ONTOX

Universiteit Utrecht

Funded by the Horizon 2020 Framework Programme of the European Union

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Computational modelling of neural tube closure defects

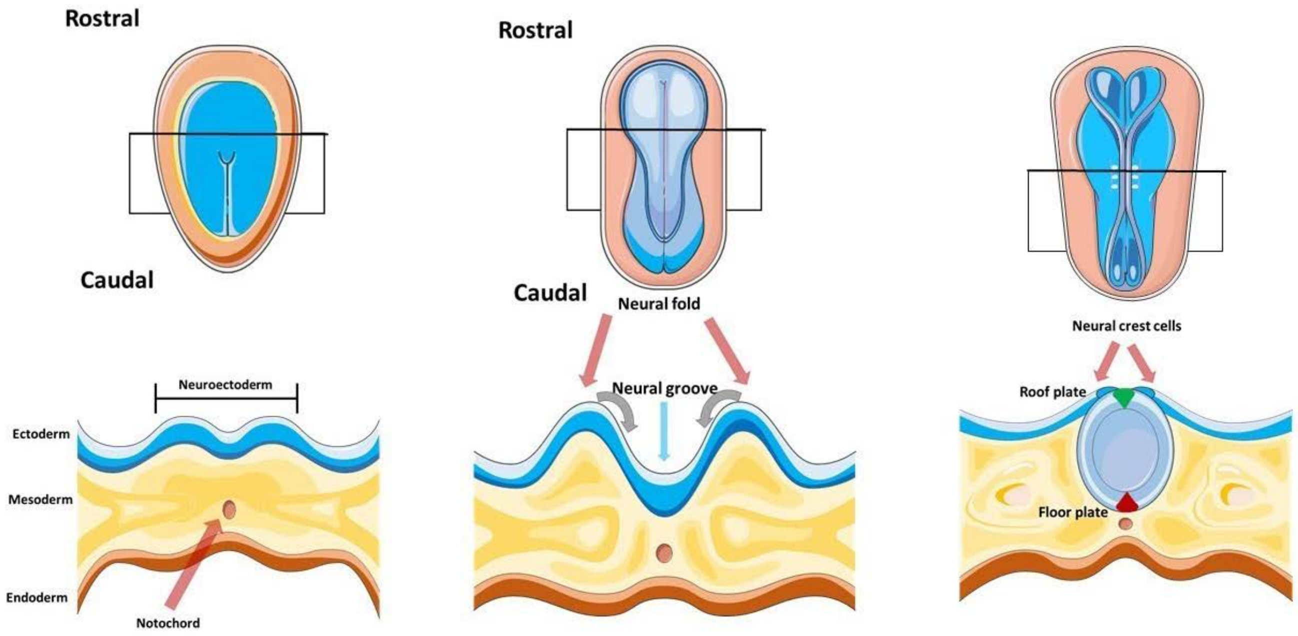
ESTIV webinar

28-04-2023

Job Berkhout

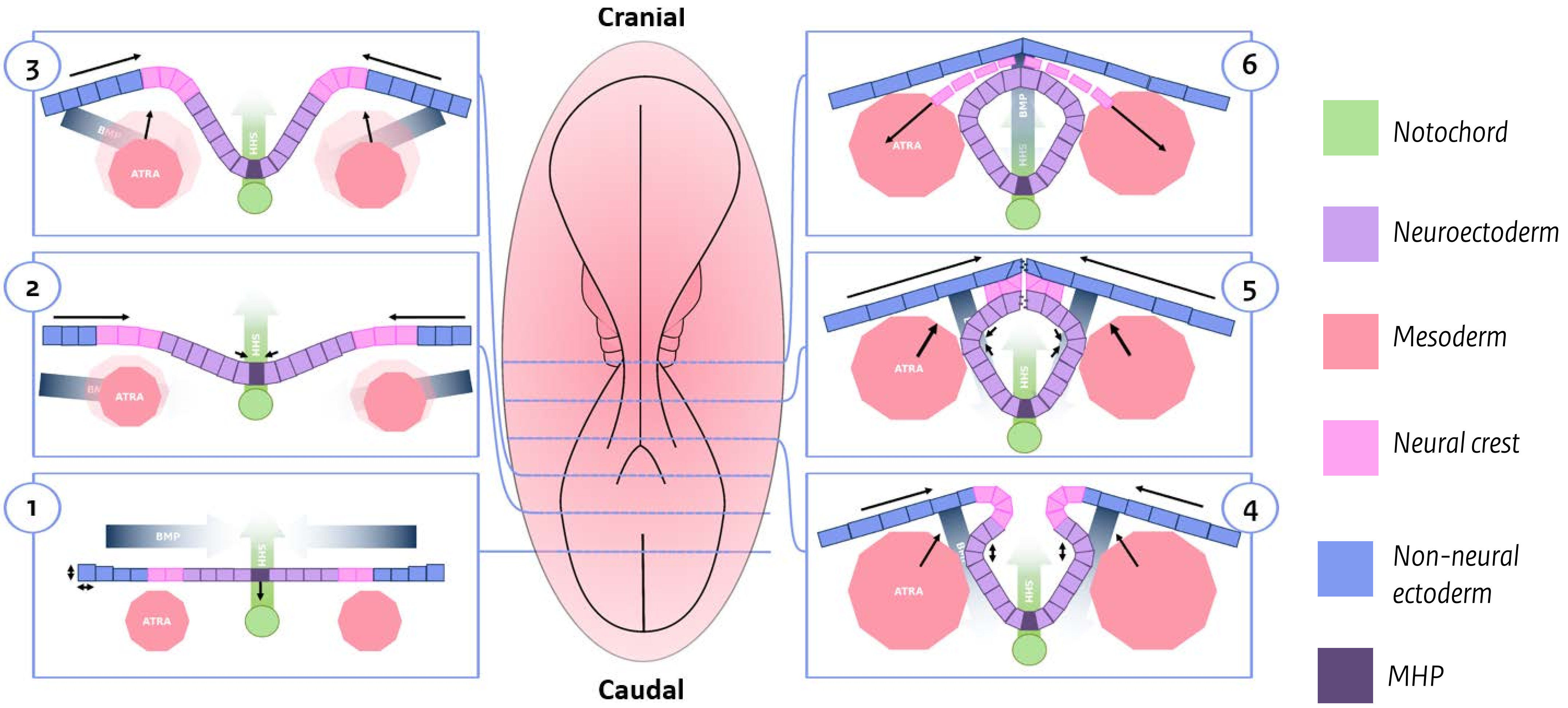
The neural tube closure

- Precursor of the brain and the central nervous system
- Early event in pregnancy
  - End of 3rd week
- Complex process that involves various cellular events



