Genome-scale Metabolic Modeling of Gut Microbiota in the Fly Gut

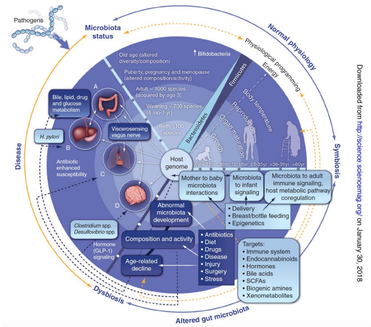
Joan Song, Brandon Barker, Nana Ankrah, and Angela Douglas

[1] Department of Electrical and Computer Engineering, [2] Center for Advanced Computing, [3] Department of Entomology,
[4] Department of Molecular Biology and Genetics at Cornell University, Ithaca, NY 14853, USA

Introduction

Gut microbiota has been demonstrated to play an integral part in influencing host metabolism and animal nutritional health; disruptions in gut microbiota have been linked to diseases such as diabetes and obesity.[1]

Bacteria have been shown to affect the breakdown of complex metabolites for host utilization and provide essential amino acids and vitamins.[2]



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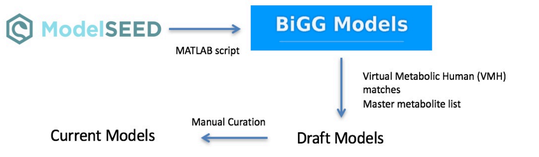
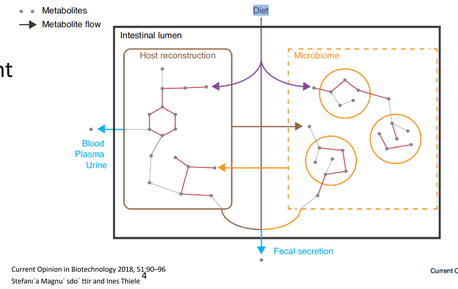
To investigate the processes shaping animal-microbe metabolic interactions and their impact on host health, we reconstructed genome scale metabolic models of the bacterial community in the *Drosophila* gut. Our aim is to derive quantitative estimates of the composition and amount of nutrients exchanged between animal and bacterial partners and the capacity of the bacterial partners to transform host derived nutrients. The use of these models will aid in elucidating the specific mechanisms underlying experimentally observed microbial contributions to host health and aid in identifying therapeutic approaches for combating metabolic diseases in humans.

Model Construction

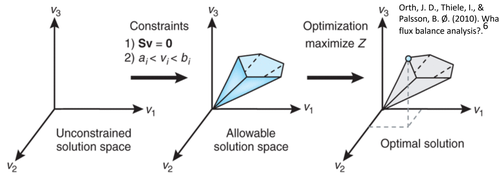


Models take into account the exchange of metabolites from the intracellular and extracellular space.



Current Opinion in Biotechnology 2018, 51:90–96
Stefanı´a Magnu´ sdo´ ttir and Ines Thiele[4]
Current Opinion in Biotechnology

Analysis- FVA/ SteadyCom



Flux balance analysis (FBA) is a computational method used to quantify fluxes using constraints.[5]

Flux variability analysis (FVA) is used to quantify the maximum and minimum fluxes through each metabolic reaction.[6]

$$v_{j,upper} / \; v_{j,lower} = \max_{v} / \min_{v} \; v_j$$

$$\text{s.t.} \quad Sv = 0, \quad l \le v \le u$$

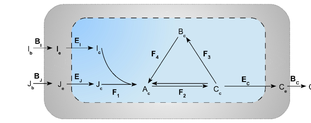
SteadyCom is based on the idea there is a steady-state community growth rate. SteadyCom FVA changes the objective function to sum of the reaction fluxes/biomass variables while the community growth rate is fixed at a value between 0 and the maximum growth rate.[7]

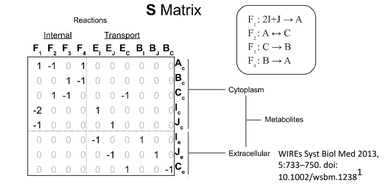
$$\max/\min \quad \sum_{j \in \mathbf{F}^k} w_{k,j}^r V_j^k + \sum_{k \in \mathbf{K}} w_k^X X^k$$

$$\text{subject to} \quad \mu = \mu_0$$

Constraints in SteadyCom

Chan, Siu Hung Joshua and Simons, Margaret N and Maranas, Costas D,PLoS computational biology 2017[7]





