COMMUNICATION

# Modeling Ebola at the Mathematical and Theoretical Biology Institute (MTBI)

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*Communicated by Steven J. Miller*

**Abstract**

Work with STEM students at MTBI advanced the possibility that quarantine can cause increased levels of Ebola transmission.[1]

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*This research has been partially supported by NSF-DMD 1263374, NSF-IRES 1261211 and DOD H98230-15-1-0021. The views expressed are the sole responsibility of the authors and not the funding agencies.*

[1] *Write-up of a Centennial Lecture by Castillo-Chavez at the 2015 MathFest of the Mathematical Association of America.*

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DOI: http://dx.doi.org/10.1090/noti1364

## Disease, Epidemics, and Models

Since twenty-first-century problems stretch across disciplines, they require interdisciplinary approaches. As Steve Strogatz [1] observes:

> Cancer will not be cured by biologists working alone. Its solution will require a melding of both great discoveries of 1953 [the Fermi-Pasta-Ulam computer experiment and the Watson and Crick discovery of the chemical structure of DNA]. Many cancers, perhaps most of them, involve the derangement of biochemical networks that choreograph the activity of thousands of genes and proteins. As Fermi and his colleagues taught us, a

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> complex system like this can't be understood merely by cataloging its parts and the rules governing their interactions. The nonlinear logic of cancer will be fathomed only through the collaborative efforts of molecular biologists—the heirs to Dr. Watson and Dr. Crick—and mathematicians who specialize in complex systems—the heirs to Fermi, Pasta and Ulam.

Per Strogatz, the future scientists at the Mathematical and Theoretical Biology Institute (MTBI), established at Cornell University in 1996, learn the problem-solving ropes by engaging in collaborative, cross-discipline efforts—often enhanced by the systematic use of computer experiments and data science—to answer focused scientific questions. The interdisciplinary research described in this note involves the dynamics of deadly diseases such as Ebola.

## Germ Theory and Epidemic Models

Aristotle's hypothesis on the existence of invisible microorganisms; Antonie van Leeuwenhoek's discovery of such germs; and the germ-theory framework advanced by Jacob Henle, Robert Koch, Joseph Lister, and Louis Pasteur served as the foundation for the study of infectious diseases. Daniel Bernoulli in 1760 introduced a mathematical model used immediately to assess the effectiveness of inoculation against smallpox virus. Much later, W. N. Hamer developed and analyzed a discrete-time mathematical model to help understand the recurrence of measles epidemics.

In 1902 Sir Ronald Ross was awarded the Nobel Prize for tying malaria to *Plasmodium* parasites carried by mosquitoes. He formulated a nonlinear system of differential equations that captured its transmission dynamics. His clear understanding of host-vector-pathogen dynamics drove him to consider the impact of such interactions at the population level. Ross concluded from his analysis that reducing the vector (mosquito) population below some threshold would drastically decrease malaria's devastating impact on the health and survival of individuals living in malaria-infested regions. Following Ross's legacy, Kermack and McKendrick advanced the concept of epidemic threshold in the context of communicable diseases such as influenza or tuberculosis. The ideas of these pioneers were later popularized by M. Gladwell in his best-selling book *The Tipping Point*. Important expansions and variations on these foundational models have given rise to the field of mathematical epidemiology and its applications (see e.g. [2]).

Ross also highlighted in his research the power of abstraction inherent in mathematics by explicitly alluding to the applicability of his malaria framework to the study of sexually transmitted diseases (STD). Cooke and Yorke followed through on Ross's ideas and produced one of the first STD models in 1973. Hethcote and Yorke later introduced the concept of *core* group, a concept which has had a tremendous impact on policies aimed at reducing gonorrhea incidence.

## Ebola Control and Ebola Spatial Dynamics

As the Ebola outbreak spread across West Africa in 2014–2015, 24/7 cable news coverage ensured that fear of the disease spread among large subpopulations of individuals living far outside affected areas.

