Cholera dynamics and climate variability

Mercedes Pascual

University of Michigan
and
Howard Hughes Medical Institute

UNIVERSITY OF MICHIGAN

HHMI
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MEDICAL INSTITUTE

Climate variability

Ocean regions that act as global drivers of regional climate variability

→

feedbacks within the disease system itself
(epidemiological processes that depend on the current or past state of the system → immunity; control measures)

Spatial heterogeneity in vulnerability
(in large urban environments of the developing world)

Limitation of ‘correlative’ approaches:

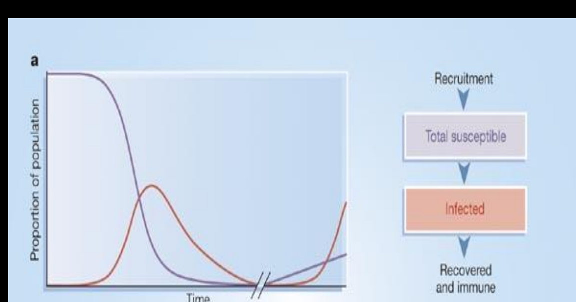
1 – Nonlinear responses to environmental forcing
Epidemiological models, extrinsic vs. intrinsic factors

2 – Spatial (and other forms) of population heterogeneity
ENSO, flooding and spatial disease dynamics

3 – Demographic stochasticity
Size distribution of outbreaks in epidemic regions
and forest fire models

Infectious disease dynamics:

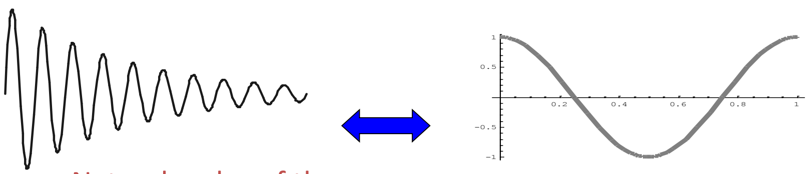
‘natural’ oscillators / consumer-resource systems/ nonlinear systems



$$\beta \frac{I}{N} S$$

From Bryan Grenfell, Ottar Bjornstad (2004)

when two cycles interact…



Natural cycles of the disease

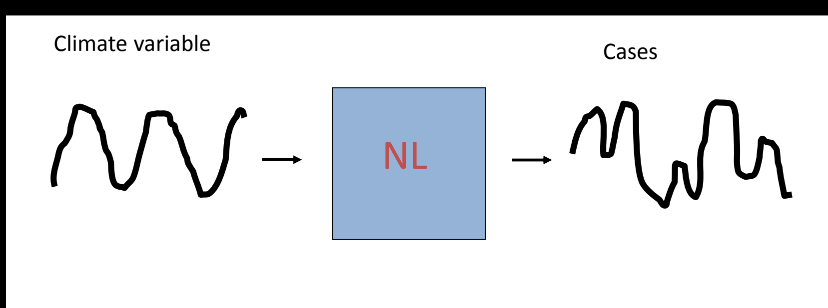
Seasonal transmission

Annual cycles

Biennial cycles or cycles of longer period

Multiple coexisting cycles

Chaos

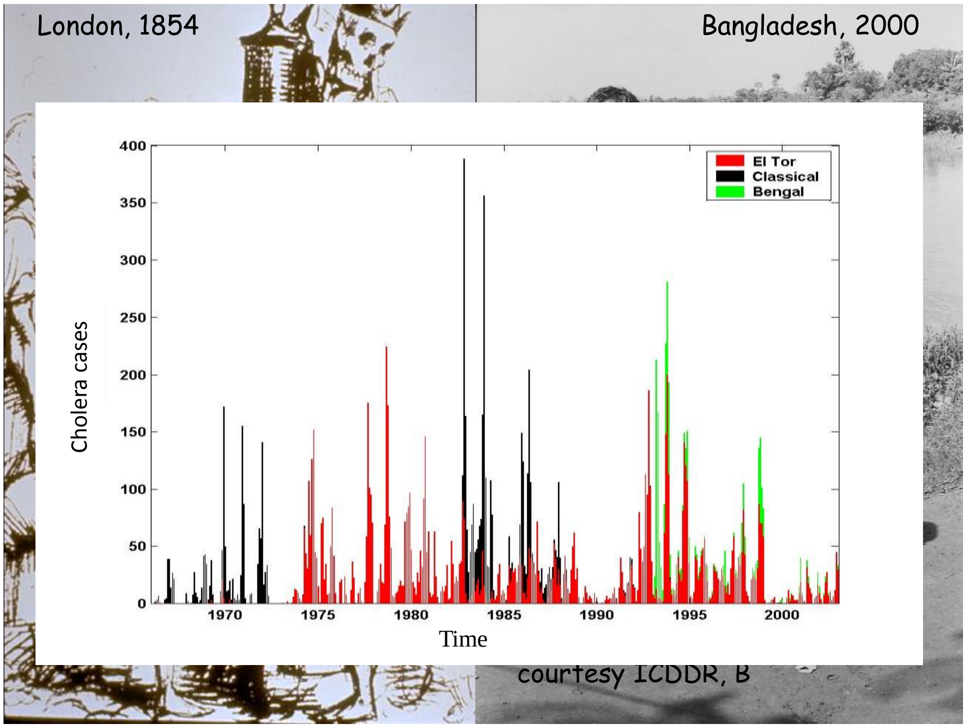


Model + statistical inference methods

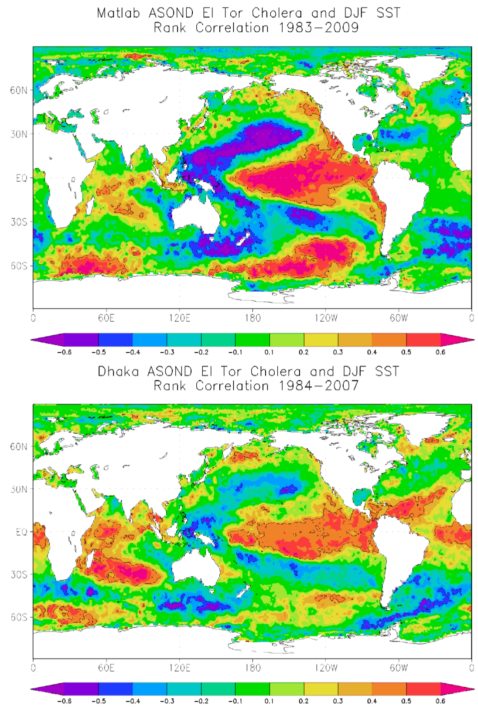
Intrinsic dynamics

Extrinsic drivers

Koelle and Pascual (Am. Nat. 2004)
Koelle, Rodo, Pascual et al. (Nature 2005)


London, 1854
Bangladesh, 2000
400
350
300
250
200
150
100
50
0
Cholera cases
1970
1975
1980
1985
1990
1995
2000
Time
El Tor
Classical
Bengal
courtesy ICDDR, B

