Identifying spatiotemporal dynamics of Ebola in Sierra Leone using virus genomes

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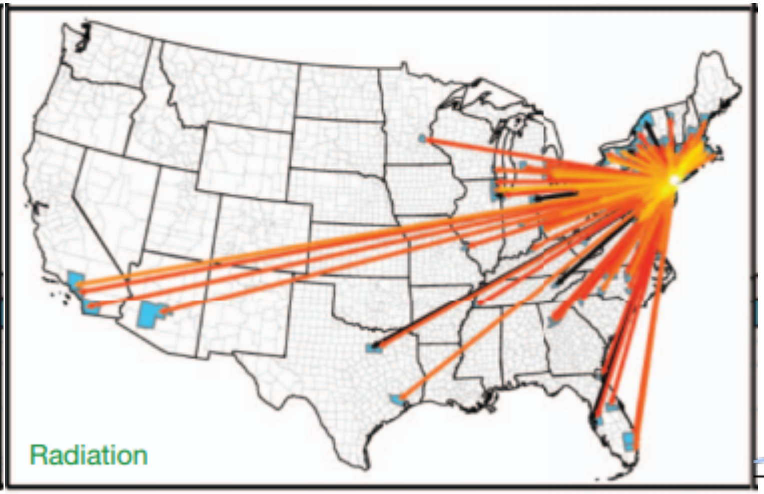
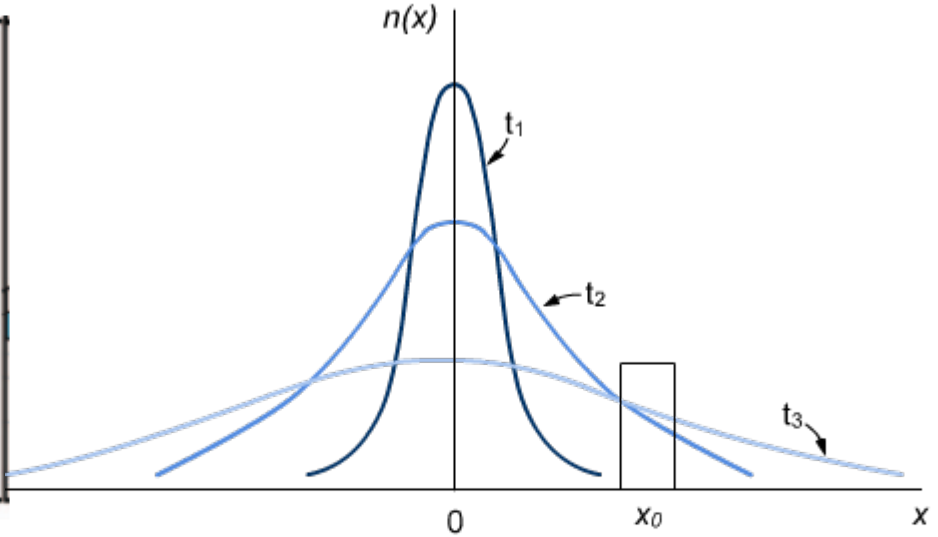
INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

IDM Symposium 2017

Modeling human mobility using physics analogies





Gravity

Ravenstein, E.G.,
J Roy Stat Soc, (1889)

Truscott and Ferguson,
PLoS Comp Bio (2012)

Radiation

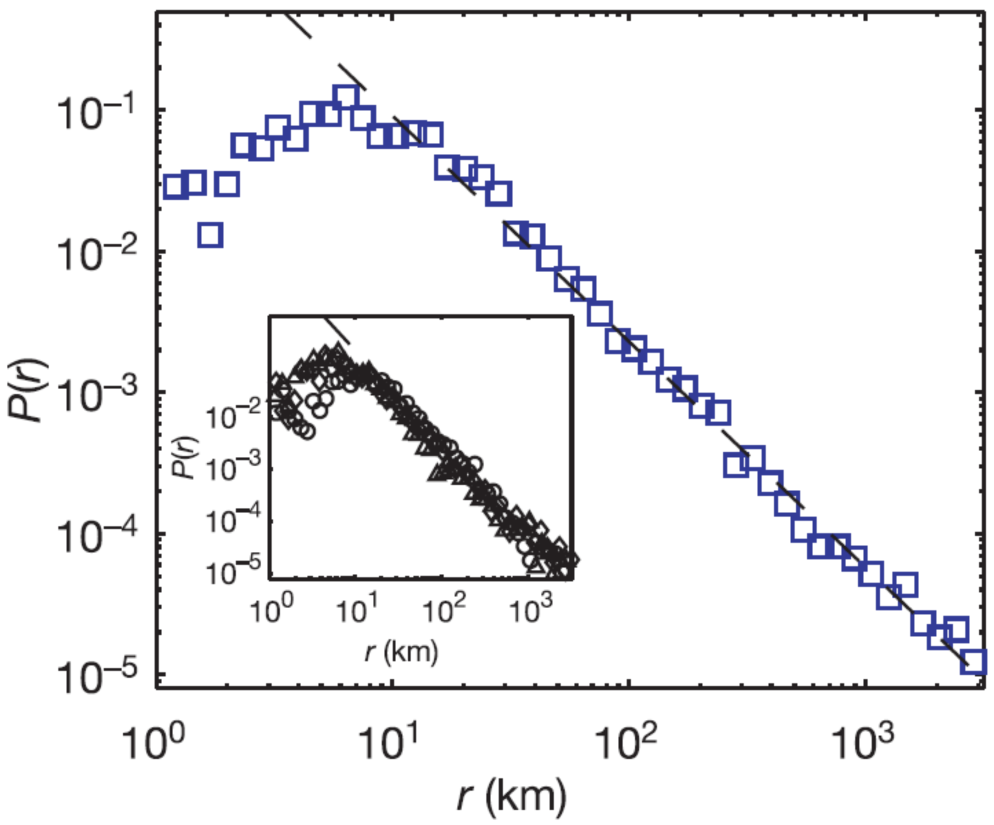
Simini *et al.* Nature (2012)

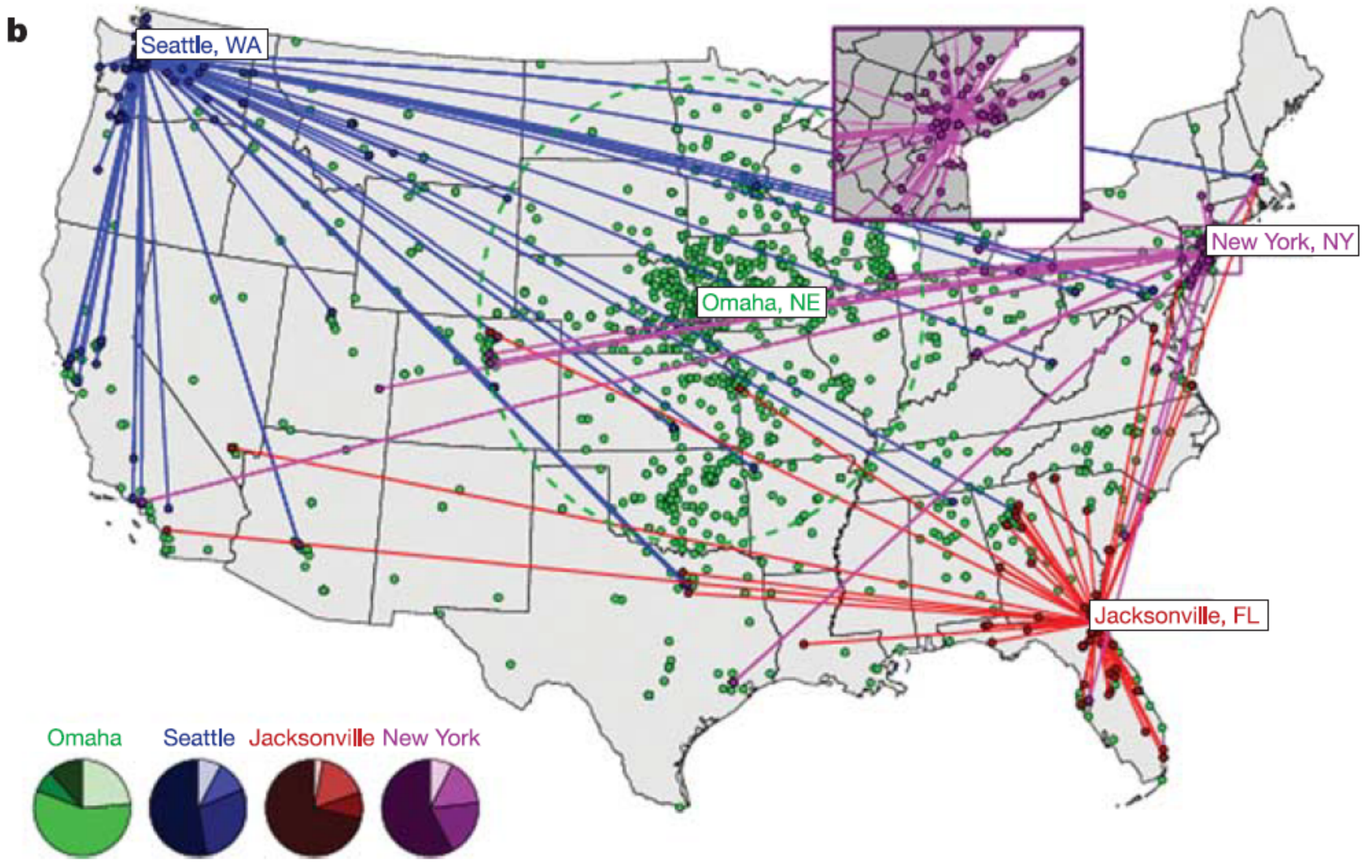
Random walks

Rhee *et al.* IEEE Trans. Networking (2012)

