Multi-strain disease dynamics on metapopulation networks.
Response to Reviewers' Comments (Not invited to resubmit)

February 25, 2020

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Reviewer 1

This work focuses on combining multi-strain disease dynamics and metapopulation network structure connected by movement and shows how their interactions affect the disease dynamics.

Authors used the multi-strain model framework developed by Gupta et al, 1998 as well as the framework developed by Xiao et al, 2011 to model the movement between populations. Combination of these two frameworks will help us better understand the disease dynamics and although authors have made some assumptions to simplify the model, I think this is a valuable work.

Below I have few minor comments:

Lines 100-105 discusses the results shown in Figure 3. It is mentioned that when origin populations have both cyclical and steady state dynamics, the destination population inherits the cyclical dynamics. Please mention in the text that the steady state dynamic also dampens the cyclical dynamics of the destination population. Also, please refer to figure 3 in the text.

Done.

Lines 129-130, the difference in mean time between epidemic peaks across network types does not seem to be significant in Figure 4. If their differences are statistically significant, please mention it in the text.

As these are simulation results, any difference, no matter how small, will become significant with a large enough number of simulations. For this reason, we have opted to not run statistical tests on these data.

Please in the discussion section, discuss how considering a discrete movement between individuals in the population can change the results of this work.

Please fix these:
Line 225: individuals moving from from

Done

Line 232: movement of between 0 *and* 100%*...*

Not sure what is wrong about this construction.

Line 234: each non-zero off-diagonal element of of

Done

Reviewer 2

The Writing

Abstract: I find the language and general writing of this abstract to be below the level that I have come to expect from this journal. It sounds very choppy and doesn't fully convey the brief contents of the paper.

We have reworked the abstract to hopefully improve flow and comprehension.

line 39: "as IT would be"

Done

Results: PLOS comp. bio. requires past tense results section like most academic journals.

Done

lines 52-53: The comparison between the two approaches is written in a confusing way where the reader thinks the next approach is going to be mentioned but it already has.

We have rewritten this sentence for greater clarity.

lines 75-81: I dont think it is necessary to describe the figures you are aiming to present before you present them. If you want to include a paragraph describing the layout of the results section, be more general. Describe figures in the appropriate results sub-sections and figure captions.

We'll leave this in for now and see what other reviewers think. I think this paragraph helps to orient the reader and provides the important clarifications regarding the presentation of only one strain and strain equivalence.

Methods: Well written and clear.

Discussion: Well written and clear.

The Study

Introduction: a good framing of the problem although it is at first difficult to understand whether the authors are referring to a network-based meta-population of susceptibles with containing a distribution of various strains associated with the structure or if they are referring to a genotype network subdivided into meta-populations. I think clarifying the representation after the problem is framed would be helpful as the this format jumps into the results before the methods.

I don't know what a "genotype network subdivided into meta-popuations" means, so going to hold out on any changes here.

Figure 1: lay out the classes described again in the caption and/or figure labels. Its unclear.

This is already laid out in the figure (right strip labels), but has now also been added to the legend.

Figure 2: very interesting

Figures: Font size can be increased in these figures and make sure to properly label axis labels (i.e. Figure 4).

Figure size has been increased to improve legibility. The axes of figure 4 are now better explained in the caption.

lines 128-129: This makes sense, if dynamics are inherited in chains, networks that create hubs with high in-degrees should amplify this behavior.

lines 150-152: This is true as this model is framed very much like many ecological meta-population network models.

lines 193-195: I have seen this modeled as a decaying function of the genotype distance between two strains. How is gamma employed?

For the specific model construction, we direct the reader to [Gupta et al., 1998] and [Lourenço et al., 2015]. In short, gamma can be thought of as the percentage of full immunity afforded by exposure to a strain sharing at least one allele with the target strain in the past. That is, if exposed to strain B, an individual's infection rate for similar strain A is now modified according to a factor of $1-\gamma$.

Methods: I believe the methods are sound. A subsection devoted specifically to experimental design might help. Are their any real-world network examples of reasonable sized meta-population networks you could employ in addition to your synthetic networks?

Unfortunately there are few real-world networks with sufficient resolution and concomitant records of disease dynamics. That said, we are working on testing this model with some real-world data and hope to publish these results independently from these, more general, theoretical results.

Over-arching Thoughts

I think this is an interesting paper that combines two important fields in epidemiology (multi-strain dynamics and meta-populations dynamics). I believe the methods to be sound but is very similar to a lot of community ecology work with communities of animal species replaced with pathogen strains. Many of the observed dynamics are similar to what you would expect but framed differently. The writing in this paper could use some attention. The abstract, introduction and results dont quite meet the requirements for how a Plos paper should read but are close.

Reviewer 3

The manuscript "Multi-strain disease dynamics on metapopulation networks" by Michalska-Smith et al. tackles the interplay of a multistrain epidemic model on top of a metapopulation structure. The problem is interesting and the authors attempt to categorize both the dynamics of the model and the role of the networks structure between metapopulations. This could be a valuable study, but in its current form both conceptualization and execution of the model fall short which is why I can not recommend further consideration of this manuscript for publication at the moment.

I have two main criticisms. First, at the conceptual level, it is not clear what the authors are trying to model. They motivate both the paper and its submission to the call for papers through population movement. We therefore imagine a network of cities where people move from one city to another, as is typical in metapopulation models. Yet, some of the results (e.g. Fig. 2) fix all parameters but vary cross-immunity based on the population in which we find an individual. What is this modelling? Two populations with different immune systems but where individuals can freely move from one to the other?

While the focus of our paper is on the dynamical results more generally, this is a fair criticism and we have re-run all of our analyses to instead vary along a more biologically interpretable axis: that of R_0. We also now mention this in the text.