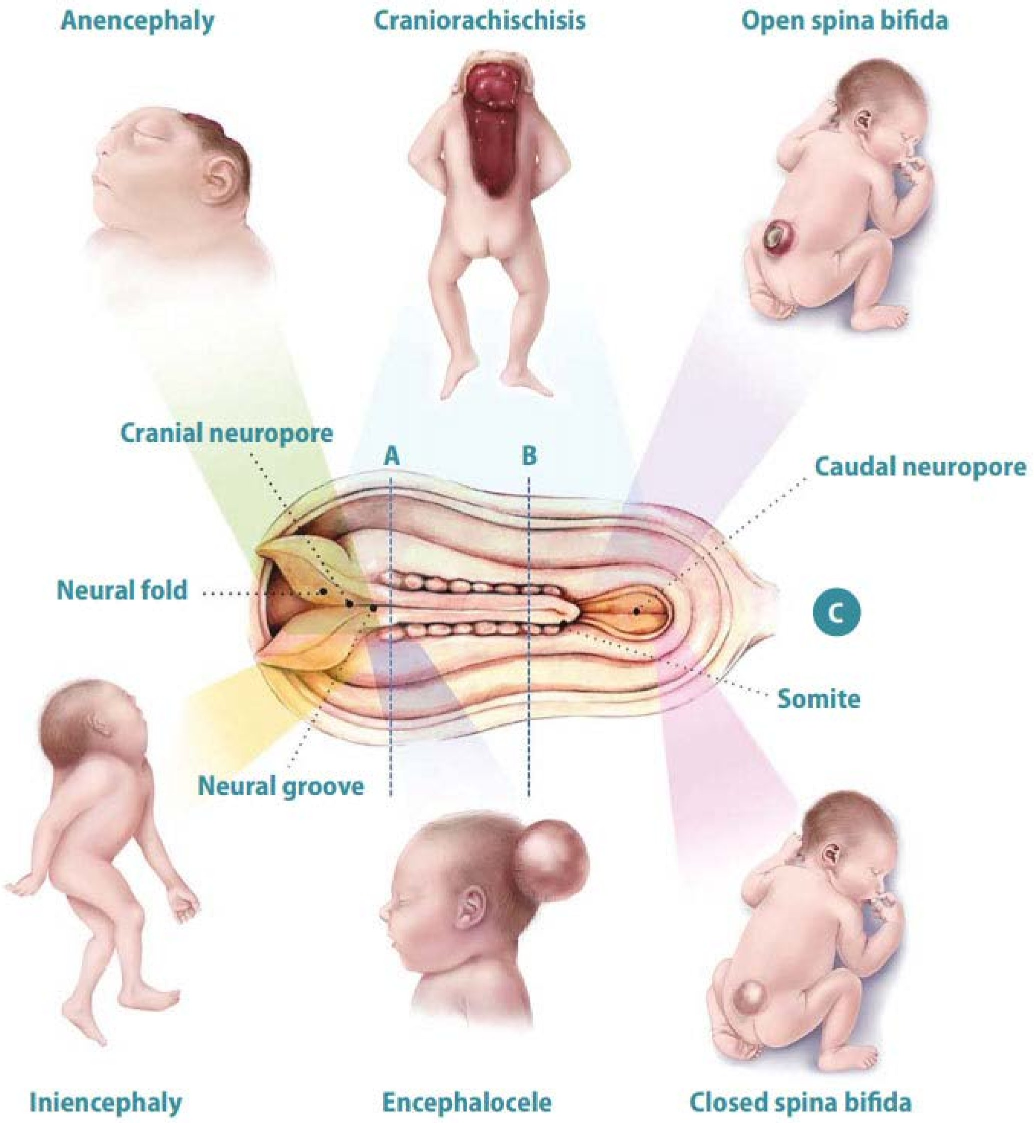
Neural tube closure

- Complex process, target for chemical disturbance



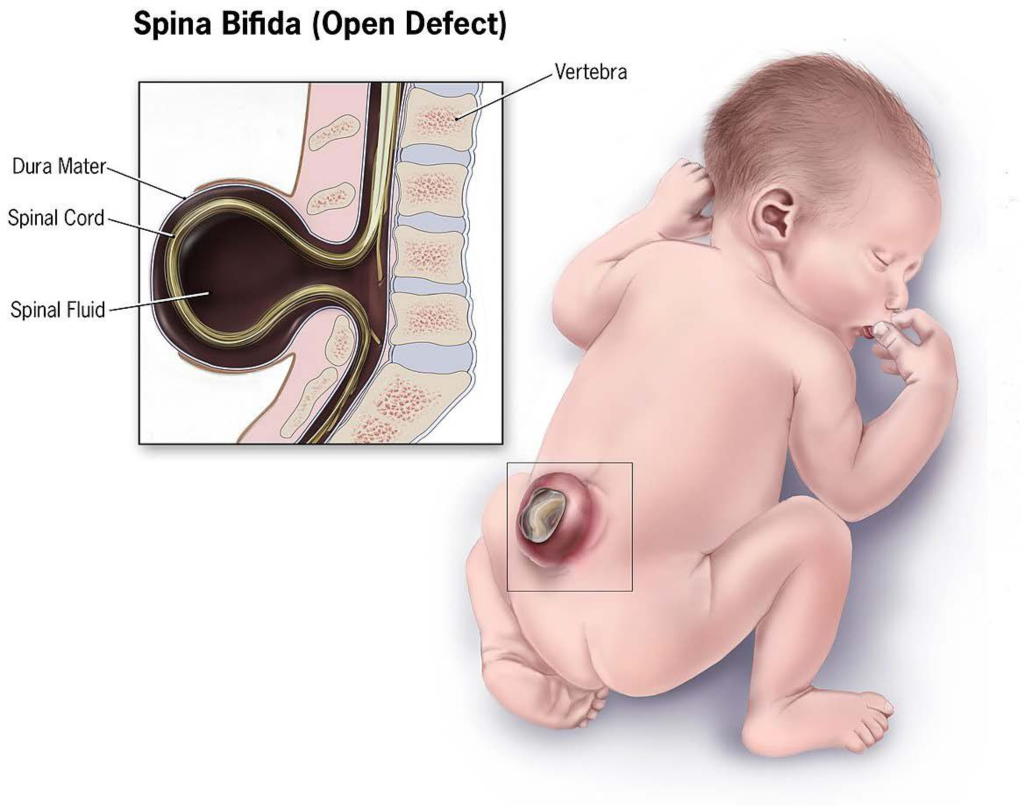
Failure of closure

- Neural tube closure defects
- Multiple variations



Failure of closure

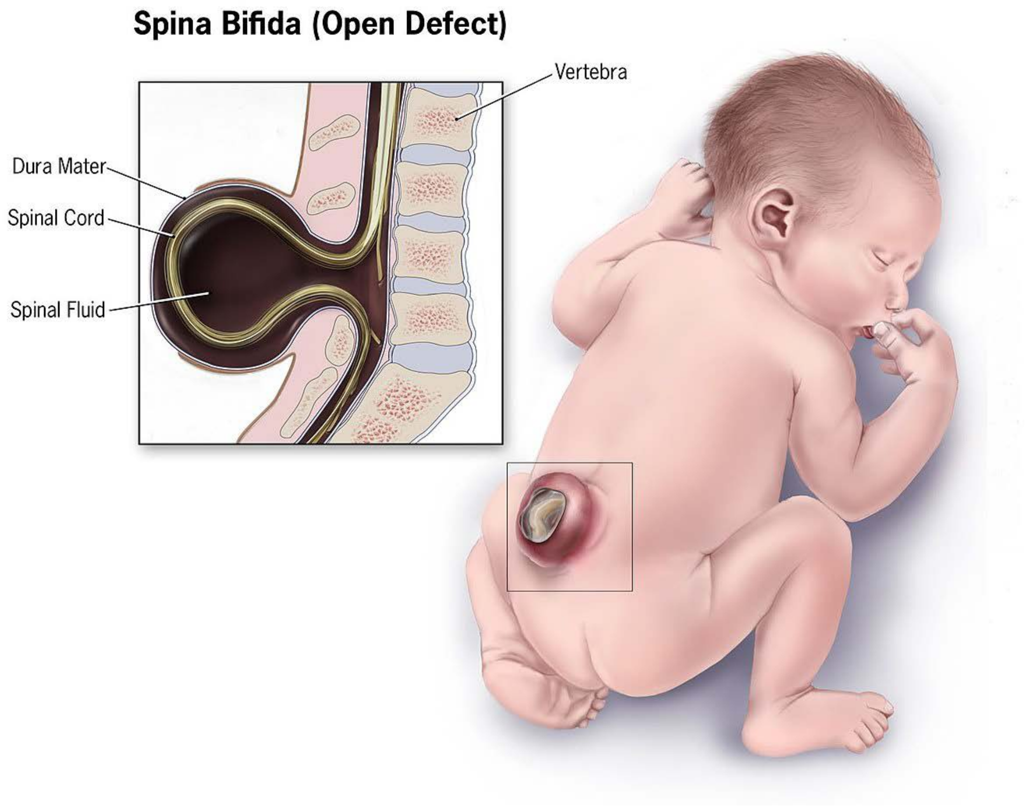
- Neural tube closure defects
- Multiple variations
- Among the most prevalent birth defects
  - Spina Bifida: 3.5/10.000 US
- No test available for risk assessment
  - *In vivo* is not sufficient



Failure of closure

- Neural tube closure defects
- Multiple variations
- Among the most prevalent birth defects
  - Spina Bifida: 3.5/10.000 US
- No test available for risk assessment
  - *In vivo* is not sufficient

- Develop a human relevant test strategy!



