National Institute for Public Health
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A developmental ontology-based computational model for mammalian neural tube closure

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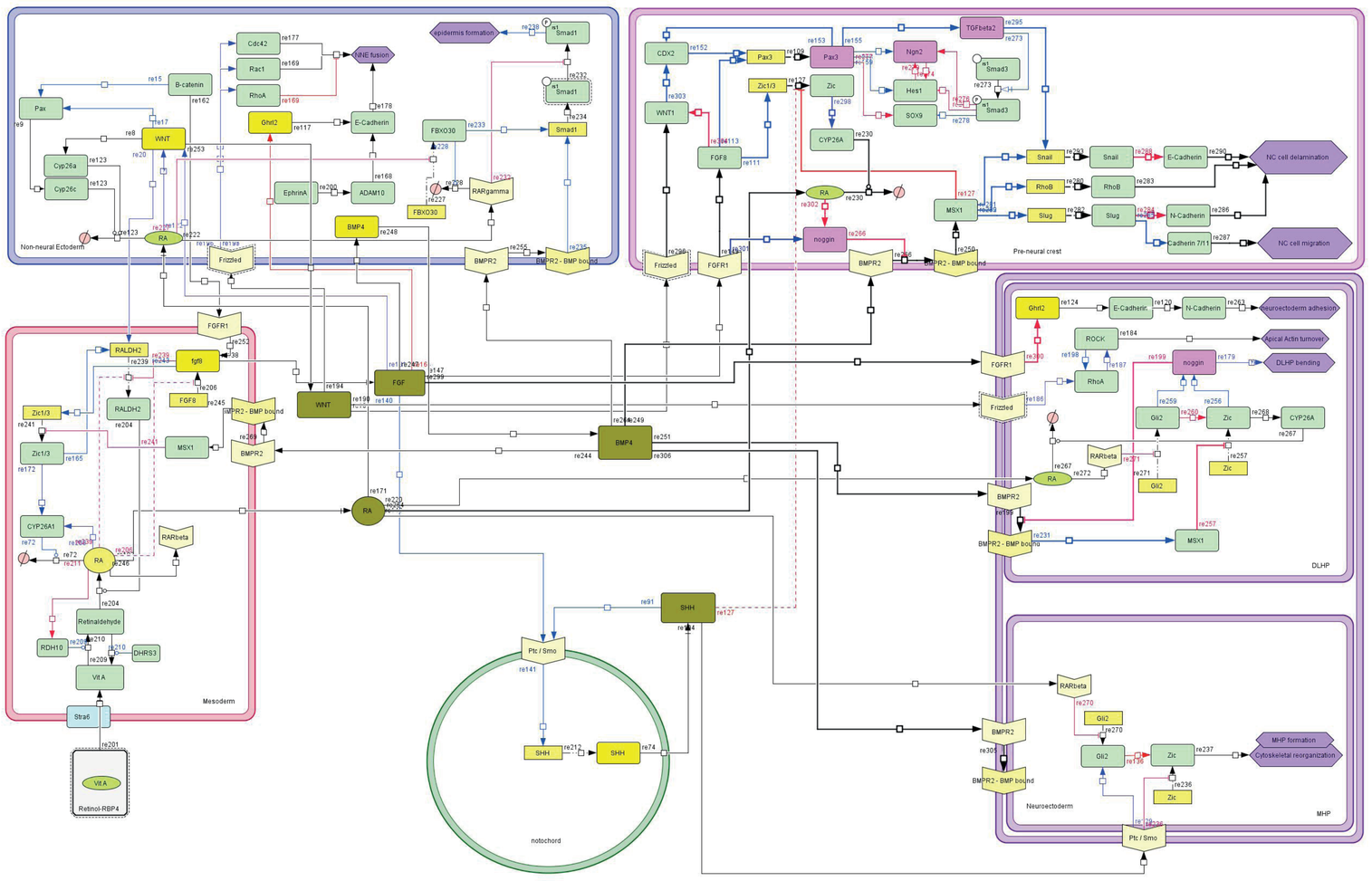
Introduction

- Computational models of biological processes are expected to revolutionize chemical safety assessment in the not too far future.
- Such models provide the template for establishing quantitative adverse outcome pathway (AOP) networks that define critical key events that need monitoring in in vitro cell models, and provide algorithms for data integration towards defining safety profiles of chemicals at the level of the intact human.
- This project aims at modelling mammalian neural tube closure in silico, as a tool for defining the related AOP network and its critical key events that need monitoring in selected in vitro assays.
- The starting point was the retinoic acid pathway, given that this morphogen plays a crucial role in cell fate, pattern formation and morphogenesis in the early mammalian embryo.

