Systems biology approaches have provided a new conceptual framework for examining complex intracellular regulatory processes, and also for hypothesizing generic rules for these regulatory events. In this context, one area of special interest is the role of signaling molecules in facilitating differential cellular responses, under diverse stimulation conditions.

In the present study we adopted a unique strategy to study receptor crosstalk events, which then facilitated an examination of the co-operative output from two different stimulation conditions. A key feature here was the approach to consider the signaling and the transcriptional machinery as a complete, integrated, unit rather than as separate parts of the larger system. Such an approach indeed provided some interesting insights into the mechanisms enforcing cell-fate decisions.

We sought to obtain a systems view on how crosstalk between the two respective cell surface receptors modulates the cellular response. We found that, in comparison to the effects of B-cell receptor activation alone, combined stimulation through both receptors enforced a marked reorientation in the 'survival versus apoptosis' axis of the signaling machinery. The consequent modulation of transcription factor activities yielded an integrated network, spanning the signaling and the transcriptional regulatory components, that was now biased towards the recruitment of molecules with a pro-survival function. This alteration in network properties influenced early-induced gene expression, in a manner that could rationalize the antagonistic effect of the IL-4 receptor on B-cell receptor signaling. Importantly, this antagonism was achieved through an expansion in the repertoire of the genes expressed, wherein the newly generated products counteracted
the effects of the B-cell receptor-specific subset. Thus the plasticity of the regulatory networks is also experienced at the level of gene expression, and it is the resultant pattern obtained that then modulates cell-fate decisions.