Test strategy for neural tube closure defects

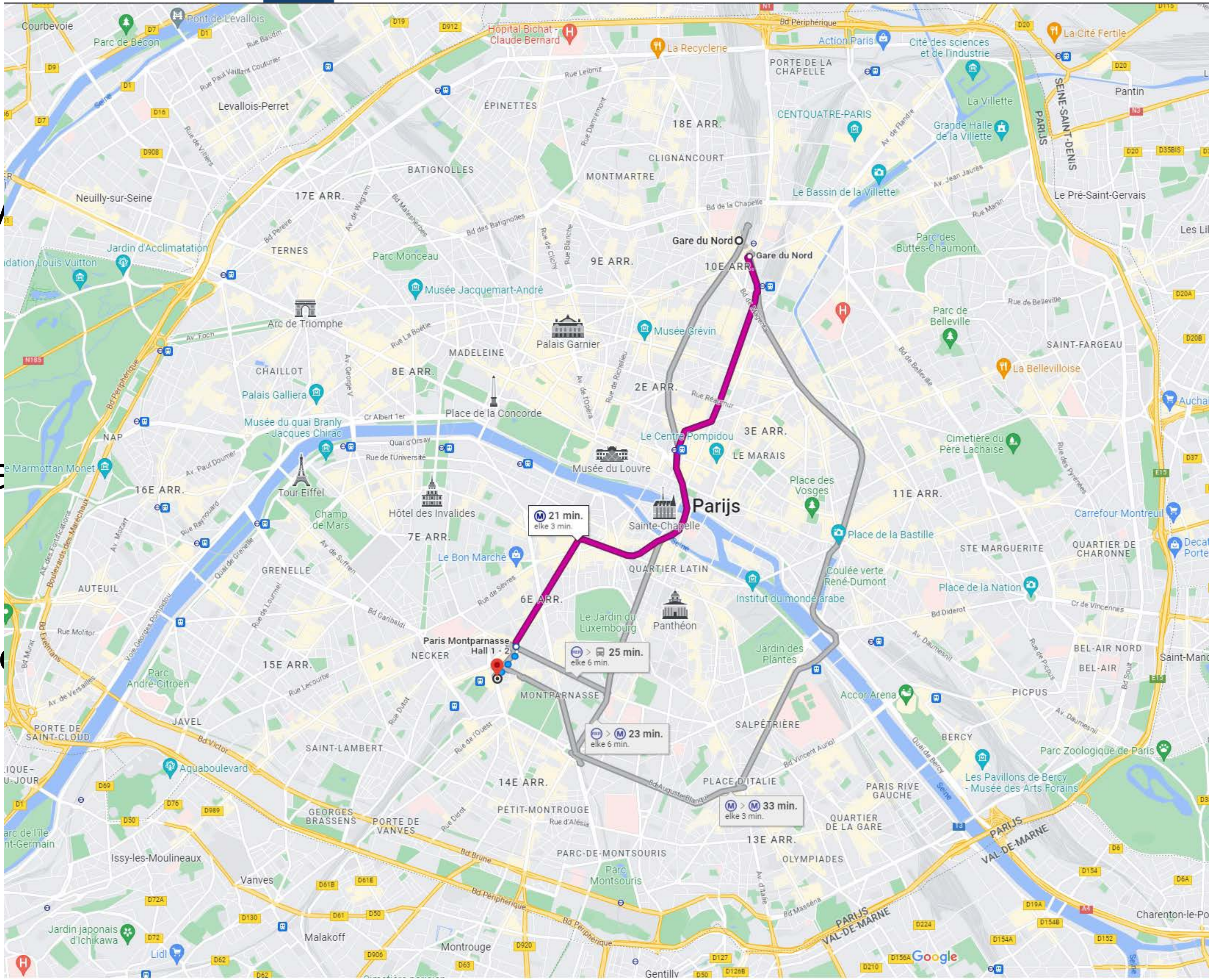
- 3R approach (Replacement, Reduction and Refinement)
  - Repeated dose toxicity
  - Focus on *In vitro* and *In silico*

- Rooted in human biology
  - Physiological maps
- Building Ontologies
  - The whole system of biology on which a test strategy is based

To model somethi

- Strategies for toxicity testing
- Paris
- Travelling by train
- Depending on the ma
    - Wrong direction
    - Dead-end street
    - Never in time for the