Whether or not Ebola-infected individuals can be detected before becoming infectious turned out to be a central question. MTBI alumnus Diego Chowell wondered how effective Ebola detection using Polymerase Chain Reaction (PCR) would be if deployed at the presymptomatic stage of the disease. Following the research carried out by MTBI alumni during the 2003 Canada SARS outbreak, Chowell et al. [3] proposed the following single outbreak epidemic model; see also Figure 1, and Tables 1 and 2.

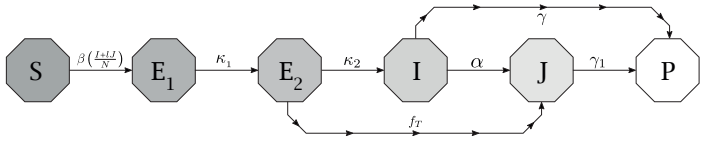


**Figure 1. Modeling the effect of early detection of Ebola.**

$$
\begin{aligned}
\dot{S} &= -\beta S\left(\frac{I+lJ}{N}\right),\\
\dot{E}_1 &= \beta S\left(\frac{I+lJ}{N}\right) - \kappa_1 E_1,\\
\dot{E}_2 &= \kappa_1 E_1 - \kappa_2 E_2 - f_T E_2,\\
\dot{I} &= \kappa_2 E_2 - (\alpha+\gamma) I,\\
\dot{J} &= \alpha I + f_T E_2 - \gamma_r J,\\
\dot{R} &= \gamma(1-\delta) I + \gamma_r (1-\delta) J,\\
\dot{D} &= \gamma\delta I + \gamma_r \delta J,\\
N &= S + E_1 + E_2 + I + J + R.
\end{aligned}
$$

**Table 1. Variables of the Model.**

| Class | Description |
|---|---|
| $S$ | Susceptible |
| $E_1$ | Latent undetectable |
| $E_2$ | Latent detectable |
| $I$ | Infectious and symptomatic |
| $J$ | Isolated |
| $R$ | Recovered |
| $D$ | Ebola-induced death |
| $P$ | $D+R$ |

**Table 2. Parameters of the Model.**

| Parameter | Description | Value |
|---|---|---|
| $\beta$ | Mean transmission rate | 0.333 |
| $1/k_1$ | Mean period between undetectable state and latent detectable state | 4 days |
| $1/k_2$ | Mean period between latent detectable state to infectious state | 3 days |
| $1/\alpha$ | Mean period between infectious state and isolation state | 3 days |
| $1/\gamma$ | Mean period between infectious state and recovery or Ebola-induced death state | 6 days |
| $1/\gamma_I$ | Mean period between isolation state and recovery or Ebola-induced death state | 7 days |
| $f_T$ | Fraction of latent individuals diagnosed before onset of symptoms | (0.1) |
| $\delta$ | Fatality rate | 0.7 |
| $l$ | Relative transmissibility of isolated individuals | (0.1) |

This transmission model was parameterized using prior MTBI research on Ebola dynamics. It was determined, via simulations, that the use of modern technologies (PCR) are indeed insufficient to stop an Ebola outbreak unless enough facilities are available to isolate a *significant* proportion of Ebola-diagnosed individuals (see Figure 2). Moreover, the DNA polymerase used in the PCR reaction is prone to errors and can lead to mutations in the fragment generated. Additionally, the specificity of the generated PCR product may be changed by nonspecific binding of the primers to other similar sequences on the template DNA. Furthermore, in order to design primers to generate a PCR product, some prior information on the sequence is usually necessary.

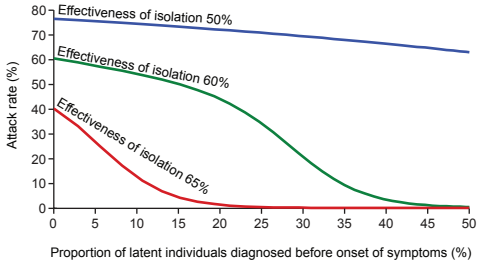


**Figure 2. Modeling the effect of early detection of Ebola. The attack rate is defined as the total number of Ebola cases per population size.**