Tracer of human mobility: US banknote random walks

Empirical power law statistics:
Lévy flight: heavy-tailed random walk

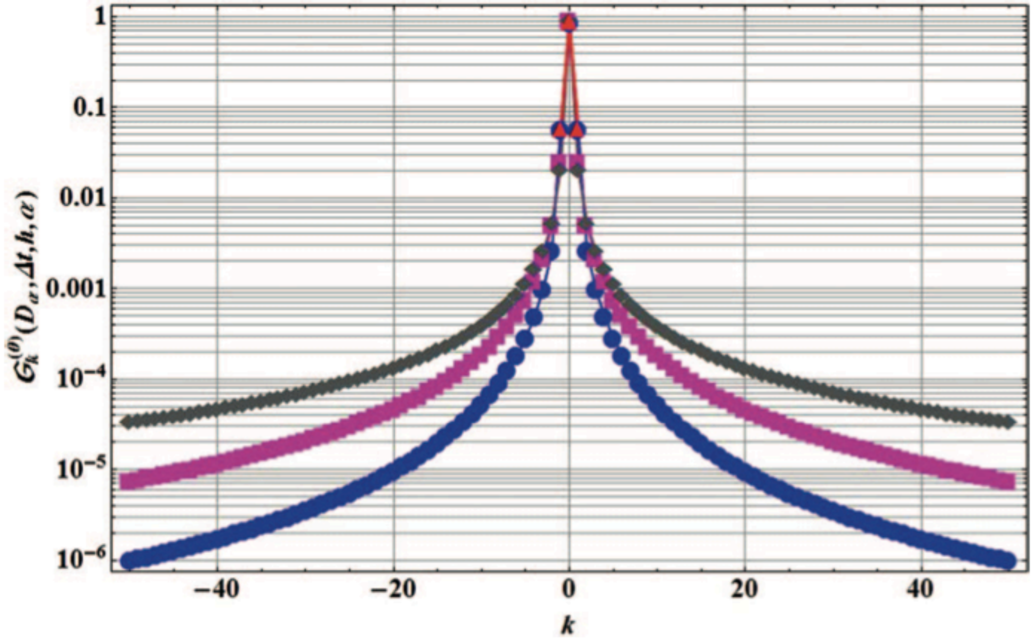




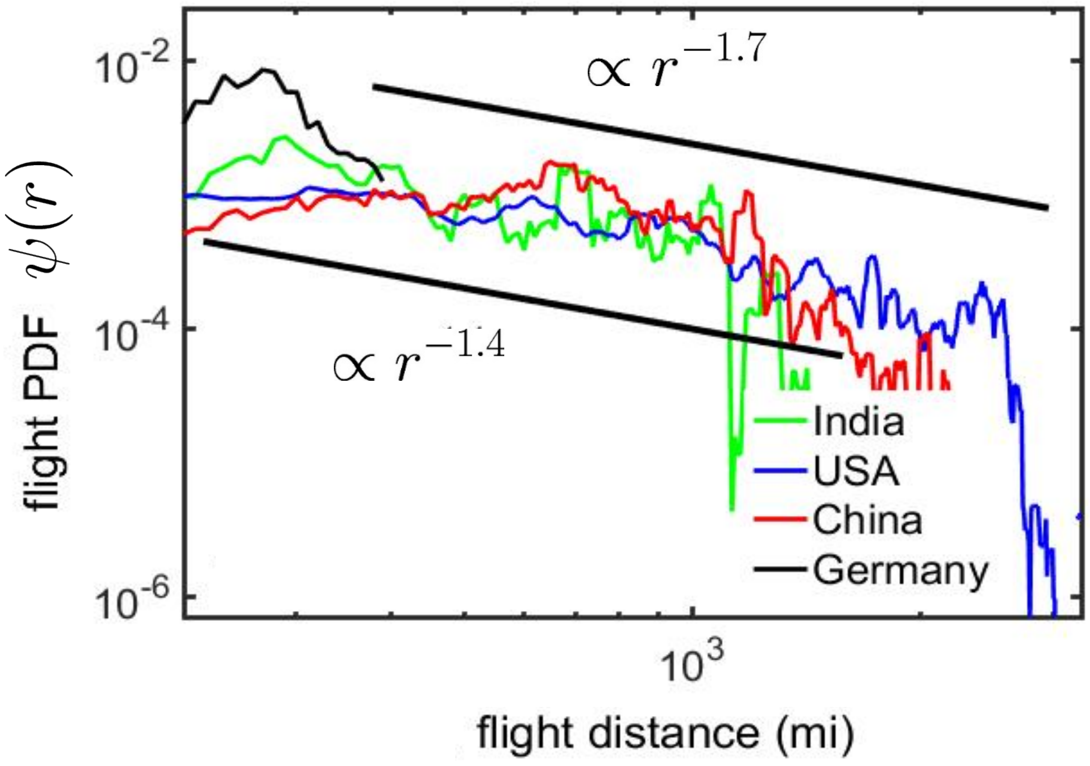
Brockmann, Hufnagel and Geisel, Nature 2006

Lévy flight is a generalization of diffusion

$$\frac{\partial \mathfrak{G}}{\partial t} = D_\alpha \frac{\partial^\alpha \mathfrak{G}}{\partial |x|^\alpha}$$



Bayati, J Chem. Phys. 2013



Gustafson, Bayati, Eckhoff
Frontiers in Ecology and Evolution, April 2017

We used space-fractional diffusion as a proxy for commercial air traffic to model outbreak dynamics

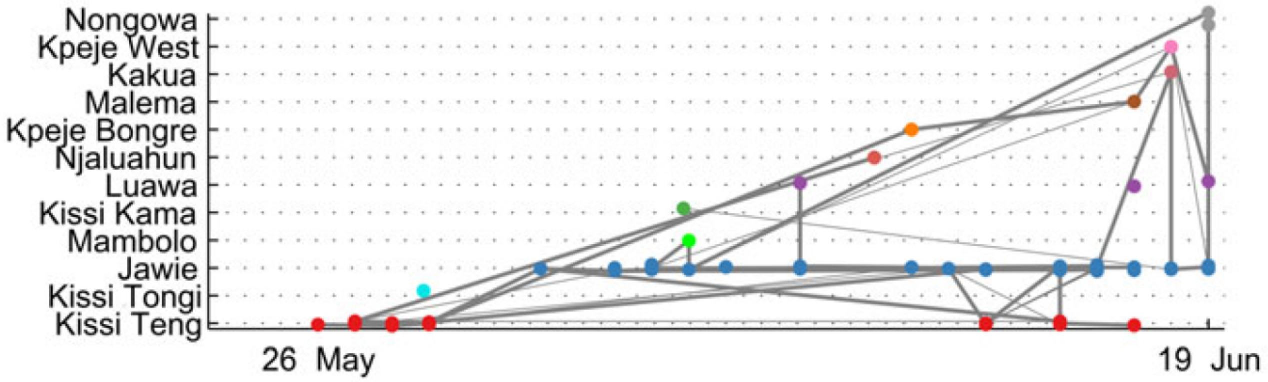
Tracking Ebola virus in Sierra Leone (2014-2015)

