How are growing cells responding to perturbations?

S. Boulineau[1], S. Tans[2]

***Short Abstract* — In order to grow and survive, E. coli bacteria must be able to adapt to fluctuating environments. Many parameters of the cell such as its macromolecular composition, its shape and size are strongly dependent on the growth conditions. These parameters of the cell have been characterized quantitatively as functions of the growth rate for E. Coli. However, it is still not well understood how the growth itself is regulated. We address this question at the single cell level with microfluidic devices. We can thus control the external environment and look at cell-to-cell variability within a population.**

***Keywords* — Bacterial growth, microfluidics, single cell, gene expression.**

I. Purpose

We are looking at two types of perturbations: internal perturbations (such as noise) and external perturbations (changes in the environment). We are interested in their effect on the growth rate of E. coli bacteria.

Experiments in the past years have shown that gene expression is a fundamentally stochastic process, with randomness in transcription and translation leading to cell-to-cell variations in mRNA and protein levels [1]. Significant cell-to-cell variations have also been reported for generation times and growth rates, as early as 1932 [2]. Stochastic gene expression has important consequences for cellular function, being beneficial in some contexts and harmful in others [3]. However, how this noise affects the growth rate or fitness of an organism is poorly understood.

A number of experiments have been done in the past where culture of bacterial cells where shifted from rich to poor medium (shift down) or from poor to rich medium (shift up) [4]. Mostly, people looked at how DNA, RNA and protein synthesis were affected by nutrient shifts [5] to [9]. However, there is little data about growth rate delays for instance, especially at the single cell level.

We monitor the cells response in microfluidic devices where single cell responses to changing conditions can be monitored. We look at the *lac* system: with a GFP reporter we can measure *lac* expression. Using automated microscopy we can measure both the expression level, by means of fluorescence, and the size of single cells over time.

[1,2] Biophysics group, FOM Institute AMOLF, Amsterdam (the Netherlands). E-mail: s.tans@amolf.nl

II. Conclusion

We have designed a simple device based on [10] and [11]. We use a membrane to separate the cells from the external flow. The cells grow in one layer for several generations and can be monitored at the single cell level in a controlled environment.

References

[1] Michael B. Elowitz, *et al.* (2002) Stochastic Gene Expression in a Single Cell. *Science* **297**, 1183-1186.

[2] Kelly C, Rahn O, (1932) The growth rate of individual bacterial cells. *J. Bacteriol.* **23**, 147-153

[3] Raj A, van Oudenaarden A, (2008) Nature, Nurture or Chance: Stochastic Gene Expression and Its Consequences. *Cell* **135**, 216-226.

[4] Schaechter M, Maaloe O, Kjeldgaard N, (1958) The Transition Between Different Physiological States During Balanced Growth of Salmonella typhirium. *J. gen. Microbiol.* **19**, 607-616.

[5] Molin S *et al.*, (1977) Control of Ribosome Synthesis in Escherichia coli: Analysis of an Energy Source Shift Down. *J. of Bacteriology* **131**, 7-117.

[6] Molin S *et al.*, (1977) Control of Protein Synthesis in Escherichia coli: Analysis of an Energy Source Shift Down. *J. of Bacteriology* **131**, 18-29.

[7] Brunschede H, Dove L, Bremer H, (1977) Establishment of Exponential Growth After a Nutritional Shift-Up in Escherichia coli B/r. *J. of Bacteriology* **129**, 1020-1033.

[8] Shepherd N, Churchward G, Bremer H, (1980) Synthesis and Function of Ribonucleic Acid Polymerase and Ribosomes in Escherichia coli B/r After a Nutritional Shift-Up. *J. of Bacteriology* **143**, 1332-1344.

[9] Zengel J, Lindahl L, (1986) Transcription of Ribosomal Genes during a Nutritional Shift-Up of E. Coli. *J. of Bacteriology* **167**, 1095-1097.

[10] Charvin G, Cross F, Siggia E (2008) A Microfluidic Device for Temporally Controlled Gene Expression and Long-Term Fluorescent Imaging in Unperturbed Dividing Yeast Cells. *PLoS ONE* **3**, e1468.

[11] Ducret A *et al.* (2009) A Microscope Automated Fluidic System to Study Bacterial Processes in Real Time. *PLoS ONE* **4**, e7282.