The research carried out in response to the 2002–2003 SARS outbreak identified specific approaches that made it possible to assess the potential of a disease outbreak with limited data. Today, epidemiologists using single outbreak epidemiological models in conjunction with incoming reported outbreak data can estimate the basic reproduction number $\mathcal{R}_0$ and often also the typically decreasing effective reproductive number $\mathcal{R}_{\text{eff}}(t)$. That is, it is possible to estimate the *initial* epidemic growth rate and associated *typically* declining rates of growth over time, the result of the depletion of susceptible individuals over the course of an outbreak. Towers et al. [4] found out that the rate of growth in West Africa was in fact not decreasing over time but increasing (see Figure 3). This group of researchers used changing epidemic growth estimates to forecast 6,800 cases by the end of September 2014, quite close to 6,553, the actual number of cases reported by the World Health Organization.

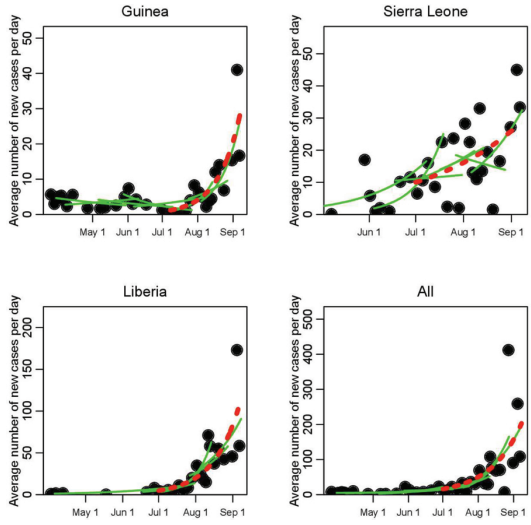


**Figure 3. Time series of recorded average number of new EVD cases per day during the initial phase of the 2014 West African outbreak for Guinea, Sierra Leone, and Liberia (dots). The green lines show a selection of the piecewise exponential fits to the data. The red lines show moving-window exponential fits from July 1 onwards.**

Our epidemiologically model-driven data analysis drove us to consider the possibility that the enforced "cordons sanitaires" mass quarantine restrictions in West Africa in late summer 2014, which forcefully restricted the movement of individuals within the most affected Ebola areas, may have in fact contributed to increased levels of Ebola transmission due to overcrowding and poor sanitation [4].

MTBI alumnus Edgar Diaz Herrera in his PhD dissertation [5] looked at the dynamics of visibly symptomatic diseases such as leprosy or Ebola on the spatial dynamics of epidemics. He asked whether individuals will aggregate in particular spatial patterns as a result of physically visible symptoms. Diaz Herrera introduced the epidemiological classes of susceptible $S(x,t)$, infectious

asymptomatic $I_1(x,t)$, and infectious *visibly* symptomatic $I_2(x,t)$ via the following nonlinear system of partial differential equations in response to his question:

$$\begin{aligned}
\frac{\partial S}{\partial t} &= -\frac{\beta}{1+I_2}SI_1 + \alpha I_2 + D_S\frac{\partial^2 S}{\partial x^2},\\
\frac{\partial I_1}{\partial t} &= \frac{\beta}{1+I_2}SI_1 - \delta I_1 + D_1\frac{\partial^2 I_1}{\partial x^2},\\
\frac{\partial I_2}{\partial t} &= \delta I_1 - \alpha I_2 + D_2\frac{\partial^2 I_2}{\partial x^2}.
\end{aligned}$$

Diaz Herrera's model incorporated a modified mass-action law, where the transmission coefficient $\hat{\beta}$ was taken to be a decreasing function $\frac{\beta}{1+I_2}$ of $I_2$. The growing population of the visibly infectious is assumed to decrease the contact rates between individuals. We found [6] that the above reaction-diffusion system was capable of supporting diffusive instabilities when $I_2$ individuals are not infectious for too long. In this case, aggregation occurs when $D_2 > D_1$, rapidly when $D_2 \gg D_1$; see Figure 4.

