Receptor cross-talk in angiogenesis: Mapping environmental cues to cell phenotype in a stochastic, Boolean signaling network model

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***Short Abstract* — Cancer invasion and metastasis depend on tumor-induced angiogenesis. Based on experimental data, we propose a Boolean signal transduction network model highlighting the cross-talk between key receptors involved in angiogenesis. We identify relationships between receptor activation combinations and cellular function, and show that cross-talk is crucial to phenotype determination. The network converges to a unique set of output states that correspond to known cell phenotypes: migratory, proliferating, quiescent, apoptotic, and it predicts one phenotype that challenges the "go or grow" hypothesis. Finally, we use the model to study protein inhibition and to suggest molecular targets for anti-angiogenic therapies.**

***Keywords* — Signal transduction, integrin, cadherin, cancer, apoptosis, proliferation, migration, Boolean network**

I. Introduction

Endothelial cells are key constituents of the interior lining of all blood and lymphatic vessels, and are the targets of biochemical agents that stimulate cell growth and motility, thereby making them the key players in angiogenesis. Many growth factors and inhibitors have been discovered to regulate angiogenesis (cf. e.g., ref. [1]).

This study [2] is the first to propose a signal transduction network model that couples VEGF-RTK, ITG, and cadherin receptor signaling cascades, to capture receptor cross-talk during angiogenesis. We use this model to investigate how cellular behavior depends on and is controlled by changing environmental signals.

II. Model

We integrate data from signaling databases (KEGG, STKE) with results from experiments to determine the dependence relation for each signalling molecule in the network. First a standard discrete Boolean network (BN) is developed, that treats molecular species as binary (on or off) Boolean variables $X_i(t)$, i.e. they are either present or absent, dependent on the state of other molecular species. Each species i has k_i regulators, $r_i^1,\ldots,r_i^{k_i}$ and a Boolean regulation function $f_i:[0,1]^{k_i}\to[0,1]$. The state of species i at time $t+1$ then is given by

$$X_i(t+1) = f_i(X_{r_i^1}(t),\ldots,X_{r_i^{k_i}}(t)).$$

Continuous time dynamics under noise then is given by the following stochastic differential equation:

$$\frac{dx_i(t)}{dt} = \left| \; f_i(X_{r_i^1}(t),\ldots,X_{r_i^{k_i}}(t)) - \delta(t) \; \right| - x_i(t),$$

$\delta(t) = 1$ with probability p and $\delta(t) = 0$ with probability $1-p$.

III. Results

The following key results were obtained in this study [2]: Both for discrete and continous time state space, Boolean network dynamics converges to a unique set of output states that correspond to known cell phenotypes: migratory, proliferating, quiescent, apoptotic, and it predicts one phenotype that challenges the "go or grow" hypothesis. Signal transduction is very robust against molecular noise, with one exception: a mixed feedback scheme between RhoA and Rac1, as sometimes discussed in the literature, is extremely sensitive to noise, leading to erreatic cell movement. After a "shock" (randomization of cell-internal concentrations), we find a transient apoptotic response that increases with molecular noise, suggesting a dynamical mechanism that ensures that when the system is under stress or shocked, that regeneration occurs preferentially from the most healthy cells, while unhealthy cells are eliminated. Finally, we use the model to study protein inhibition and show that, in principle, it is possible to suggest molecular targets for anti-angiogenic therapies.

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