Matlab



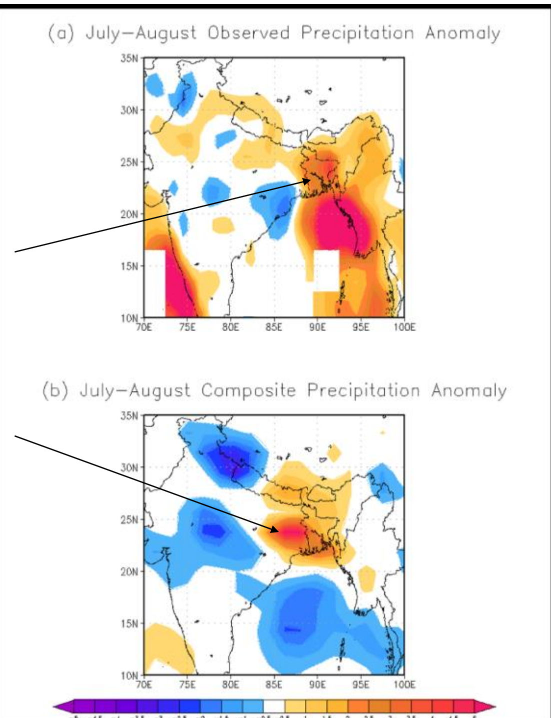
Dhaka

SST data: HadSST1:
Rayner et al. 2003

El Tor Cholera

Link between cholera and ENSO

- Observed precipitation enhanced following El Niño
- Model captures much of the observed empirical signal



Cash, Rodo and Kinter ,
J. Climate 2008

Data:

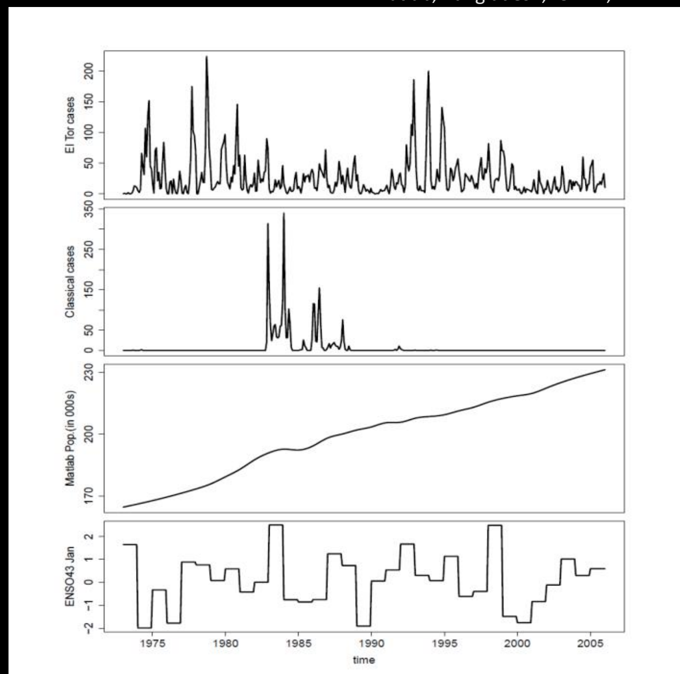
Matlab, Bangladesh, ICDDR, B

El Tor

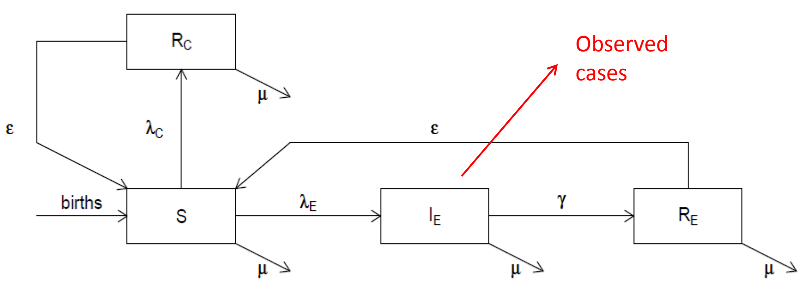
Classical

Population growth

ENSO index January



Transmission model



Force of infection

$$\lambda_E(t) = \overbrace{e^{-\eta(t-t_0)}}^{\text{long-term trend}} \left[\beta(t)\left[\frac{I(t)}{N(t)}\right]^{\alpha} + \omega\right]\frac{dW}{dt}$$

'secondary' transmission

'primary' transmission

noise

Inference method:

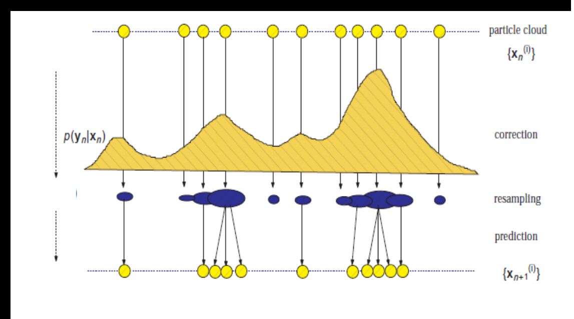
Ionides *et al*. (PNAS 2006); King *et al*. Nature 2008

Likelihood maximization by iterated filtering (based on sequential Monte Carlo methods --- particle filters)

can accommodate:

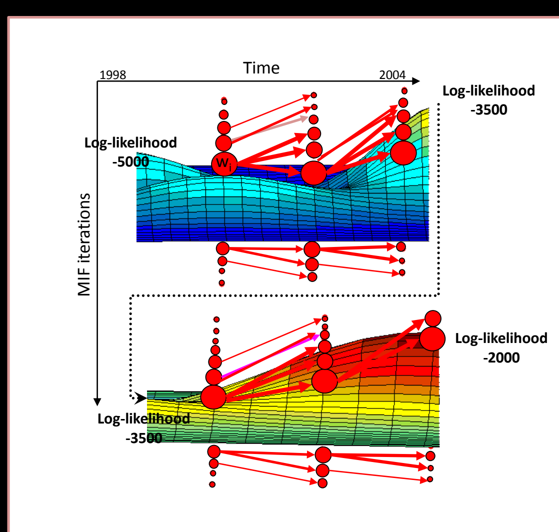
- flexible model formulations ; continuous time
- unobserved variables (e.g. susceptibles)
- stochasticity , trends
- measurement error (under-reporting)

See Laneri et al (PloS Comp. Biol.) for inclusion of covariates and pseudo-code in a malaria example



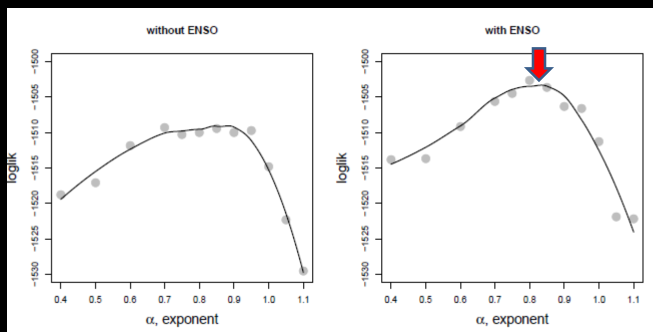
From Z. Chen 2009

Inference method:



Likelihood maximization by iterated filtering (based on sequential Monte Carlo methods --- particle filter ; Ionides and King PNAS 2006)