## Lagrangian Approach to Epidemic Models and Ebola

Lagrangian models (see e.g. [7]) keep track of each individual at all times. A general Susceptible-Infectious-Susceptible, or SIS, model involving $n$-patches is given by the following system of nonlinear equations:

$$\begin{cases}
\dot{S}_i = b_i - d_i S_i + \gamma_i I_i - \sum_{j=1}^n (S_i \text{ infected in Patch } j)\\
\dot{I}_i = \sum_{j=1}^n (S_i \text{ infected in Patch } j) - \gamma_i I_i - d_i I_i\\
\dot{N}_i = b_i - d_i N_i,
\end{cases}$$

where $b_i$, $d_i$, and $\gamma_i$ denote the per capita birth, natural death, and recovery rates respectively. Infection is modeled as follows:

$$\begin{aligned}
[S_i \text{ infected in Patch } j] = {} & \underbrace{\beta_j}_{\text{the risk of infection in Patch } j}\\
\times\ & \underbrace{p_{ij}S_i}_{\text{susceptible from Patch } i \text{ who are currently in Patch } j}\\
\times\ & \underbrace{\frac{\sum_{k=1}^n p_{kj}I_k}{\sum_{k=1}^n p_{kj}N_k}}_{\text{proportion of infected in Patch } j},
\end{aligned}$$

where the last term accounts for the *effective* infection proportion in Patch $j$ at time. The model reduces to the $n$-dimensional system

$$\dot{I}_i = \sum_{j=1}^n \left(\beta_j p_{ij}\left(\frac{b_i}{d_i} - I_i\right)\frac{\sum_{k=1}^n p_{kj}I_k}{\sum_{k=1}^n p_{kj}\frac{b_k}{d_k}}\right) - (\gamma_i + d_i)I_i, \quad i = 1,2,\dots,n,$$

with a basic reproduction number $\mathcal{R}_0$ that is a function of the risk vector $\mathcal{B} = (\beta_1, \beta_2, \dots, \beta_n)^t$ and the residence times matrix $\mathbb{P} = (p_{i,j}), i, j = 1, \dots, n$, where $p_{i,j}$ denotes the proportion of the time that an $i$-resident spends visiting Patch $j$. We show that when $\mathbb{P}$ is irreducible (patches are strongly connected), the Disease Free State is globally asymptotically stable (g.a.s.) if $\mathcal{R}_0 \le 1$, while whenever $\mathcal{R}_0 > 1$ there exists a unique interior equilibrium which is g.a.s.

The patch-specific basic reproduction number is given by

$$\mathcal{R}_0^i(\mathbb{P}) = \mathcal{R}_0^i \times \sum_{j=1}^n \left(\frac{\beta_j}{\beta_i}\right) p_{ij}\left(\frac{p_{ij}\frac{b_i}{d_i}}{\sum_{k=1}^n p_{kj}\frac{b_k}{d_k}}\right),$$

from where we see, for example, that if $p_{kj} = 0$ for all $k = 1, \dots, n$, and $k \neq i$, then the disease dies out in Patch $i$.

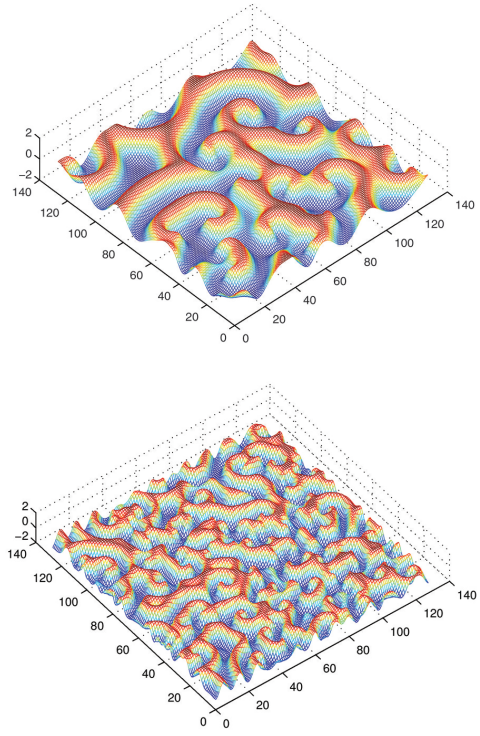

**Figure 4. The densities for the asymptomatic infectious $I_1$ are plotted for $\alpha = 0.05, \beta = 1$ and $\delta = 1.3$ for the Diaz Herrera model. Slow spatial aggregation of individuals (top) occurs when the coefficients $D_2 > D_1$ ($D_1 = 10, D_2 = 20$), and fast spatial aggregation (bottom) occurs when $D_2 \gg D_1$ ($D_1 = 10, D_2 = 80$).**

