Vascular receptor-ligand binding and signalling

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***Short Abstract* — Vascular endothelial growth factor (VEGF) is the most frequent determinant for the activation of angiogenesis (formation new blood vessels from existing vasculature). In the project we are focused on building a comprehensive mathematical model for the purpose of simulating cellular fate.**

***Keywords* — angiogenesis, stochastic model, ligand-induced dimerisation, receptor tyrosine kinase**

I. Purpose

Cellular responses are usually induced by detection of extracellular signalling molecules (ligands) through specialized cell-surface proteins called receptors [1]. An intracellular signalling cascade begins upon receptor binding and this triggers a cellular response. There are several types of membrane-bound receptors. Angiogenesis is the process of new blood vessel formation in response to substances called growth factors (GFs), which are secreted and released by the surrounding tissues [2]. Blood vessel development and vascular repair are regulated by such ligands. There are many types of GFs and cell-surface receptors involved in angiogenesis. Our focus is on vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFR). Angiogenesis is an indication of all solid tumors [3] or wound healing [4]. The vascular system is essential for normal tissue growth development and homeostasis (the ability to control internal environment of the system to maintain it in a steady-state condition). For these reasons research is conducted to develop therapies that target the VEGF pathway [5].

II. Mathematical model

In order to model cell behaviour regulated by VEGFR-VEGF signalling, initial cell surface binding events and subsequent intracellular trafficking processes must be first quantified. Once this foundation is established, cell behaviour phenomena can be more easily analysed based on the number, state, and location of all units and complexes. The receptor population is involved in coupling with other receptors or membrane associated molecules, internalisation, recycling, degradation and synthesis - the pathway termed trafficking. Both VEGFRs monomers and VEGFRs dimers undergo internalisation by the same mechanism. The molecules are absorbed and transferred to an early endosome, in the process called endocytosis. After entering the early endosome, dimer and non-dimer VEGFRs follow different pathways. The former are transported to the late endosome and then to lysosomes to be degraded, where the latter are rapidly recycled to the membrane [6].

Stochastic models of the trafficking and binding dynamics of VEGFR to the bivalent VEGF have been developed in terms of Markov processes. Using the definition of the moment generating function, a partial differential equation for the moment generating function is derived. Also through the approach proposed in [7], the expansion of the master equation is performed to go from a stochastic description to a deterministic one. That approach enables analysis of fluctuations around the steady states. On the other hand, the differential equations for the first and second moments are obtained. The approximated solutions of the moments are found using moment closure techniques.

III. Conclusion

In view the low VEGF concentration in vivo and in vitro, stochastic modelling of molecular interactions may be necessary. The number of VEGFR-1 relative to VEGFR-2 is small; therefore VEGFR-1 might be neglected for the study of trafficking events. The binding is two-step process, depending on transport and intrinsic binding coefficient.

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