Infections as a tracer of human mobility

Stochastic process

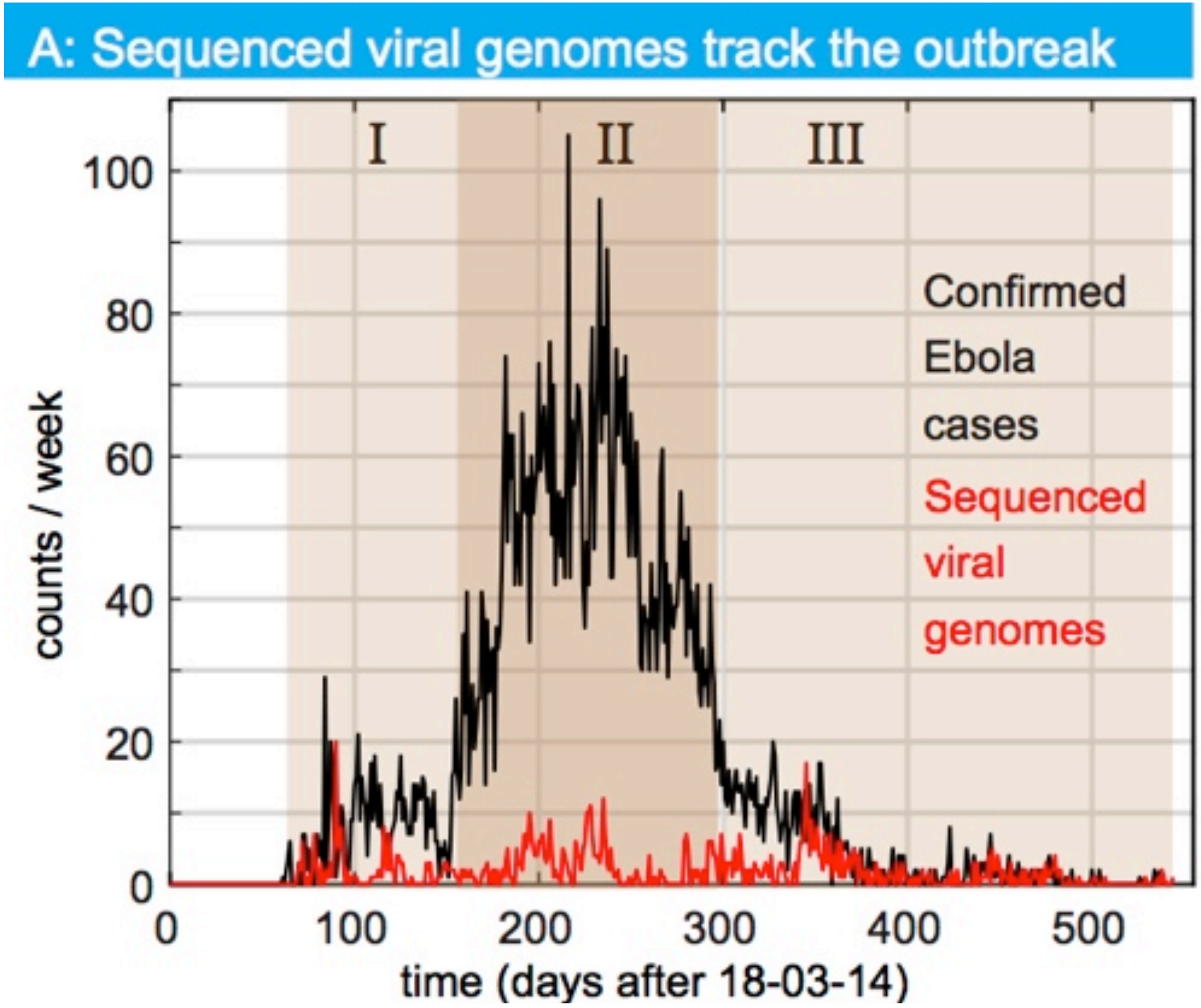
Human behavior is dynamic

Population landscape is inhomogeneous



Famulare and Hu, Int. Health (2015)

Need: a tool to decide which spatial model explains the epidemic dynamics



Focus on Sierra Leone

Sequenced cases tracked the course of all cases

Peak of cases in Freetown in December 2014

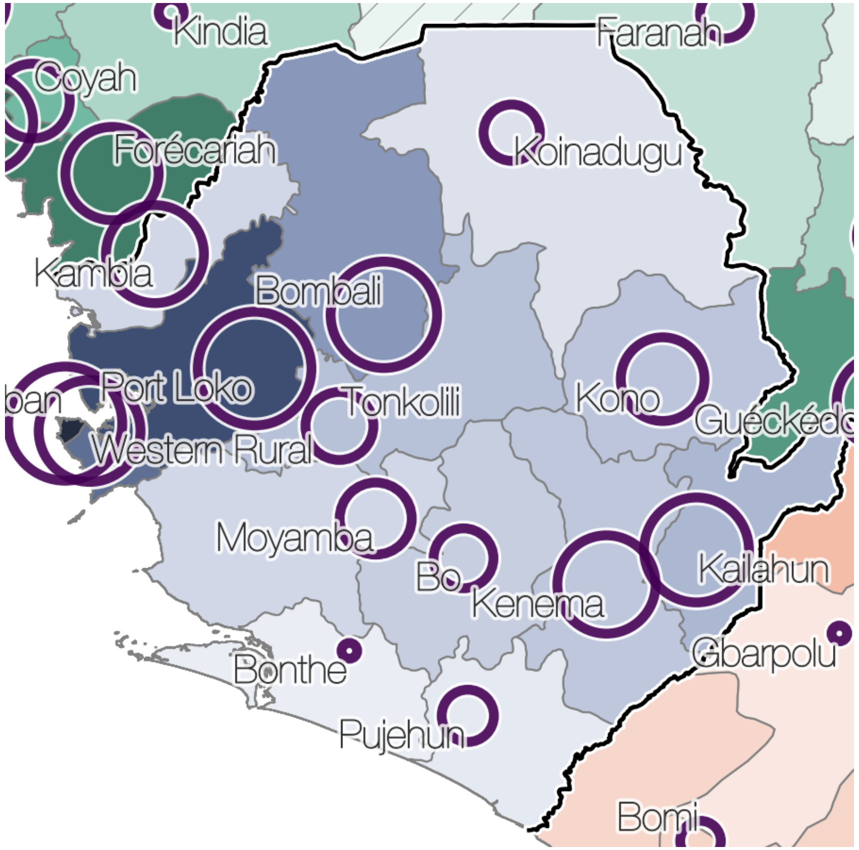
“Surge” of interventions reduced transmission in Freetown

Dudas *et al.* Nature 2017
Fang *et al.* PNAS 2016

Using open data

FASTA file with >1000 district-localized genomes from Sierra Leone

Dudas *et al.* bioRxiv 2016



Sierra Leone data

Arias *et al.* Virus Evolution (2016)

554 sequences

Tong *et al.* Nature (2015)

175 sequences

Park *et al.* Cell (2015)

232 sequences

Gire *et al.* Science (2014)

78 sequences

Smits *et al.* Euro Surveillance (2015)

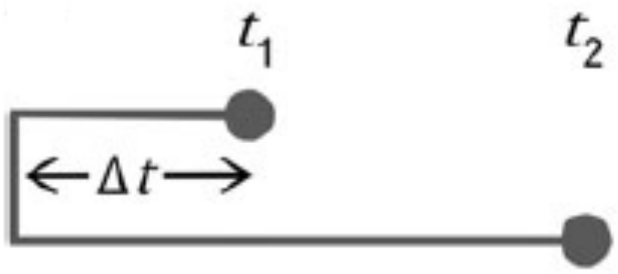
49 sequences

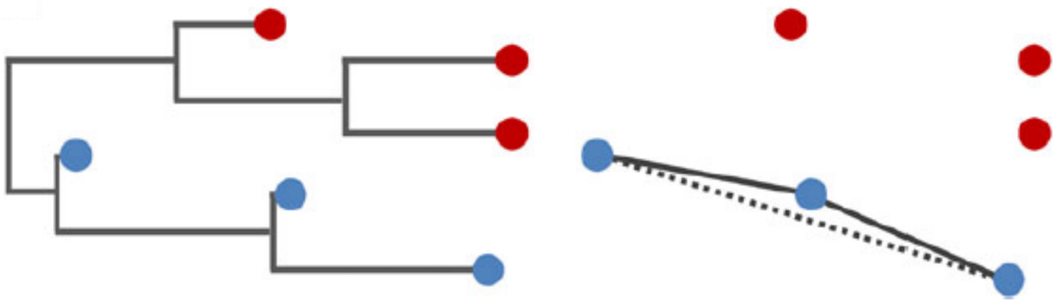
Partially observed transmission network (POTN): fast and adaptable

Famulare and Hu, Int. Health (2015)