Ongoing MTBI alumni work [7] uses this model to test whether movement restrictions reduce overall transmission. We embed susceptible, exposed, infectious, dead, and removed categories into the simple and basic single-patch (S E I D R) model

**Table 3. Variables and Parameters of the Contagion Model.**

| Parameter | Description | Base model values |
|---|---|---|
| $\alpha$ | Rate at which asymptomatic individuals recover (not infectious due to acquired immunity) | $0 - 0.458\ \text{day}^{-1}$ |
| $\beta$ | Per susceptible infection rate | $0.3056\ \text{day}^{-1}$ |
| $\gamma$ | Rate at which an infected recovers or dies | $\frac{1}{6.5}\ \text{day}^{-1}$ |
| $\kappa$ | Per capita progression rate | $\frac{1}{7}\ \text{day}^{-1}$ |
| $\nu$ | Per capita body disposal rate | $0.5\ \text{day}^{-1}$ |
| $f_{\text{dead}}$ | Proportion of infected who die due to infection | 0.708 |
| $\varepsilon$ | Scale: Ebola infectiousness of dead bodies | 1.5 |

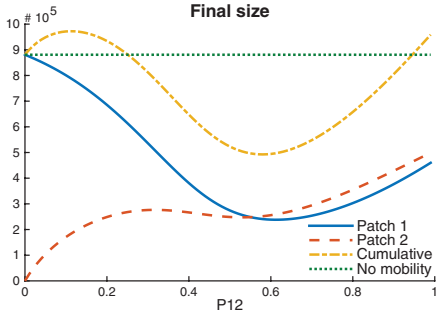


**Figure 5. Dynamics of maximum final size in the one-way case with parameters:** $\varepsilon_{1,2} = 1, \beta_1 = 0.305, \beta_2 = 0.1, f_{\text{death}} = 0.708, k = 1/7, \alpha = 0, \nu = 1/2, \gamma = 1/6.5$**. The initial populations are** $N_1 = N_2 = 1,000,000$**. For most values of the one-way mobility from Patch 1 (high risk) to Patch 2 (low risk), the cumulative final size of the epidemic is smaller than for no mobility.**

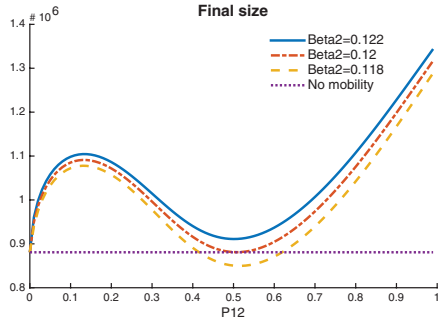


**Figure 6. Dynamics of maximum final size in the one-way case with parameters:** $\varepsilon_{1,2} = 1, \beta_1 = 0.305, \beta_2 = 0.122, 0.12, 0.118, f_{\text{death}} = 0.708, k = 1/7, \alpha = 0, \nu = 1/2, \gamma = 1/6.5$**. The initial populations are** $N_1 = N_2 = 1,000,000$**. As the level of risk** $\beta_2$ **in the low-risk patch increases, the value of positive mobility disappears.**

given by the following set of equations:

$$\begin{cases} N = S + E + I + D + R \\ \dot{S} = -\beta S \frac{I}{N} - \varepsilon\beta S \frac{D}{N} \\ \dot{E} = \beta S \frac{I}{N} + \varepsilon\beta S \frac{D}{N} - (\kappa + \alpha)E \\ \dot{I} = \kappa E - \gamma I \\ \dot{D} = f_{\text{dead}}\gamma I - \nu D \\ \dot{R} = (1 - f_{\text{dead}})\gamma I + \nu D + \alpha E. \end{cases}$$

See Table 3 for a description of the parameters. The transition from $D$ to $R$ represents the proper and appropriate handling of dead bodies during the burial or ritual services.

