**Chemical reaction networks for modelling colorectal cancer signaling: a focus on MAPK pathway**

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The G1-S phase of life of a cell involves numerous proteins, interacting through many chemical reactions. Mutations in the genes responsible for the synthesis of these proteins can be problematic, causing diseases as cancer. Therefore, learning to predict the effects of such mutations is a first crucial step to identify which targeted drugs to administer and their dosage.

The dynamic over time of proteins concentrations inside the cell can be described through a powerful tool named Chemical Reaction Network (CRN) [1]. Specifically, we focus on the CRN devised for modeling colorectal (CRC) cells, which involves many chemical species belonging to several interacting pathways, e.g. WNT, MAPK, TGF, EGF. From a mathematical viewpoint, the mass-action law allows to model a CRN as a large system of ODEs depending on a set of kinetic parameters.

Computing the steady states of such systems is a key step for understanding the local and global effects of mutations and drugs on the network since it reveals which proteins concentrations vary the most at equilibrium when the healthy cell and the mutated one are compared. Here a fast and accurate optimization method, the NonLinearly Projected Combined (NLPC) algorithm, that we propose in [2], is applied for studying one of the most frequent mutations involving the MAPK (mitogen-activated protein kinase) pathway found in colorectal cancer.

Specifically, the talk focuses on a quantitative analysis of the impact of the gain of function mutation of KRAS [3], a widely expressed GTP/GDP-binding protein located inside MAPK pathway, whose mutated version is very common in colorectal cancer.

We will show how the NLPC algorithm allows to compute the impact of KRAS mutations both on the CRC network’s global proteomic profile and on the expression of MAPK key species: k-Ras, B-Raf, MEK and ERK and their phosphorylated version. Furthermore, we will simulate the impact on the whole cell of single and combined drugs that target species belonging to MAPK pathway, by computing the equilibrium states and analyzing the dynamic behavior of specific species when different dosages of drug are considered.

Finally, by using a dynamic approach, we will see how the impact of drugs on KRAS mutated colorectal cells could slow down the phosphorylation of ERK, responsible of cancer development and progression [4].

**References**

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