# Metabolic modelling reveals pH-dependent differences in pathogenic and commensal ***Staphylococcus epidermidis*** **strains**

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(12+333/ 350 word max including title)

**Background:** *Staphylococcus epidermidis*, a common human skin colonizer, causes infections associated with the use of medical devices. Strains belonging to clonal complex 2 (CC2) and non-CC2 coexist in human skin as commensals, but have different pathogenic potential[1]. This dual behavior is poorly understood and improved knowledge on the factors that determine the pathogenicity of *S. epidermidis* is needed to design more effective prevention and treatment strategies.

**Methods:** To investigate the differences in metabolism of CC2 and non-CC2 *S. epidermidis* strains at different pH that mimic skin and blood (5.5 and 7.4), we collected time-course exometabolomic data during bacterial growth and integrated it with genome-scale metabolic models (GEM). The models specific to CC2 and non-CC2 strains were built based on the genome annotation of representative strains, using a manually curated model of a reference strain (RP62 strain of CC2 lineage) as a template[2]. To simulate the two strain metabolisms at different pH, we performed flux balance analysis using biomass production as optimization function and exometabolomic data as constraints. Previously acquired intracellular metabolomics and proteomics data under these pH conditions[3] were further used to constrain and validate the GEMs.

**Results:** Unique genes were associated with each of the lineages: 73 genes associated with antibiotic resistance, virulence, and their regulation were specific to the CC2 strain; while 55

genes associated with sulfur metabolism, metal ion resistance, detoxification, membrane transport, and osmoregulation were specific to the non-CC2 strain. Exometabolomics analysis revealed that the two strains had different uptake patterns of several amino acids and saccharides. For several metabolites (2,3-butanediol, acetoin, and formate) the effluxes were discriminative between each of the strains at different pH. Differences in the genomic background and the influx/efflux rates were used to constrain the GEMs, leading to more reliable metabolic models under relevant biological pH states.

**Conclusions** The generated experimental datasets and strain-specific GEMs provide an important tool to investigate *S. epidermidis* metabolism and to predict the responses of CC2 and non-CC2 strains to compounds used to prevent or treat *S. epidermidis* infections.

**References (28/30 words):**

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2. Calvo, T. D. *et al. Metabolites* **12**, 136 (2022).
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