ENSO and 'self-limiting' effect



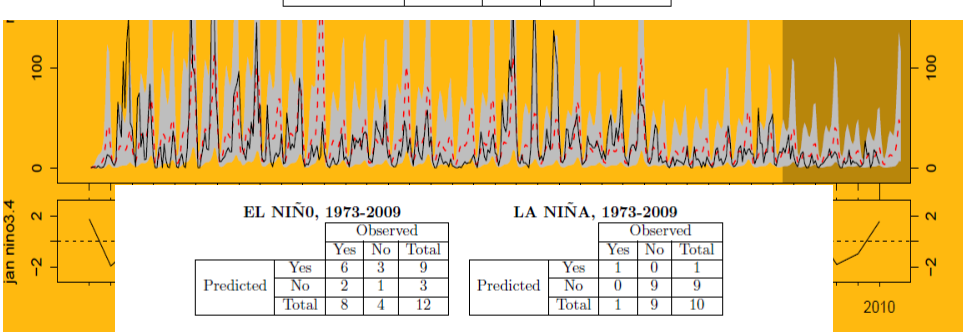
- The model that includes ENSO in the force of infection better fits the data

- Also a 'self-limiting' effect: without it, the epidemics are too explosive and lead to too much extinction of the disease → a feedback mechanism curtailing this explosiveness:
a rapid 'depletion' of susceptibles? (short immunity); 'behavioral immunity'?; phages?

Shrestha *et al. , in prep.*

TABLE 1. Contingency Table of epidemic forecasts for 37 years (1973-2009). The epidemics are defined as fall months with more than 150 reported cases.

		Observed		
		Yes	No	Total
Predicted	Yes	11	6	17
	No	4	16	20
	Total	15	22	37



EL NIÑ0, 1973-2009

		Observed		
		Yes	No	Total
Predicted	Yes	6	3	9
	No	2	1	3
	Total	8	4	12

LA NIÑA, 1973-2009

		Observed		
		Yes	No	Total
Predicted	Yes	1	0	1
	No	0	9	9
	Total	1	9	10

Highly localized sensitivity to climate forcing drives endemic cholera in a megacity

Robert C. Reiner, Jr.,[a,1], Aaron A. King[a,b], Michael Emch[c], Mohammad Yunus[d], A. S. G. Faruque[d], and Mercedes Pascual[a]

[a]University of Michigan, Ann Arbor, MI; [b]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; [c]University of North Caroli Chapel Hill, NC; and [d]International Centre for Diarrheal Disease Research, Dhaka 1000, Bangladesh

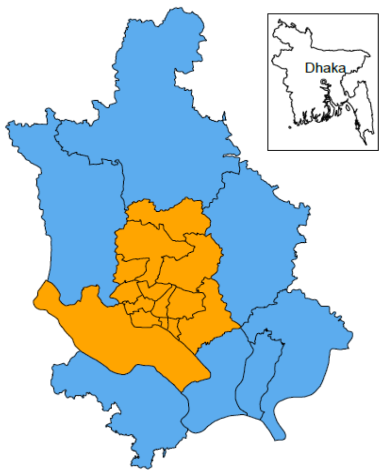
Image courtesy of http://news.bbc.co.uk

Image courtesy of http://www.purefilteredwater.com/

Motivation

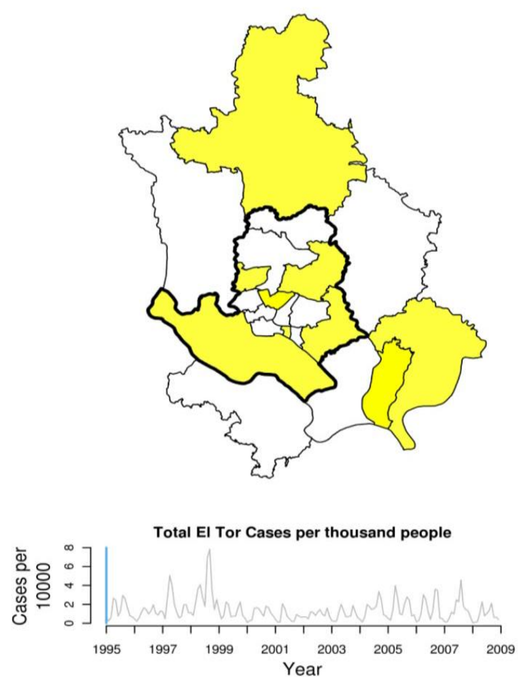
- Spatial effects have not been considered before in the response of cholera to climate variability. We may expect global climate drivers such as ENSO to operate at regional scales.
- We still have a poor understanding of proximal mechanisms that mediate the effect of global climate drivers in urban environments
- Statistical models in the literature cannot be used effectively for prediction because of their short lead times (ranging from 0 to 1 months)

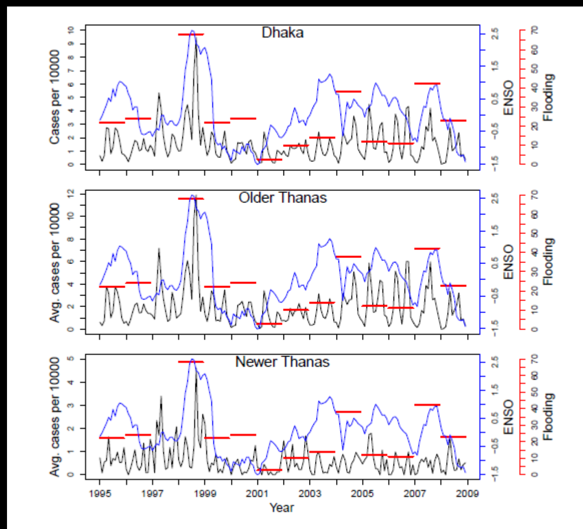
Data Description



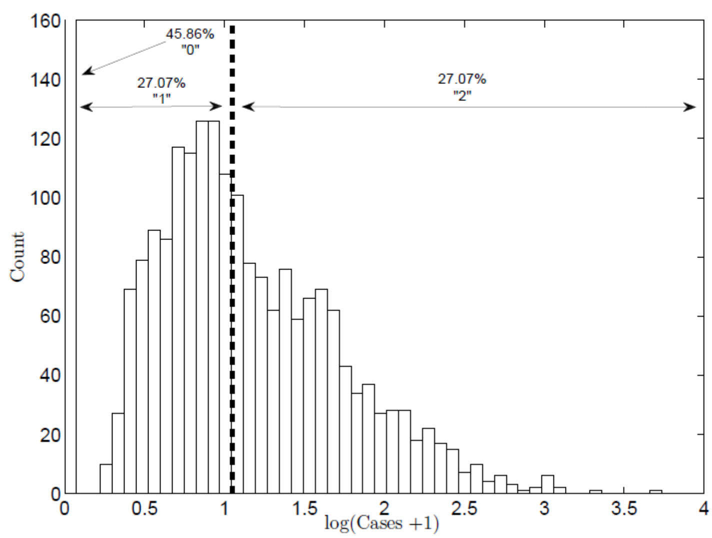
- Dhaka, the capital of Bangladesh, contains more than 14 million people (almost tripled in last 25 years, projected to double in next 25).
- The data we analyze is the number of cases of cholera of the O1 El Tor biotype over 14 years (1995-2008), broken down by thana (i.e. administrative region).

