Dynamics of control and cell fate in the chondrocyte network: a preliminary study

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INTRODUCTION

Background

- Developmental engineering: an *in vivo*-like *in vitro* process to engineer tissues[1]
- Understanding of combination and interplay of signals directing chondrocyte development is required

Growth plate regulation

- BMP, Wnt, FGF, Ihh/PTHrP, TGFβ and IGF-I are important paracrine signals
- Sox9 is the master regulator of chondrogenesis
- Runx2 controls chondrocyte hypertrophy

Modelling

- What is the influence of individual factors on cell fate?
- What is the effect of the speed classes on this influence?

GENE NETWORK AND DYNAMICS

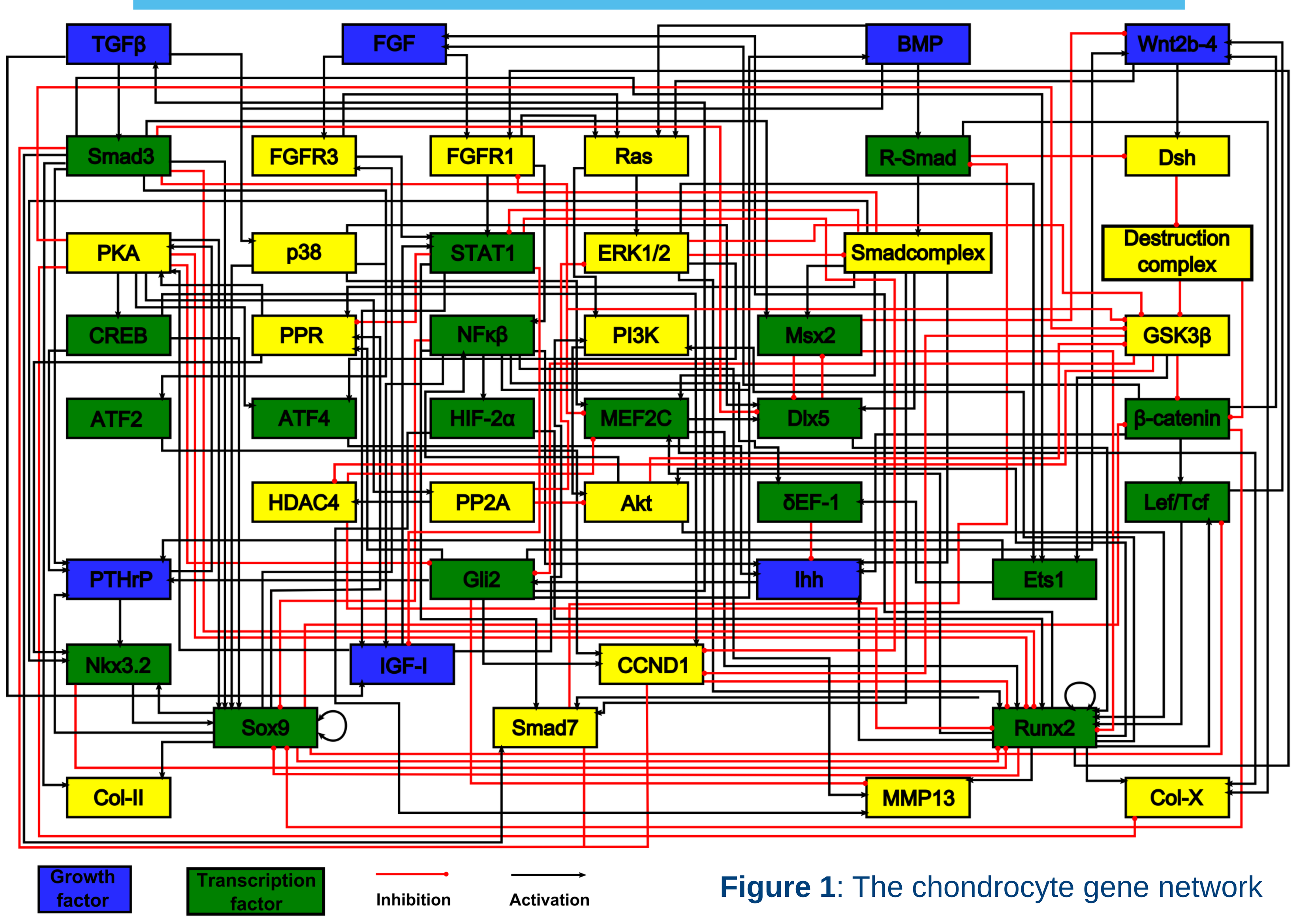

Figure 1: The chondrocyte gene network

- A **literature-based network** comprising several influences on the balance between Sox9 and Runx2
- 46 nodes and 161 interactions
- 2 competing set of transcription factors lead to formation of 2 attractors (Runx2 and Sox9-associated)
- Discrete dynamics using **additive** functions
- Allows measurement of the size of the attractor basins and the sensitivity to perturbation of attractors

