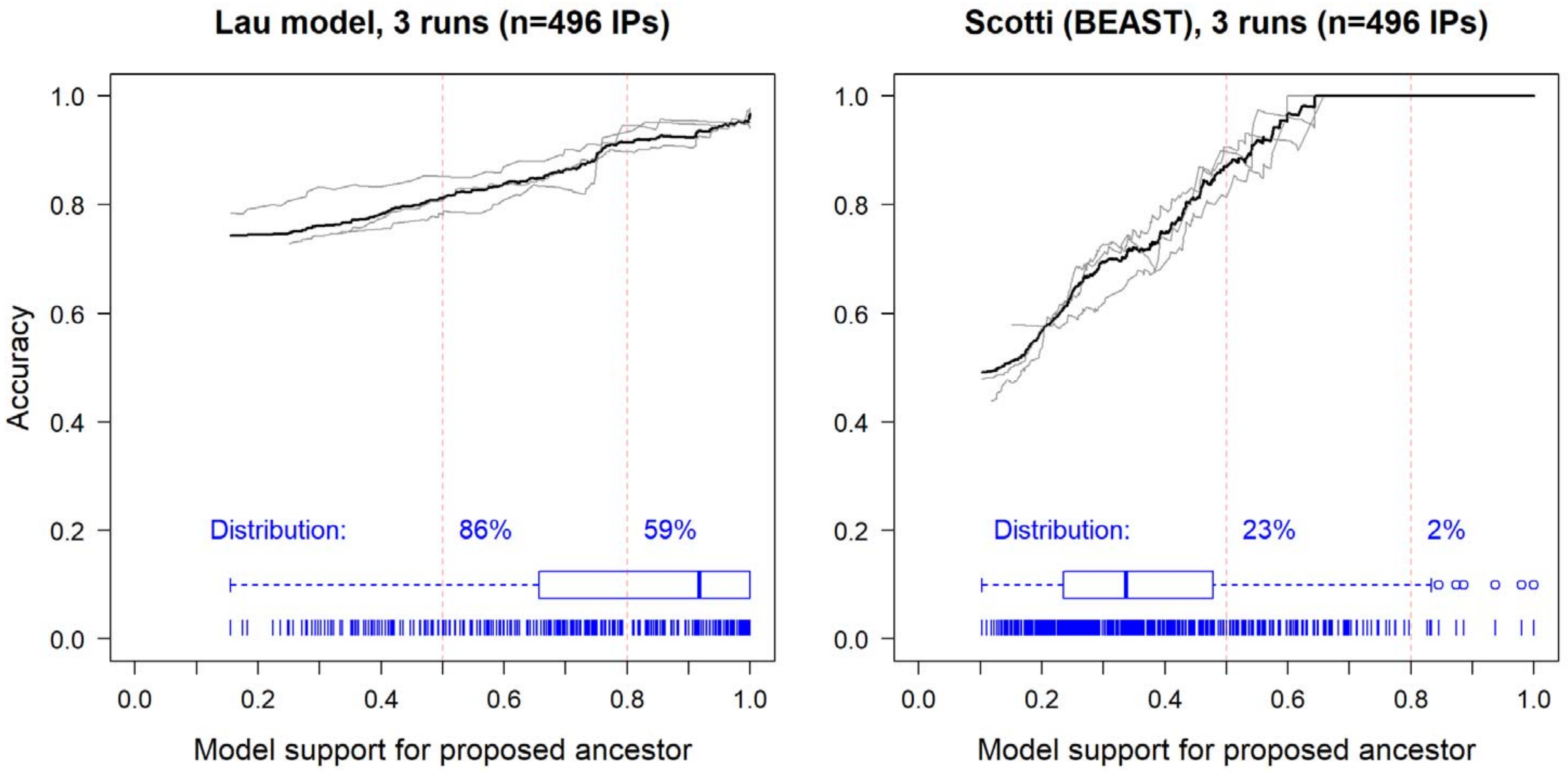
Adapted from Ypma, et al (2013) Genetics

