



Invited Talk Julio Saez:

Comparative logical models of signaling networks in normal and transformed hepatocytes

Protein interaction networks (PINs or interactomes), protein signaling networks (PSNs) and gene regulatory networks have successfully been used to classify drug-target interactions, identify master transcriptional regulators and uncover new disease genes.

Unfortunately, PINs and PSNs are rarely cell-type specific and do not encode the input-output relationships required for analyzing receptor-mediated signaling cascades and the drugs that target them. Conversely, traditional approaches to studying cell signaling do not make use of the wealth of information that is now encoded in PINs and PSNs. Here we describe a hybrid to convert PSNs into logical models that can be trained against data in which cells are exposed to-combinations of ligands and drugs followed by multiplex biochemical measurement of intracellular responses, and its implementation in the toolboxes CellNetOptimizer (Mol. Sys. Biol., 5:331, 2009) and DataRail (Bioinformatics, 15(24):840, 2008). We apply the method to distinguishing the topologies of immediate early signaling networks in primary human hepatocytes and four hepatocellular carcinoma (HCC) cell lines. We show that five distinct models cluster topologically into normal and diseased sets, revealing three functional differences between normal and diseased cells that involve activation of growth factor receptors and intracellular kinase cascades. In a proof-of-principle experiment we also infer a target for an I-kappa B kinase inhibitor developed to treat arthritis and airway inflammation.

Date: Friday 29th October .

Place: Hotel Son Don Pablo. Sala Toledo.