A mechanistic modeling approach relating human gut microbial community to physiologically-relevant biomarkers

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Background

The adult human gut houses a microbial community which contains a large number of bacteria species. It is well-known that the actual composition of this community has a significant influence on human vital functions and may be an important determinant of various pathologies (*e.g.*, obesity, inflammation). However, the mechanisms controlling the assembly of gut microbiota and its relationship with human host tissues remain poorly understood. For example, there were several attempts to find such relationship in patients with obesity, where a possible mechanistic connection between microbial community and host tissues may be explained by various short chain fatty acids (SCFA) production specific for particular community compositions.

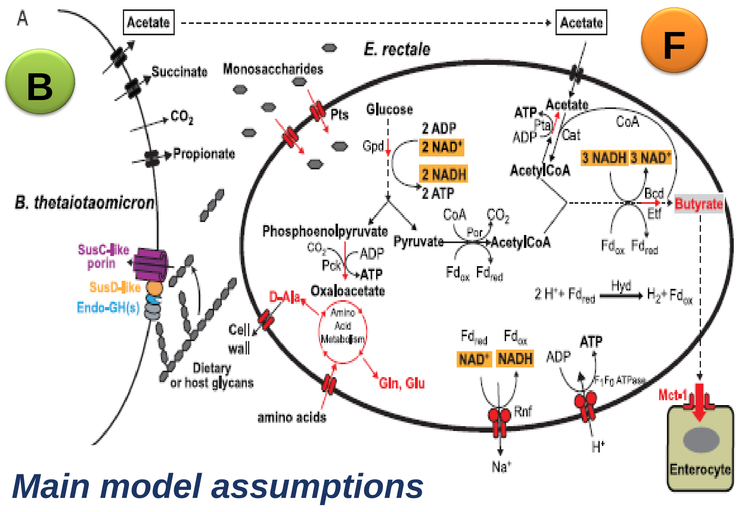
Objective

This work represents a first attempt in developing an integrated quantitative understanding of factors relating gut microbiota to measures of physiologically-significant biomarkers.

Methods

Based on the results of Turnbaugh. *et al.*, 2009, which showed that the human gut microbial community is typically formed by two bacterial phyla (Firmicutes and Bacteroidetes), we developed various sub-models describing generalized metabolic signatures of these bacteria, as well as the processing of their endpoint metabolites such as SCFA. Individual sub-models were integrated to provide a unified model of microbiota relationships with host tissues. Model predictions were verified against experimental data from the literature, on qualitative and quantitative gut microbial composition, biochemical characterization of particular bacteria, and results of gnotobiotic mice colonization by various microbial cultures. Final model simulations were used for the analysis of two datasets with microbiomic data about gut microbial composition in healthy volunteers and patients with obesity (individual experimental data for 197 subjects *were obtained in frame of Russian metagenome project, http://metagenome.ru)*

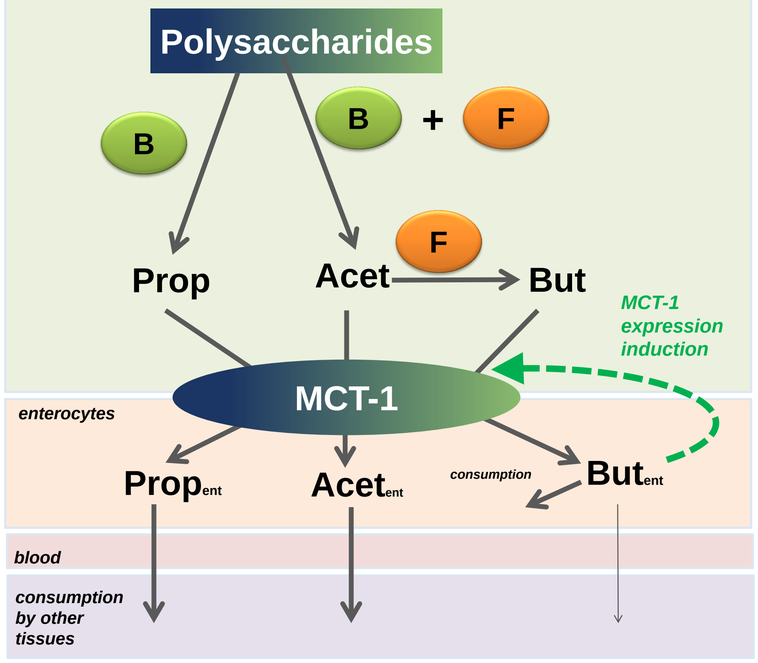
Scheme of the Bacteroidetes (B)/ Firmicutes (F) metabolism [taken from Mahowald M. et al., 2009]



