

Title: Causal Effects in Microbiomes Using Interventional Calculus

Log-likelihood : -15071.78

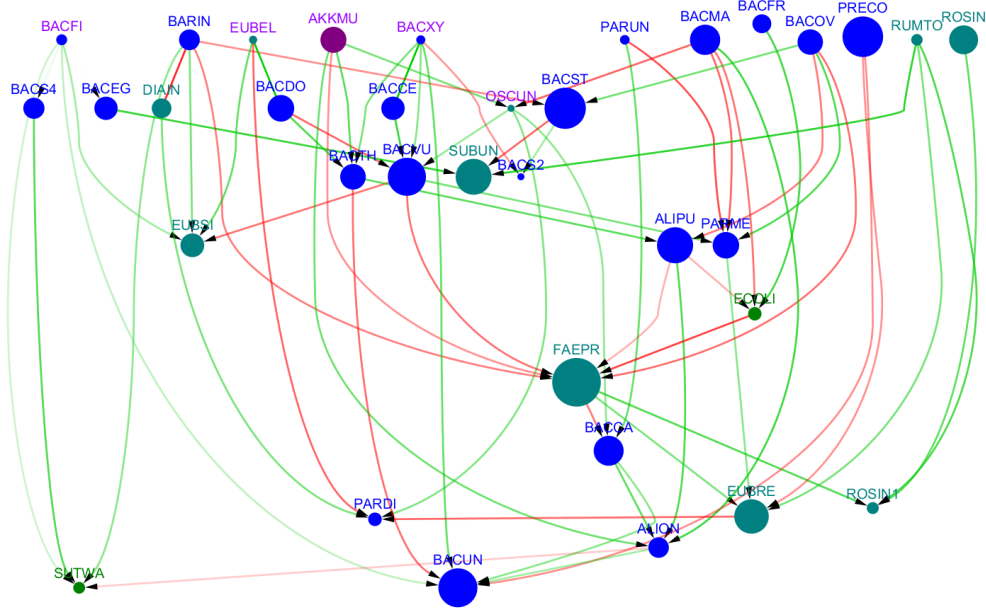


Figure S1. Causal network for non-IBD (healthy) data from iHMP data set. The labels of beneficial bacteria are in purple font. This figure was generated using the R package, `bnlearn`¹, and visualized using `Cytoscape` 3.5.0².

Crohn's disease (CD) is another form of IBD that may potentially affect parts of the digestive system. Unlike UC, the links between microbiomes and CD are less established and may be linked to host genetic factors³. However, some bacteria are suspected as either beneficial or harmful for subjects with CD. As with the UC data, we calculated the causal influence from the microbiome data for the CD cohort.

A brief discussion on causal analysis of *Disease* (CD-healthy) network

While *R. inulinivorans* is not known to be directly causally linked to CD, evidence suggests that *R. inulinivorans* is more abundant in CD patients⁸. The taxon *B. finegoldii* is present in the fecal microbiome. While its exact role may be unclear,

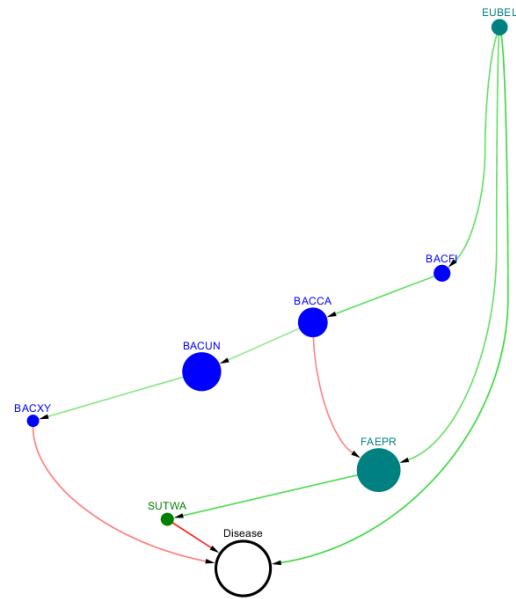


Figure S2. Sub-network of taxa reachable through directed path from *E. eligens* in the *disease* network for Ulcerative Colitis as shown in figure 9 in the paper. This figure was generated using the R package, bnlearn¹, and visualized using Cytoscape 3.5.0².

