

PROTOCOL FOR:

Sex-assortativity and the spread of TB on contact networks

Spring 2019

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Background:

TB is a respiratory-transmitted infectious disease that is heterogeneously distributed globally and concentrated in Africa and Asia. In addition, TB is heterogeneously distributed within populations; in particular, men face higher risk factors than women. The global male:female TB case ratio is 1.9, a pattern strikingly consistent across countries.

Male-bias in TB case reports is thought to be due to sex-specific differences in exposure to Mtb or susceptibility to disease following exposure, or a combination of the two. Exposure rates could be mediated by differences in behaviors and societal gender roles. For example males may have more contacts or be more central in social networks though previous studies have failed to substantiate this (Miller et al. *in prep*, Mossong et al. 2008, etc.). Alternatively, sex-specific exposure rates could be driven by differences in the types of contacts that males have in comparison to females. Specifically, exposure could be higher in males due to assortative mixing which is where individuals tend to associate with others similar to them, creating sub-groups within a social network. However, we lack studies analyzing the role of hypothesized exposure mechanisms at driving male-bias. More studies identify sex-specific susceptibility (smoking, hormones, genetics, immunology) as the key component driving male bias.

We wondered whether the types of contacts that men have, specifically their preferential social mixing with other men, could contribute to male-bias in TB case reports per se or if previously described differences in susceptibility between the sexes are necessary to explain male-bias

Research questions:

1. Can sex-assortative mixing lead to male-bias by itself or is sex-specific susceptibility required to explain male-bias?
2. What are the effects of sex-assortative mixing on disease spread (peak size/time, variation in outbreak size/duration)?

Study design:

We will examine the effects of sex-assortativity and sex-specific susceptibility on the ratio of male to female cases using models of disease spread on simulated networks. In the simulated networks, each node will represent an individual and each link is a connection between individuals that infection can spread.

Network simulation:

Simulated networks will vary in level of sex-assortativity, r , calculated according to Newman (2003) as

$$r = \frac{\sum_i e_{ii} - \sum_i (a(i)b(i))}{1 - \sum_i (1 - a(i)b(i))} = \frac{Tr\mathbf{E} - ||E^2||}{1 - ||E^2||}$$

where e_{ij} is the fraction of edges connecting vertices of type i and j , $a(i) = \sum_j e_{ij}$ and $b(j) = \sum_i e_{ij}$. Alternatively, if \mathbf{E} is the matrix of e_{ij} and $\|\mathbf{x}\|$ is the sum of all elements in a matrix \mathbf{X} , then assortativity can be calculated with the fraction of edges within-sex ($Tr\mathbf{E}$) and the fraction of edges that would be within groups if connections were random $\|\mathbf{E}^2\|$. Here, if edges were distributed randomly, $Tr\mathbf{E} = \|\mathbf{E}^2\| = 0.5$ and $r = 0$. Typically, r ranges from $0 \gg r \geq 1$ because disassortative networks are much closer to random networks than are assortative networks.

Network modularity (Q) is another measure of non-random mixing in networks: $Q = \sum_i e_{ii} - a_i^2$ where e_{ij} is the fraction of edges in the network that link nodes in community i to community j and $a_i = \sum_j e_{ij}$ represents the fraction of edges in the network that link nodes to community i . In this formulation, if edges were to fall between nodes without any regard for communities, $e_{ij} = a_i a_j$ and have $Q=0$. The maximum value of Q is $1 - \frac{1}{K}$ where K is the number of modules.

We will generate scale-free networks according to the parameters listed in Table 1 using the classic BA-algorithm. Following network generation, we will update the networks as following:

1. Assign nodes randomly as male (0) or female (1).
2. Calculate temporary value of sex-assortativity in the network (r_t).
3. If r_t is not within ϵ of r , randomly choose a proportion α of 0–1 edges (i.e, a male–female edge) if $r \geq 0$ and re-wire them or if $r < 0$, choose a proportion α of 0–0 and 1–1 edges and re-wire them.
4. Repeat step 3 until $|r_f - r_t| \leq \epsilon$.

Network will be generated with parameters shown in Table 1.

Table 1: Network parameters.

