**The search for a core functionality network in chondrocyte differentiation using heuristic and genetic algorithms**

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*Introduction:* In the growth plate a continuing process where cartilage is replaced by bone provides the fuel for bone growth until its closure towards the end of puberty. At the cellular level the growth rate is maintained by proliferation and enlargement of maturing cells (hypertrophy). Mature cartilage cells (hypertrophic chondrocytes) secrete Ihh, a growth factor that induces expression of PTHrP, another growth factor, in immature proliferating chondrocytes. Since PTHrP in turn inhibits chondrocyte maturation, Ihh secretion limits the number of maturing chondrocytes through a negative feedback loop, striking a balance between proliferation and hypertrophy [Kronenberg, 2003].

*Materials and methods:* A gene network centering on the control of Ihh, PTHrP and transcription factors Sox9 and Runx2, which are the master regulators of early and late chondrocyte differentiation respectively, was manually constructed from literature. The dynamics of this network are simulated in a discrete framework that divides reactions into two speed classes. In this framework all interactions are considered additive, and each interaction is associated with a weight. Starting from the observation that the gene network must activate Runx2 in the presence of Ihh and Sox9 in the presence of Ihh and PTHrP, we investigate which edges are vital in achieving this. To this end, we employ both a heuristic and a genetic algorithm where the weights attached to the edges function as variables. *In the heuristic algorithm weights are uniformly distributed in [0,1] and the means (based on 450 samples) of the weights that satisfy the above mentioned observations are contrasted with those that do not. If the difference of the means passes a certain threshold, the weight of the corresponding edge is fixed at 1.*

*Results and discussion:* Preliminary results from the heuristic algorithm show that fixing 14 weights (out of 147) is sufficient to match the biological observations in about 22% of cases, all other weights being selected randomly. The selected edges show that the BMP pathway is crucial in effecting a switch between hypertrophy in the absence of PTHrP and proliferation in its presence. This observation can be substantiated by earlier findings that BMP signalling plays a crucial role in prehypertrophic cells that are on the verge of hypertrophy [Yoon, 2006].

*References:* Kronenberg, 2003, Nature, 423:332-336; Yoon et al.,2006, Development, 133:4667-4678.