A Complex Systems Theory of Disease

Samuel V. Scarpino
Omidyar Fellow
Santa Fe Institute

scarpino@santafe.edu
@svscarpino
scarpino.github.io

Juan Genoves
Where will the next pandemic emerge?
Where will the next **influenza** pandemic emerge?
What factors are important for pandemic flu?

Air travel

Density of pig farms
Worldwide pig density

Source: Gridded Livestock of the World
Worldwide pig density

**Pigs density map matching FAOSTAT 2005 (modelled)**

**Source:** Gridded Livestock of the World
and it happened again with Ebola
and it happened again with Ebola

### Table I. — Age distribution of persons positive for either Lassa (LAS), Ebola (EBO) or Marburg (MAR) virus antibodies.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Nb tested</th>
<th>LAS-positive (prevalence %)</th>
<th>EBO-positive (prevalence %)</th>
<th>MAR-positive (prevalence %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>49</td>
<td>5 (10 %)</td>
<td>2 (4 %)</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>68</td>
<td>11 (16 %)</td>
<td>5 (7 %)</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>108</td>
<td>21 (19 %)</td>
<td>6 (6 %)</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>94</td>
<td>16 (17 %)</td>
<td>5 (5 %)</td>
<td>1</td>
</tr>
<tr>
<td>40-59</td>
<td>88</td>
<td>9 (10 %)</td>
<td>6 (7 %)</td>
<td>1</td>
</tr>
<tr>
<td>60 plus</td>
<td>26</td>
<td>5 (16 %)</td>
<td>2 (8 %)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>433</td>
<td>67 (16 %)</td>
<td>26 (6 %)</td>
<td>5 (1 %)</td>
</tr>
</tbody>
</table>
and it may happened again with Chagas

Brumpt et al. 1912
Salazar et al. 2015
and it may happened again with Chagas

Brumpt et al. 1912
Salazar et al. 2015
Modeling infectious diseases

Inequality & disease

Social clustering & Ebola
Compartmental models

Susceptible (S)
Compartmental models - Mass Action Assumption

Susceptible (S)  Infectious (I)
Compartmental models

Susceptible (S) → Infectious (I) → Removed (R)

- $\beta SI$
- $\gamma I$

Recovery or Death
Lions, Tigers, and Boxes … oh my

Fig. 1 The general transfer diagram for the MSEIR model with the passively immune class M, the susceptible class S, the exposed class E, the infective class I, and the recovered class R.

\[
S'(t) = \mu \cdot (1 - wP - aP) - \beta[I_s(t) + I_a(t)]S(t) - \nu S(t) \\
I'_s(t) = \beta\sigma[I_s(t) + I_a(t)]S(t) - \gamma_s I_s(t) - \nu I_s(t) \\
I'_a(t) = \beta(1 - \sigma)[I_s(t) + I_a(t)]S(t) + \beta[I_s(t) + I_a(t)]V(t) - \gamma_a I_a(t) - \nu I_a(t) \\
V'(t) = \mu \cdot aP - \beta[I_s(t) + I_a(t)]V(t) - \nu V(t) \\
R'(t) = \mu \cdot wP + \gamma_s I_s(t) + \gamma_a I_a(t) - \nu R(t)
\]
Lions, Tigers, and Boxes … oh my

\[ S'(t) = \mu \cdot (1 - \beta \sigma [I_s(t)] \cdot (1 - \alpha) \cdot \alpha \cdot \lambda V_1) \]

\[ I_s'(t) = \beta \sigma [I_s(t)] \cdot (1 - \alpha) \cdot \lambda V_1 \]

\[ I_a'(t) = \beta (1 - \alpha) \cdot \lambda V_1 \]

\[ V'(t) = \mu \cdot aP \]

\[ R'(t) = \mu \cdot wP \]

**FIG. 3.** Transfer diagram for the pertussis model with vaccination.
Reproduction Number

Expected number of secondary cases in the beginning of an outbreak
Compartmental models

Susceptible (S) → Infectious (I) → Removed (R)

\[ R_0 = \frac{\text{Infection rate}}{\text{Recovery rate}} = \frac{\beta S}{\gamma} \]
# Reproduction Numbers