Tree that only retains likely direct descendants

Good for finding transmission chains





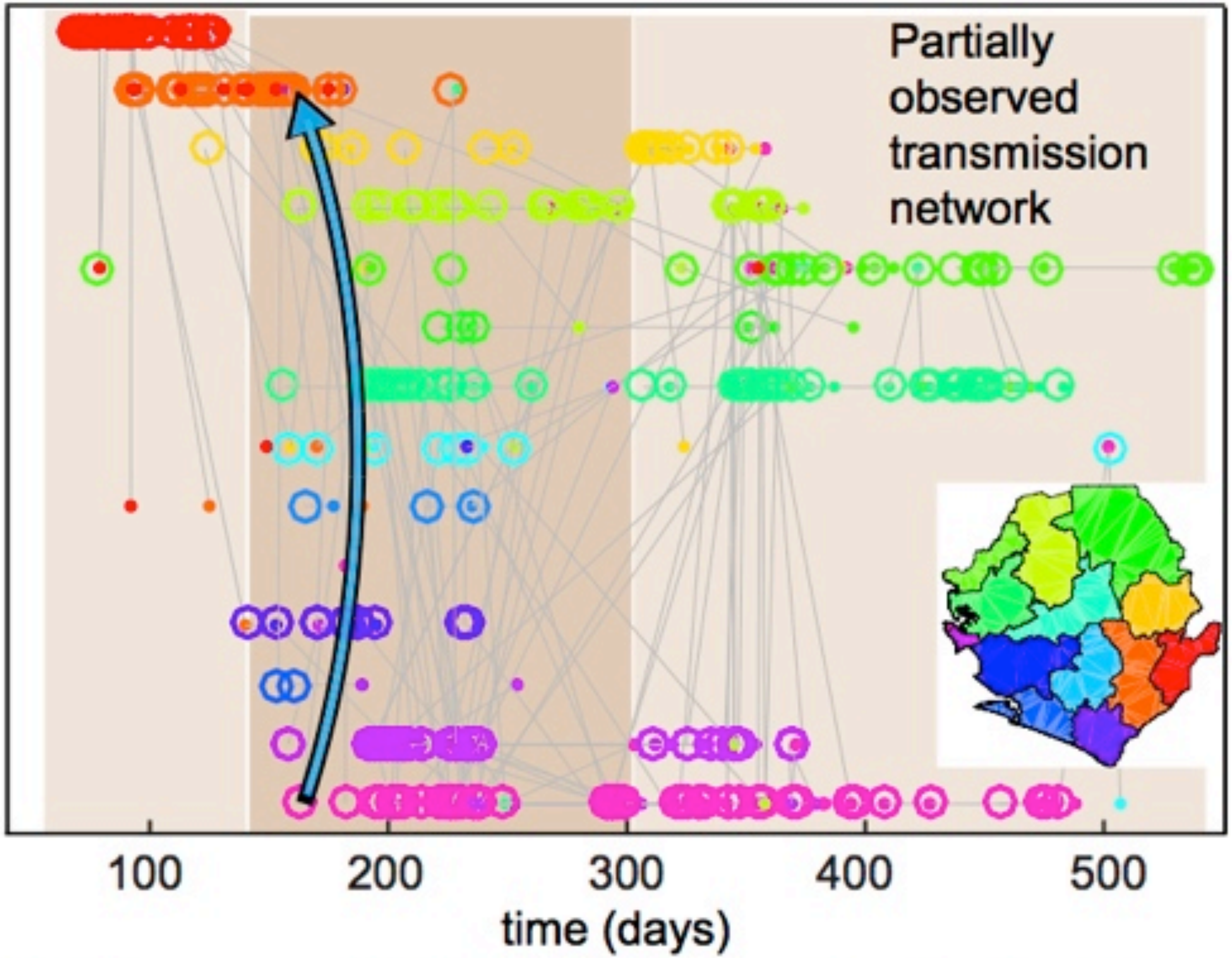
Likelihood ratio

$$H_{12} = \frac{L(\Delta t = 0 | t_1, t_2, d_{12}, \mu)}{L(\Delta t = \widehat{\Delta t} | t_1, t_2, d_{12}, \mu)}$$

Poisson mutation model

$$L(\Delta t | t_1, t_2, d_{12}, \mu) = \frac{(\mu(t_2 - t_1 + 2\Delta t))^{d_{12}}}{\Gamma(d_{12} + 1)} \exp(-\mu(t_2 - t_1 + 2\Delta t))$$

B: Genetic linkages infer spatial connectivity



POTN:

$\mu = 2\text{x}10^{-3}$ bp/site/year

Gire *et al.* Science 2016

Open circle: origin
Closed dot: destination

No inferred ancestors,
only likely descendants

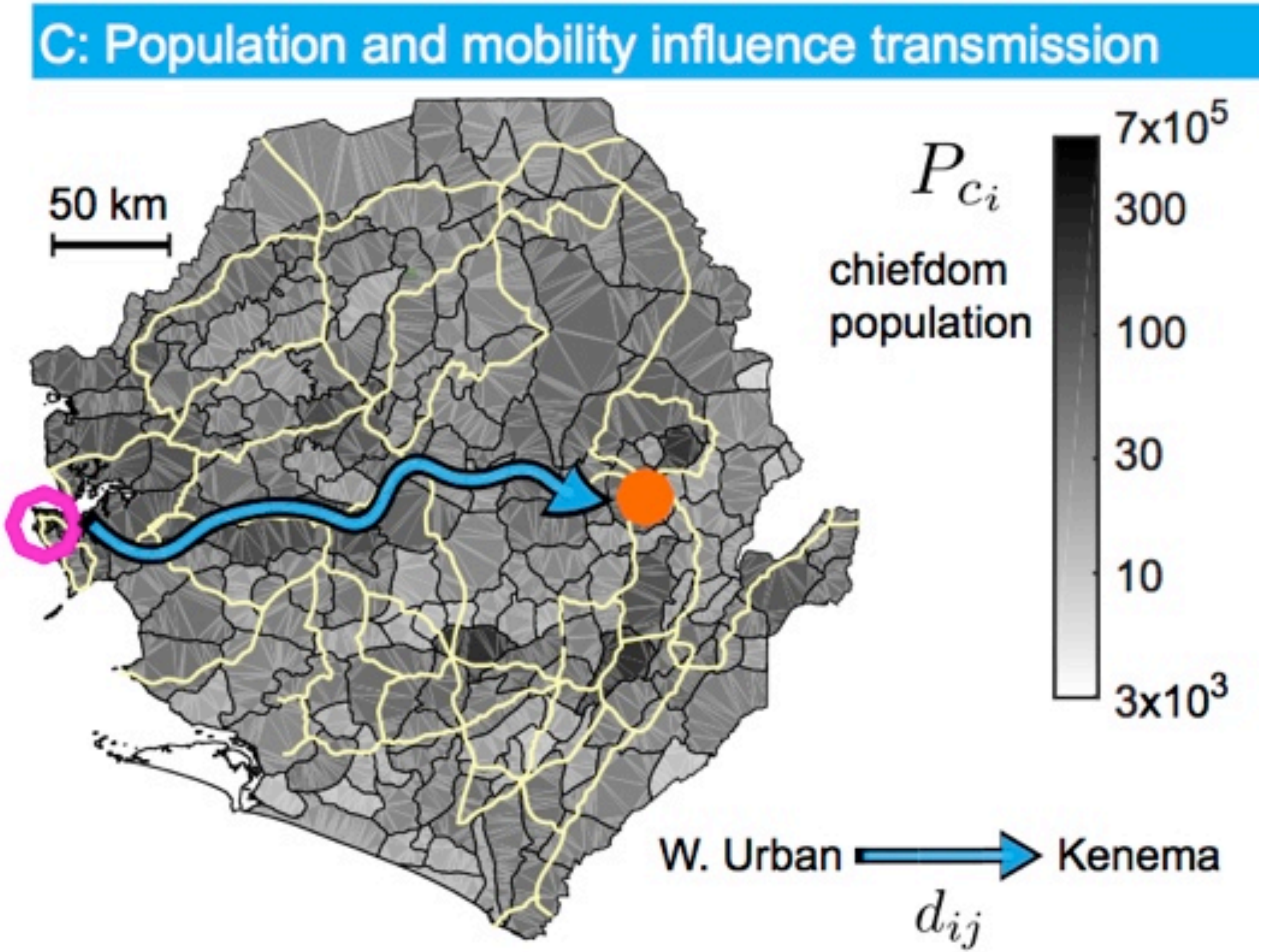
Pruned to shortest linkages
for plot

Our innovations

Lévy flight fitting for POTN transmission distances

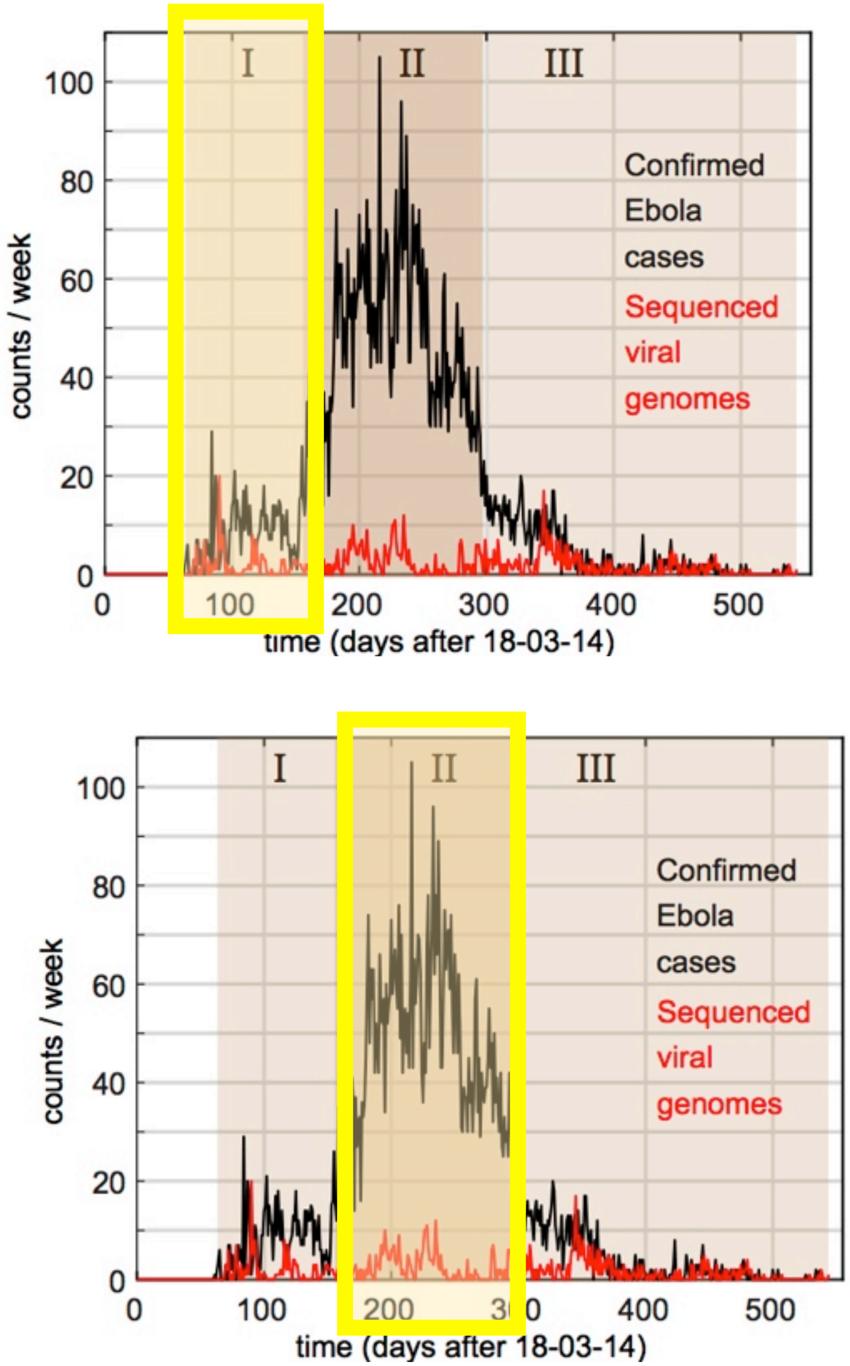
Dynamic spatial model selection using genetic linkages

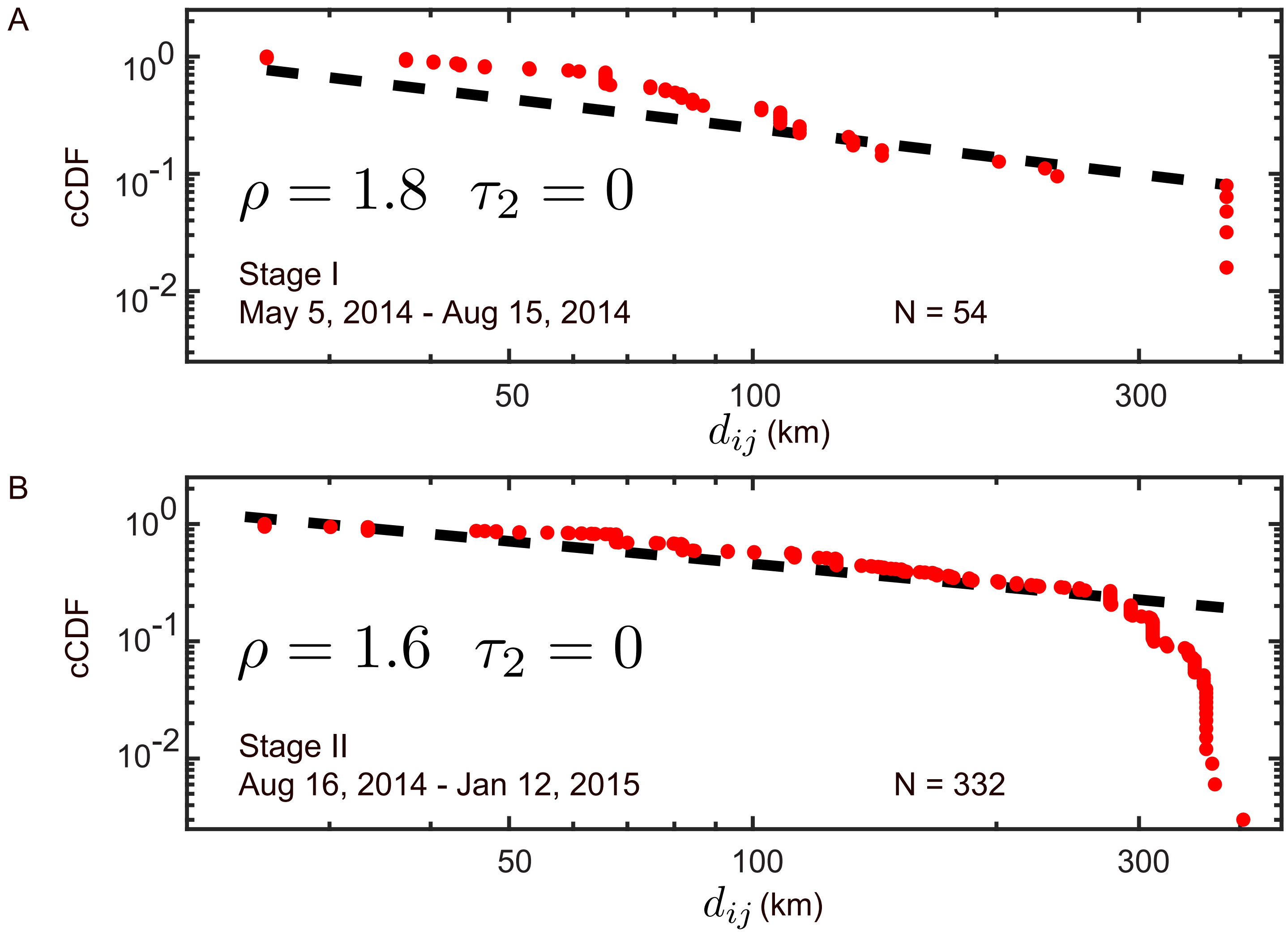
A decision tool for adaptable spatial pattern prediction