- Better maps needed
- Ontologies

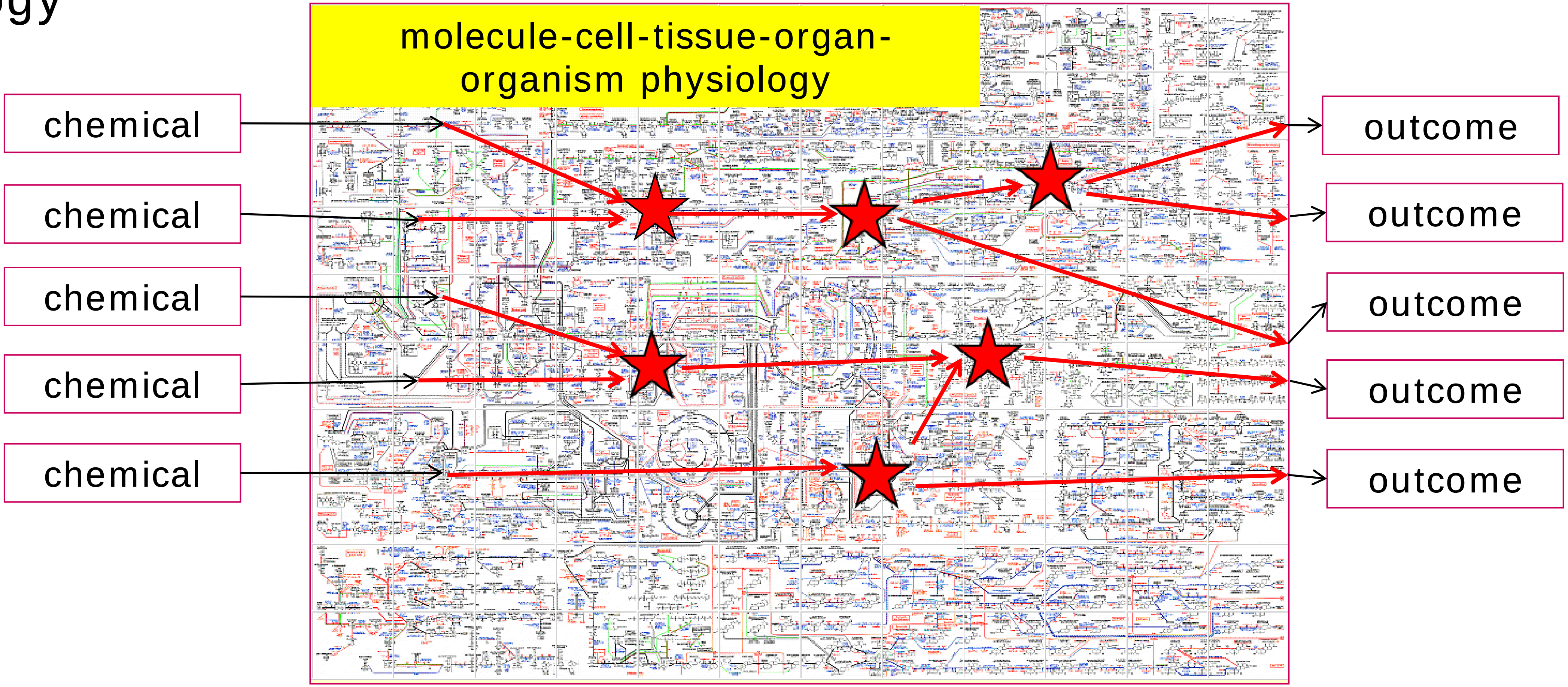


Adopted from H. Heusinkveld

Ontologies

Normal physiology

Human



Adopted from H. Heusinkveld

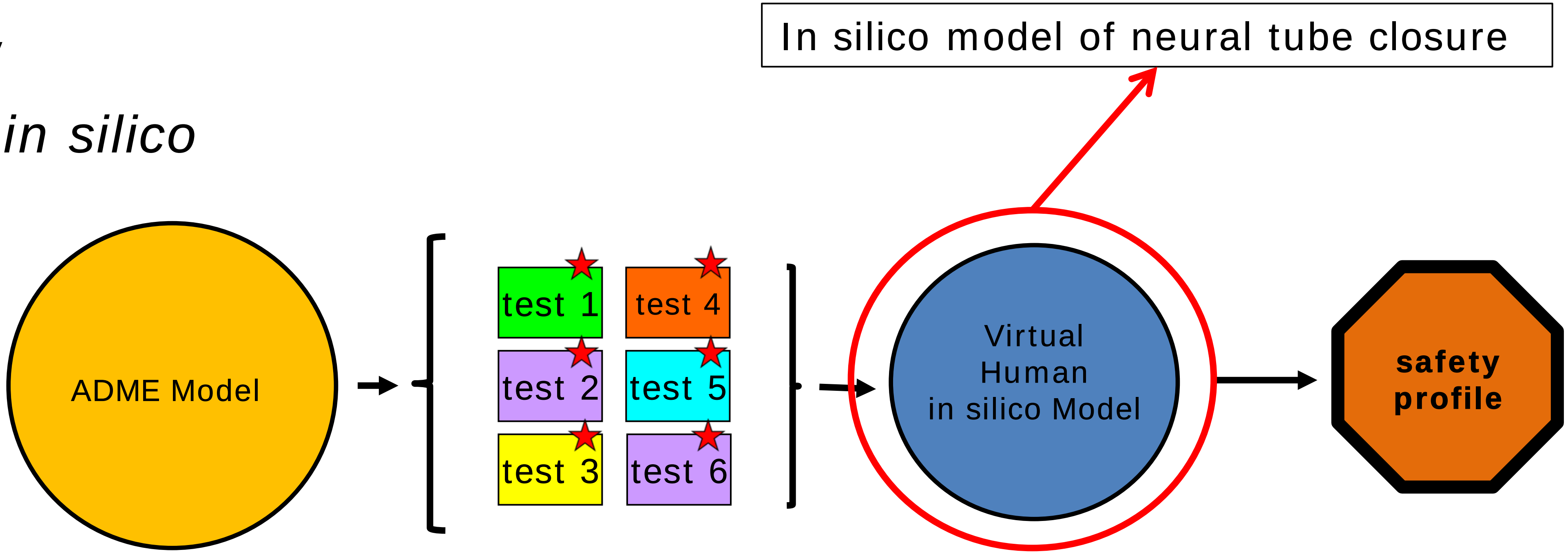
From Ontology to test strategy

Key elements

AOPs

Test battery

Integration *in silico*



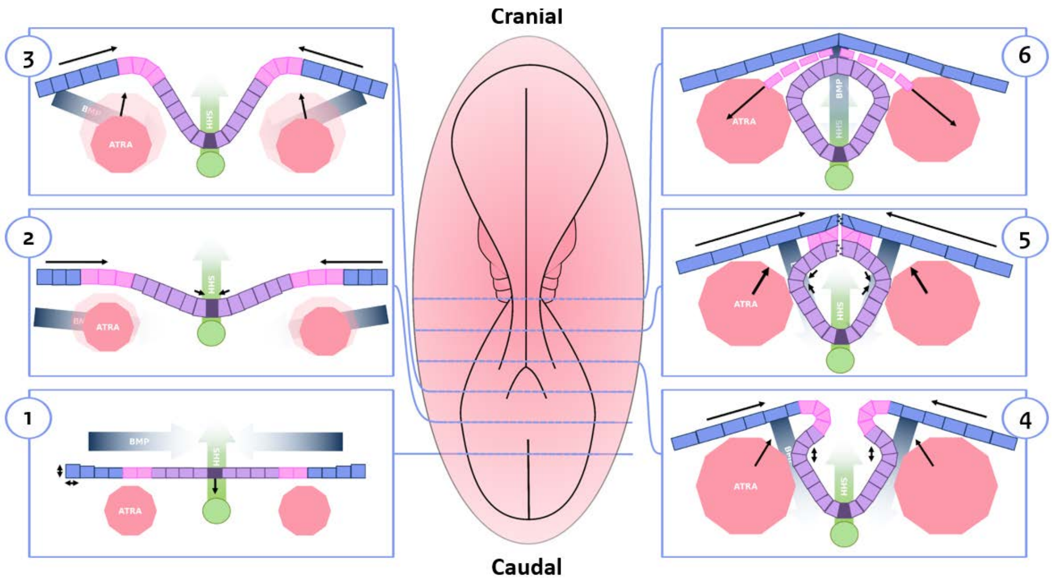
Adopted from H. Heusinkveld

Computational modeling of neural tube closure

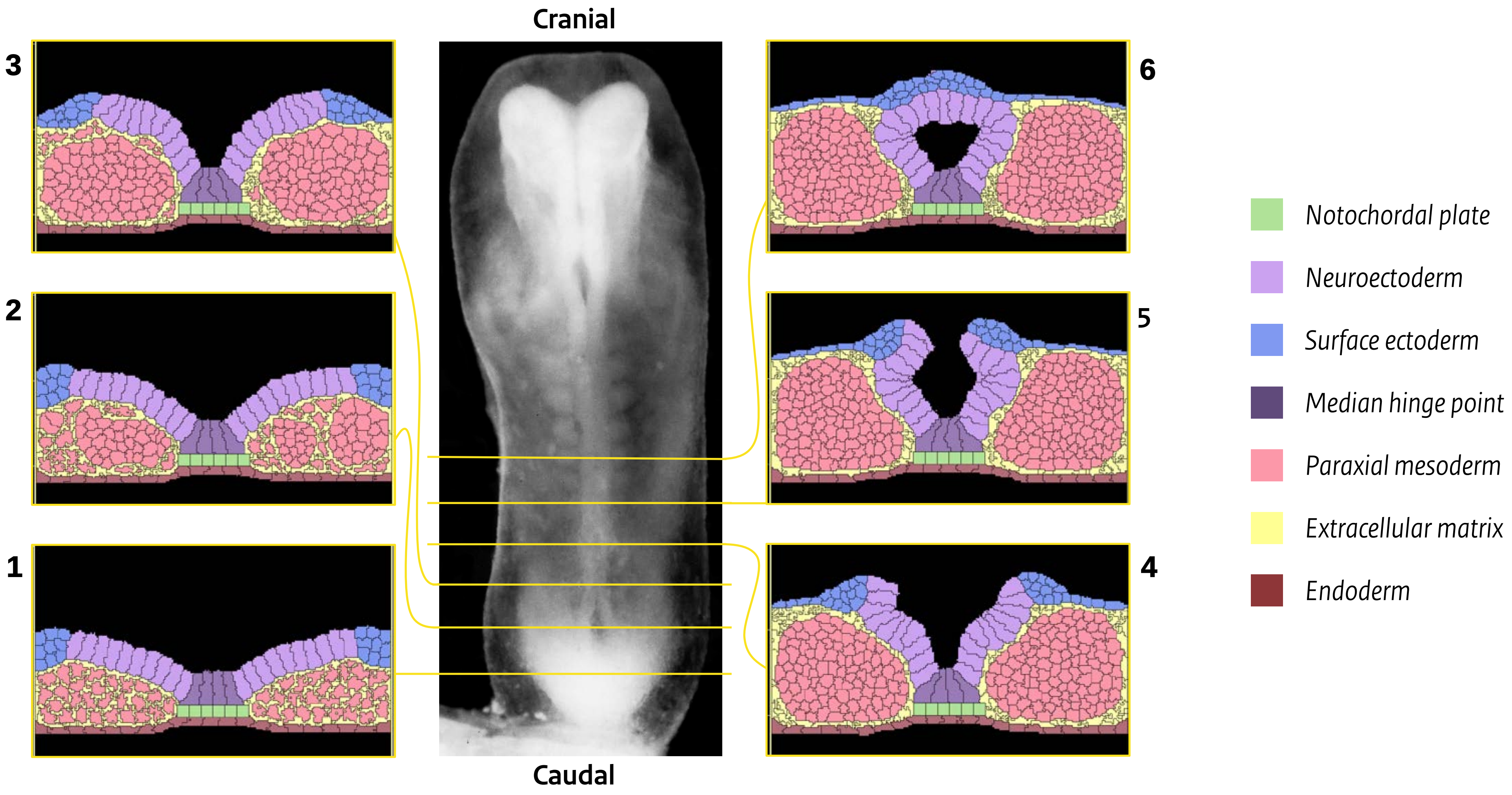
- Cellular-Potts in Compucell 3D
- Agent-based

