# Differential Signaling with a Single Ligand

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***Short Abstract* — the VEGF family contains many related ligands and receptors. VEGFR-1 and -2 are both expressed by endothelial cells, and both have the capacity to bind the same ligand, VEGF-A. We investigate the possibility that different concentrations of the same ligand may lead to different physiological response, due to excitation of different pathways.**

***Keywords* — signaling, receptor clustering, inhibition.**

## I. Background

The Vascular Endothelial Growth Factor or VEGF cytokine and receptor family forms a complex ligand-receptor system, involved in the development of blood vessels. The five different ligand genes (VEGF-A through VEGF-D, and PlGF) and three VEGFR receptor genes give rise to several different splice variants, with further complexity resulting through dimerization [1]. All variants of VEGF are normally dimers and act as a bivalent ligand to their receptors. The initial VEGF signaling unit consists of two ligand-bound receptors, which cross-activate. Due to its bivalence, VEGF binding may precede and induce the dimerization of its receptors, by the binding of a second receptor to the free binding site of the ligand. Bivalence may also lead to *high dose inhibition*, when most receptors are bound to one site of a VEGF ligand but dimerization is inhibited due to the lack of free receptors. The vast majority of VEGF ligands bind to more than one receptor type, with all but 4 of the 15 VEGF-A subtypes binding to both VEGFR-1 and VEGFR-2 [1]. Endothelial cells express both receptors, whose binding to the same VEGF-A ligand triggers different pathways, with additional downstream signals activated by the receptor heterodimers.

Why is it useful to have different receptors for the same extracellular signal, instead of a single receptor to induce all pathways that are activated by a given ligand? A possible explanation is that *different activation profiles arise from different ligand signal intensities or time patterns,* mapping different physiological situations onto specific activation profiles. We examine the feasibility of differential signaling, the *selective induction of specific signaling units* resulting from different concentration profiles of a single ligand.

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## II. Results and Outlook

We rely on a computational model of the two-receptor VEGF system with one ligand [2], consistent with human vascular endothelial cells. The ODE-based model is solved analytically at steady state. Together with fast ODE simulations, this allows efficient exploration of different conditions, represented as changes in parameter values. The original parameter set is a characterization of long-term, average behavior of a large number of cells, since it relies essentially on equilibrium binding experiments.

### *A. High dose inhibition creates resonance-like response*

The number of activated complexes of each type (homodimers and heterodimers) first increases with ligand concentration, then decreases, approaching zero as the concentration exceeds the binding constants for the receptors. The curves are several orders of magnitude wide if the original model parameters are used, exceeding the separation between the peaks.

### *B. Receptor clustering broadens the response curves*

Experimental and computational evidence [1,3] indicates that RTK receptors, including VEGFR, accumulate in a small fraction of the cell surface; this *clustering* occurs after ligand binding. Higher density increases dimerization rates, therefore *pre-clustering kinetics* should have *lower dimerization rates* than the regime described by the original model. Lowered dimerization response curves have narrower resonances, indicating that early responses may be more dose-specific. Further parameter space exploration reveals regimes with differential signaling.

In summary, (1) VEGF has resonance-like dose response curves (2) receptor clustering widens these peaks (3) if clustering *follows* exposure, the initial response is narrow, with signaling profiles dependent on ligand concentration. Ongoing numerical investigation will identify experimental circumstances where our hypothesis may be tested.

## References

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