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Bachelorthesis

A genome-scale metabolic model of *Klebsiella pneumoniae* HS11286

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1 Background and Motivation

Klebsiella pneumoniae is a Gram-negative bacterium belonging to the *Enterobacteriaceae* family [1]. It is one of the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) making it one of the six most dangerous pathogens known today [2]. This is because *K. pneumoniae* is multi-drug resistant. Subsequently, infections related to this bacterium no longer only pose a threat to immunocompromised individuals, but can also lead to severe damages in healthy individuals [3]. Infections are often acquired in hospitals, and lead to pneumonia, urinary tract infections and bacteremia [1]. Normally, *K. pneumoniae* resides in soil and surface water and on medical devices [3]. From there, it can colonize different human mucosal surfaces and spread to other tissues like the respiratory tract [4]. Besides that, *K. pneumoniae* is also used

Figure 1 | Secondary electron microscopy of *Klebsiella pneumoniae*. Image source: Wikipedia

in biotechnology. Multiple metabolically engineered strains exist that produce beneficial chemicals, such as 1,3-propanediol [1].

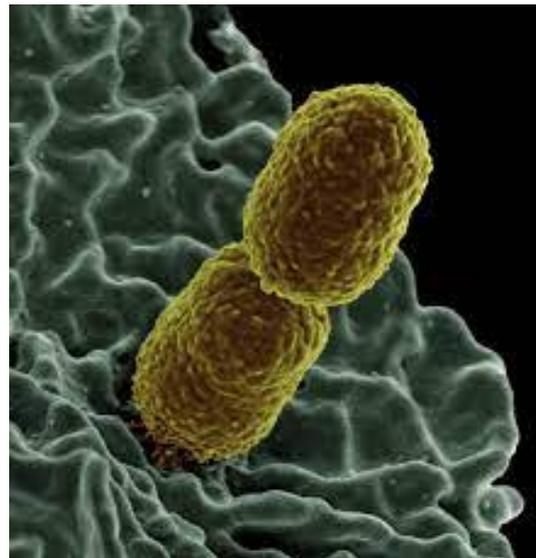The particular strain that this thesis will focus on is the HS11286 which was found in China. Its genome consists of one chromosome with 5.3 Mb and six plasmids. It was found that this strain has an extremely plastic genome, which contributes to the dangerous spread of antibiotic resistance among different genera [5].

There are currently two manually curated genome-scale metabolic models (GEMs) for *K. pneumoniae*. Both of them model different strains than the one that this thesis will focus on. Liao et al. [1] reconstructed and experimentally validated the MGH78578 strain by mapping the current GEM for *E. coli* onto the genome of MGH78578 and improving the model with the help of experimental data. The other existing model recon-

structed the KPPR1 strain of *K. pneumoniae* using the Propagate Model to New Genome application. Gap-filling was performed on the glucose minimal medium [6]. Besides those manually curated GEMs, a metabolic model for strain MGH78578 was created in an automated way and is available at the Virtual Metabolic Human (VMH) database. Especially the experimentally-validated GEM for strain MGH78578 proved helpful by providing a deeper understanding of the metabolic network of *K. pneumoniae* and by identifying potential drug targets [4, 7].

For the HS11286 strain, there is no GEM available, yet. Creating a model for the HS11286 strain is therefore an important contribution to further deepen the understanding of the metabolic network of *K. pneumoniae* and to provide a useful tool in the fight against multidrug-resistant pathogens. Such a GEM could help to save time and money in laborious experiments (e.g., determininig gene essentialities via knockout experiments) by providing predictions and promising hypotheses that can be further evaluated.

Henry et al. [6] not only constructed a model for KPPR1, but also compared it to the strain MGH78578. This revealed differences in virulence and adaption to different carbon sources. Therefore, a model for strain HS 11286 can clarify differences between different strains, their adaption to different tissues and varying drug targets.

2 Aim and Approach

The aim is to create a high-quality systems biology model of *K. pneumoniae* HS11286 and compare it to the existing reconstructions for the strains MGH78578 [1] and KPPR1 [6]. The reconstruction of the metabolic network will be done using automated tools like CarveMe [8] and will be improved by manual curation through literature research. MEMOTE [9] and the SBML validator [10] will be used to ensure the quality of the model.