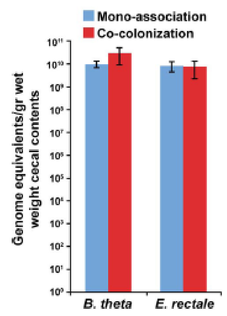
Main model assumptions

- Microbial community consists of two main metabolism types, Firmicutes (F) and Bacteroidetes (B), which process the fermentation of polysaccharides to endpoint short chain fatty acids (acetate, butyrate, propionate).
- Intake of the dietary glycans is non-limiting and permanent.
- Short chain fatty acids are transported to gut enterocytes via MCT-1
- Expression of MCT-1 is regulated by butyrate concentration
- Butyrate is mainly consumed by enterocytes. Acetate and propionate are commonly passed to the blood and consumed by other tissues.

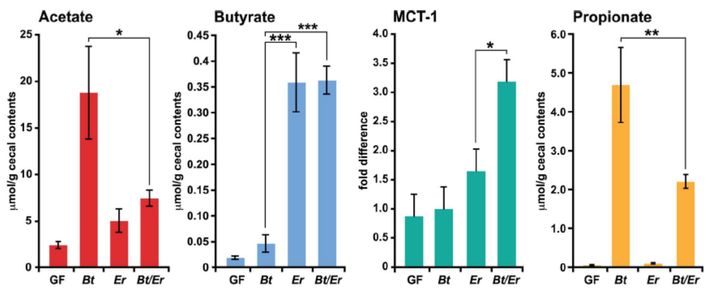
Scheme of the mechanistic model



Different types of experimental data have been used for model verification



- Critical model parameters have been verified against experimental data published by Mahowald *et al.*, 2009, who measured SCFAs and MCT-1 for three bacterial composition ratios: (1) B:1, F:0; (2) B:0, F:1 (3) B:2, F:1



- Parameters for the MCT-1 transporter sub-model were found *via* various literature sources (Table 1)

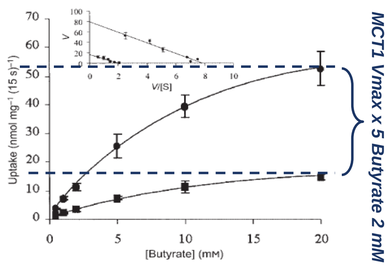


Table 1. Specificity of MCT1 to different short chain fatty acids

Fatty acid	Value (mM)	Ref.
Acetate	3.5	Jackson et al, 1996
Propionate	1.5	Broer S. et al, 1998
Butyrate	10	Cuff et al, 2002

Results

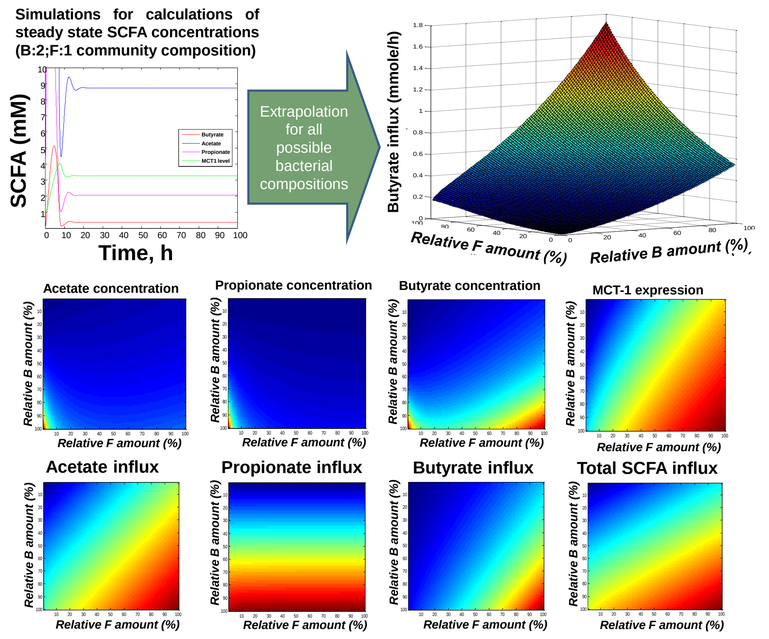
All individual sub-models provided adequate description of isolated interactions. The integrated model provided a good description of literature-reported changes in butyrate, acetate, propionate and MCT-1 expression (Table 2), in response to varying bacterial composition (in accordance to data by Mahowald *et al*., 2009).