Driving distances from Google Maps API

Populations from 2010 census





Clauset, Shalizi, and Newman
SIAM Rev., 2009

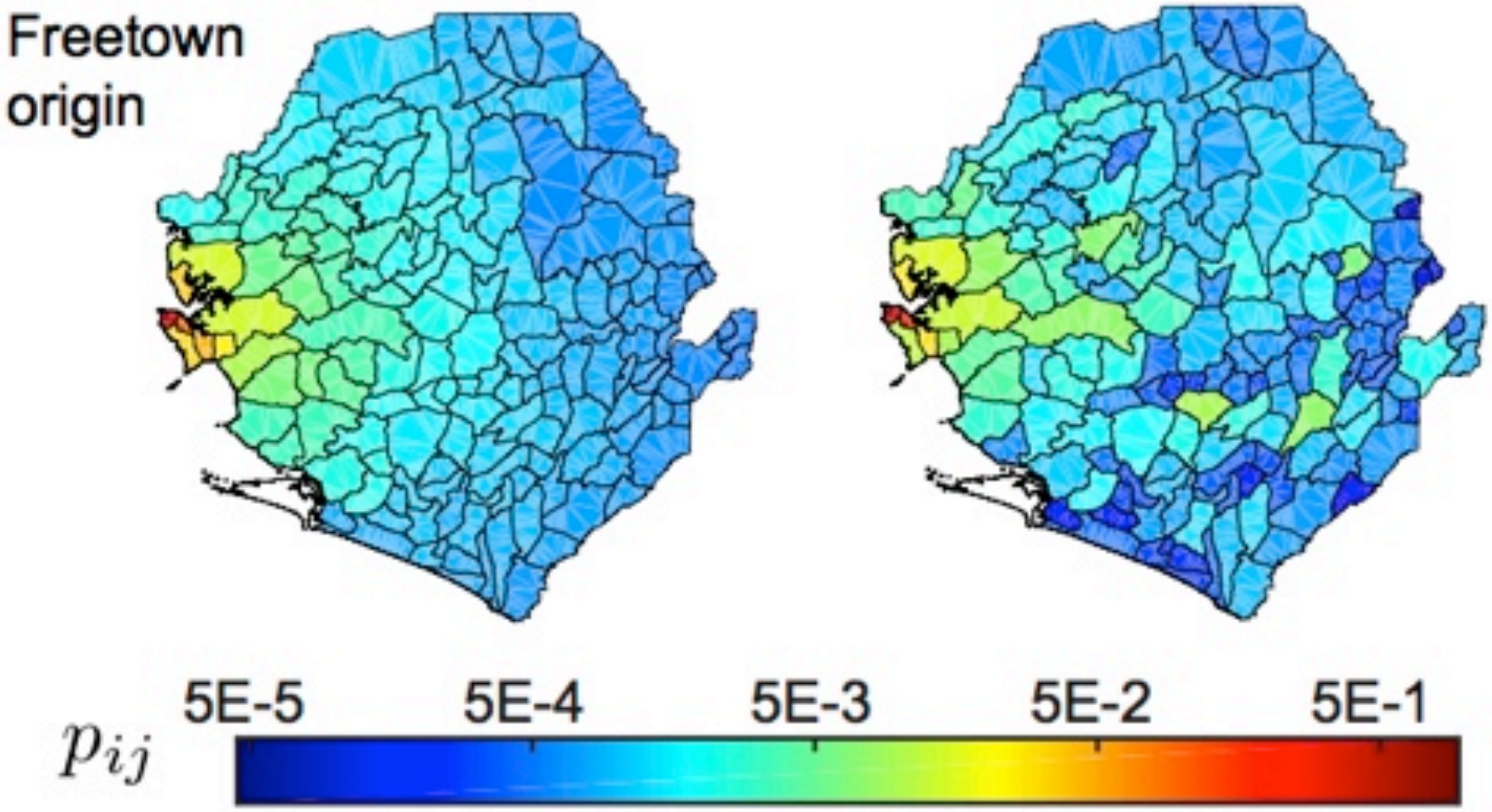
E: Disease mobility models are calibrated to data

Power law

$$p_{ij}^{L} = C_i^{L} \frac{1}{d_{ij}^{\rho}}$$

Gravity

$$p_{ij}^{G} = C_i^{G} \frac{P_{c_i}^{\tau_1} P_{c_j}^{\tau_2}}{d_{ij}^{\rho}}$$



Let the gravity model become a population-weighted random walk

Normalized origin by origin

50% chance of staying in origin chiefdom

Gravity model concentrates probability in population centers

Likelihood ratio for model selection

Power law

$$p_{ij}^L = C_i^L \frac{1}{d_{ij}^\rho}$$

Gravity

$$p_{ij}^G = C_i^G \frac{P_{c_i}^{\tau_1} P_{c_j}^{\tau_2}}{d_{ij}^\rho}$$

$$\mathcal{R}(\rho, \tau_2) = \sum_{\mathcal{S}} [ln(p_{ij}^G) - ln(p_{ij}^L)]/\sqrt{N}$$

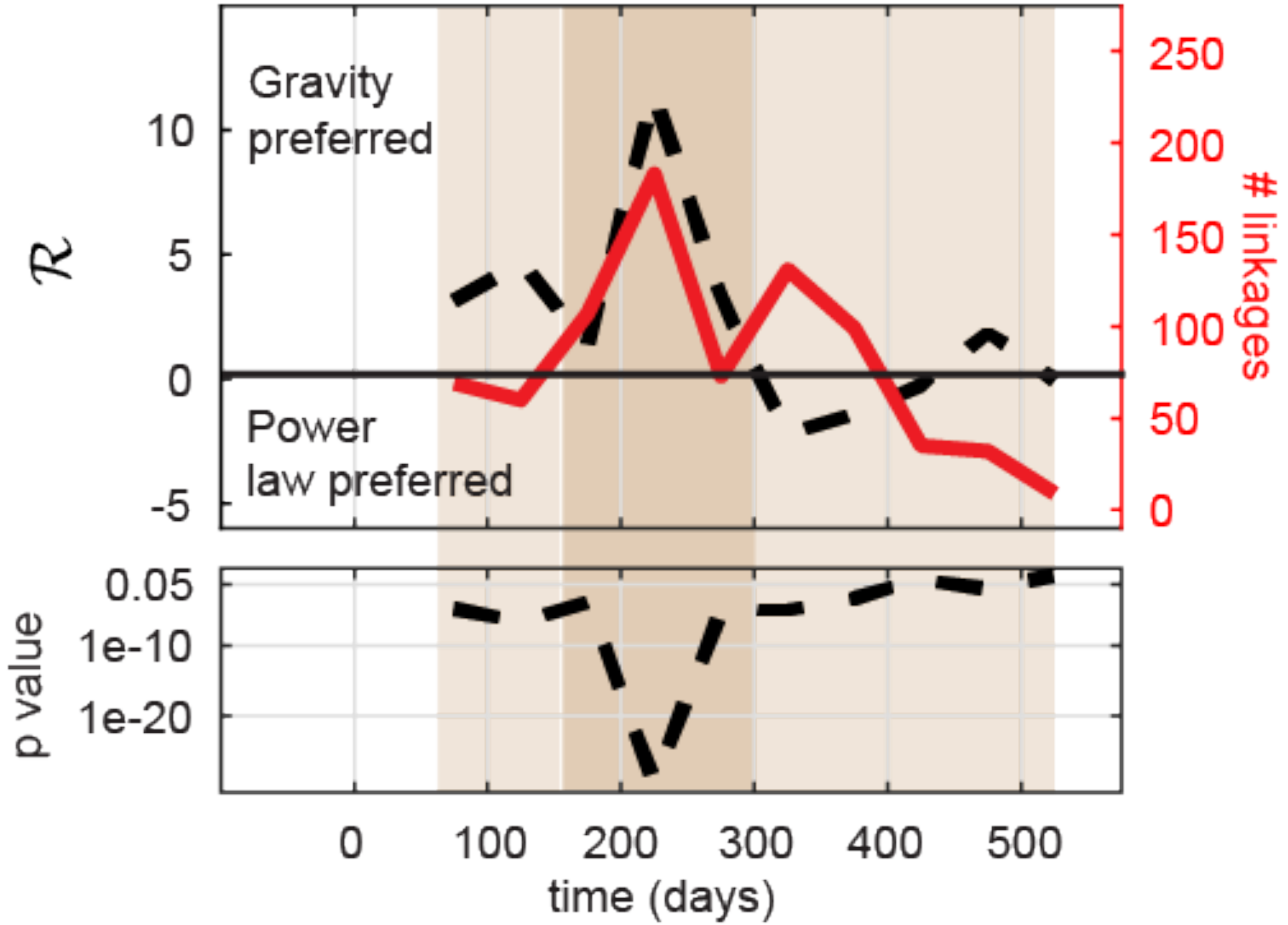
N genetic linkages

Two options:

1) Compare power law with classical $\tau_2 = 1$ gravity using same ρ

2) Scan through ρ and τ_2 to determine maximum likelihood gravity, compare to power law

