Acknowledgements. We would like to thank Xinying Ren, John Marken, William Poole, and the Murray lab for useful discussions and insights throughout the project. This research is supported in part by the Institute for Collaborative Biotechnologies through contract W911NF-19-D-0001 from the U.S. Army Research Office. The content of the information on this page does not necessarily reflect the position or the policy of the Government, and no official endorsement should be inferred.

Code Availability. All code for figures and results of this study can be found at https://github.com/sophiejwalton/dosage_control.

Bibliography

- Stephen R. Lindemann, Hans C. Bernstein, Hyun-Seob Song, Jim K. Fredrickson, Matthew W. Fields, Wenying Shou, David R. Johnson, and Alexander S. Beliaev. Engineering microbial consortia for controllable outputs. *The ISME Journal*, 10(9):2077–2084, Sep 2016. ISSN 1751-7370. doi: 10.1038/ismej.2016.26.
- Katie Brenner, Lingchong You, and Frances H. Arnold. Engineering microbial consortia: a new frontier in synthetic biology. *Trends in Biotechnology*, 26(9):483–489, Sep 2008. ISSN 0167-7799. doi: 10.1016/j.tibtech.2008.05.004.
- Corentin Briat, Ankit Gupta, and Mustafa Khammash. Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks. *Cell Systems*, 2(1):15–26, Jan 2016. ISSN 2405-4712. doi: 10.1016/j.cels.2016.01.004.
- Chelsea Y. Hu and Richard M. Murray. Design of a genetic layered feedback controller in synthetic biological circuitry. bioRxiv, 2019. doi: 10.1101/647057.
- Tau-Mu Yi, Yun Huang, Melvin I. Simon, and John Doyle. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proceedings of the National Academy of Sciences*, 97(9):4649–4653, 2000. ISSN 0027-8424. doi: 10.1073/pnas.97.9.4649.
- Steven T. Rutherford and Bonnie L. Bassler. Bacterial quorum sensing: Its role in virulence and possibilities for its control. Cold Spring Harbor Perspectives in Medicine, 2(11), 2012. doi: 10.1101/cshperspect.a012427.
- Eric L. Haseltine and Frances H. Arnold. Implications of rewiring bacterial quorum sensing. Applied and Environmental Microbiology, 74(2):437–445, 2008. ISSN 0099-2240. doi: 10.1128/AEM.01688-07.
- Tal Danino, Octavio Mondragón-Palomino, Lev Tsimring, and Jeff Hasty. A synchronized quorum of genetic clocks. *Nature*, 463(7279):326–330, Jan 2010. ISSN 1476-4687. doi: 10.1038/nature.07575
- Arthur Prindle, Jangir Selimkhanov, Howard Li, Ivan Razinkov, Lev S. Tsimring, and Jeff Hasty. Rapid and tunable post-translational coupling of genetic circuits. *Nature*, 508(7496): 387–391, Apr 2014. ISSN 1476-4687. doi: 10.1038/nature13238.
- Lingchong You, Robert Sidney Cox, Ron Weiss, and Frances H. Arnold. Programmed population control by cell-cell communication and regulated killing. *Nature*, 428(6985):868–871, Apr 2004. ISSN 1476-4687. doi: 10.1038/nature02491.
- Xinying Ren and Richard M. Murray. Layered feedback control improves robust functionality across heterogeneous cell populations. bioRxiv, 2020. doi: 10.1101/2020.03.24.006528.
- A. Vignoni, D. A. Oyarzún, J. Picó, and G. . Stan. Control of protein concentrations in heterogeneous cell populations. In 2013 European Control Conference (ECC), pages 3633– 3639, 2013.
- A. Vignoni, D. A. Oyarzún, J. Picó, and G. . Stan. Control of protein concentrations in heterogeneous cell populations. pages 3633–3639, 2013. doi: 10.23919/ECC.2013.6669828.
- Yadira Boada, Alejandro Vignoni, and Jesús Picó. Engineered control of genetic variability reveals interplay among quorum sensing, feedback regulation, and biochemical noise. ACS Synthetic Biology, 6(10):1903–1912, 2017. doi: 10.1021/acssynbio.7b00087. PMID: 28581725.
- L. Pasotti, M. Bellato, N. Politi, M. Casanova, S. Zucca, M. G. Cusella De Angelis, and P. Magni. A synthetic close-loop controller circuit for the regulation of an extracellular molecule by engineered bacteria. *IEEE Transactions on Biomedical Circuits and Systems*, 13(1):248–258, 2019.
- Timothy S. Gardner, Charles R. Cantor, and James J. Collins. Construction of a genetic toggle switch in escherichia coli. *Nature*, 403(6767):339–342, Jan 2000. ISSN 1476-4687. doi: 10.1038/35002131.
- Nicolo' Politi, Lorenzo Pasotti, Susanna Zucca, Michela Casanova, Giuseppina Micoli, Maria Gabriella Cusella De Angelis, and Paolo Magni. Half-life measurements of chemical inducers for recombinant gene expression. *Journal of Biological Engineering*, 8(1):5, Feb 2014. ISSN 1754-1611. doi: 10.1186/1754-1611-8-5.
- L. M. Posnick and L. D. Samson. Influence of s-adenosylmethionine pool size on spontaneous mutation, dam methylation, and cell growth of escherichia coli. *Journal of bacteriology*, 181(21):6756–6762, Nov 1999. ISSN 0021-9193. doi: 10.1128/JB.181.21.6756-6762. 1999. 10542178[pmid].
- Bryson D. Bennett, Elizabeth H. Kimball, Melissa Gao, Robin Osterhout, Stephen J. Van Dien, and Joshua D. Rabinowitz. Absolute metabolite concentrations and implied enzyme active site occupancy in escherichia coli. *Nature Chemical Biology*, 5(8):593–599, Aug 2009. ISSN 1552-4469. doi: 10.1038/nchembio.186.
- Susanna Zucca, Lorenzo Pasotti, Nicolò Politi, Michela Casanova, Giuliano Mazzini, Maria Gabriella Cusella De Angelis, and Paolo Magni. Multi-faceted characterization of

- a novel luxr-repressible promoter library for escherichia coli. *PLOS ONE*, 10(5):1–26, 05 2015. doi: 10.1371/journal.pone.0126264.
- Nitzan Rosenfeld, Michael B Elowitz, and Uri Alon. Negative autoregulation speeds the response times of transcription networks. *Journal of Molecular Biology*, 323(5):785 – 793, 2002. ISSN 0022-2836. doi: https://doi.org/10.1016/S0022-2836(02)00994-4.

Walton et al. | Dosage Control | 11