<table>
<thead>
<tr>
<th>Disease</th>
<th>$R_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles &amp; Whooping Cough</td>
<td>5 - 18</td>
</tr>
<tr>
<td>Chicken Pox</td>
<td>7 - 12</td>
</tr>
<tr>
<td>Polio</td>
<td>5 - 7</td>
</tr>
<tr>
<td>Smallpox</td>
<td>1.5 - 20+</td>
</tr>
<tr>
<td>Seasonal flu</td>
<td>1.1 - 1.5</td>
</tr>
<tr>
<td>Ebola</td>
<td>1.1 - 3</td>
</tr>
</tbody>
</table>


Problems with the Reproduction Number
Ebola virus genomic data

Modified from Gire et al. 2014
Reconstructed transmission network

Mean infection date
- 19th May 2014
- 26th May
- 2nd June
- 9th June
- 16th June

Number of mutations
- 0
- 1
- 2
Posterior number of secondary infections

Count

Number of secondary infections
Problems with the Reproduction Number
Contact Patterns Vary
Ebola Predictions from mass-action models

Meltzer et al. 2014
Ebola Predictions from mass-action models

Meltzer et al. 2014
Ebola Predictions from mass-action models

Estimated - 100,000

Meltzer et al. 2014
Ebola Predictions from mass-action models

Estimated - 100,000

Observed - 10,000

Meltzer et al. 2014
Why do these problems exist?
Why do these problems exist?

1. Intrinsic properties of the pathogen

2. Contact patterns of the host
Network Epidemiology
Network Epidemiology

\[ R_0 = T \left( \frac{\langle K^2 \rangle - \langle K \rangle}{\langle K \rangle} \right) \]
Network Epidemiology Vs. Standard Calculation

\[ R_0 = T \left( \frac{\langle K^2 \rangle - \langle K \rangle}{\langle K \rangle} \right) \]

\[ R_0 = \frac{\beta S}{\gamma} \]
Model complexity
Modeling infectious diseases

Inequality & disease

Social clustering & Ebola
The Cholera Outbreak of 1854

Snow 1855
Poverty and the Cholera Outbreak of 1854
Modern Inequality and health

Life Expectancy

Income Inequality

Primary Care

Life Expectancy

modified from Shi et al. 1999
The current Ebola outbreak
Poverty and the current Ebola virus outbreak

Physicians Per 1,000 Citizens
(log scale)

Health Care Expenditure Per Person U.S.D.
(log scale)

Nigeria
L Liberia
S Sierra Leone
G Guinea

Scarpino 2015
Poverty and the current Ebola outbreak
Influenza in El Paso, TX

El Paso, TX, USA

Number of rapid positive tests

October
January 2014
April

2013 - 14 Influenza Season
El Paso, TX
2014 - 15 Influenza Season
Poverty and flu in El Paso

El Paso, TX, USA

9.5 Km
At least two strongly correlated groups
It’s not geographic
It’s poverty and …
It’s poverty and vaccination

Geographic proximity (pca 1 score)

Proportion in poverty

Proportion vaccinated

First Correlation Group

Second Correlation Group
Poverty and influenza in Dallas, TX
Higher hospitalization rates in poorer zip codes
Poorer zip codes are in sync

Pairwise correlation vs Percent in poverty
Predicting hospitalizations

Influenza-associated hospitalizations

Influenza-like Illness (ILINet)

Patients with U.R.I. (Biosense 2.0)

Influenza-like Illness (Google Flu Trends)
Predicting hospitalizations in the richest areas

Hospitalizations

0 - 7.5% in poverty

- Observed
- Fitted

2007  2009  2011
Predicting hospitalizations in the poorest areas

>21.5 % in poverty
Modeling infectious diseases

Inequality & disease

Social clustering & Ebola
Clustering and disease transmission

High clustering  Low clustering

t0
Clustering and disease transmission

High clustering

Low clustering

$t_0$

$t_1$
Clustering and disease transmission

High clustering | Low clustering
---|---
t0 | ![Graph at t0 for high clustering](image1)
   | ![Graph at t0 for low clustering](image2)
t1 | ![Graph at t1 for high clustering](image3)
   | ![Graph at t1 for low clustering](image4)
t2 | ![Graph at t2 for high clustering](image5)
   | ![Graph at t2 for low clustering](image6)
Outbreak in Sierra Leone