Switching between Lévy flight and gravity



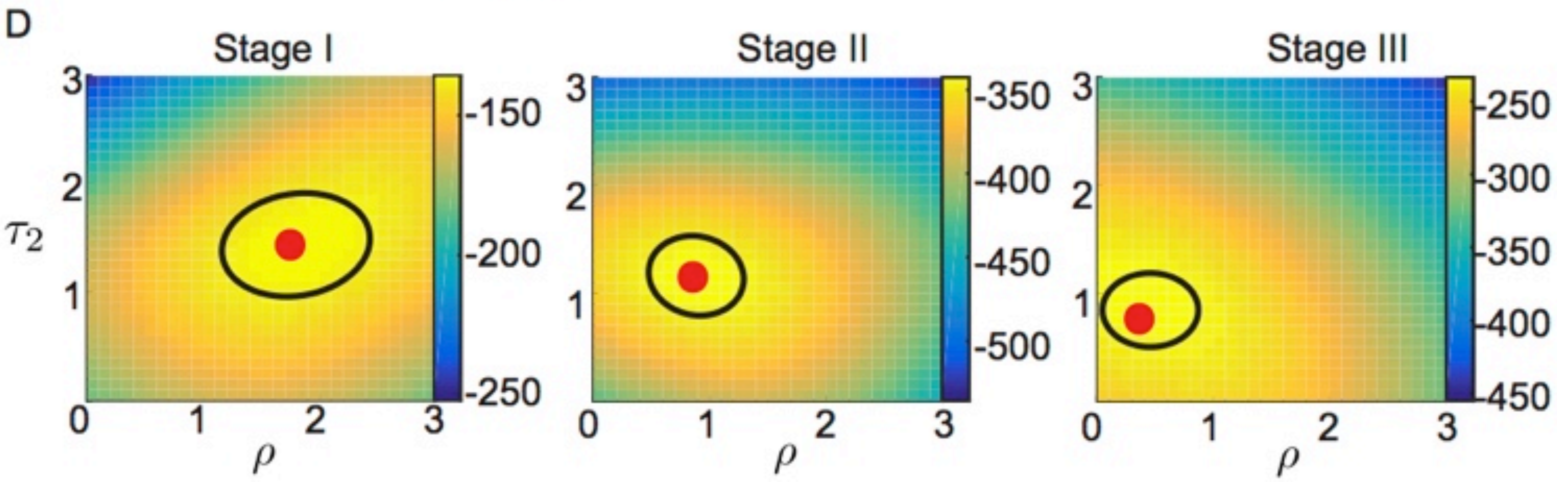
$\rho = 1.7 \quad \tau_2 = 1$

50 day windows

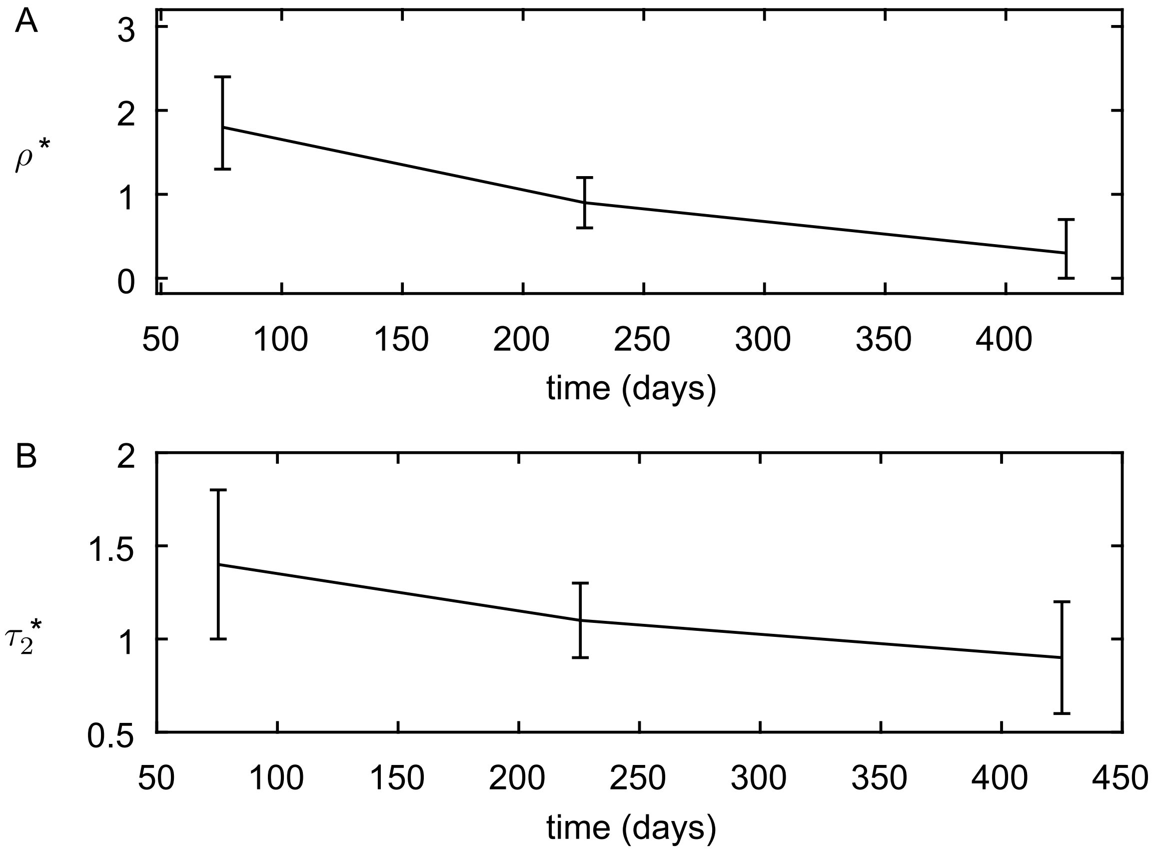
Each window for descendant linkages

Using median chiefdom population

Maximum likelihood for gravity model



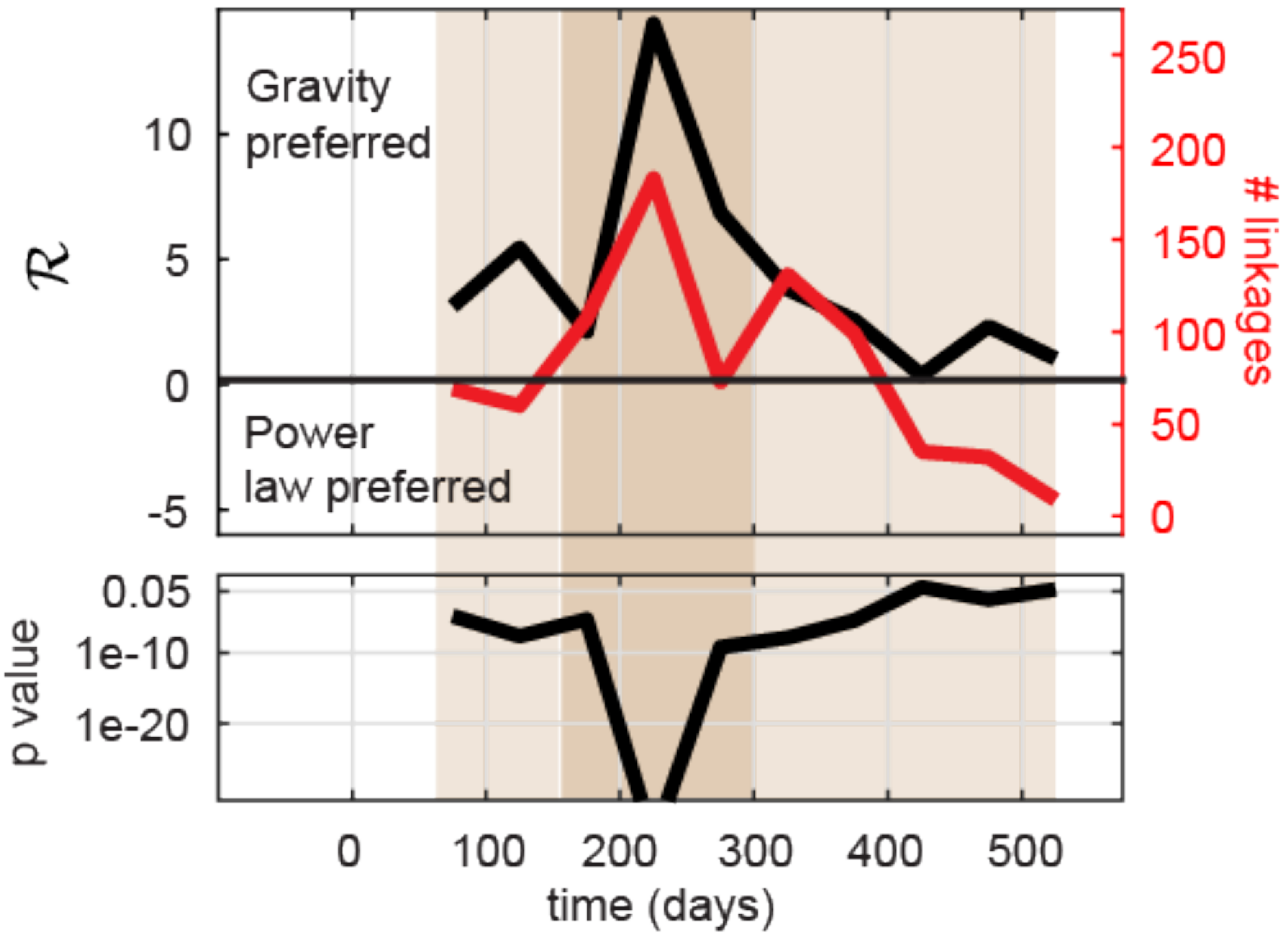
$$p_{ij}^{G} = C_i^{G}\,\frac{P_{c_i}^{\tau_1} P_{c_j}^{\tau_2}}{d_{ij}^{\rho}}$$



