

# Context-dependent Signaling in Autocrine Loops: Modeling and Experiments in the Epidermal Growth Factor Receptor System

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## ABSTRACT

We describe a mechanism for context-dependent cell signaling mediated by autocrine loops with positive feedback. We demonstrate both computationally and experimentally that the extracellular environment can critically influence the dynamic characteristics of intracellular signaling induced by extracellular stimuli. Specifically, in the Epidermal Growth Factor Receptor (EGFR) system, both the amplitude and the duration of MAP Kinase pathway activation are modulated by the positive feedback that joins the EGFR, the Ras-MAPK signaling pathway, and a ligand-releasing protease. The signaling response to a transient input is short-lived when most of the released ligand is lost to cellular microenvironment. The response is prolonged, or even persistent, in a cell that is efficient in recapturing the ligand.

To study the functional capabilities of autocrine loops with positive feedback, we have developed a mathematical model that accounts for ligand release, transport, binding, and intracellular signaling.

We have used Brownian motion theory, Monte Carlo simulations and reaction-diffusion models to relate the spatial characteristics of autocrine loops to measurable parameters of ligand receptor systems. Applying our models to autocrine loops in the EGFR system, we find that it can operate with tight spatial localization – even at the level of a single cell [1].

The localized autocrine loops can establish positive feedback in growth factor systems when recaptured ligands can stimulate the activity of ligand-releasing proteases [2]. Multiparameter sensitivity and bifurcation analysis of our integrated transport/signaling/release model indicates that such feedback can result in steady state multiplicity and excitability. This dynamic behavior endows autocrine loops with context-dependent signal processing capabilities.

Using the model, we can directly interpret the context-dependent responses of autocrine cells to ionizing radiation [3]. In human carcinoma cells, MAPK signaling patterns induced by a short pulse of ionizing radiation can be either transient or sustained, depending on the cell type and the composition of the extracellular medium. Based on our model, we propose that autocrine loops in this, and potentially other growth factor and cytokine systems, may serve as modules for context-dependent cell signaling [4].

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