Computational modeling of neural tube closure

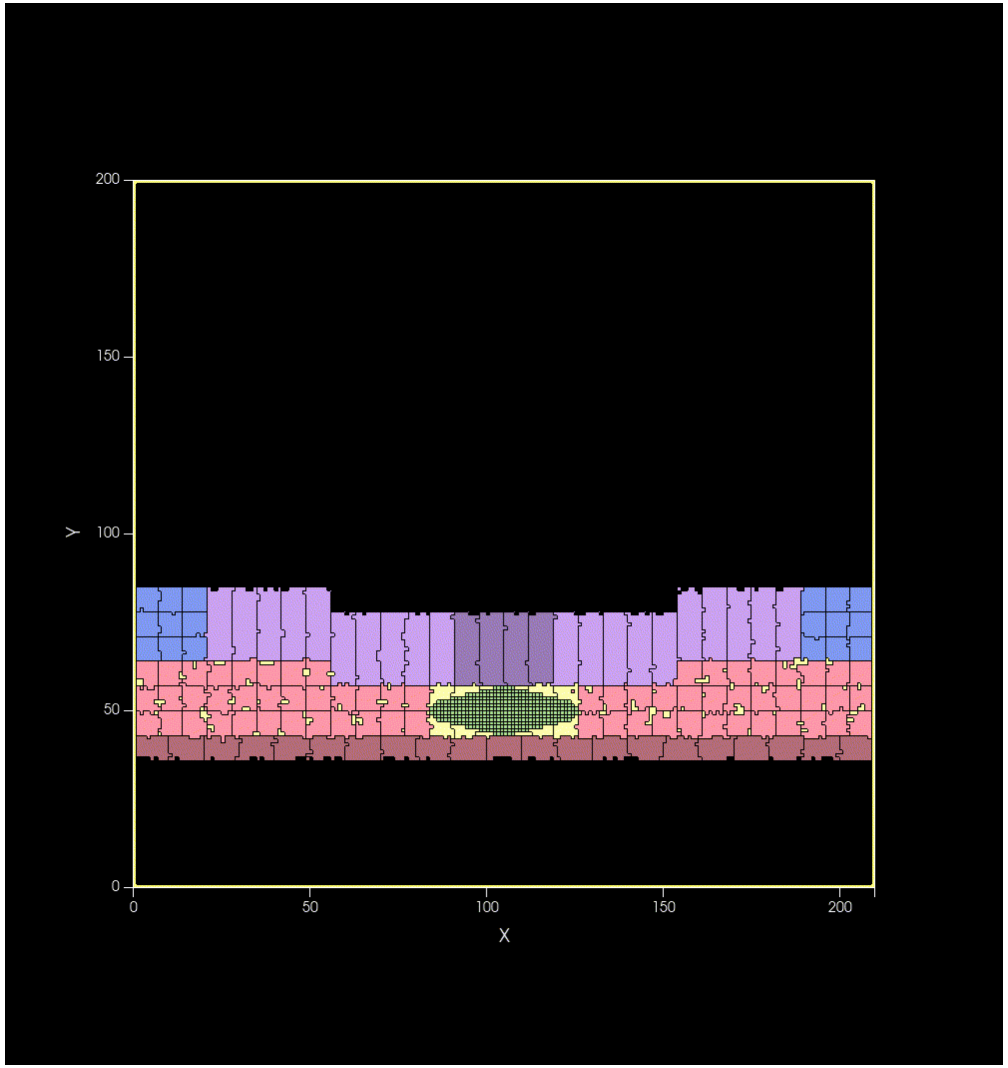
- Cellular-Potts in Compucell 3D
- Agent-based
- Start with a 2D model
- First include relevant cell behaviors
- Implement biologically relevant triggers afterwards



The CC3D model reflects the progressive closing neural tube



A computational model of neural tube closure build in CC3D



- Notochordal plate
- Neuroectoderm
- Surface ectoderm
- Median hinge point
- Paraxial mesoderm
- Extracellular matrix
- Endoderm

Components of the current neural tube closure model

- Spatial organization based on human physiology
- Apical constriction induced by relevant protein gradients
  - For DLHP and MHP formation
- Somite formation

Components of the current neural tube closure model

- **Spatial organization based on human physiology**
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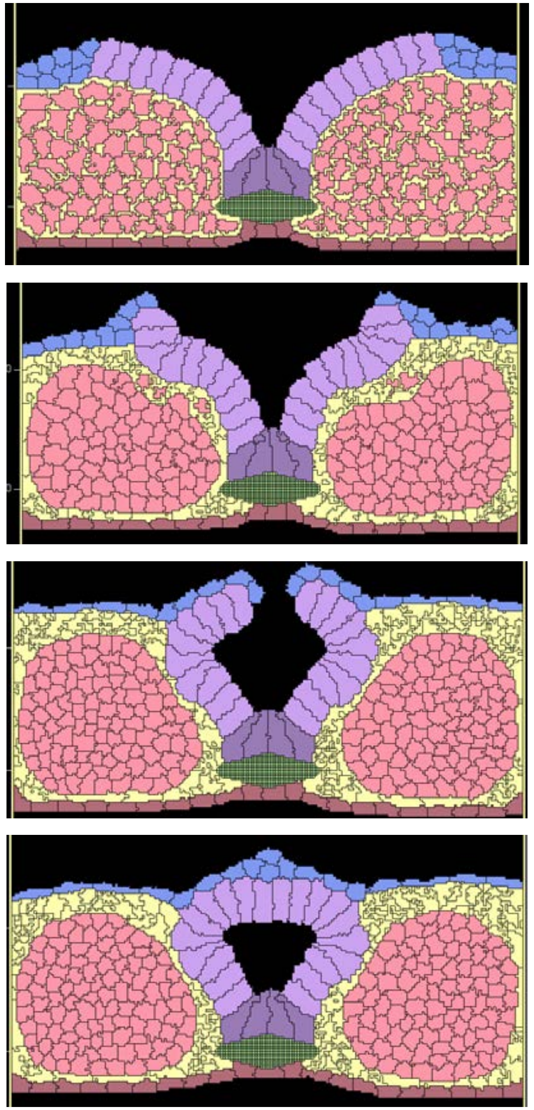
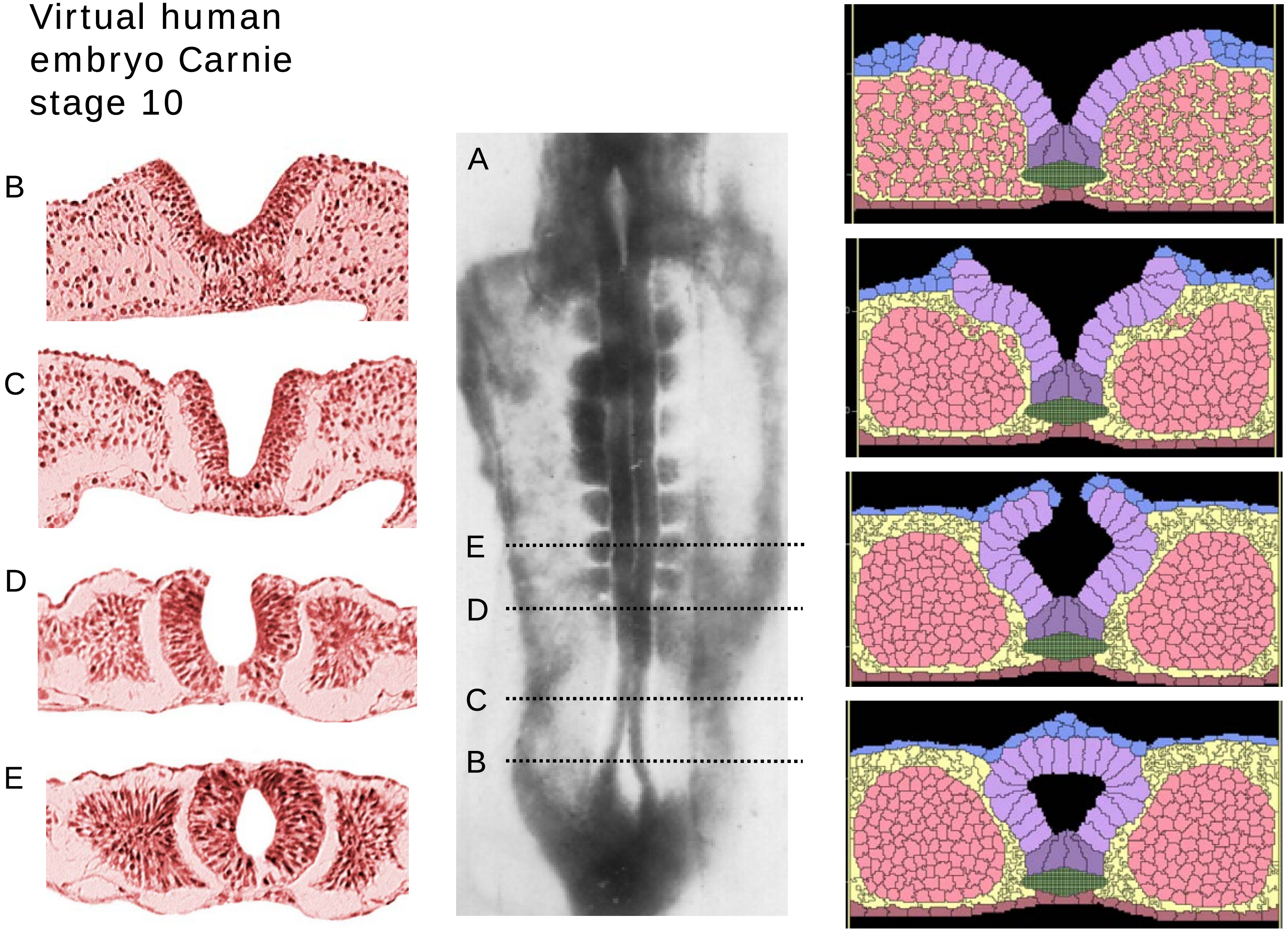
Spatial organization of the model



