Poster 3

Systems genome, Gene Activity Networks, and Recurrent Activity Motifs in control of genome homeostasis; role of nuclear FGFR1

J. Diehl[a], N. Manoj[b], A. Sangwan[c], J. Jornet[c], Y. Bae[d], A. Dutta[a,d], M.K.Stachowiak[a,d]
a UB BME, b UB GGB, c NEU Electrical Engineering, dUB Pathology and Anatomical Sciences

During transition of human Neural Progenitor Cells (NPC) to Neuronal Committed Cells (NCC) activities of 4706 genes change their activities. These changes obey the Gaussian principle whereby the majority are moderate and few represent extreme up- or down-regulations. Inhibition of pan-ontogenic nuclear Fibroblast Growth Factor Receptor 1 (nFGFR1) signaling, which mediates the NPC to NCC differentiation, affected the activities of hundreds of genes in NPC and in NCC. Our new results show that nFGFR1 acts as a Band-Path filter that maintains global genome function within a homeostatic range by diminishing extreme changes and promoting moderate changes. To elaborate on the underlying mechanism, we analyzed Pearson correlation among the genes of the regulated genome. The majority of 4007 gene activities were highly coordinated and their frequencies were increased during the NPC to NCC transition while the low coordinated genes were decreased. The frequencies of high and low coordinated genes were affected by the inhibition of endogenous nFGFR1 and by the overexpression of constitutively active nFGFR1.

Analysis of Gene Activity Networks (GANs) formed by the most coordinated neurodevelopmental genes showed that NPC to NCC transition is accompanied by a deconstruction of NPC GANs and construction of new NCC GANs and that the formation of GANs is largely dependent on the endogenous levels of nFGFR1. Within the GANs we identified several overrepresented Recurring Correlation Motifs (RCM) which undergo frequency redistribution during differentiation. The high complexity motifs (with a high number of connections) increased during GANs' construction and decreased during GANs' deconstruction. The ability of the RCM to counteract excessive gene activity oscillation during differentiation was analyzed by modelling their function as electrical RLC equivalent networks with genes serving as inductors (L) and the equivalent Spring-mass oscillator model. In RLC circuits, where the reduced inductance value from star network arrangement dampens the oscillations, increased motifs complexity dampens down the oscillations in the individual nodes (genes) activities as the network transits between different activity levels. In conclusion, deselection of low complexity of motifs and selection of more complex motifs by nFGFR1 serve to maintain the genome homeostasis during development.

A Proportional–Integral–Derivative (PID) controller model with the RLC lumped element equivalents is proposed employing nFGFR1 feedback as a control system of the ontogenic gene programs.