[Movie]

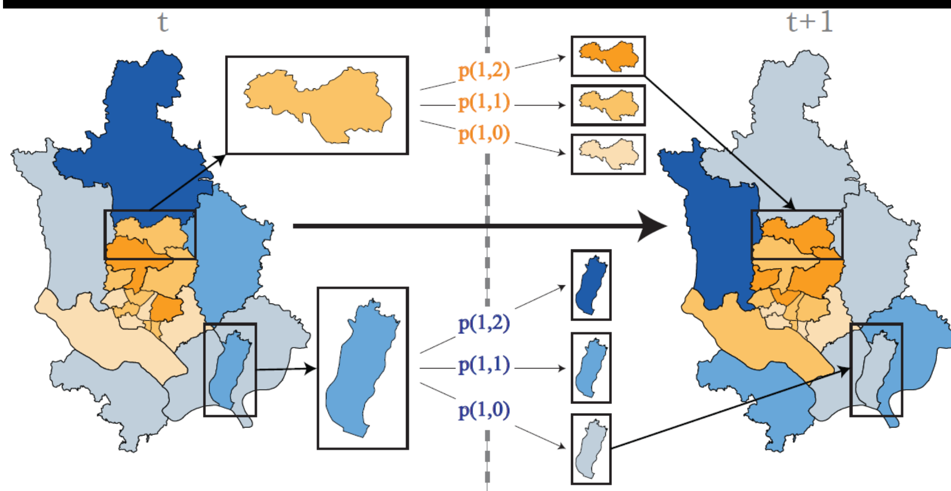




Data Transformation



Probabilistic model (discrete state Markov chain model): probabilities a function of group , season, neighbors' states, and climate covariates.



Model Description

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Markov Chain Model

- We start with a simple Markov Chain model to describe the data.
- This model assumes the only difference between any two observations is what the value of the thanas were the month before.

Model Description

Older

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Newer

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Multiple Markov Chain Model

- We add complexity by allowing the transition matrices to be different depending on the area of the city where the thana is located.
- There are several ways to identify which thana should be in which area, but eyeballing the timeseries worked well for this problem.

Model Description

NN=0

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=1

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Multi-Dimensional Markov Chain Model

- To account for local spatial effects, we expand the model to allow for a different transition matrix depending on the maximum state of the nearest neighbors of that thana.
- All thanas must now be simultaneously tracked, hence we now have a multi-dimensional model (21 dimensions, one for each thana).

Model Description

Spring

NN=2	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Summer

NN=0	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

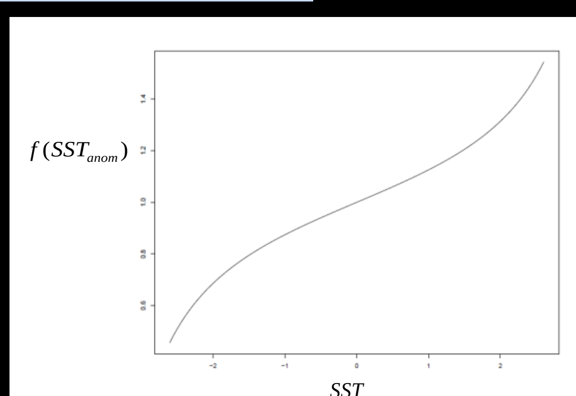
NN=0	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=0	Older 0	Older 1	Older 2	Newer 0	Newer 1	Newer 2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Multi-Dimensional Inhomogeneous Markov Chain (MDIMC) Model

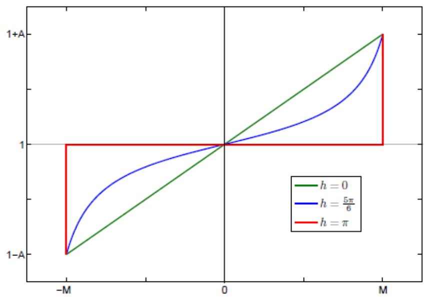
- Allowing the transitions to vary by season, our model is no longer temporally homogeneous, but allows for the known two-peak-per-year dynamics to emerge. Unfortunately there are way too many variables in this model. Only Spring and Summer are shown here in a four season model. One could imagine a different set of matrices for each month.

$$P_{ENSO}(i,j) = P(i,j) * [1 + f(SST_{anom})]$$



$$\mathrm{P}\left(X_{k,t} = j \mid X_{k,t-1} = i, \max_{l \in \mathcal{N}(k)} X_{l,t-1} = v, \mathrm{ENSO} = s\right) =$$

$$= \mathbb{P}_{i,j,\mathcal{D}(k)} \times \mathrm{Neigh}(i,j,v,\mathcal{D}(k)) \times \mathrm{Seas}(i,j,t,\mathcal{D}(k)) \times \mathrm{Nino}(j,s,\mathcal{D}(k))$$



$$p'_{i,2,k,t} = f\left(p_{i,2,k,t} \times \mathrm{Nino}(t-1, \mathcal{D}(k))\right),$$

where the El Niño function has the sigmoidal form

$$\mathrm{Nino}(t,d) = 1 + A_d \frac{\tan\left(\frac{h_d}{2} \cdot \frac{\mathrm{ENSO}(t-10)}{M_d}\right)}{\tan\left(\frac{h_d}{2}\right)}$$

$$p'_{i,0,k,t} = \left(1 - p'_{i,2,k,t}\right)\frac{p_{i,0,k,t}}{p_{i,0,k,t} + p_{i,1,k,t}}$$

$$p'_{i,1,k,t} = \left(1 - p'_{i,2,k,t}\right)\frac{p_{i,1,k,t}}{p_{i,0,k,t} + p_{i,1,k,t}}.$$

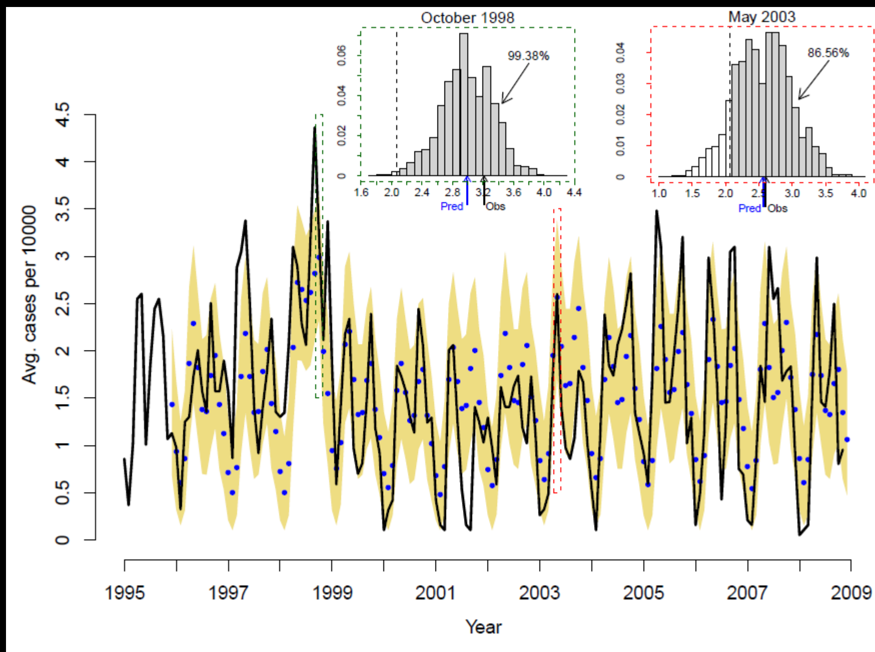
- Spatial heterogeneity: the dynamics between groups are significantly different (p-value=0.0001)
- Local effect: the state of neighboring districts matters (p-value =0.01) but a weaker effect
- Interaction between spatial structure and climate forcing: the parameters governing the effect of ENSO are significantly different between the groups (p-value= 0.03); and similarly for flooding (p-value= 0.015)

> ENSO is a significant covariate (p=value < 0.0001); lag of 11 months for the spring months and 9 months for the fall ones.