WIREs Syst Biol Med 2013, 5:733–750. doi: 10.1002/wsbm.1238[1]

$$\max \quad \mu$$

$$\text{s.t.} \quad \sum_{j \in \mathbf{J}^k} S_{ij}^k V_j^k = 0, \qquad \forall i \in \mathbf{I}^k, k \in \mathbf{K}$$

$$LB_j^k X^k \le V_j^k \le UB_j^k X^k, \qquad \forall j \in \mathbf{J}^k, k \in \mathbf{K}$$

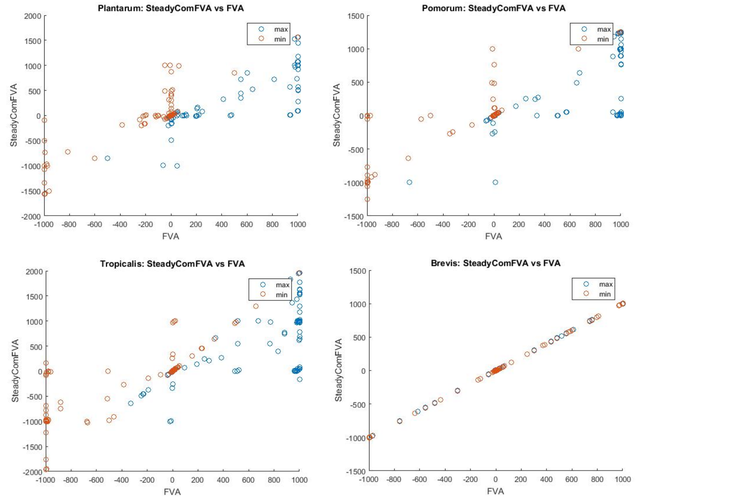
$$\sum_{k \in \mathbf{K}} V_{ex(i)}^k + u_i^{com} \ge 0, \qquad \forall i \in \mathbf{I}^{com}$$

$$V_{biomass}^k = X^k \mu, \qquad \forall k \in \mathbf{K}$$

$$\sum_{k \in \mathbf{K}} X^k = 1$$

$$X^k, \quad \mu \ge 0, \qquad \forall k \in \mathbf{K}$$

$$V_j^k \in \Re, \qquad \forall j \in \mathbf{J}^k, k \in \mathbf{K}$$



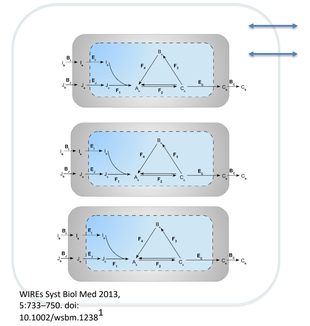
Comparing the results of FVA and SteadyCom FVA shows that the SteadyCom method yields different results.

Results/Future Work

The final product is a *L. plantarum* model with 1028 reactions and 933 metabolites, a *L. brevis* model with 946 reactions and 840 metabolites, *A. tropicalis* with 1228 reactions and 1108 metabolites, and *A. pomorum* with 1058 reactions and 938 metabolites. There are 313 non–exchange reactions which are unique to an individual model.

Our model reconstruction indicates that the microbial partners encode fermentative pathways necessary for the breakdown of complex polysaccharides into short chain fatty acids which can be utilized by the host. The bacterial partners also encode metabolic pathways for the production of essential amino acids and vitamins which can be made available to the host.

Through the creation of these models, we have taken an important step in quantifying the amount of nutrients exchanged among a bacterial community. Future work included creating a composite model of the bacteria models to simulate a microbe/host system.



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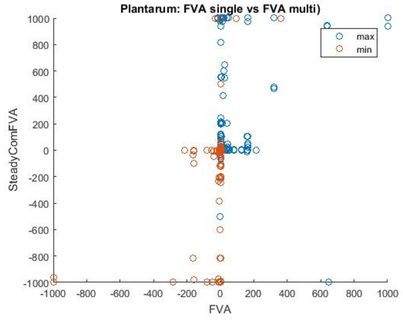

Although we do expect different calculated fluxes from SteadyComFVA and FVA, we do not expect differences between a compartmentalized model and a non-compartmentalized model. Therefore, we need to understand how the current microbe/host system is apparently relaxing constraints.

Additionally, future work involves quantifying fluxes at varying microbial relative abundances and compositions to determine how such differences may affect the ability of the host to transform and use metabolites.

References

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Acknowledgements

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