Second, I do not think the Ordinary Differential Equations (ODEs) given in Eqs. (1-2) are correct.

We regret that the reviewer did not understand our model formulation (largely taken from [Lourenço et al., 2015]).

(i) Using forms like $(1 - z_{i,k})$ assumes that the population in k is conserved (i.e. sums to 1) which is not the case with the asymmetric mobility patterns used in the paper. Population sizes on the different nodes of the metapopulation network vary (in theory) but are always fixed and equal in the ODEs.

This construction does not assume contant population sizes, but rather is modeling the proportion of a population in each class (hence the summing to 1). The reviewer is correct that the modelling of migration in this way makes an implicit assumtion that populations are of the same size (that is, that 20% of population A corresponds to 20% of population B.) We now discuss this limitation.

(ii) There are death terms (e.g. $-\mu * y_i$) but no birth terms. Are we modelling a shrinking population? If the population size is conserved, all the ODEs should sum to zero.

This absence of birth terms stems from the proportional modelling framework and the implicit modelling of susceptibles [Lourenço et al., 2015]. As such, these need not be shrinking populations.

(iii) *Similarly, if traditional recovered individuals are found in w and z, why are there no positive terms proportional to σ ?*

There is no positive σ term in the equations for w and z because individuals are already members of these classes as soon as they are infected (their recovery does not affect their class status except for removal from y)

(iv) *Lastly, I am very confused by the infection terms (those proportional to β). Shouldn't the total number of exposure to i (positive rate in z_i) be exactly equal to the number of new infections by strain i? If so, why are the positive terms in dy_i/dt and dz_i/dt different? Those are all people newly exposed to strain i.*

This discrepancy is a result of partial immunity. While those with partial immunity do not become infectious when exposed (*i.e.* they do not end up in a y class), they nonetheless develop specific immunity to the challenging strain. Put another way, while all individuals in y_i are simultaneously in z_i (and w_i for that matter), that is not the only way to get specific immunity. z_i also contains individuals that have recovered from the disease and those that were exposed but protected from infection due to partial cross-protective immunity.

(v) *In the second system (with more than one population), there might be some typos in the mobility terms. Usually the element $A_{i,j}$ of a matrix A refers to the j-th column of the i-th row. Given the matrix Δ given in Section 5.3.1, the sum in Eq. (2) should be over elements $\Delta_{l,k}$ or the matrices shown should be transposed. Also, I believe the strain should be i in those terms and not j.*

We thank the reviewer for catching these errors in notation. We have fixed Eq. 2 and added clarification in the methods.

I might be misunderstanding the equations completely. If so, the authors should describe them much more clearly. Currently, I am too worried about the formulation of the model to be able to trust the results presented.

As our contribution is more a combination of theoretical frameworks than a novel set of equations, we deferred much of the details to the source references [Gupta et al., 1998, Lourenço et al., 2015]. Nevertheless, we have corrected the typo mentioned by the reviewer above.

Minor comments

1. *The model should be fully explained before results are discussed. Otherwise readers can't know what parameters are being varied or what they mean.*

   This organization was constrained by the PLOS Computational Biology requirements. We now place the methods after the introduction and before the results.

2. *In most figures, e.g. the top-middle panel of Figure 3, there is highly noisy and aperiodic behaviour. This could be interesting. What is going on exactly?*

   This is actually complex cyclical behavior (*i.e.* not aperiodic), as expected based on prior results [Gupta et al., 1998].

3. *Authors should be careful when discussing disease burden and explicitly mention whether they mean "per capita" or total incidence or exposure.*

   We have clarified our usage of this term throughout.

4. *Network structures should be better explained. What parameters are used and what constraints are enforced? Is the total number of interactions kept constant? Or is the average in- and out-degree kept fixed? More details are needed. In fact, why is the connectance of trees so noisy (Figure S4)? I have a hard time understanding the ensembles of random networks used in Fig. 4.*

   These statistics are reported in the SI. Also all code is publicly available...

5. *Barabási-Albert networks are trees (when m=1 in their original model) and their clustering always vanish wi..he original Watts & Strogatz paper). Otherwise, random trees are also small-world networks.*

   We thank the reviewer for catching this misstep and have corrected the reference in the text. We have also clarified the relationship between Barabási-Albert random graphs and trees.

6. *In figure 4, are random parameters randomized for every node in a given network or equal in every node but randomized from one network to the next? The caption says "randomized between each simulation" and "in each population", so I am guessing the latter is correct, but that should be a bit clearer.*

   We have tried to make this more clear.

7. *The comment that scale-free networks have increased epidemic size (line 161) is not quite right, or should come with some caveat. They have low (or vanishing) epidemic thresholds, but at high transmission rates they tend to have smaller epidemic size than an equivalent homogeneous network with the same density.*

   We now mention this holds in the case of sufficiently low spreading rate.

8. *I recommend changing the color scheme used in Fig. S3.*

   We have lightened the colors, but opt to keep the overall palette to match the rest of the figures.

9. *Mobility rates should not be described as "proportions of source population". While I understand what the authors mean, it could be confusing to some readers since it is a "proportion of population per unit time" (i.e. a rate on the population) and can therefore be greater than 1.*

We have clarified this in the methods and corrected the axis label of figure S2.

References

Sunetra Gupta, Niel Ferguson, and Roy Anderson. Chaos persistence, and evolution of strain structure in antigenically diverse infectious agents. *Science*, 280(5365):912–915, may 1998. doi: 10.1126/science.280.5365.912.

José Lourenço, Paul S Wikramaratna, and Sunetra Gupta. MANTIS: an R package that simulates multilocus models of pathogen evolution. *BMC Bioinformatics*, 16(1), may 2015. doi: 10.1186/s12859-015-0598-9.