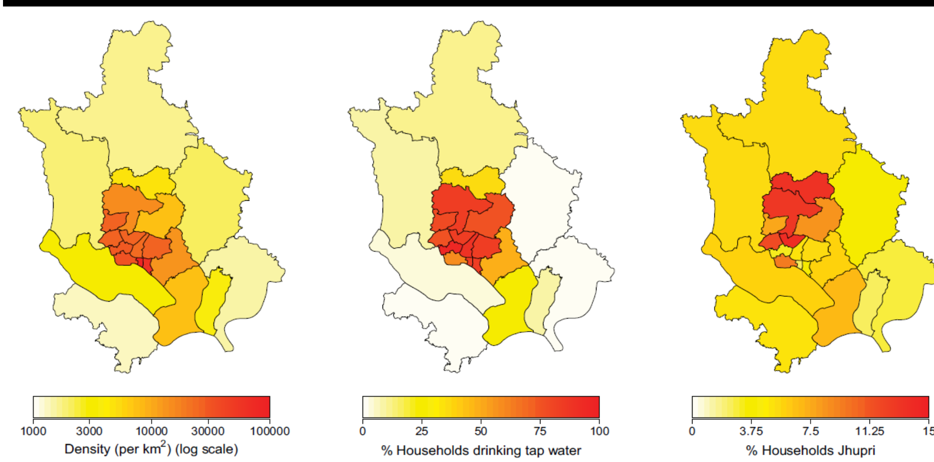
> Flooding is also significant (p-value < 0.0001)

> Flooding still significant when tested in the presence of ENSO (p-value = 0.008) and vice-versa (p-value < 0.0001)

Reiner *et al. (PNAS 2012)*



Socio-economic conditions



Summary so far:

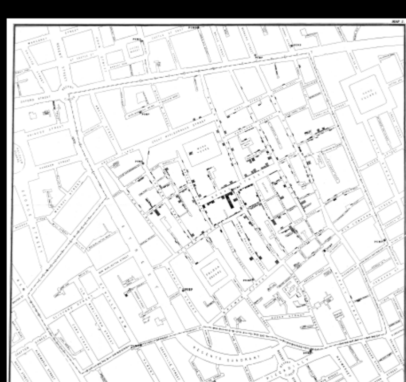
Climate change
El Niño / floods frequency and intensity?

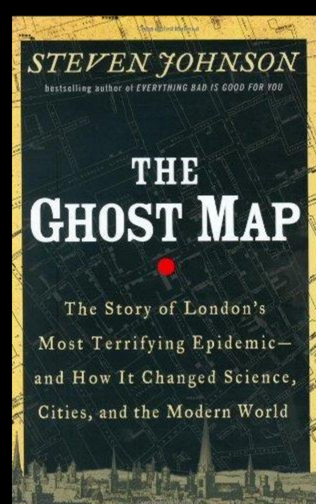
➢ Cholera outbreaks in Dhaka (and Bangladesh) are strongly driven by climate variability (ENSO and flooding). The effect of El Niño is partly through precipitation and associated flooding.

Urban population growth:
access to clean water and sanitation

➢ Population susceptibility shows pronounced geographic variation within Dhaka, with a part of the city acting as a susceptible core, in a way that highlights the key role of sanitary and associated socio-economic conditions.

In 1864, Dr John Snow became the first to link cholera to drinking water, when he plotted the proximity of victims' homes to drinking wells in London



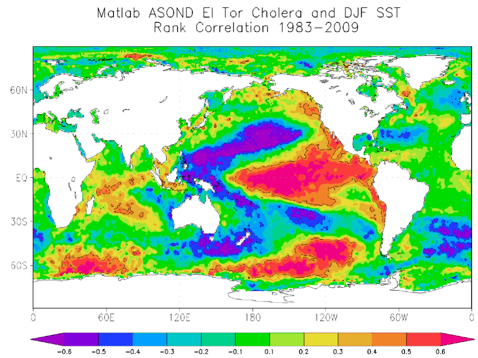


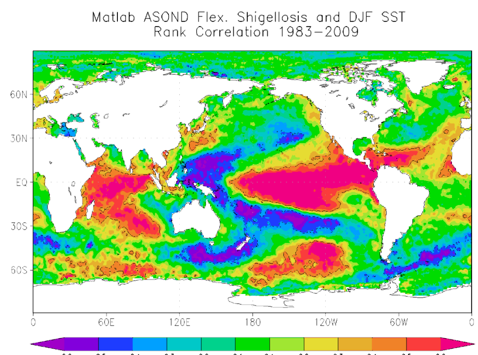
John Snow 'revisited' but in the context of climate forcing and a megacity of the developing world.

Different diarrheal diseases:

Similar responses to forcing but different epidemiology?

SST data: HadSST1: Rayner et al. 2003





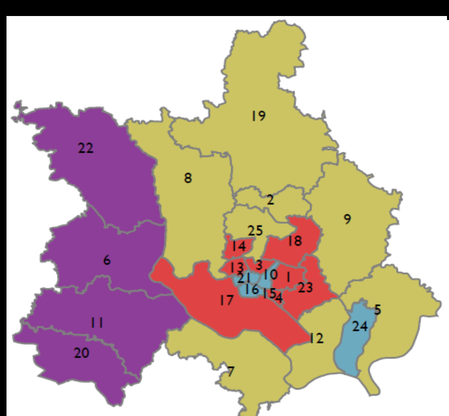
Matlab

El Tor Cholera

Shigellosis (*S. flexneri*)

(Cash *et al., in prep.*)

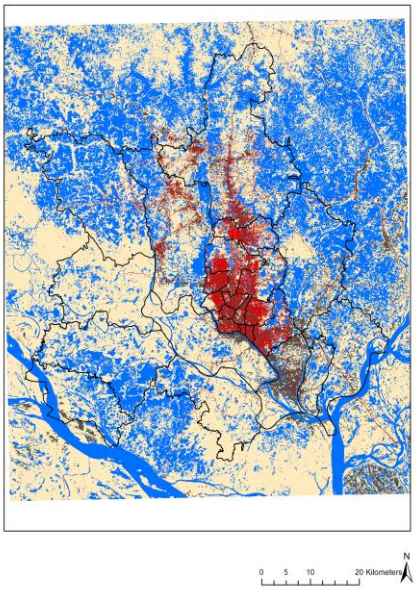
Search algorithms to identify 'groups ' of locations with similar dynamics …

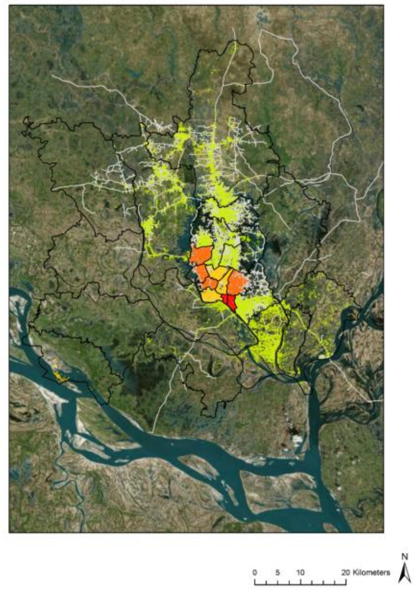


There are $\mathcal{S}_{25}^{(2)} = 16,777,215$ distinct groupings.