Variable	Value
Sex-assortativity, r	(-0.5, 0.5) by 0.1
Degree distribution, $p(K)$	$\frac{k^{-\alpha}}{\zeta(\alpha)}$
Mean degree, $\langle K \rangle$	10
Network size, N	500, $1 \cdot 10^3$, $2 \cdot 10^3$, $5 \cdot 10^3$
Tolerance, ϵ	0.035
Rewiring proportion, α	0.2

Disease transmission modeled as SIR:

Nodes can exist as either susceptible, infected, or recovered (Table 2).

We will model disease spread on networks as a continuous time Markov chain with infection spreading along an edge at rate τ and recovery happening at rate γ .

An infected node transmits to each of its uninfected neighbors independently with probability $p(T) = 1 - e^{-\tau T}$ where T is the duration of infection for the infected node.

We will use an event-driven algorithm for simulations on synthetic networks implemented in the python module EoN (Kiss, Miller & Simon 2017).

We will assume SIR dynamics as our model of disease spread (Table 2).

Table 2: Disease parameters.

Variable	Value
Initial susceptible, S_0	$N - 0.05 \cdot N$
Initial infected, I_0	$0.05 \cdot N$
Infection rate, τ	0.125, 0.25, 0.375
Recovery rate, γ	1

Variable	Value
Estimated R_0	$\left[\frac{\tau}{\tau+\gamma}\right]\left[\frac{\langle K^2 \rangle - \langle K \rangle^2}{\langle K \rangle}\right]$

Analysis:

Network structure:

- Relationship between network structure (clustering, degree assortativity, diameter, degree variation) and assortativity

Case ratio:

- Relationship between assortativity and M:F case ratio
- Variation by network size and R_0

Disease spread:

- Relationship between assortativity and epidemic peak size, peak time, variation in outbreak size, variation in epidemic duration
- Variation by network size and R_0

Checklist:

- Understand the relationship between measures of community structure (Q vs. r) for K=2 modules
- Run study across larger parameter grid and more replicates
- Understand and relate results to Salathe and Sah research
- Decide on next steps which could be: (1) Seed epidemics disproportionately in one module; (2) Incorporate sex-specific susceptibility; (3) Incorporate latent class of individuals; (4) Sample epidemics according to COHSONET and validate results

Important background papers:

Kiss, I Z, J C Miller, and PL Simon Cham Springer. 2017. “Mathematics of Epidemics on Networks.” Springer.

Newman, MEJ. 2003. “Mixing Patterns in Networks.” Physical Review E 67 (2). American Physical Society. doi:10.1103/PhysRevE.67.026126.

Nhamoyebonde, Shepherd, and Alasdair Leslie. 2014. “Biological Differences Between the Sexes and Susceptibility to Tuberculosis.” Journal of Infectious Diseases 209 (suppl 3): S100–S106. doi:10.1093/infdis/jiu147.

Pastor-Satorras, R, and A Vespignani. 2001. “Epidemic Dynamics and Endemic States in Complex Networks.” Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics 63 (6 Pt 2): 066117. doi:10.1103/PhysRevE.63.066117.

Perkins, S E, M F Ferrari, and P J Hudson. 2008. “The Effects of Social Structure and Sex-Biased Transmission on Macroparasite Infection.” Parasitology 135 (13): 1561–69. doi:10.1017/S0031182008000449.

Sah, Pratha, Stephan T Leu, Paul C Cross, Peter J Hudson, and Shweta Bansal. 2017. “Unraveling the Disease Consequences and Mechanisms of Modular Structure in Animal Social Networks..” Proceedings of the National Academy of Sciences of the United States of America 114 (16). National Academy of Sciences: 4165–70. doi:10.1073/pnas.1613616114.

Sah, Pratha, Lisa O Singh, Aaron Clauset, and Shweta Bansal. 2014. “Exploring Community Structure in Biological Networks with Random Graphs.” *BMC Bioinformatics* 15 (220). BioMed Central. doi:10.1186/1471-2105-15-220.

Salathé, Marcel, and James H Jones. 2010. “Dynamics and Control of Diseases in Networks with Community Structure.” Edited by Christophe Fraser. *PLoS Computational Biology* 6 (4). Public Library of Science: e1000736. doi:10.1371/journal.pcbi.1000736.

CHANGE-LOG:

- [bullet list of changes to protocols with reasons for each change]