Both population and distance parameters shrink

Uncertainty in fit is high

Trend away from gravity – using MLE estimates



50 day windows

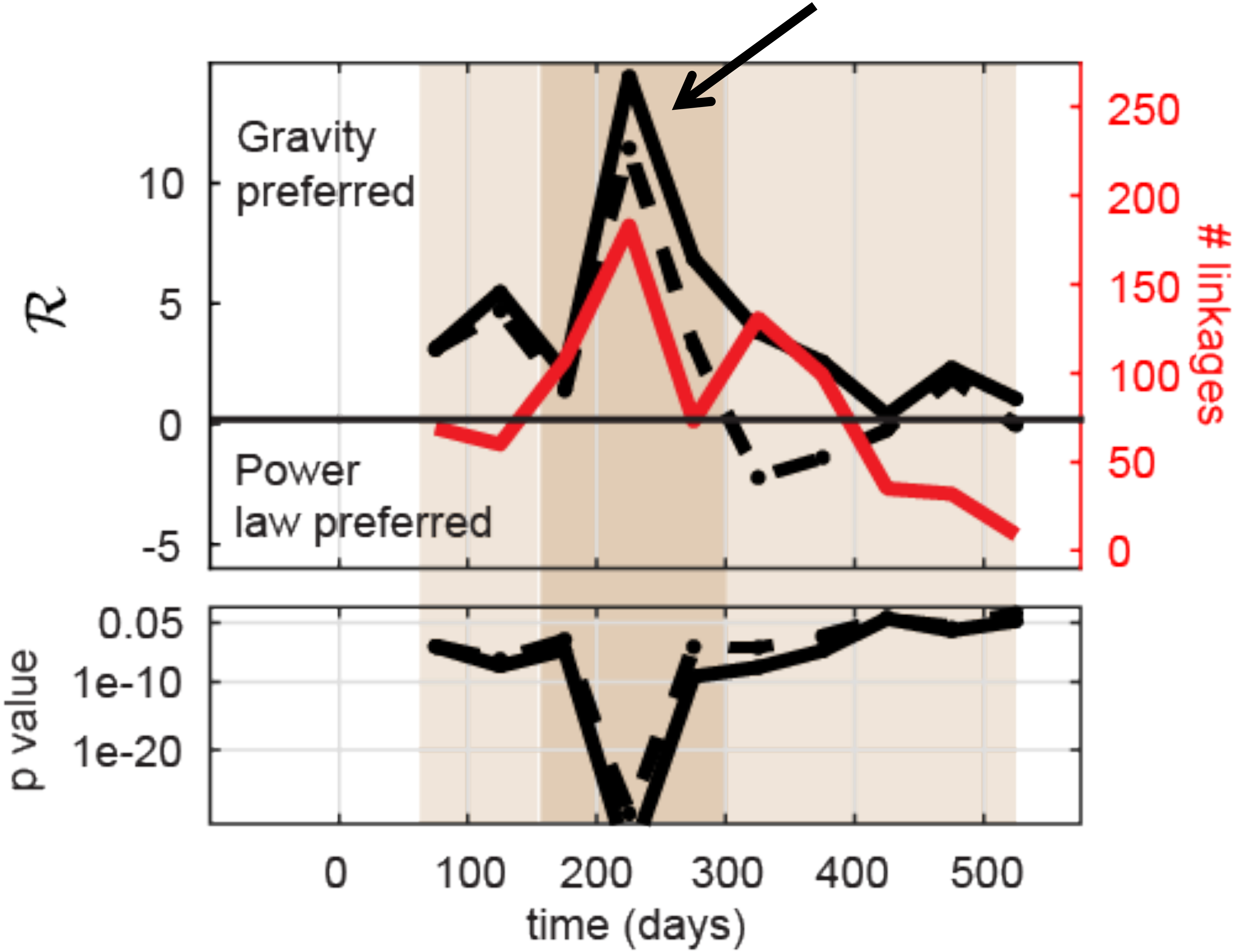
Gravity model preferred until 400 days

Uncertainty in MLE estimate is large

Significance of model preference low after 400 days

Comparison

Intervention surge in Freetown

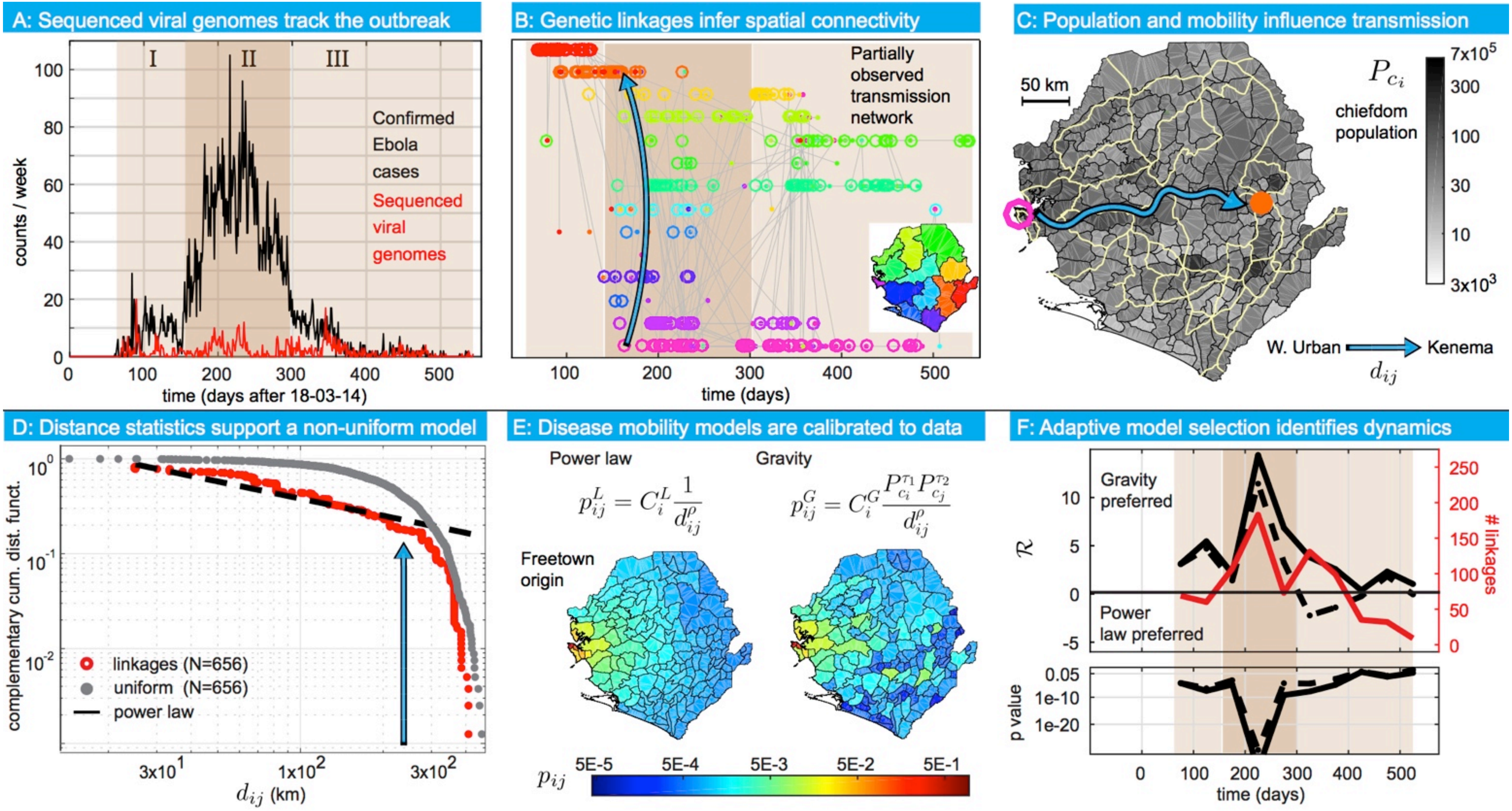


MLE estimates

$\rho = 1.7 \quad \tau_2 = 1$

Best to use both methods

Clear success of Operation Western Area Surge



A: Sequenced viral genomes track the outbreak
I
II
III
Confirmed Ebola cases
Sequenced viral genomes
counts / week
time (days after 18-03-14)
B: Genetic linkages infer spatial connectivity
Partially observed transmission network
time (days)
C: Population and mobility influence transmission
50 km
P_{c_i}
chiefdom population
7x10^5
3x10^3
W. Urban
Kenema
d_{ij}
D: Distance statistics support a non-uniform model
complementary cum. dist. funct.
linkages (N=656)
uniform (N=656)
power law
d_{ij} (km)
E: Disease mobility models are calibrated to data
Power law
Gravity
$p^L_{ij} = C^L_i \frac{1}{d^\rho_{ij}}$
$p^G_{ij} = C^G_i \frac{P^{\tau_1}_{c_i} P^{\tau_2}_{c_j}}{d^\rho_{ij}}$
Freetown origin
p_{ij}
5E-5
5E-4
5E-3
5E-2
5E-1
F: Adaptive model selection identifies dynamics
Gravity preferred
Power law preferred
$\mathcal{R}$
linkages
p value
time (days)

Summary and next steps

Phylogeography indicates a Lévy flight or weighted Lévy flight / gravity

Population size is not always predictive of transmission pattern

Adaptable model selection for real-time spatial dynamics of outbreaks

Other models and geographies can be implemented for next outbreak

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