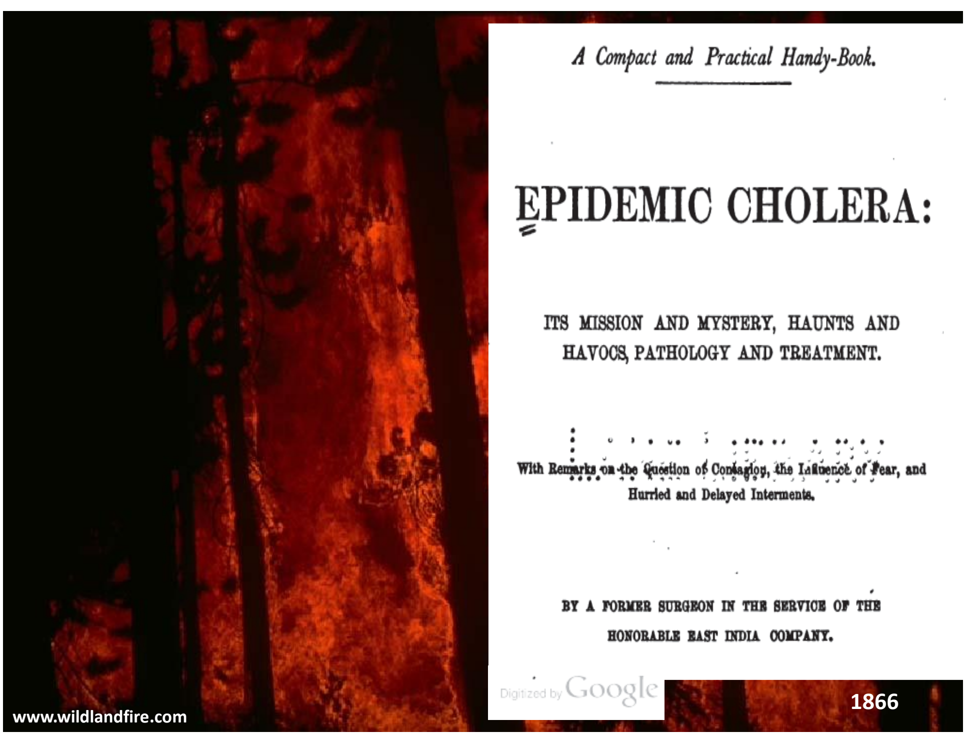
Bayesian approach to classify districts based on a dynamical model and time series data:

Baskerville et al. 2011. Spatial Guilds in the Serengeti Food Web Revealed by a Bayesian Group Model. PloS Computational Biology 7(12)





With Francisco Javier Perez , E. Bertuzzo, A. Rinaldi (EPFL)


A Compact and Practical Handy-Book.

EPIDEMIC CHOLERA:

ITS MISSION AND MYSTERY, HAUNTS AND HAVOCS, PATHOLOGY AND TREATMENT.

With Remarks on the Question of Contagion, the Influence of Fear, and Hurried and Delayed Interments.

BY A FORMER SURGEON IN THE SERVICE OF THE HONORABLE EAST INDIA COMPANY.

Epidemics and Critical Phenomena (1)

letters to nature

Nature **381**, 600 - 602 (13 June 1996); doi:10.1038/381600a0

Power laws governing epidemics in isolated populations

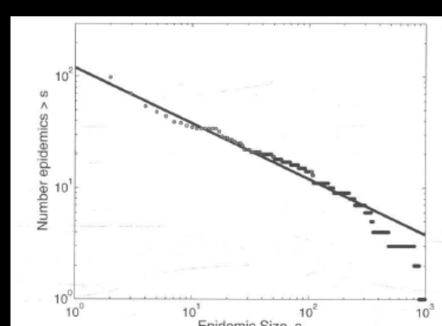
C. J. RHODES & R. M. ANDERSON

Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, South Parks Road, Oxf
OX1 3PS, UK

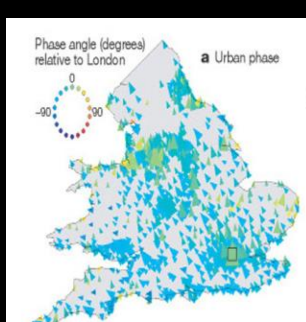
TEMPORAL changes in the incidence of measles virus infection within large urban communities in the developed world have been the focus of much discussion in the context of the identification and analysis of nonlinear and chaotic patterns in biological time series[1–11]. In contrast, the measles records for small isolated island populations are highly irregular, because of frequent fade-outs of infection[12–14], and traditional analysis[15] does not yield useful insight. Here we use measurements of the distribution of epidemic sizes and duration to show that regularities in the dynamics of such systems do become

Epidemic Dynamics and Critical Phenomena (2)

Measles cases ‘in a small fairly isolated population in East Anglia, UK’ 1944-1968

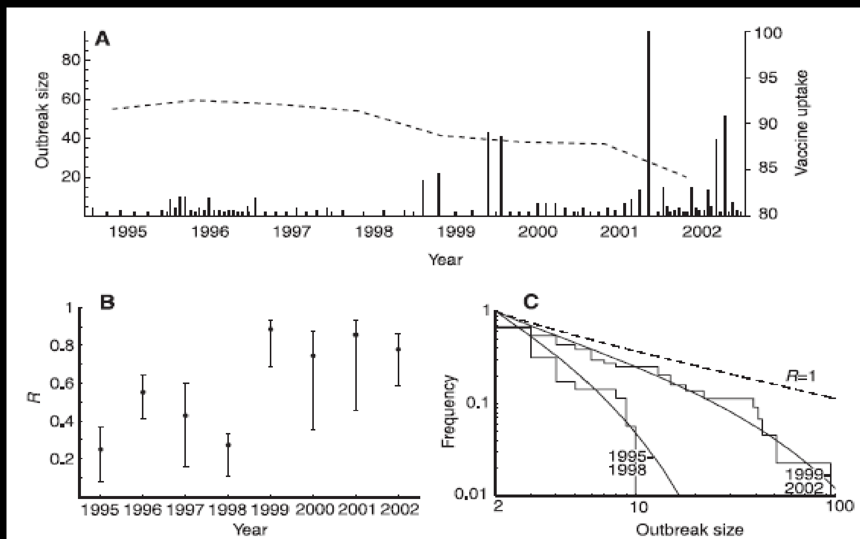


M. Keeling 2005



Grenfell *et al.* Nature 2001

Epidemic Dynamics and Critical Phenomena (3)



