



PATRICK D SCHLOSS, PHD
Department of Microbiology & Immunology
1150 W MEDICAL CENTER DR. 1526 MSRB I
ANN ARBOR, MICHIGAN 48109-0620
Phone: (734) 647-5801
Fax: (734) 764-3562
pschloss@umich.edu

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To the editors of mSystems:

We **resubmit** for your review: “Biogeography and Environmental Conditions Shape Phage and Bacteria Interaction Networks Across the Healthy Human Microbiome” by Geoffrey Hannigan and colleagues. This manuscript was reviewed once at mSystems by **Dr. Mani Arumugam** as manuscript **mSystems00056-17**. Because of the time required to incorporate the reviewer comments, the manuscript was rejected but invited for resubmission. We found the reviewer comments to be incredibly helpful and feel that addressing the comments has substantially improved the manuscript.

In addition to this letter, we have provided a revised version of the manuscript and a point-by-point response to the reviewer comments.

The reviewers’ primary concerns for the manuscript were 1) overstatements with underpowered datasets, 2) flaws in network analysis and inference, and 3) filtering actual viral sequences from the bacterial metagenomes. Although we attempted to present the underpowered sections of the manuscript as “case studies/observations”, we realize we fell short and further clarified this in the text. We addressed the perceived flaws in the network analysis and inference (second point) by clarifying our methods and interpretations. It appears our own inadequate descriptions and ambiguity resulted in the misunderstandings. We addressed the third point by including more robust quality control information done in the original studies (both computational and molecular QC) and our own supplemental analyses. We also addressed the other minor points raised by the reviewers.

In addition to the reviewer points, we addressed an issue a collaborator raised with our data analysis and presentation. We initially presented our random forest model performance using cross-validation results, but we should have shown nested cross-validation so as to avoid reporting an over fit model by parameter tuning during the cross-validation procedure. This change is represented in the manuscript and in Figure 1A.

We thank you for your consideration and look forward to your response.

Sincerely,

A handwritten signature in black ink, appearing to read 'P. Schloss'.

Patrick D. Schloss
Associate Professor
Frederick G. Novy Collegiate Professor of Microbiome Research