3 Requirements

For this thesis, a good knowledge of python and basic biochemistry is required. As well as the motivation and interest to learn more about systems biology, constrained-based modeling and how to build a GEM using different modeling tools and Python packages.

References

[1] Y.-C. Liao, T.-W. Huang, F.-C. Chen, P. Charusanti, J. S. J. Hong, H.-Y. Chang, S.-F. Tsai, B. O. Palsson, and C. A. Hsiung. "An Experimentally Validated Genome-Scale Metabolic Reconstruction of *Klebsiella pneumoniae* MGH 78578, *i*YL1228". In: *Journal of Bacteriology* 193.7 (2011), pp. 1710–1717. DOI: 10.1128/JB.01218-10.

[2] C. J. Norsigian, H. Attia, R. Szubin, A. S. Yassin, B. Ø. Palsson, R. K. Aziz, and J. M. Monk. "Comparative Genome-Scale Metabolic Modeling of Metallo-Beta-Lactamase–Producing Multidrug-Resistant *Klebsiella pneumoniae* Clinical Isolates". In: *Frontiers in Cellular and Infection Microbiology* 9 (2019). ISSN: 2235-2988. DOI: 10.3389/fcimb.2019.00161.

[3] M. K. Paczosa and J. Mecsas. "Klebsiella pneumoniae: Going on the Offense with a Strong Defense". In: *Microbiology and Molecular Biology Reviews* 80.3 (2016), pp. 629–661. DOI: 10.1128/MMBR.00078-15.

[4] M. F. Cesur, B. Siraj, R. Uddin, S. Durmuş, and T. Çakır. "Network-Based Metabolism-Centered Screening of Potential Drug Targets in *Klebsiella pneumoniae* at Genome Scale". In: *Frontiers in Cellular and Infection Microbiology* 9 (2020). ISSN: 2235-2988. DOI: 10.3389/fcimb.2019.00447.

[5] P. Liu, P. Li, X. Jiang, D. Bi, Y. Xie, C. Tai, Z. Deng, K. Rajakumar, and H.-Y. Ou. "Complete Genome Sequence of *Klebsiella pneumoniae* subsp. pneumoniae HS11286, a Multidrug-Resistant Strain Isolated from Human Sputum". In: *Journal of Bacteriology* 194.7 (2012), pp. 1841–1842. DOI: 10.1128/JB.00043-12.

[6] C. S. Henry, E. Rotman, W. W. Lathem, K. E. J. Tyo, A. R. Hauser, and M. J. Mandel. "Generation and Validation of the iKp1289 Metabolic Model for *Klebsiella pneumoniae* KPPR1". In: *The Journal of Infectious Diseases* 215.suppl_1 (Mar. 2017), S37–S43. ISSN: 0022-1899. DOI: 10.1093/infdis/jiw465.

[7]   M. L. Jenior, M. E. Dickenson, and J. A. Papin. "Genome-scale metabolic modeling reveals increased reliance on valine catabolism in clinical isolates of *Klebsiella pneumoniae*". In: *bioRxiv* (2021). DOI: 10.1101/2021.09.08.459555.

[8]   D. Machado, S. Andrejev, M. Tramontano, and K. R. Patil. "Fast automated reconstruction of genome-scale metabolic models for microbial species and communities". In: *Nucleic Acids Research* 46.15 (2018), pp. 7542–7553. DOI: https://doi.org/10.1093/nar/gky537.

[9]   C. Lieven, M. E. Beber, and B. G. Olivier. "MEMOTE for standardized genome-scale metabolic model testing". In: *Nature Biotechnology* 38 (2020), pp. 272–276. DOI: https://doi.org/10.1038/s41587-020-0446-y.

[10]   B. J. Bornstein, S. M. Keating, A. Jouraku, and M. Hucka. "LibSBML: An API Library for SBML". In: *Bioinformatics* 24.6 (2008), pp. 880–881. ISSN: 1367-4803. DOI: 10.1093/bioinformatics/btn051.