Periodic forcing of the ERK pathway

Nguyen Tran[1] and Andrew H.A. Clayton[2]

***Short Abstract* — Signal transduction networks respond to stimuli from the environment. Depending on the dynamics of these stimuli, the network may exhibit different output dynamics and, consequently, induce different cell outcomes. The ERK pathway is one such system – displaying different outputs for different stimuli patterns, which go on to dictate different cell functions. Here we show how different periodic forcing dynamics lead to different ERK pathway dynamics and, consequently, different cell functions.**

***Keywords* — ERK pathway, EGF, NGF, PC12 cells, periodic forcing, frequency domain, transfer function**

I. Introduction

The ERK pathway is a signal transduction network that starts with receptors on the cell surface and ends with the activation of a family of proteins in the cytoplasm, collectively called ERK. ERK controls a wide range of cell functions in metazoans including survival, growth, metabolism, migration, and differentiation [1]. Different ERK activation dynamics dictate different cell functions. In PC12 cells, transient ERK activation induces cell proliferation while sustained ERK activation induces cell differentiation [2]. In MCF-10A cells, the duration of ERK activation pulses controls entry rate into S phase [3]. In NRK-52E cells, the presence of oscillations in ERK activation increases proliferation rate [4].

The idea of timescales appears to be a recurring theme in these examples – from timescales of transient versus sustained dynamics, to timescales of pulses, to timescales of oscillations. The natural language of timescales is frequency. And so, we are motivated to ask how the ERK pathway transforms inputs into outputs in the frequency domain. More concretely, this question becomes: "What is the transfer function of the ERK pathway?" Such a function would allow us to map inputs to outputs. And if the connection between outputs and cell outcomes are known, we have a mapping from inputs to cell outcomes.

II. Results

We study the EGF- and NGF-activated ERK pathway model presented in [2] and derive its transfer function. Using this function, we predict how different periodic forcing dynamics of EGF and NGF yield different ERK activation dynamics and, consequently, different cell outcomes in literature.

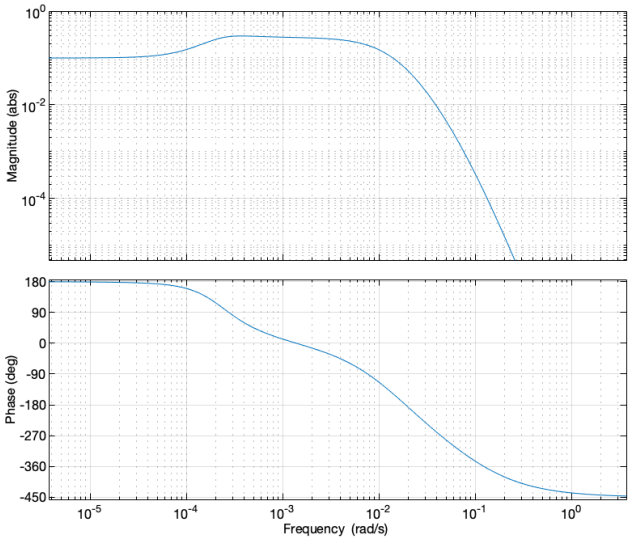

Figure 1: Bode plots of the transfer function describing how the ERK pathway modulates and phase shifts periodic EGF input signals, centred at 3.3 ng/mL, into phosphorylated ERK output signals.

III. Conclusion

Our work aims to provide a predictive tool for experimentalists to relate desired inputs and outputs in conducting frequency domain experiments. It also provides insight into the regions of dynamics that may be useful for treating diseases associated with dysfunctional ERK activation.

References

[1] Lavoie, H., Gagnon, J., & Therrien, M. (2020). ERK signalling: a master regulator of cell behaviour, life and fate. *Nature Reviews Molecular Cell Biology*, *21*(10), 607-632.

[2] Ryu, H., Chung, M., Dobrzyński, M., Fey, D., Blum, Y., Lee, S. S., ... & Pertz, O. (2015). Frequency modulation of ERK activation dynamics rewires cell fate. *Molecular systems biology*, *11*(11), 838.

[3] Albeck, J. G., Mills, G. B., & Brugge, J. S. (2013). Frequency-modulated pulses of ERK activity transmit quantitative proliferation signals. *Molecular cell*, *49*(2), 249-261.

[4] Aoki, K., Kumagai, Y., Sakurai, A., Komatsu, N., Fujita, Y., Shionyu, C., & Matsuda, M. (2013). Stochastic ERK activation induced by noise and cell-to-cell propagation regulates cell density-dependent proliferation. *Molecular cell*, *52*(4), 529-540.

Acknowledgements: This work was funded by a Swinburne University Postgraduate Research Award to Nguyen Tran.

[1]Optical Sciences Centre, Swinburne University of Technology, Hawthorn, Australia. E-mail: nhtran@swin.edu.au

[2]Optical Sciences Centre, Swinburne University of Technology, Hawthorn, Australia. E-mail: aclayton@swin.edu.au