True network in arbitrary space




Lau model inferred network (iteration = 100)
91
27
58
67
89
31
78
46
60
69
52
28
53
57
8
7
32
24
84
30
9
22
12
50
61
26
64
88
20
15
14
49
65
1
4
19
11
21
2
17
97
96
95
6
77
3
13
48
16
98
87
5
55
80
71
51
35
10
36
54
74
68
23
29
59
75
94
34
18
56
39
38
79
40
33
93
47
72
37
25
62
44
83
43
42
76
82
45
86
70
41
63
85
90
73
66
81
92
100% support
80% support
50% support
20% support
10% support

Results: Comparison of accuracy and confidence



Results: Comparisons (summary)

Crude mean accuracy, 3 runs (n=98, 100, 298)

Model	100% IPs sampled	50% IPs sampled
Just reading phylogeny	21%	na
Cottam	54%	na
Cottam (modified)	**70%**	na
Lau	**76%**	**61%**
SCOTTI	49%	na
Phybreak	49%	na
Outbreaker	49%	6%
Outbreaker2	34%	0%

Note: ‘na’ = method doesn’t account for missing sequence data

Results: Comparisons (summary)

>50% support: mean accuracy, 3 runs (n=98, 100, 298)

Model	100% IPs sampled	50% IPs sampled
Just reading phylogeny	na	na
Cottam	**76%** (0.18)	na
Cottam (modified)	na	na
Lau	**81% (0.86)**	**65% (0.49)**
SCOTTI	**87%** (0.23)	na
Phybreak	**81%** (0.40)	na
Outbreaker	53% (0.88)	0% (0.07)
Outbreaker 2	47% (0.12)	na

(proportion of IPs > this level of support for inferred ancestor)

Note: ‘na’ = method doesn’t account for support OR missing sequence data

Results: Comparisons (summary)

>80% support: mean accuracy, 3 runs (n=98, 100, 298)

Model	100% IPs sampled	50% IPs sampled
Just reading phylogeny	na	na
Cottam	90% (0.10)	na
Cottam (modified)	na	na
Lau	**91% (0.59)**	**82% (0.19)**
SCOTTI	**100% (0.02)**	na
Phybreak	**95% (0.18)**	na
Outbreaker	63% (0.64)	0% (0.05)
Outbreaker 2	48% (0.07)	na

(proportion of IPs > this level of support for inferred ancestor)

Note: ‘na’ = method doesn’t account for support OR missing sequence data

Conclusions

- We all know to read the assumptions of modelling papers closely, **read the validation section very closely too**

- A number of transmission models benchmarked
- Lau *et al*'s model reasonably fit for purpose
- SCOTTI (BEAST) & Cottam (modified) good backups

- Further research
  - Applying Lau's model on more actual outbreak datasets
  - Test more iterations of sequence generation
  - Extending models: contact-tracing data, within-farm repeated sampling, farm covariates, within-host genomic models

THE UNIVERSITY OF MELBOURNE

FACULTY OF VETERINARY & AGRICULTURAL SCIENCES

Thank you … questions

Australian Government
Australian Research Council

NARO 農研機構
National Agriculture and Food Research Organization

APCAH
Asia Pacific Centre for Animal Health

Australian Government
Department of Agriculture and Water Resources

cebra
Centre of Excellence for Biosecurity Risk Analysis

OIE
The University of Melbourne

OIE Collaborating Centre
Diagnostic Test Validation Science

Acknowledgements

- This research was supported by an Australian Research Council Discovery Early Career Researcher Award (project number DE160100477)
- Components of this research were undertaken on the Victorian Life Sciences Computation Initiative (VLSCI) Peak Computing Facility (grant number VR0277)
- NARO, Viral Disease and Epidemiology Research Division, National Institute of Animal Health, Japan.
- Exotic Diseases Research Station, NARO, Kodairo, Japan
- Graeme Garner (Australian Govt, DAWR)
- Asia-Pacific Centre for Animal Health (APCAH): Glenn Browning, James Gilkerson, Carol Hartley
- Max Lau, Don Klinkenberg, Chris Jewell, Thibaut Jombart, Finlay Campbell, Sebastián Duchêne
- Soren Alexandersen, Anthony Chamings (Geelong Centre for Emerging Infectious Diseases)

Vet Epi @ Melbourne: http://fvas.unimelb.edu.au/veam