Log-likelihood : -16701.78

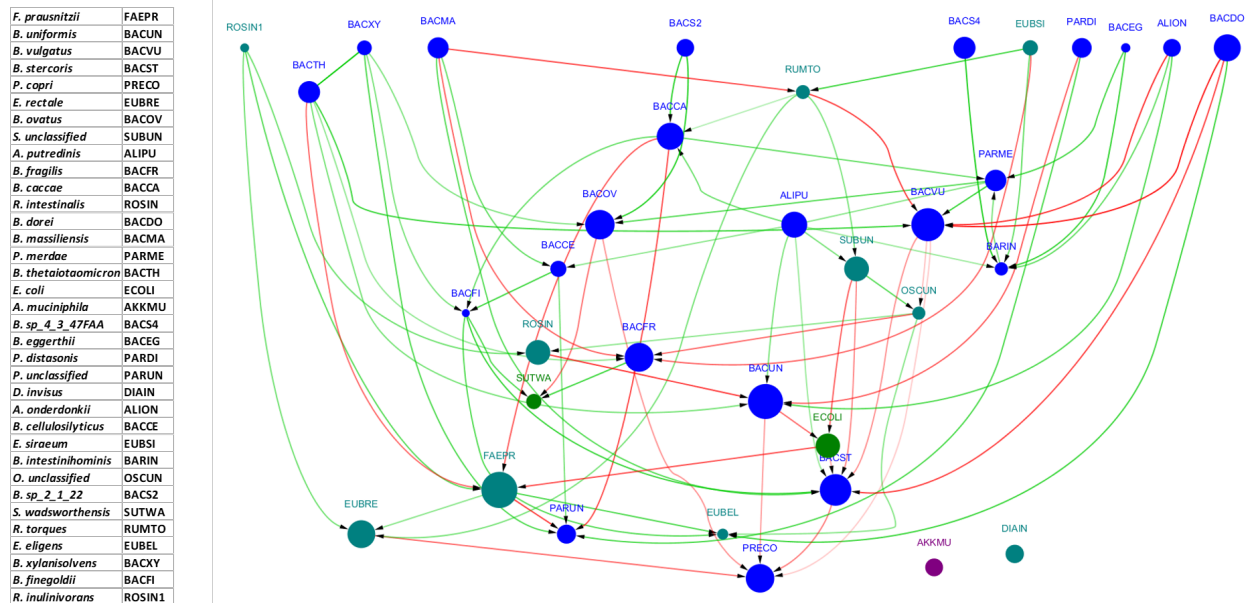


Figure S3. Causal network inferred from Crohn's disease (CD) data set of iHMP database. This figure was generated using the R package, bnlearn¹, and visualized using Cytoscape 3.5.0².

emerging reaserch suggests that it may play a role in maintaining a healthy colon, as well as potentially acting as a probiotic to help patients recover from illnesses such as inflammatory bowel disease and *Clostridium difficile* infection⁹. *E. eligens* is known for its beneficial behavior as a prebiotic in IBD⁶. *B. caccae* can be harmful in some cases for CD and IBD¹⁰ and *R. torques* is a pathogenic taxon for both UC and CD⁴. Thus similar to disease (UC) network analysis we found that the bacterial taxa with the highest causal effect on the disease node are primarily from the beneficial or pathogenic group.

References

1. Scutari, M. Bayesian network constraint-based structure learning algorithms: Parallel and optimised implementations in the bnlearn R package. *arXiv preprint arXiv:1406.7648* (2014).
2. Shannon, P. *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome research* **13**, 2498–2504 (2003).
3. Gevers, D. *et al.* The treatment-naïve microbiome in new-onset Crohn's disease. *Cell host & microbe* **15**, 382–392 (2014).
4. Mishra, S. & Imlay, J. A. An anaerobic bacterium, *Bacteroides thetaiotaomicron*, uses a consortium of enzymes to scavenge hydrogen peroxide. *Mol. microbiology* **90**, 1356–1371 (2013).
5. Ricanek, P. *et al.* Gut bacterial profile in patients newly diagnosed with treatment-naïve Crohn's disease. *Clin. experimental gastroenterology* **5**, 173 (2012).
6. Chung, W. S. F. *et al.* Prebiotic potential of pectin and pectic oligosaccharides to promote anti-inflammatory commensal bacteria in the human colon. *FEMS microbiology ecology* **93**, fix127 (2017).
7. Chassard, C., Delmas, E., Lawson, P. A. & Bernalier-Donadille, A. *Bacteroides xylanisolvens* sp. nov., a xylan-degrading bacterium isolated from human faeces. *Int. journal systematic evolutionary microbiology* **58**, 1008–1013 (2008).
8. Ananthakrishnan, A. N. *et al.* Gut microbiome function predicts response to anti-integrin biologic therapy in inflammatory bowel diseases. *Cell host & microbe* **21**, 603–610 (2017).
9. Microbewiki. *Bacteroides fingoldii*. (Date last accessed 30-June-2020).
10. Wei, B. *et al.* Molecular cloning of a *Bacteroides caccae* TonB-linked outer membrane protein identified by an inflammatory bowel disease marker antibody. *Infect. immunity* **69**, 6044–6054 (2001).