Abstract Submitted
for the MAR10 Meeting of
The American Physical Society

NF-κB dynamics show digital activation and analog information processing in cells SAVAS TAY, Stanford University, JAKE HUGHEY, TIMOTHY LEE, TOMASZ LIPNIACKI, MARKUS COVERT, STEPHEN QUAKE — Cells operate in ever changing environments using extraordinary communication capabilities. Cell-to-cell communication is mediated by signaling molecules that form spatiotemporal concentration gradients, which requires cells to respond to a wide range of signal intensities. We used high-throughput microfluidic cell culture, quantitative gene expression analysis and mathematical modeling to investigate how single mammalian cells respond to different concentrations of the signaling molecule TNF-α via the transcription factor NF-κB. We measured NF-κB activity in thousands of live cells under TNF-α doses covering four orders of magnitude. In contrast to population studies, the activation is a stochastic, switch-like process at the single cell level with fewer cells responding at lower doses. The activated cells respond fully and express early genes independent of the TNF-α concentration, while only high dose stimulation results in the expression of late genes. Cells also encode a set of analog parameters such as the NF-κB peak intensity, response time and number of oscillations to modulate the outcome. We developed a stochastic model that reproduces both the digital and analog dynamics as well as the gene expression profiles at all measured conditions, constituting a broadly applicable model for TNF-α induced NF-κB signaling in various types of cells.

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Date submitted: 02 Oct 2009 Electronic form version 1.4