Spatial organization of the model

Virtual human embryo Carnie stage 10



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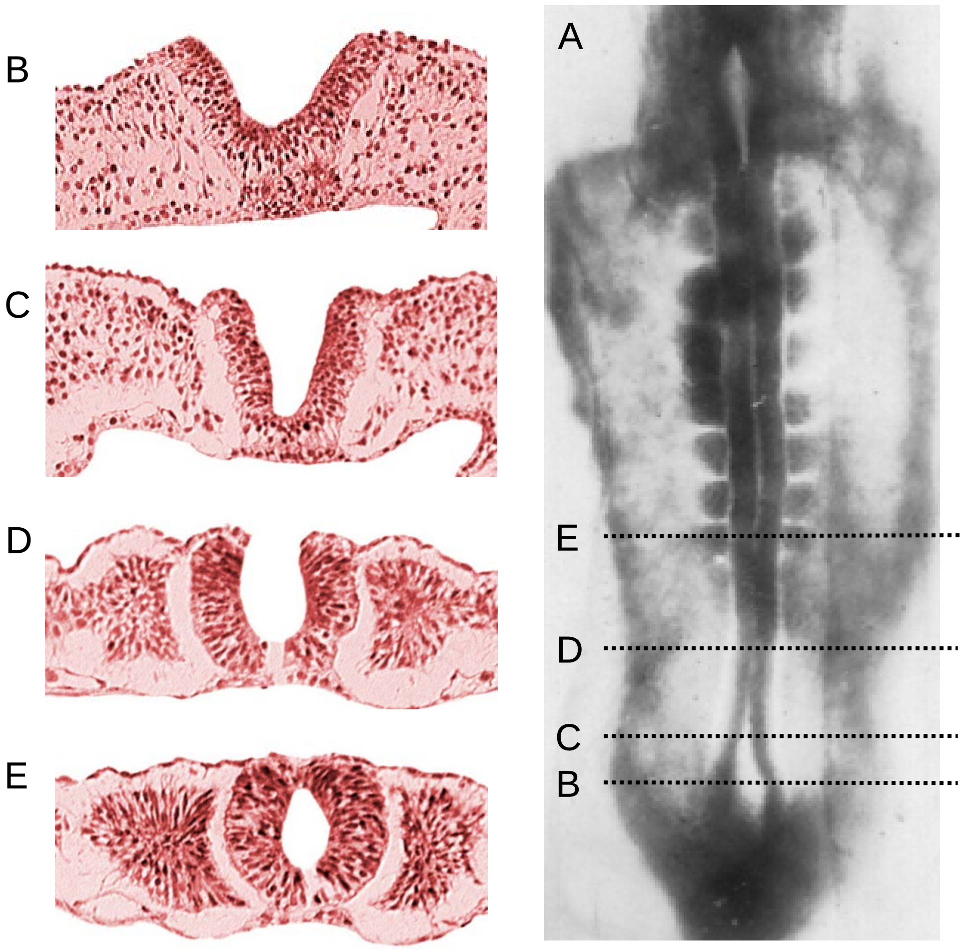
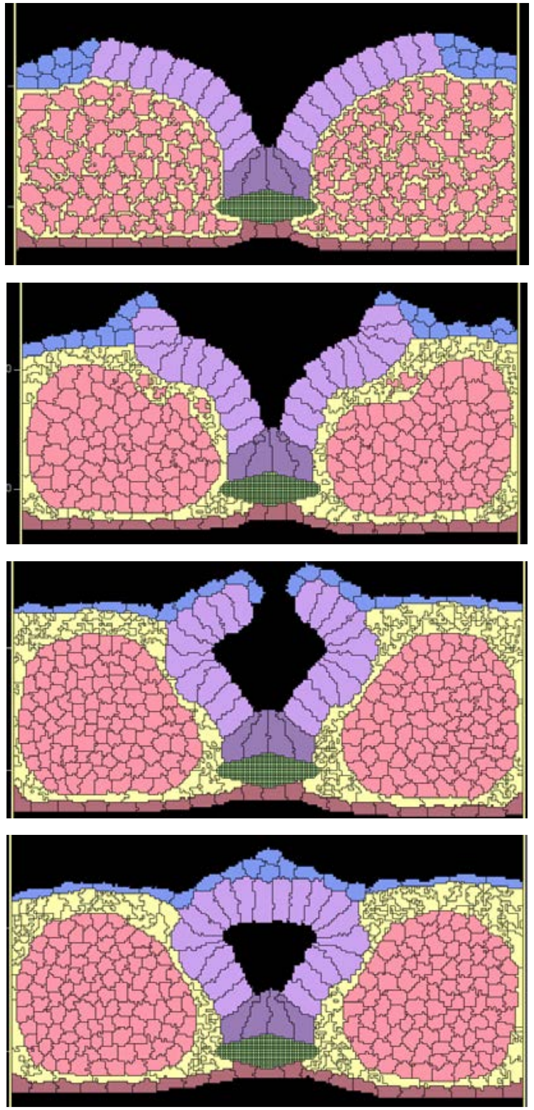
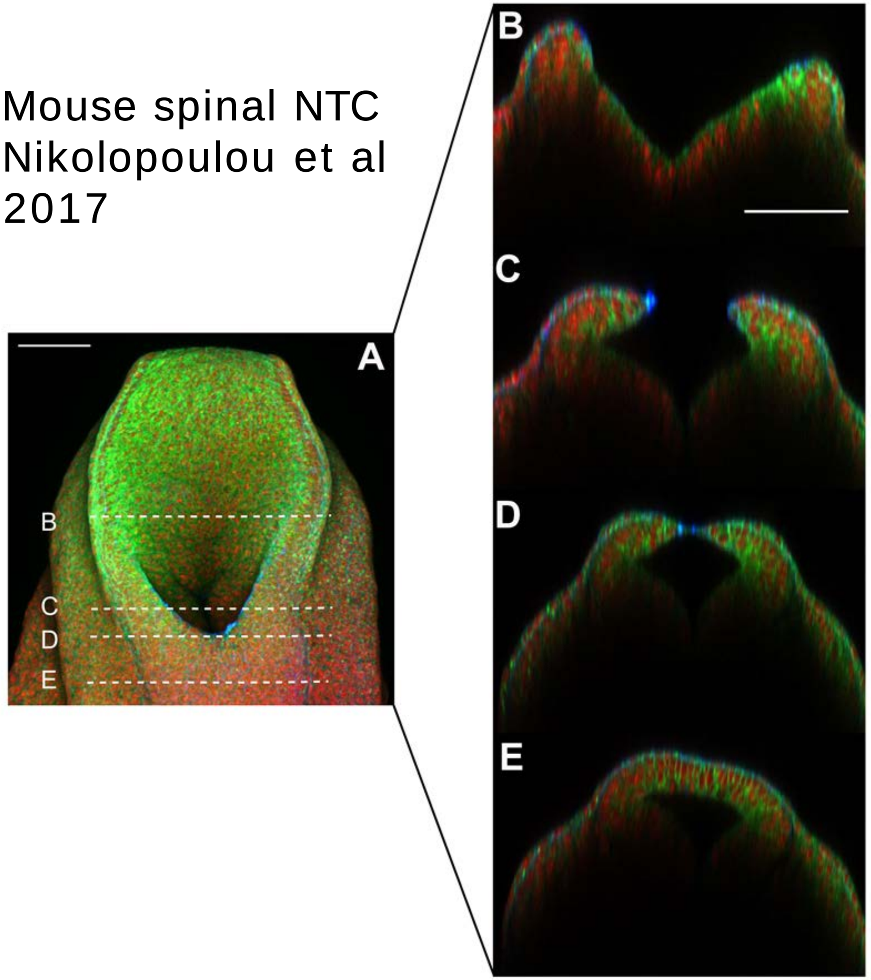