In the simplest version of our Lagrangian framework, there is a *two-patch* world of "residents" and "visitors", connected by a residence time matrix

$$\mathbb{P} = \begin{pmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{pmatrix}.$$

We explore, via simulations, the role of restrictions in movement between patches. Preliminary simulations assume that the patches have equal populations, but the high-risk area is assumed to have a high population density, poor health facilities, and limited resources, while the low-risk area is assumed to host a sparsely distributed population and solid health facilities and resources. This is a standard hypothesis for communicable diseases in general, and it applies to Ebola in particular. The parts of West Africa where Ebola exploded are poverty-stricken areas, with much higher density than middle or upper middle class neighborhoods, so the hypothesis is reasonable. Figures 5 and 6 show how mobility and risk affect the final size of the epidemic. Sometimes quarantining the high-risk area yields a larger epidemic.

All differences are assumed to be captured by the assigned $\beta$-values.

Figure 5 and Figure 6 provide some ideas of the role that mobility and risk play in the dynamics of Ebola in connected high/low-risk environments. Figure 5 plots both the global and the *per* patch final epidemic size as a function of mobility from Patch 1 (high risk) to Patch 2, exclusively. We see,

for example, that high single-direction mobility leads to a smaller cumulative final epidemic size in this case.

Of course, Figure 5 provides only part of the story. In Figure 6 we plot global epidemic size as a function of the level of risk in the low-risk patch ($\beta_2$). We see from simulations that the quality of services in Patch 2, as defined by $\beta_2$, would lead to a beneficial global result only if $\beta_2 \leq 0.12$. Also, simulations suggest that the choice $\alpha > 0$ brings the reproduction number $\mathcal{R}_0$ below one much faster for a wide range of residence times.

## Final Remarks and Acknowledgements

This article has provided the opportunity to showcase the type of research carried out by MTBI students over the past twenty years. Members of the Simon A. Levin Mathematical, Computational and Modeling Sciences Center, many of them external faculty members, join forces in addressing the research agenda proposed by undergraduate students. The research has been funded via NSF, NIH, DOD, and Sloan grants over the past two decades. We want to particularly thank Fred Brauer, Ted Greenwood, James Schatz, and our friends and supporters at NSF for their continuous support for this experimental model of education and mentorship through research, a model that has contributed to the education of a significant number of minority students and women.

## References

[1] Steven Strogatz, The real scientific hero of 1953, *The New York Times*, November 4, 2003.

[2] Herbert W. Hethcote, The mathematics of infectious diseases, *SIAM Review* **42** (2000), no. 4, 599–653. MR1814049 (2002c:92034)

[3] Diego Chowell, Carlos Castillo-Chavez, Sri Krishna, Xiangguo Qiu, and Karen S. Anderson, Modelling the effect of early detection of Ebola, *The Lancet Infectious Diseases* **15** (2015), no. 2, 148–149.

[4] Sherry Towers, Oscar Patterson-Lomba, and Carlos Castillo-Chavez, Temporal variations in the effective reproduction number of the 2014 West Africa Ebola Outbreak, *PLoS currents* **6** (2014).

[5] Edgar Diaz Herrera, *Diffusive Instability and Aggregation in Epidemics*, Arizona State University, 2010. MR2792949

[6] Kamuela E. Yong, Edgar Díaz Herrera, and Carlos Castillo-Chavez, From bee species aggregation to models of disease avoidance: The Ben-Hur effect, preprint, arXiv:1510.04364, 2015.

[7] Derdei Bichara, Yun Kang, Carlos Castillo-Chavez, Richard Horan, and Charles Perrings, SIS and SIR epidemic models under virtual dispersal, *Bulletin of Mathematical Biology* (2015), DOI 10.1007/s11538-015-0113-5. MR3427113

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