Determinants of Bistability in Induction of the *Escherichia coli lac* Operon

David W. Dreisigmeyer[1], Jelena Stajic[2], Ilya Nemenman[3,2], William S. Hlavacek[1,2] and Michael E. Wall[3,4,2]

***Short Abstract* — We have developed a mathematical model of regulation of expression of the *Escherichia coli lac* operon, and have investigated bistability in its steady state induction behavior in the absence of external glucose. We validated the model by finding a family of biophysically reasonable systems that are consistent with an experimentally determined bistable region for induction by thio-methylgalactoside (TMG). We then extended it to describe regulation by lactose, in which allolactose, a metabolic intermediate in lactose metabolism and a natural inducer of *lac*, is the inducer. For biophysically reasonable parameter values, the model yields no bistability in response to induction by lactose; however, systems with an unphysically small permease-dependent export effect can exhibit small amounts of bistability for limited ranges of parameter values. These results cast doubt on the natural relevance of bistability in the *lac* operon, and help shed light on the controversy among existing theoretical studies that address this issue. They also emphasize the importance of the nature of the input signal in determining the functions of genetic regulatory circuits**

I. Background

IN 1957, Novick and Weiner discovered that *Escherichia coli* can exhibit discontinuous switching in expression of the *lac* operon, with some cells expressing a large amount of β-galactosidase (β-gal), other cells expressing a small amount, and an insignificant number of cells expressing an intermediate amount [1]. Recently, this effect was further characterized using single cell assays of fluorescence levels in a population of *E. coli* cells carrying a *lac::gfp* reporter [2]. The population exhibited a bimodal distribution, with induced cells having over 100 times the fluorescence level of uninduced cells. Both of these studies were conducted using the artificial inducer TMG, and theoretical studies disagree in their assessment of whether bistability is present [3, 4, 5] or absent [6, 7] in expression of *lac* among *E. coli* cells in a natural context. In addition, both Savageau [8] and van Hoek & Hogeweg [7] found that bistability increases the time required to respond to sudden increases in environmental lactose, which can be a disadvantage in competition for nutrients. These results argue against the natural relevance of bistability in *lac* expression.

Acknowledgements: Supported by the US Department of Energy through contract DEAC5206NA25396, and grant GM 80216 from the National Institutes of Health. The collaboration was facilitated by the First q-bio Summer School on Cellular Information Processing, which was sponsored by the New Mexico Consortium's Institute for Advanced Studies, and the Center for Nonlinear Studies at Los Alamos National Laboratory.

[1]Theoretical Division, [2]Center for Nonlinear Studies, [3]Computer, Computational and Statistical Sciences Division, [4]Bioscience Division, Los Alamos National Laboratory, Los Alamos, NM 87545 USA

II. Results

We developed ODE models of induction of *lac* by either TMG or lactose [9]. Both models involve inducer-dependent expression of permease and β-gal; permease-dependent and passive transport of TMG or lactose; and dilution of intracellular species by cell growth. However, the models are topologically distinct because lactose induction occurs through a metabolic intermediate (allolactose) whereas TMG is not metabolized; both lactose and allolactose are degraded by β-gal in the lactose induction model. We analyzed the behavior of the models for a wide range of biophysically reasonable parameters. TMG induction exhibited bistability for all parameter values, with 65% of the systems being favorable for experimental detection. The bistable behavior matched the experiments [2] for an appropriate choice of parameters. By contrast, lactose induction only exhibited bistability for an unphysically small permease-dependent export effect.

III. Conclusions

The lack of bistability for induction by lactose agrees with modeling studies concluding that bistabity in *lac* expression is irrelevant to *E. coli* in a natural context [6, 7, 8]. Analysis of the lactose induction model predicts that bistable behavior can be promoted by (1) hindering the kinetics of permease transport and β-gal catalysis; (2) lowering the level of allolactose required for half-maximal *lac* expression; (3) accelerating cell growth; and (4) decreasing the Michaelis constant for permease influx relative to that for efflux. Overall, the results emphasize the importance of the nature of the input signal in determining the functions of genetic regulatory circuits.

References

[1] A. Novick and M. Weiner, *PNAS* **43**, 553 (1957).
[2] E. M. Ozbudak, M. Thattai, H. N. Lim, B. I. Shraiman, and A. Van Oudenaarden, *Nature* **427**, 737 (2004).
[3] N. Yildirim and M. C. Mackey, *Biophys J* **84**, 2841 (2003).
[4] N. Yildirim, M. Santillan, D. Horike and M. C. Mackey, *Chaos* **14**, 279 (2004).
[5] M. Santillan, M. C. Mackey and E. S. Zeron, *Biophys J* **92**, 3830 (2007).
[6] M. J. van Hoek and P. Hogeweg, *Biophys J* **91**, 2833 (2006).
[7] M. J. van Hoek and P. Hogeweg, *PLoS Comput Biol* **3**, e111 (2007).
[8] M. A. Savageau, *Math Biosci* **180**, 237 (2002).
[9] D. W. Dreisigmeyer, J. Stajic, I. Nemenman, W. S. Hlavacek and M. E. Wall. *IET Syst Biol*. In press.