Mouse spinal NTC Nikolopoulou et al 2017

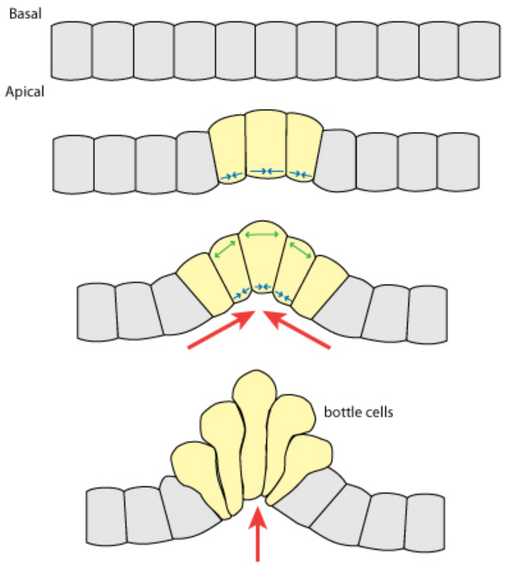


Components of the current neural tube closure model

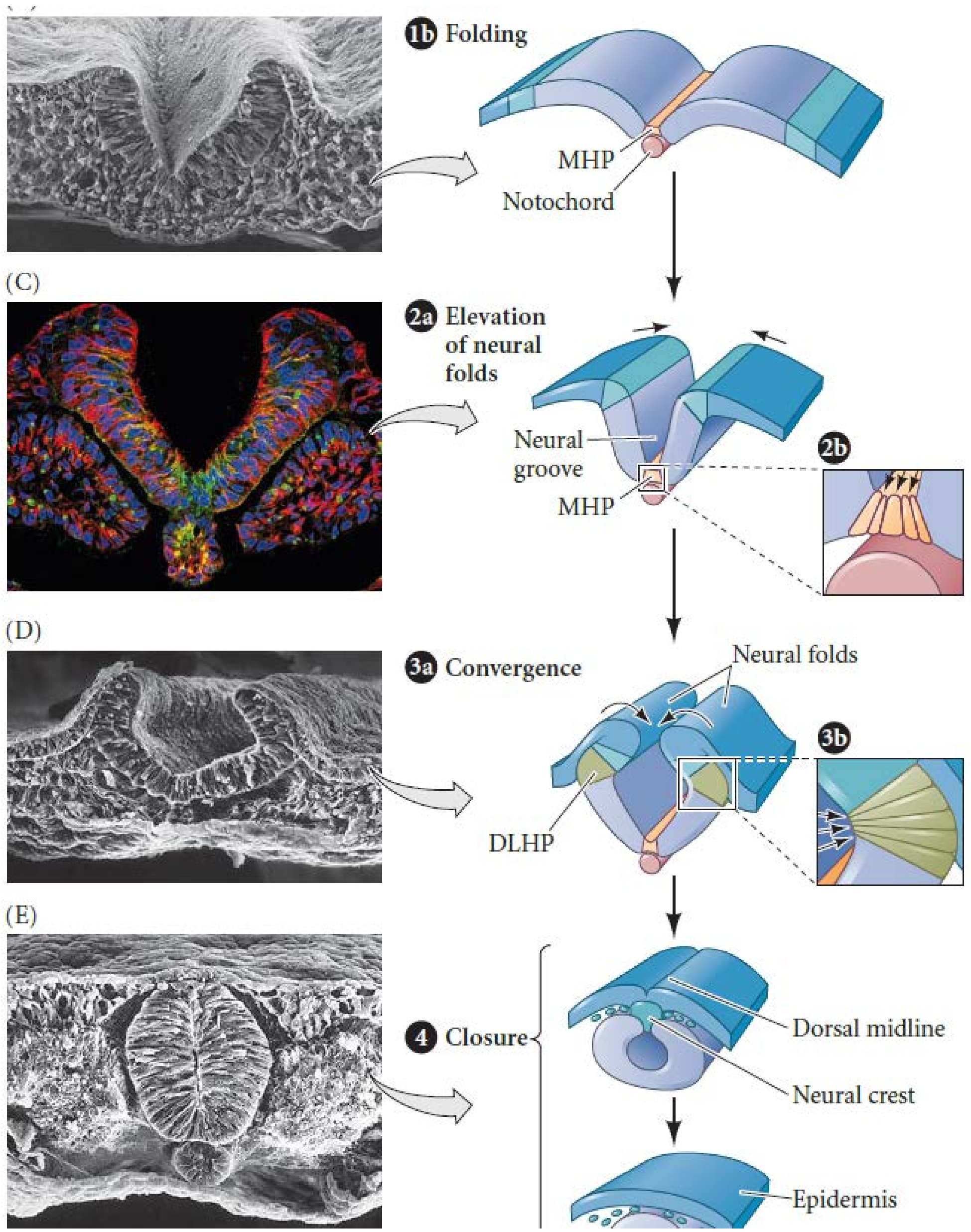
- Spatial organization based on human physiology
- **Apical constriction induced by relevant protein gradients**
  - For DLHP and MHP formation
- Somite formation

