Role of gut microbiota and their temporal interactions in kidney transplant recipients

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Abstract

The impact of the gut microbiome on the recovery of kidney transplant recipients has been previously shown, but the current understanding remains superficial. Bayesian Networks were applied to longitudinal data from kidney transplant patients, including sequence data and clinical information, with the goal of understanding the role microbes play in the recovery and health of these patients.

1 Introduction and Motivation

The number of microbes inside the human body is of the same order as the number of human cells (1), with their metabolism so tightly connected to the host's that humans are being referred to as a superorganism (2). It is known that the microbiome affects the outcome of a kidney transplant, but its role remains to be elucidated (3). Toward this goal, stool samples were collected from 79 kidney transplant patients from two tertiary centers in South Korea. For all subjects, samples were collected before transplant, and at 3 and 12 months after transplant. Bayesian techniques were applied to generate new hypotheses and to find evidence for previous ones about the effect of microbiome on transplant outcome.

2 Methods

Microbial composition was inferred from the Illumina MiSeq sequence data using the software CL community by ChunLab and UCHIME (4). Study participants with missing samples were discarded, leaving a total of 24 subjects with 3 measurements each. The 40 most abundant taxa were selected along with different clinical variables. The temporal information of the bacteria was unrolled with the new nodes represented by additional subscripts, allowing them to be processed by a Bayesian Network (BN). This way, the measurements at the three time points for bacteria A will be replaced by the three attributes: A_{t0}, A_{t3}, and A_{t12}, corresponding to the measurements at time points 0, 3 and 12 respectively, instead of being treated as new samples. The clinical information and time invariant outcomes were left without transformation. The data were further analyzed using Bayesian Networks, which are probabilistic graphical models that uncover interactions between the variables. The structure learning of the algorithm was done using Greedy Hill Climbing and restricting the maximum number of parents of a node to 3. This was done using a modified version of the R library `bnlearn` (5) to allow for categorical variables. Also, intrinsic information about the real world was encoded in the form of restrictions; the network only needs to learn edges that follow the flow of time (from present to future). Also, as the focus was on predicting certain kind of interactions, only the following edges were allowed: microbe to microbe, microbe to baseline clinical variable (clinical), microbe to transplant outcome (outcome), clinical to outcome, outcome to clinical. This was done during the network structure learning by checking if the candidate edge is in the allowed list. The parameter learning step of the BN learning consisted of calculating the Pearson correlation coefficient between the two nodes involved. Finally, the network was visualized using Cytoscape (6) and the predicted interactions were interpreted.

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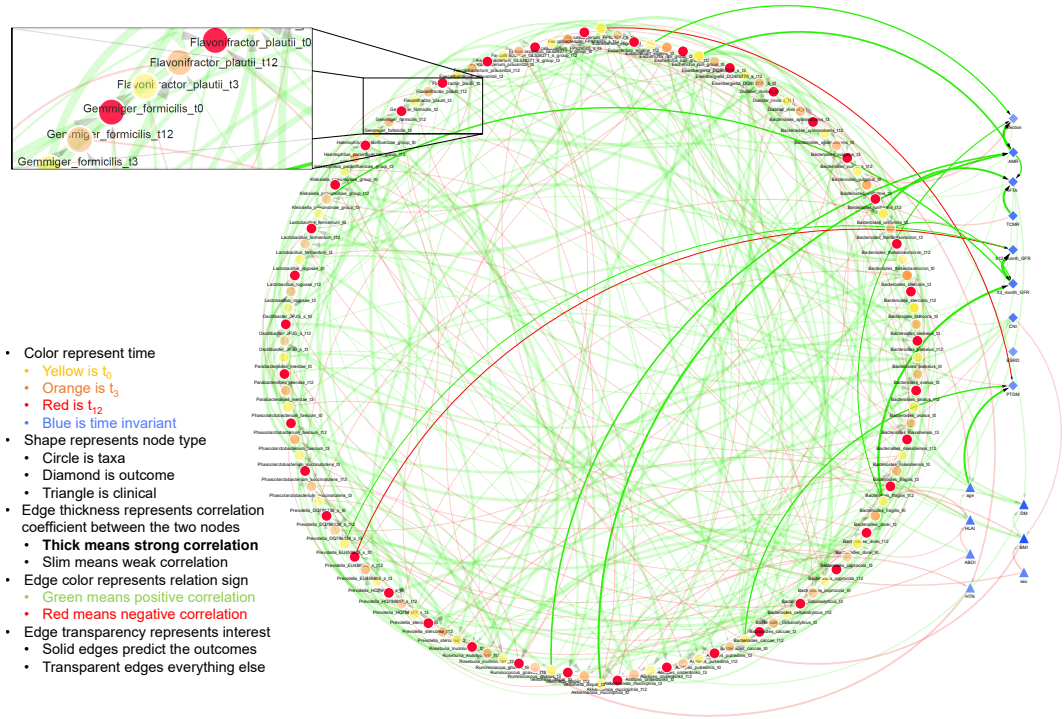

Figure 1: **Inferred Bayesian Network**. The three representations of each bacteria (0, 3 and 12) months are arranged in the big circle, while the clinical information and outcomes are outside.

3 Results and Discussion

A single Bayesian network (BN) was computed using bacterial abundance at all time points, clinical data and transplant outcomes and visualized in Figure 1. Many of the interactions computed in the inferred BN are well known in the literature. For example, higher BMI correlates with higher prevalence of diabetic nephropathy, and older age correlates with more frequent occurrence of *post-transplantation diabetes mellitus* (PTDM).

Antibody-mediated rejection (AMR) was correlated with higher abundance of *Escherichia coli*, *Veillonella dispar*, and *Akkermansia muciniphila* just prior to transplant. *V. dispar* has been shown to be significantly associated with autoimmune hepatitis (7) and *Veillonella spp* have been shown to be associated with severe inflammatory conditions such as recurrent Crohn's disease (8), osteomyelitis (9), and endocarditis (10). It produces bacterial lipopolysaccharides and can contribute to activation of immune reaction (11). On the other hand, T cell-mediated rejection was not correlated with the abundance of any bacterial taxa, but associated with AMR. Interstitial fibrosis/tubular atrophy (IFTA) were positively correlated with higher level of *Lactobacilus fermentum* and *Eisenbergiella* at 0m and *Bacteroides caccae*, *Alistipes onderdonkii* and *Veilonella dispar* at 12 months. In particular, IFTA was mostly was mostly associated with bacteria at 12 months after kidney transplantation. IFTA causes chronic lesions and is associated with worsening of kidney function which would bring systemic change of patients. Therefore, those bacterial changes may be a result of kidney function deterioration and systemic inflammation. Infection, one of the most dangerous post-transplant complications, showed positive correlations with *Bacteroides fragilis* and *Eubacterium eligens* at 0 month. *B. fragilis* is generally known to be an important commensal for the development of the gastrointestinal tract and immune system (12), as well as for protection against colonization by pathogens. *E. eligens* has also been shown to display anti-inflammatory properties (13). PTDM was positively correlated with *Faecalibacterium* and *Bacteroides caccae* at 0 month, and negatively with *E. coli*. In one study, kidney recipients who need tacrolimus dose escalation during the first month of transplant showed higher abundance of *Faecalibacterium prausnitzii* in the first week of kidney transplantation (14). It is possible that *Faecalibacterium* could cause PTDM by leading patients to have larger dose of tacrolimus.

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