Current Progress

- We have extensively mined the developmental biology and toxicology literature to generate the gene and cell compartment interaction map shown below (figure left).
- A cascade of gene expression changes programmed in the embryo in space and time causes location-specific cell proliferation and differentiation patterns, ultimately resulting in the development of a closed neural tube from the initial neural plate (figure right).
- We are currently translating this map, produced in CellDesigner software, into a three-dimensional in silico neural tube closure model, produced in CC3D software, which is driven by the gene expression map.
- This model will allow to study in silico the consequences for neural tube closure of model compound-induced gene expression changes detected in relevant in vitro assays.



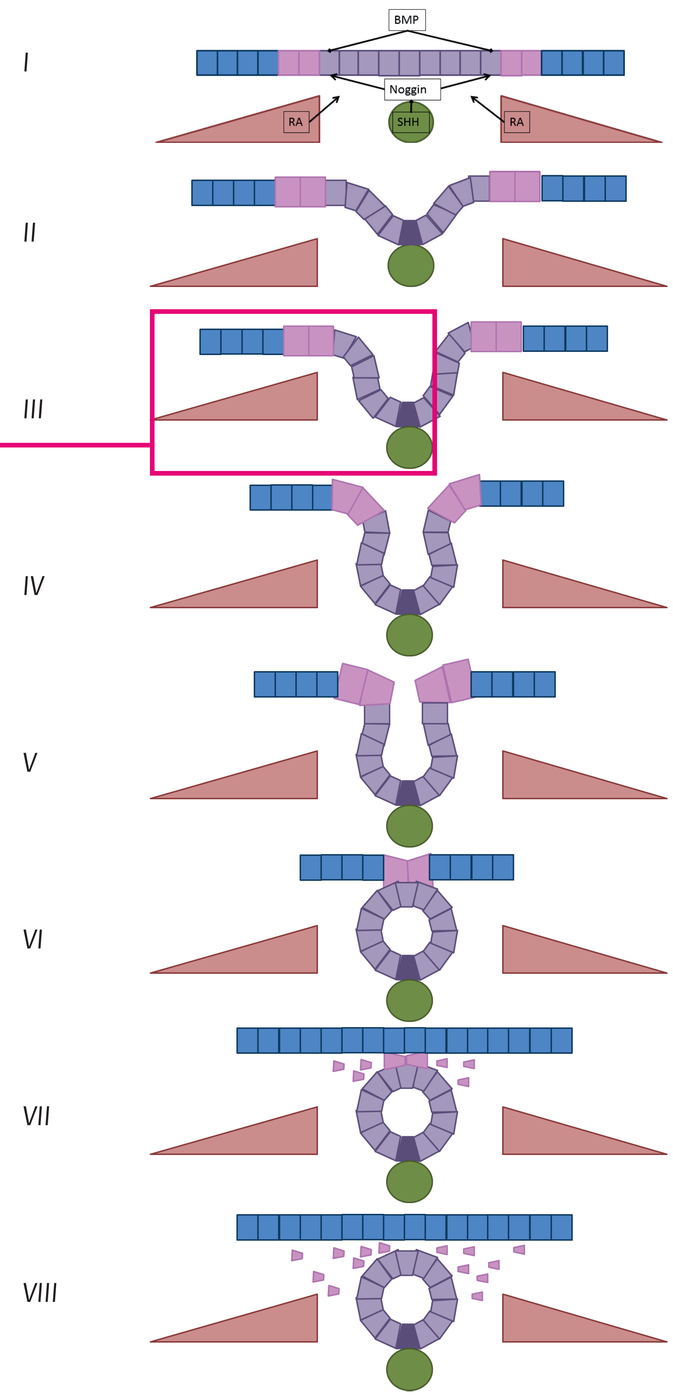


Figure: *Signaling network underlying the process of closure of the mammalian neural tube (left). Neural tube closure (right) starts with a flat surface of ectoderm (I) in which the notochord (dark olive) will trigger formation of the median hinge points (dark purple) (II – III) causing the first invagination of the plate after which the bending of the tube will occur following formation of the dorsolateral hinge points (IV - VI). Subsequently, the neuroectoderm (light purple) and the non-neuroectoderm (blue) will fuse (VII) and the neural crest cells (pink) will detach and move away (VII – VIII). Red box indicates section represented in signaling network.*