

Modeling Delta-Notch signaling during Somitogenesis: selection, analysis and extension.

1 Background

Somitogenesis is a dynamic morphogenetic process during which the paraxial mesoderm of the trunk and tail of vertebrate embryos is segmented. The Delta1 (Dll1) gene encodes one of the Notch ligands in mice and is required for the generation of epithelial somites and the maintenance of boundaries between mesodermal segments.

The Dll1 5' upstream region was screened for potential cis-regulatory elements, which could drive Dll1 expression during somitogenesis. One particular element (MSD) directed reporter gene expression in the presomitic mesoderm (PSM) and somites in transgenic mice. It contains T/Tbx6 and LEF/TCF binding sites, which are necessary for reporter gene expression in the PSM and tail bud of transgenic mice.

Tbx6 itself is a T-Box transcription factor and is expressed exclusively in the PSM during development. In addition, Tbx6 protein was shown to bind to MSD *in vitro*. Interestingly the Tbx6 regulatory region itself contains a RPBjk binding site suggesting a feedback loop of Tbx6, Dll1 and NICD.

2 Objectives

For our analysis we use qPCR data of Dll1, Notch and Tbx6 from seven different mouse lines: wild type, Tbx6^{tm1pa/+}, Tbx6^{tm1pa/+} Dll1^{tm1.1Ieg/+}, Tbx6^{tm1pa/+} Dll1^{tm1.1Ieg/tm1.1Ieg}, Tbx6^{tm1pa/tm1pa}, Dll1^{tm1.1Ieg/+} and Dll1^{tm1.1Ieg/tm1.1Ieg}. Initially, a qualitative two-compartment model based on prior knowledge is used to define a proper model space. Assuming a steady state condition for each mouse line, an ABC method based [1] model selection approach should be performed.

The goal of the thesis is to find a model or a set of models that best fit to the data. These should then be further tested for robustness and stability. The models should then be discussed towards their biological relevance. The results will be the basis for hypothesis generation and further experiments.

Thereby several open questions should be answered:

- self activation of Tbx6?
- feedback loop Tbx6 – Dll1?
- regulation of Notch?
- further unknown influences, miRNAs?

The project is a collaboration with the ‘institute of experimental genetics (IEG)’ of the Helmholtz Zentrum Muenchen.

References

- [1] Tina Toni and Michael P H Stumpf. Simulation-based model selection for dynamical systems in systems and population biology. *Bioinformatics*, 26(1):104–110, Jan 2010.

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