PHENOTYPICAL STABILITY

- **Stability to perturbation** in a random node
- **Higher stability** of Runx2-associated state

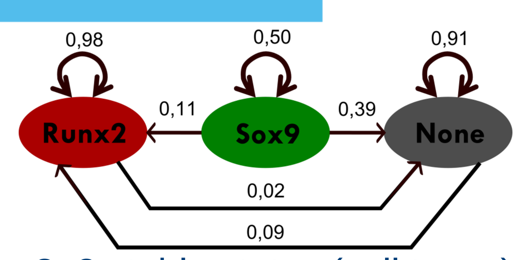

Figure 3: 3 stable states (cell types) and their transition likelihoods

DISCUSSION

- Analysis based on topological information reveals the relative stability of the possible chondrocytic cell types
- **Slow control** seems to confer **higher influence**, but results are not unequivocal

TWO SPEED CLASSES

- Ideal separation between fast (posttranslational processes) and slow time scale (transcriptional processes)
  - Quasi-steady state approach

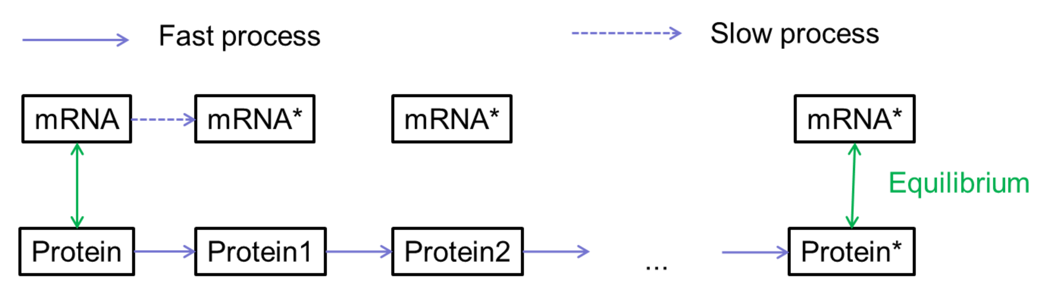

Figure 2: Fast variables are in equilibrium with the slow variables at all times.

DYNAMICS OF CONTROL

- Do nodes under slow control have a higher influence on cell fate (choice of attractor)?
- Switching from fast to a slow speed class gauges **effect of the speed class on cell fate**
- Effect of higher influence is estimated through a constitutive activation of the respective node, lower influence via knockout
- **Table 2** compares the effects of the change in speed class with the estimated change in influence of the node

Node	Speed	Result	Perturbation	Result	Match?
Wnt	S→F	-1,1%	KO	-7,7%	
Dsh	F→S	2,2%	CA	6,2%	
IGF-I	S→F	-0,7%	KO	-1,3%	
R-smad	F→S	7,0%	CA	13,4%	
Ihh	S→F	-2,3%	KO	-8,5%	
Gli2	F→S	3,2%	CA	-12,5%	
β-catenin	F→S	3,4%	CA	6,0%	
PTHrP	S→F	1,9%	KO	3,5%	
PKA	F→S	0,1%	CA	-1,0%	
FGF	S→F	-1,4%	KO	-2,9%	
STAT1	F→S	2,1%	CA	3,2%	
Smadcomplex	F→S	7,3%	CA	13,9%	
Nkx3.2	S→F	1,0%	KO	1,2%	
ERK1/2	F→S	5,7%	CA	11,5%	
TGFβ	S→F	-3,3%	KO	0,4%	
Smad7	S→F	1,5%	KO	4,5%	
Smad3	F→S	-2,6%	CA	-69,5%	
NFκβ	F→S	4,1%	CA	9,5%	
HDAC4	F→S	-1,2%	CA	-34,0%	
BMP	S→F	1,6%	KO	-9,7%	
p38	F→S	-0,5%	CA	5,2%	
GSK3β	F→S	0,6%	CA	0,7%	
DC	F→S	-1,8%	CA	-6,1%	
PP2A	F→S	-0,2%	CA	-3,0%	
δEF-1	S→F	-0,4%	KO	0,0%	
ATF4	F→S	3,6%	CA	1,4%	
HIF-2α	S→F	-1,6%	KO	-0,6%	

F→S: fast to slow switch
S→F: slow to fast switch
CA = constitutive activation
KO = knockout

Table 2: Assessing whether nodes under slow control have a higher influence on cell fate (attractor) choice.'Speed' indicates the change in speed class. 'Perturbation' shows the corresponding perturbation, either upward for going to the slow class, or downward for the fast class. The results columns show the change in size of the Runx2-assiocated attractor basin. The last column assesses whether the slow control does indeed result in a higher influence.

CONTACT DETAILS & REFERENCES

[1] Lenas P. et al. (2009) *Tissue Eng Part B Rev*, **15**, 381.

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