From Stress to Adaptive Success: A systematic investigation of physiological adaptation of *Escherichia coli* facing harsh environments

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Bacteria continually experience heterogeneous and rapidly changing environments. To survive and thrive, bacteria must quickly sense and respond to environmental shifts [1, 2]. This requirement is exemplified in pathogens during host colonisation [3, 4]. To successfully transition from the intestine to the urinary tract, uropathogenic *Escherichia coli* must rapidly switch from an energy-rich to an energy-poor nutritional environment with fewer sugars and metals [5]. Similarly, *Mycobacterium tuberculosis* must adapt to more acidic and oxidative conditions when infecting alveolar macrophages [6, 7].

Successful adaptation to different environments is regulated by a plethora of mechanisms. These regulatory mechanisms range from swift and transient protein-metabolite interactions to long-term and slow changes in gene expression [8–11]. Differential gene expression frequently entails modulating transcriptional initiation by transcription factors [12, 13, 14]. Understanding how changes in transcriptional regulation affects fitness can thus unveil fundamental aspects of bacterial adaptability and potentially expose vulnerabilities in pathogen metabolism [15, 16, 17, 18]. However, systematic understanding of the extent to which bacterial populations maintain metabolic stability or adapt their metabolism to challenging environments under transcriptional misregulation remains pending.

In this poster, I will present our approach to systematically unravel and model the interplay between transcriptional regulation and metabolism in *E. coli* by combining tuneable interference of transcription factor expression with high-throughput metabolomics. Our strategy involves integrating metabolic profiles with growth phenotypic data and existing knowledge of the regulatory network. Through this integration, we aim to develop mathematical models that shed mechanistic insights into bacterial adaptation to harsh environments. Such an approach could hold clinical potential to predict new ways to interfere with essential pathogenic regulation during host infection.

[1] H. Link *et al.*, Nat. Methods **12**, 1091 (2015).
[2] O. Kotte, J. B. Zaugg, and M. Heinemann, Mol. Syst. Biol. **6**, 355 (2010).
[3] T. M. Fuchs *et al.*, FEMS Microbiol. Rev. **36**, 435 (2012).
[4] A. A. Crofts *et al.*, Proc. Natl. Acad. Sci. U. S. A. **115**, E8968 (2018).
[5] C. C. Y. Chan, and I. A. Lewis, Trends Microbiol. **30**, 1174 (2022).
[6] J. J. Baker, S. J. Dechow, and R. B. Abramovitch, Trends Microbiol. **27**, 942 (2019).
[7] P. Chandra, S. J. Grigsby, and J. A. Philips, Nat. Rev. Microbiol. **20**, 750 (2022).
[8] D. W. Erickson *et al.*, Nature **551**, 119 (2017).
[9] R. Tollerson, and M. Ibba, J. Biol. Chem. **295**, 10434 (2020).
[10] M. Zampieri *et al.*, Nat. Commun. **10**, 3354 (2019).
[11] D. Ledezma-Tejeida, E. Schastnaya, and U. Sauer, Curr. Opin. Syst. Biol. **28**, 100404 (2021).
[12] D. Browning, and S. Busby, Nat. Rev. Microbiol. **14**, 638 (2016).
[13] C. Lamoureux *et al.*, Nucleic Acids Res., gkad750 (2023).
[14] L. Gerosa *et al.*, Cell Syst. **1**, 270 (2015).
[15] V. Parisutham *et al.*, Mol. Syst. Biol. **18**, e10843 (2022).
[16] T. Fuhrer *et al.,* Mol. Syst. Biol. **13**, 907 (2017).
[17] D. Giacalone *et al.*, PLoS Genet. **18**, e1010331 (2022).
[18] V. Naveen *et al.*, PLoS One **11**, e0157165 (2016).