Scarpino & Iamarino et al. 2015

Cumulative Incidence (observed)

Cumulative Mortality (observed)

May 27th  June 16th  July 6th  July 26th  Aug. 15th  Aug. 30th

Scarpino & Iamarino et al. 2015
Evidence for clustered transmission

- Incidence (observed)
- Incidence (Fitted Values - No Clustering)
- Mortality (observed)
- Mortality (Fitted Values - No Clustering)

Cumulative

May 27th | June 16th | July 6th | July 26th | Aug. 15th | Aug. 30th
Evidence for clustered transmission
1. Dynamic importance of clustering

Predicting Confirmed Cases
(Nov. 2nd 2014)

Proportion Error

Clustered | Unclustered

-0.2 | 0.3
-0.1 | 0.2
0.0 | 0.1
0.1 | 0.0
Predicting Confirmed Cases
(Nov. 2nd 2014)

Proportion Error

Clumped

Unclumped
3. Perhaps we can forecast outbreaks

Predicting Confirmed Cases
(Nov. 2nd 2014)

- Clustered
- Unclustered

Proportion Error

-0.2
-0.1
0.0
0.1
0.2
0.3
What happens when you replace sick workers?
What happens when you replace sick workers?
What happens when you replace sick workers?
How does *Relational Exchange* work?
How does *Relational Exchange* work?
Accelerating exponential growth
Accelerating exponential growth

![Graph showing exponential growth](image)

Proportion infectious

Time

- Relational Exchange
- Standard Model
- Exp.
Empirical evidence for *Relational Exchange*
Empirical evidence for *Relational Exchange*

**Influenza**

- Observations (Obs. data)
- Training data
- Exponential model fit
- Acc. exp. growth

**Dengue**

- Observations (Obs. data)
- Acc. exp. growth

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**Graph Details**

- **X-axis:**
  - **Influenza:** Oct. 2012 – May 2013
  - **Dengue:** May 21st 2005 – Oct. 29th 2005

- **Y-axis:**
  - **Percent I.L.I.** (log-scale)
  - **Dengue cases** (log-scale)

- **Data Points:**

---

**Legend:**

- **Obs. data**
- **Training data**
- **Exp. model fit**
- **Acc. exp. growth**
Empirical evidence for *Relational Exchange*

**Influenza**

**Percent I.L.I.**

|------|------|------|------|------|------|------|------|------|------|

**Dengue**

**Cases**

<table>
<thead>
<tr>
<th>Year</th>
<th>1991</th>
<th>1993</th>
<th>1995</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1991</td>
<td>1993</td>
<td>1995</td>
<td>1997</td>
<td>1999</td>
<td>2001</td>
<td>2003</td>
<td>2005</td>
</tr>
</tbody>
</table>
Empirical evidence for *Relational Exchange*

Influenza in the U.S.A. 1926 - 1951

Proportion of influenza seasons w/ accelerating spread

- 1.00
- 0.75
- 0.50
- 0.25
- 0.00
- State avg.
- Missing

N: 516 Km
Why do predictions fail?

\[ R_0 = T \left( \frac{\langle K^2 \rangle - \langle K \rangle}{\langle K \rangle} \right) \]

\[ R_0 = \frac{\beta S}{\gamma} \]
Why do predictions fail?

El Paso, TX, USA

First Correlation Group

Second Correlation Group

9.5 Km
Why do predictions fail?

High clustering       Low clustering

\[ t_0 \]
\[ t_1 \]
\[ t_2 \]
Why do predictions fail?

- **Influenza**

  ![Influenza Graph](image)

- **Dengue**

  ![Dengue Graph](image)
Toward a complex systems theory of disease

Modified from Gire et al. 2014
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Questions?

Samuel V. Scarpino  
Omidyar Fellow  
Santa Fe Institute

scarpino@santafe.edu  
@svscarpino  
scarpino.github.io