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Epidemics and Critical Phenomena (4): Forest Fire Model (Drossel Schwabl) SOC

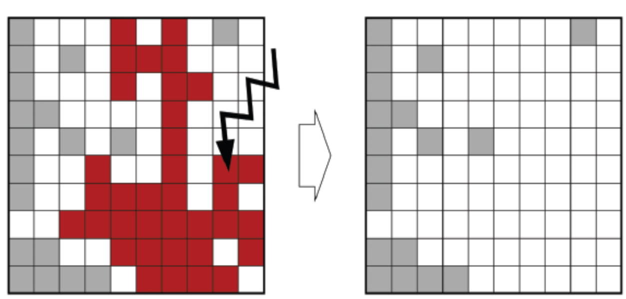
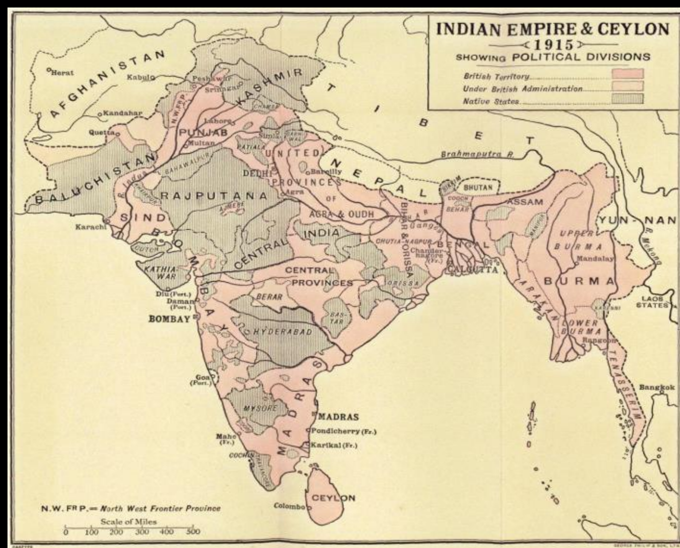


Figure 16. Lightning strikes at random positions in the forest fire model, starting fires that wipe out the entire cluster to which a struck tree belongs.

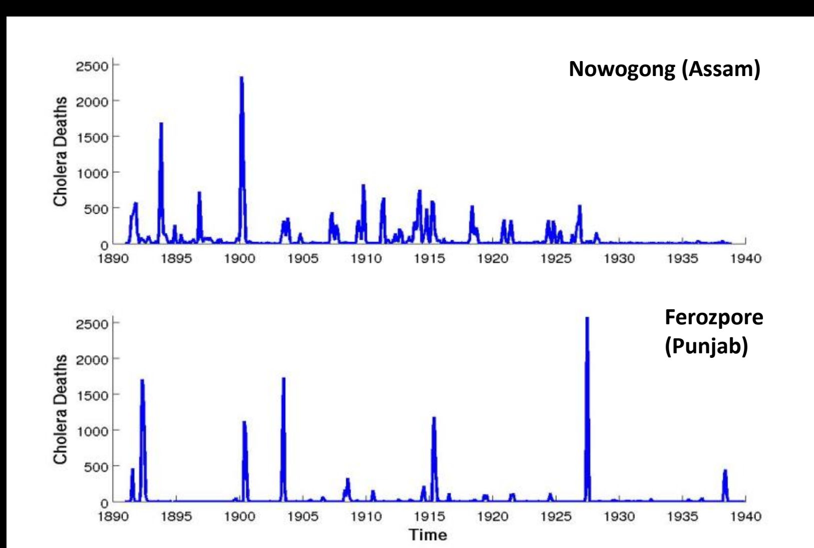
From M. Newman
Contemporary Physics 2005

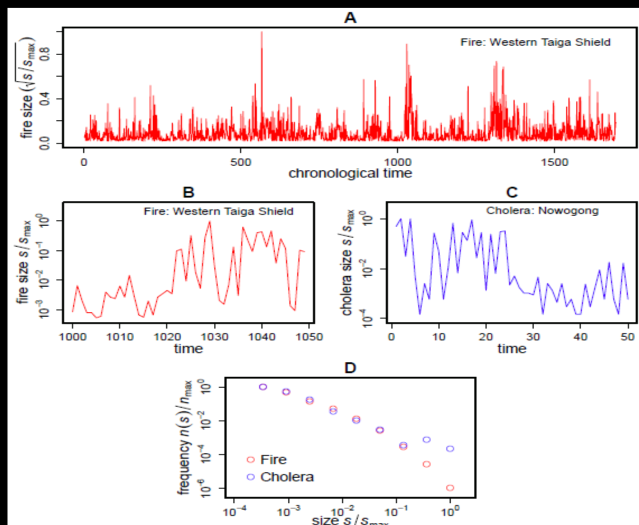
But model generates only one value of the power-law exponent in the fire size distribution!

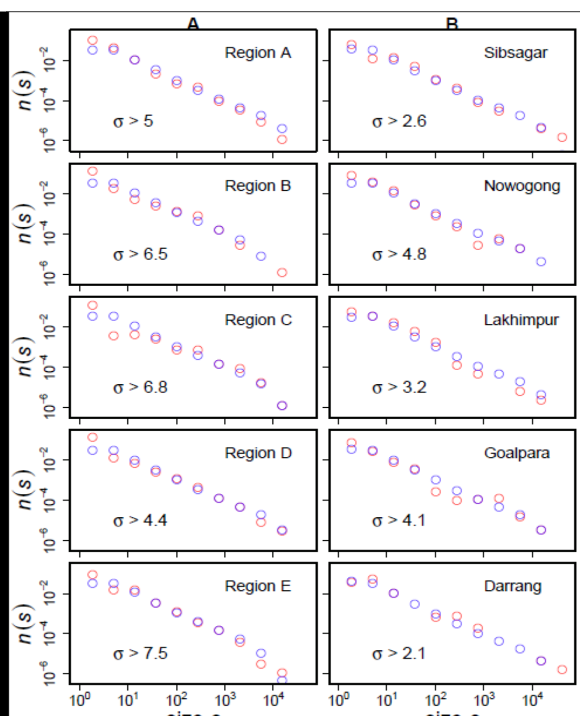


Vincent Smith's – India in the British Period, Oxford, Clarendon Press, 1920

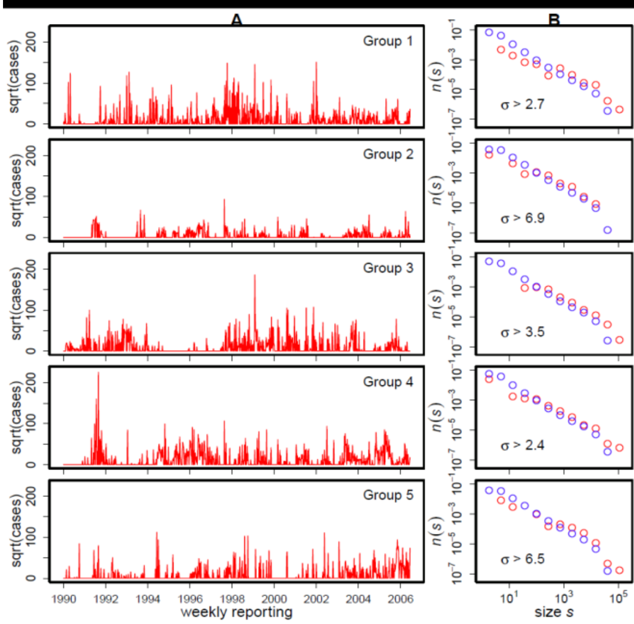
Historical cholera: epidemic dynamics

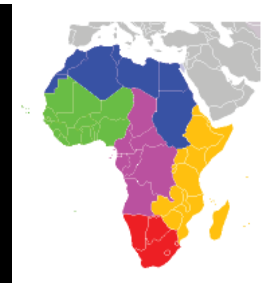



A
Fire: Western Taiga Shield
chronological time
B
Fire: Western Taiga Shield
time
C
Cholera: Nowogong
time
D
Fire
Cholera
frequency $n(s)/n_{max}$
size s/s_{max}

