# Impact of Asymmetric Activation and Membrane Landscape on ErbB1 Receptor State

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***Short Abstract* – ErbB1 is a key membrane signaling protein whose overexpression is strongly linked to cancer. Due to this key role and link to cancer, understanding the kinetics and dynamics of this protein is important. Single particle tracking has enabled experimentalists to observe and measure ErbB1 interaction dynamics on the single molecule level, giving deeper insight into how specific receptor states interact. Here we describe a spatial-stochastic model of receptor state and interactions based upon these SPT measurements and incorporate an asymmetric phosphorylation mechanism for receptor activation. A complex interplay between receptor states and the influence of membrane landscape on receptor state is revealed.**

***Keywords* — EGFR/ErbB, Spatial Stochastic Modeling, Computational Methods, Signal Transduction**

## I. Background

ERBB1 is a critical membrane signaling protein which plays a key role in cell proliferation, growth, and apoptosis, among other cell functions [1,2]. ErbB1 is activated via ligand binding and subsequent formation of homo and heterodimers [1]. Structural evidence for extracellular domain fluctuation of unliganded receptors [2] and asymmetric tail orientation [4] plays a large role in the mechanisms of dimer formation [3] and activation [5]. Given the important role ErbB1 plays in normal cell development, it is not surprising that the overexpression of ErbB1 is implicated in the progression of cancers [1]. Due to the strong link between ErbB1 and cancer, it is important to understand the kinetics and dynamics of these receptors.

## II. Approach

One method of investigating the complex interplay of receptor interactions and activation is through mathematical modeling. Here we build a spatial stochastic model directly implementing SPT [6] and receptor activation [7] data. Receptor activation is modeled based upon an asymmetric tail phosphorylation mechanism and repeated receptor interactions.

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## III. Results

### A. Membrane Domains Promote Repeated Interactions

Repeated interactions between receptors, as observed during SPT experiments [6], are reproduced in simulations. The number of repeat interactions between each pair of receptors varies broadly, with the number of binding interactions between a given pair exceeding 100. A large number of rebinding reactions occur faster than the frame rate of the data collection, suggesting the number of repeated encounters may be underrepresented during image acquisition.

### B. Implications of the asymmetric model for receptor transphosphorylation

Asymmetric tail phosphorylation allows only one tail in the dimer to be phosphorylated per dimer event. Serial interactions are therefore required for full dimer phosphorylation. Rapid receptor re-encounters permit the system to quickly reach equilibrium, providing a significant pool of phosphorylated receptors for recruitment of signaling partners.

### C. Membrane Landscape Impacts Receptor State

Receptor co-confinement in membrane domains promotes repeated interactions, even at low density of receptors. In the absence of domains, repeated interactions between the same pair of receptors are more rare events. Repeated interactions due to domain confinement causes receptors to shuffle quickly between different activation states.

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