Dynamic response mapping of cell signaling effectors

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***Short Abstract* — To support the prediction of cell regulatory actions through to new protein expression and fate, we characterize dynamic response models of transcription factor expression using quantitative live cell imaging. Complementing existing modeling of major signaling pathways, we fit parsimonious models of the dynamic response of select transcription factors, as well as end phenotype, to the activity of the terminal kinases ERK and Akt. Data are generated by time lapse imaging of MCF-10A cells expressing both a kinase reporter and a fluorescently labeled transcription factor. The characterized models demonstrate a predictive capacity for the response to terminal kinase activity.**

***Keywords* — Cell signaling, signal dynamics, ERK, Akt, transcription factor, live cell imaging, mathematical modeling.**

I. Background

CELL regulatory signaling represents a broad category referring to the joint action of a group of more restricted pathways. Each pathway is initiated by inputs, largely from cell surface receptors, and activates a sequence of phosphorylation events resulting the activity of a terminal kinase that acts to modify gene expression via transcription factors.

Information transduced through signaling pathways may be encoded both through the combination of multiple pathways and through the dynamic pattern of signaling. Extracellular signal regulated kinase (ERK) has previously been observed acting in a dynamically complex manner [1,2] as well as acting in conjunction with protein kinase B/Akt to affect differentiation and proliferation [3].

Past modeling of signal transduction has focused dynamic and mechanistic studies on the response of terminal kinases to receptor activation, generating a growing body of knowledge on the function of these pathways [4].

II. Approach

To supplement the body of knowledge on signal transduction, we collect new data simultaneously observing dynamic ERK or Akt activity and target gene levels under varied growth conditions. Data is collected for ERK with the transcription factors Fos related antigen 1 (FRA-1) or early growth response protein 1 (EGR-1) and for Akt with forkhead box O 3a (FOXO3a) and cyclin-dependent kinase inhibitor 1B/p27.

A. Modeling

With an emphasis on dynamic response over detailed mechanism, this study employs parsimonious models, the simplest of which is a linear time invariant (LTI) system. LTI systems are inferred as transfer functions in the frequency space, based on the coherent input/output time series data generated.

B. Experiments

For each measurement, a cell line expressing the desired pair of a Förster resonance energy transfer (FRET) based reporter for either ERK or Akt kinase activity [5], and a genomically targeted fluorescent protein fusion to the target gene of interest [6] is generated. Cells are treated with varied levels of extracellular ligands and therapeutic drugs to elicit varied responses, and imaged over time to develop coherent time series data.

III. Conclusion

The inferred response models demonstrate the capacity to predict the response of transcription factor expression to the activity of the terminal kinases, ERK and Akt. These models augment the existing body of work describing the activity of these kinases resulting from receptor stimulation, and further the applicability of control strategies to direct cellular response and fate.

References

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