VEGF Binding with High Affinity Domains

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***Short Abstract* — TEM imaging indicates that VEGF receptors tend to co-locate in clusters ranging from a few to a hundred molecules. Dimerization of receptors (usually ligand dependent) is necessary for signaling, but there is no known mechanism for larger bound aggregates.**

We hypothesize pre-existing high affinity regions on the cell membrane that preferentially exchange receptors with the remaining part of cellular membrane. This would increase the observed dimerization rates by increasing the concentration of receptors in the high affinity regions. We explore the implications of this mechanism through a compartmentalized version of a kinetic model of VEGF signal initiation [1].

***Keywords* — Chemical Reaction Networks, Receptors, Ligands, VEGF, Clustering**

I. Background

We discuss a Chemical Reaction Network (CRN) model of the binding of Vascular Endothelial Growth Factor (VEGF) to its receptors. VEGF has important roles in the spread of cancer; it facilitates tumor growth by summoning blood vessels to continue to feed the tumor once it has surpassed the size at which diffusion alone can provide oxygen and necessary nutrients [2].

High resolution imaging studies have revealed that the cell membrane is far from homogeneous; it has a varied landscape with elements of the cytoskeleton, accumulations of membrane proteins, and inhomogeneities in the lipid composition of the membrane. This landscape is reflected in the mobility and localization of membrane receptors and of other molecules involved in early signaling.

Certain families of membrane bound receptors, such as receptor tyrosine kinases (RTK), require dimerization in order to activate. Ligand-induced dimerization is a central feature of the respective signaling machinery, whose precise kinetics ensures the proper behavior of cells. Molecular changes that result in increased or decreased dimerization rates may have far reaching consequences. The mobility of membrane-bound receptors can potentially have a similar impact on signaling, by facilitating or hindering receptor-receptor collisions and impacting dimer formation.

II. CRN Model of VEGF Signal Initiation

Our starting point is a mathematical model [1] developed by Mac Gabhann and Popel (MGP), based on experiments quantifying the binding of VEGF to cells and the overall cellular response. VEGF receptors are monovalent (they bind to only one ligand) whereas the VEGF ligand is bivalent, binding to two receptors. The MGP model allows for a direct receptor-receptor bond, resulting in ligand independent dimer species; for a single receptor type, the resulting CRN has 7 species and 14 reactions [1]. This baseline model represents a spatially homogeneous, "well-mixed" system where the receptors are distributed evenly and can move unobstructed over the entire membrane.

III. Model with High Affinity Domains

Based on TEM imaging of VEGF receptors, as well as a host of indications of clustering behavior in other receptor systems [3], we developed the following hypothesis. The membrane contains small attractive regions that concentrate the receptors in their random movement. The observed clusters reflect the size and distribution of these "high affinity domains".

We explore this hypothesis with a version of the MGP model where copies of the VEGF system are placed in multiple domains. Transfer reactions added to the system allow movement between the high affinity regions and the rest of the membrane. Computer simulations of this model indicate increased receptor concentrations in the attractive regions result in increased signaling as compared to the baseline MGP model. Analytical calculations provide an independent check of the simulations, as well as more direct insight into the behavior of the system. We are investigating the possibly multiple steady states, which are not forbidden by basic CRN theory.

IV. Outlook

Beyond this, we are interested in the effect high affinity regions have on the speed at which cellular response occurs, which must be done through simulation. We plan to use our framework of combining spatial and chemical networks for stochastic simulations of early VEGF signaling on the scale of the entire cell.

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