Emergent intracellular network states and cell fate decision: a dynamically integrated study of the epidermal growth factor receptor network with an agent based model

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In biological networks (e.g. protein-protein) component interactions are highly nonlinear. Theoretical models based on ordinary differential equation (ODE) have dominated the simulation of intracellular networks in the literature of theoretical cell biology. This approach is parameter driven and therefore motivated by the data currently available for well studied signalling systems such as the epidermal growth factor receptor (EGFR). Although these models are incredibly detailed they become unmanageable with the increase of network size and hence lose their predictive power. Simplified techniques such as discrete time Boolean networks which strip completely the dynamical system of kinetic parameters and evaluate qualitative network behaviour have been an alternative option for large networks. The network studied in this work involves the extended EGFR signalling pathway and its validated nuclear targets [Oda,K., et al.Mol Syst Biol 1:2005.0010] for which only a small part has been modelled using ODEs.The epidermal growth factor receptor (EGFR) has been implicated in the regulation of cell proliferation, survival and differentiation via activation of signalling pathways. Overexpression or constitutive activation of EGFR has been associated with in-vitro tumourigenic transformation and linked for example to non-small cell lung carcinoma (NSCLC), breast and colon cancers. Small molecule kinase inhibitors of the EGFR have been developed and two of them, Gefitinib and Erolitinib, have already been licensed for clinical use in NSCLC. These drugs have been found to have positive impact — reduction in cell proliferation and induction of apoptosis — in patients with mutated EGFR. Nevertheless, the action of the inhibitors has many non-specific interactions [Fabian, M, et al., (2005), Nat. Biotechnol, 23, 329]. Both pro-cancerous and anti-cancerous kinases, in addition to EGFR, are inhibited exerting therefore additional effects on the cell. To study the possible consequences of an EGFR signalling network perturbation and devise strategic methods for cell fate decision control, through the administration of drugs, an Agent Based Modelling (ABM) approach was used. Cell phenotype is identified with particular network emergent dynamical states. An extension of a class of continuous time Boolean networks was analysed under the ABM paradigm. Each agent, seen as a control gate, represents a 'molecular species' (signalling protein or transcription factor) with a normalized concentration value but with only ON/OFF output states determined by a threshold value. Its concentration evolution is represented by a piece-wise linear differential equation with time delays. The time delays stand for diffusion associated effects or other processes that escape the usual assumption of a well mixed system in cell simulations. Higher autonomy of each node is secured by the existence of an internal noise term associated with each time delay. Agents representing transcription factor nodes exhibit higher time delays which stand for the differences in time scale of signal transduction and gene transcription processes. Node targeting is performed by node removal, by modulation of the internal noise term or partial inhibition according to the binding assay data [Fabian et al (2005)]. This modelling approach is the simplest possible one retaining important properties of biological systems such as distributed control, asynchrony and noise.