Table 2. Comparison of experimental data and values predicted by the model at different compositions of microbial gut community

	B:1,F:0 exp	B:1,F:0 pred	B:0,F:1 exp	B:0,F:1 pred	B:2,F:1 exp	B:2,F:1 pred
Acetate (mM)	18±5	13	5±1.5	1.6	7±1	8.7
Propionate (mM)	4.6±1	4.7	0.1±0.1	0.01	2.2±0.3	2.1
Butyrate (mM)	0.04±0.02	0.04	0.35±0.07	0.045	0.35±0.03	0.38
MCT-1	1±0.4	1	1.6±0.4	1.73	3.2±0.4	3

Results

Model simulations were performed to calculate steady-state SCFA concentrations and their influx into host tissues.

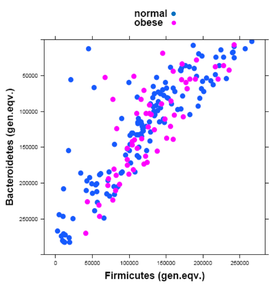


As seen from such simulations:

- Only colon butyrate is suggested to be a biomarker, sensitive of changes in a variety of community compositions. Though, accumulation of acetate can found only at specific conditions when bacterial community consists only from Bacteroidetes.
- Profiles of various SCFAs influx into host tissues are strongly dependent upon bacterial composition ratios.

Integration and analysis of microbiomics data

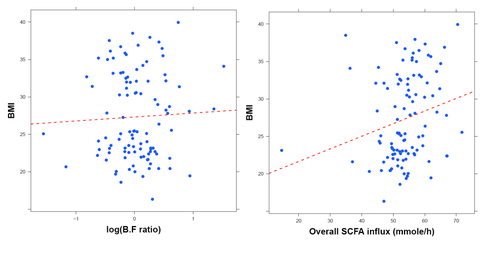
Steady-state SCFA concentrations and their influx into host tissues calculated from model simulations have been used for the analysis of the combined dataset, which consisted of microbiomic data on gut microbial composition in healthy volunteers and in patients with obesity.



- It is well-known that body mass index (BMI) correlates with age, so we subdivided datasets for three groups (<30,30- 60,60<)
- We found that biomarker behavior and correlation between them and BMI are different within these age groups (Table 3).

Table 3. Results (p-values) of Pearson test for possible correlation between BMI and one of tested biomarkers.

Biomarker	Pool (n=197)	<30 (n=59)	30-60 (n=104)	60< (n=34)
Bacteroidetes amount	0.0034	0.04	0.31	0.81
Firmicutes amount	0.76	0.073	0.9	0.26
B/F ratio	0.7	0.54	0.88	0.29
Acetate concentration	0.59	0.88	0.2	0.4
Propionate concentration	0.63	0.85	0.21	0.34
Butyrate concentration	0.56	0.0974	0.045	0.77
Acetate influx	0.35	0.5	0.07	0.31
Propionate influx	0.05	0.028	0.34	0.73
Butyrate influx	0.578	0.2	0.9	0.33
Overall SCFA influx	0.018	0.1447	0.023	0.54



As it can be seen correlation between B/F and BMI ratio is much less significant than correlation between overall SCFA influx

As it can be seen, there is a statistically significant correlation between overall SCFA influx and BMI. This dependence is the most relevant in the middle age group. It can be explained by the too-large variability of bacterial community compositions in the young age group.

Conclusions

A mechanistic model establishing a relationship between human gut microbial community and host tissues was developed. Based on the analysis of the model behaviour, we found that butyrate concentration in the colon may be used as a sensitive biomarker, because only this SCFA accumulates at steady state over a sufficiently broad range *vs*. community compositions. Influx of total SCFAs is determined not only by the qualitative composition of bacterial community (B/F ratio), but also quantitatively (level of colonization). Integration to the model and analysis of microbiomics data about gut microbial community obtained for the 197 individuals shows that there are weak but statistically significant correlation between overall SCFA influx to the host tissues and BMI.

Acknowledgments

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References:

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