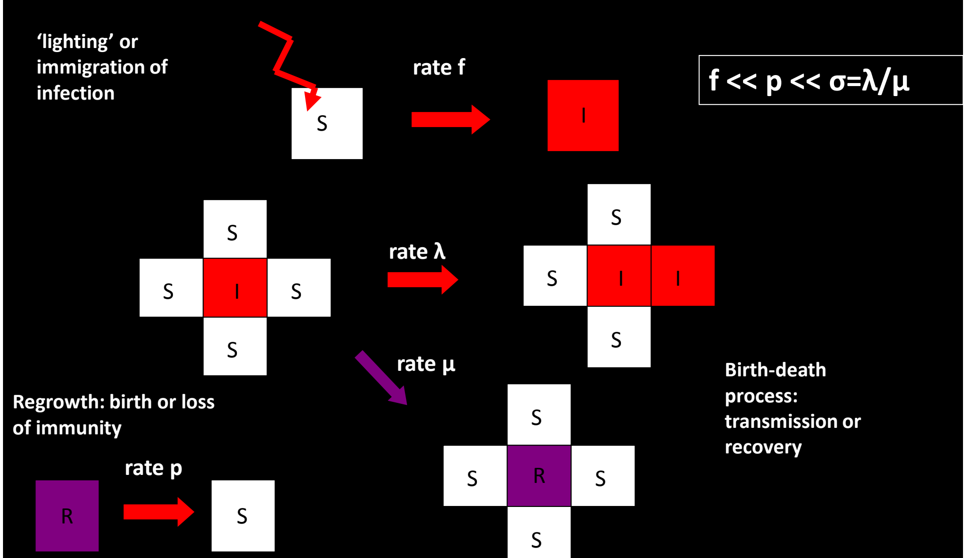

A
B
Region A
σ > 5
Sibsagar
σ > 2.6
Region B
σ > 6.5
Nowogong
σ > 4.8
Region C
σ > 6.8
Lakhimpur
σ > 3.2
Region D
σ > 4.4
Goalpara
σ > 4.1
Region E
σ > 7.5
Darrang
σ > 2.1
n(s)
size s
size s

Cholera in Africa: WHO weekly reports 1990-2006

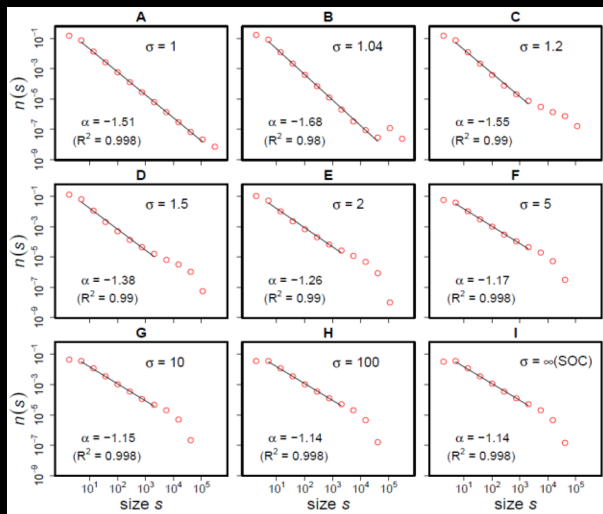


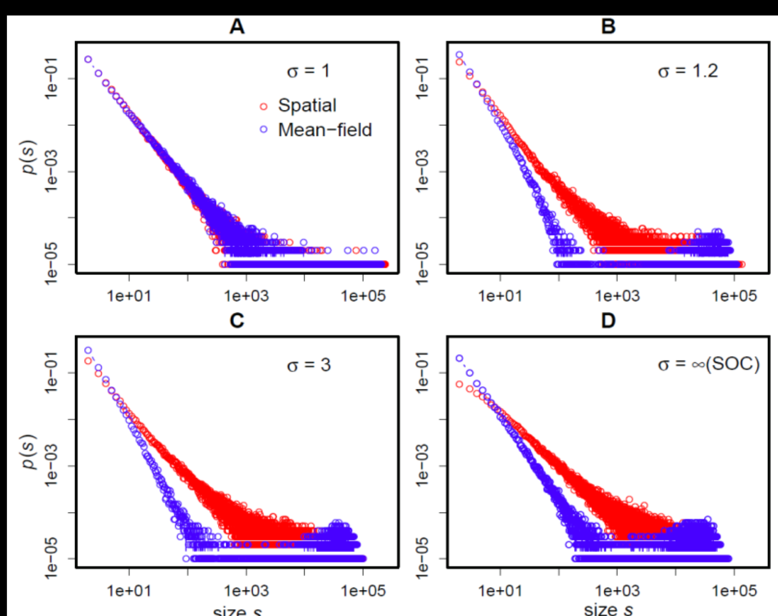


Forest-Fire Model: Richard Zinck *et al.* (Am. Nat. 2011)



Predicted size distributions for different 'R0s' > 1





Conclusions and Implications

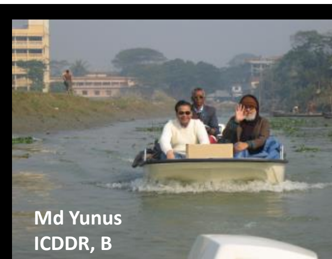
- Heavy-tailed distributions in epidemic size distributions are a more general pattern than previously appreciated
- A simple, generic, forest-fire model can explain the observed patterns
- We can classify epidemic dynamics into subcritical and supercritical behavior; this indicates which mechanism controls epidemic dynamics:
  a poor propagation or the local depletion of susceptibles
- The model can also be used to estimate a lower bound for the local R0

Conclusions and Implications

- Cholera epidemics appear primarily limited by the local depletion of susceptibles
- Explicit 'space' matters (the dynamics are distributed in space or in a network)
- **Stochasticity (demographic noise) might be essential to the epidemic dynamics of infectious diseases, beyond the recognized effect of small population size on extinction.**

Gracias

Robert Reiner, UC Davis



Md Yunus
ICDDR, B

Aaron King, UM

Menno Bouma, LSHTM

Ben Cash: COLA (Center for Ocean Land and Atmosphere Studies)

Xavier Rodó (IC3 Barcelona)

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