Reconstruction of *Dolosigranulum pigrum*

Research Project

Background and Motivation

Dolosigranulum pigrum is a Gram-positive coccus, which may be organized in pairs, tetrads, and clusters [1]. The bacterium is mainly a commensal of the upper respiratory tract, but can also be isolated from blood, eye cultures, spinal cord, urine, and the stomach [1], [2]. Until now, *D. pigrum* was only rarely associated with human diseases, such as sepsis, synovitis, nosocomial pneumonia, cholecystitis, and pancreatitis. Moreover, it was—in some cases—found to be Erythromycin-resistant [1], [2].

In contrast, Liu *et al.* have identified *D. pigrum* to be a negative predictor for *Staphylococcus aureus* presence in the nasal microbiome [3]. It was shown that only 16% of *D. pigrum* positive individuals were habituated by *S. aureus*, while 56% of negative individuals carried the pathogen [3]. Consequently, *D. pigrum* is, on the one hand, a determinant for *S. aureus* presence with potential use as nasal probiotic and, on the other hand, a virulent pathogen, especially in immunodeficient hosts [2], [3].

Genome-scale reconstructions (GEM) have been used to successfully predict biological features and targetability of reactions for treatment and other applications. However, by now, no curated GEM is available for *D. pigrum*. A genome-scale metabolic model of *D. pigrum* may be a substantial improvement for the understanding of the organism and its interactions with the host and bacterial community, especially its interaction with *S. aureus*.

Aim

This project aims to create the first version of a curated genome-scale reconstruction (GEM) of the organism's metabolic capabilities in the SBML Level 3 Version 1 format [4] by following the standard reconstruction protocol [5].

Approach

The following steps will be executed:

(1) Download the genome of the organism from NCBI[1].
(2) Apply automatic reconstruction tools, such as CarveMe [6], ModelSEED [7], and KBase [8].
(3) Compare all models, possibly by using libSBML [9], e.g., for Python and model annotation, e.g., using ModelPolisher [10].
(4) Simulate model growth in relevant media using COBRApy [11], including the synthetic nasal medium SNM3 [12].
(5) Draw parts of the model in the form of a metabolism chart using software such as Escher [13].

[1] https://www.ncbi.nlm.nih.gov/assembly/GCF_000245815.1

Literature

[1] L. LaClaire and R. Facklam, “Antimicrobial susceptibility and clinical sources of Dolosigranulum pigrum cultures,” *Antimicrob. Agents Chemother.*, vol. 44, no. 7, pp. 2001–2003, Jul. 2000.

[2] H. Lécuyer *et al.*, “Dolosigranulum pigrum causing nosocomial pneumonia and septicemia,” *J. Clin. Microbiol.*, vol. 45, no. 10, pp. 3474–3475, Oct. 2007.

[3] C. M. Liu *et al.*, “Staphylococcus aureus and the ecology of the nasal microbiome,” *Sci. Adv.*, vol. 1, no. 5, Jun. 2015.

[4] M. Hucka *et al.*, “The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2,” *J. Integr. Bioinform.*, vol. 0, no. 0, Jun. 2019.

[5] I. Thiele and B. Palsson, “A protocol for generating a high-quality genome-scale metabolic reconstruction,” *Nat. Protoc.*, vol. 5, no. 1, pp. 93–121, Jan. 2010.

[6] D. Machado, S. Andrejev, M. Tramontano, and K. R. Patil, “Fast automated reconstruction of genome-scale metabolic models for microbial species and communities,” *Nucleic Acids Res.*, vol. 46, no. 15, pp. 7542–7553, Sep. 2018.

[7] C. S. Henry, M. DeJongh, A. A. Best, P. M. Frybarger, B. Linsay, and R. L. Stevens, “High-throughput generation, optimization and analysis of genome-scale metabolic models,” *Nat. Biotechnol.*, vol. 28, no. 9, pp. 977–982, Sep. 2010.

[8] A. P. Arkin *et al.*, “KBase: The United States Department of Energy Systems Biology Knowledgebase,” *Nat. Biotechnol.*, vol. 36, no. 7, pp. 566–569, Jul. 2018.

[9] B. J. Bornstein, S. M. Keating, A. Jouraku, and M. Hucka, “LibSBML: an API Library for SBML,” *Bioinformatics*, vol. 24, no. 6, pp. 880–881, Mar. 2008.

[10] M. Römer, J. Eichner, A. Dräger, C. Wrzodek, F. Wrzodek, and A. Zell, “ZBIT Bioinformatics Toolbox: A Web-Platform for Systems Biology and Expression Data Analysis,” *PLoS One*, vol. 11, no. 2, p. e0149263, Feb. 2016.

[11] A. Ebrahim, J. A. Lerman, B. O. Palsson, and D. R. Hyduke, “COBRApy: COnstraints-Based Reconstruction and Analysis for Python,” *BMC Syst. Biol.*, vol. 7, no. 1, p. 74, Aug. 2013.

[12] B. Krismer *et al.*, “Nutrient limitation governs Staphylococcus aureus metabolism and niche adaptation in the human nose.,” *PLoS Pathog.*, vol. 10, no. 1, p. e1003862, Jan. 2014.

[13] Z. A. King, A. Dräger, A. Ebrahim, N. Sonnenschein, N. E. Lewis, and B. O. Palsson, “Escher: A Web Application for Building, Sharing, and Embedding Data-Rich Visualizations of Biological Pathways,” *PLOS Comput. Biol.*, vol. 11, no. 8, p. e1004321, Aug. 2015.