Apical constriction

- Critical for Neural tube closure
- Wedge shaped cells

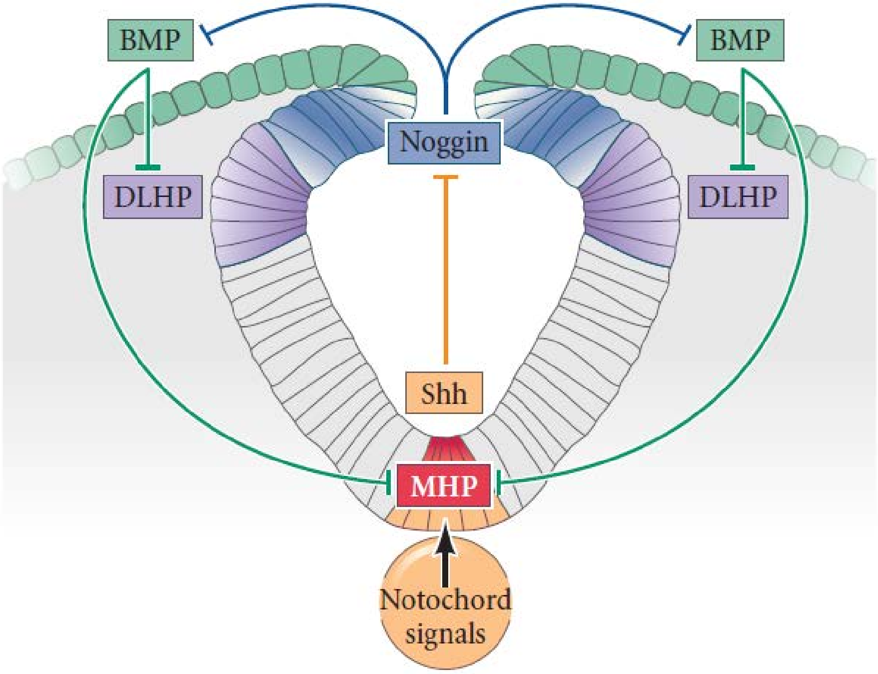


Apical constriction

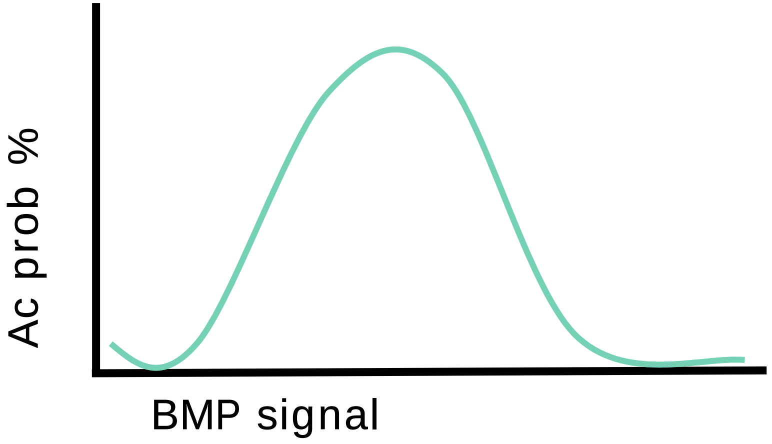


Apical constriction

- Mediated by BMP and SHH
  - BMP ⟶ Apical constriction
  - SHH ⊣ Apical constriction
- Requires intermediate levels of BMP
  - Inhibited by high BMP



P_{ac} →



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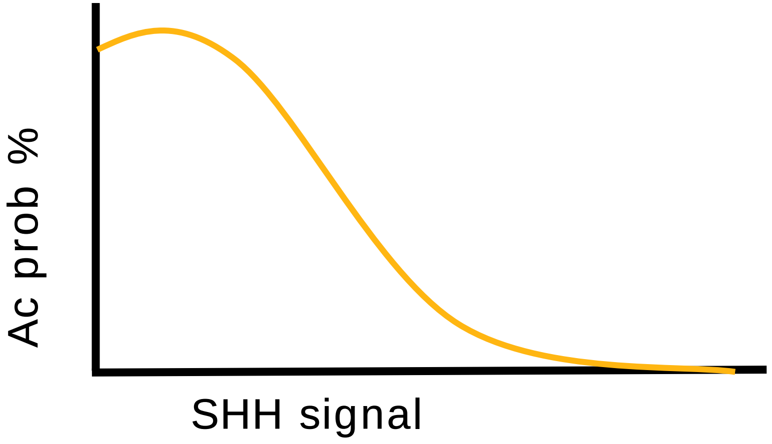
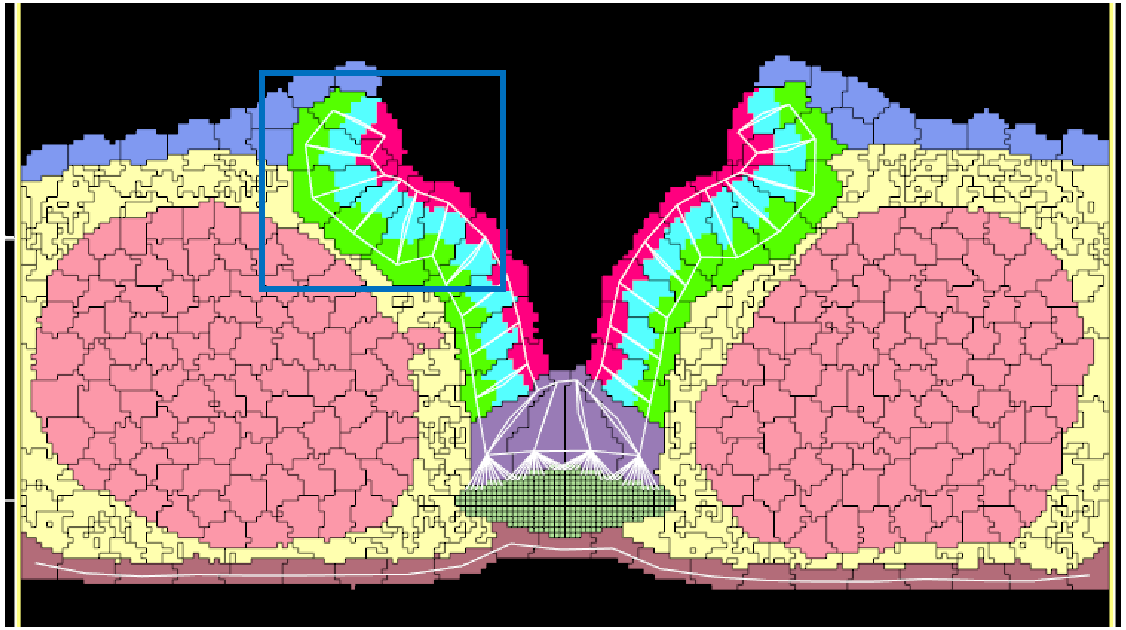
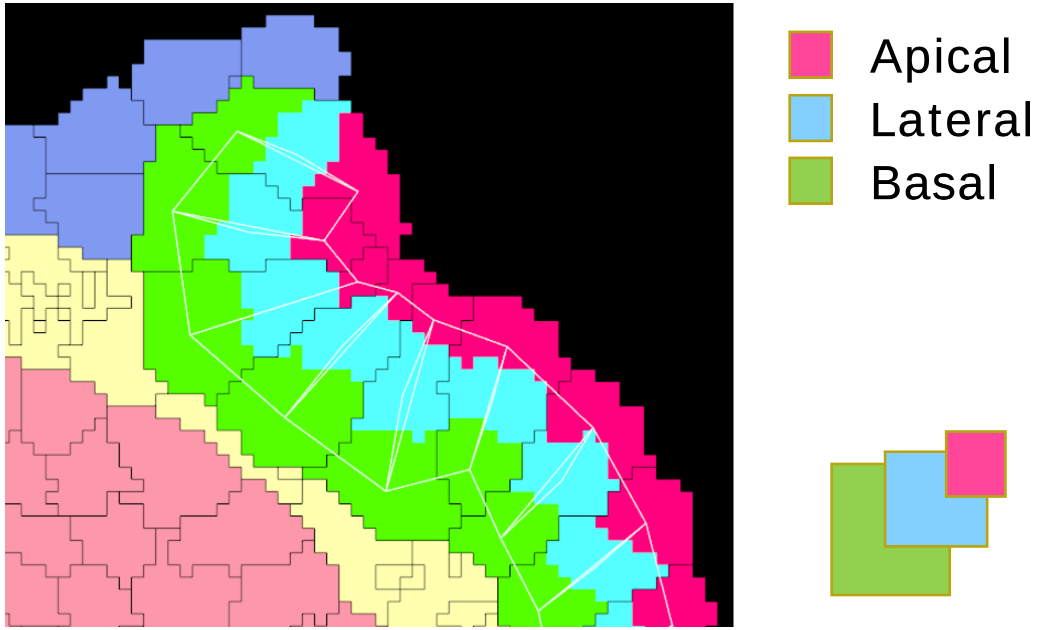


Gonzales, et al 2007; gilbert & Barresi 11th edition

Apical constriction in the NTC CC3D model DLHP

- Reduce apical cell volume, increase basal cell volume
- “Springs” Between cells to simulate contractile forces
  - actomyosin machinery

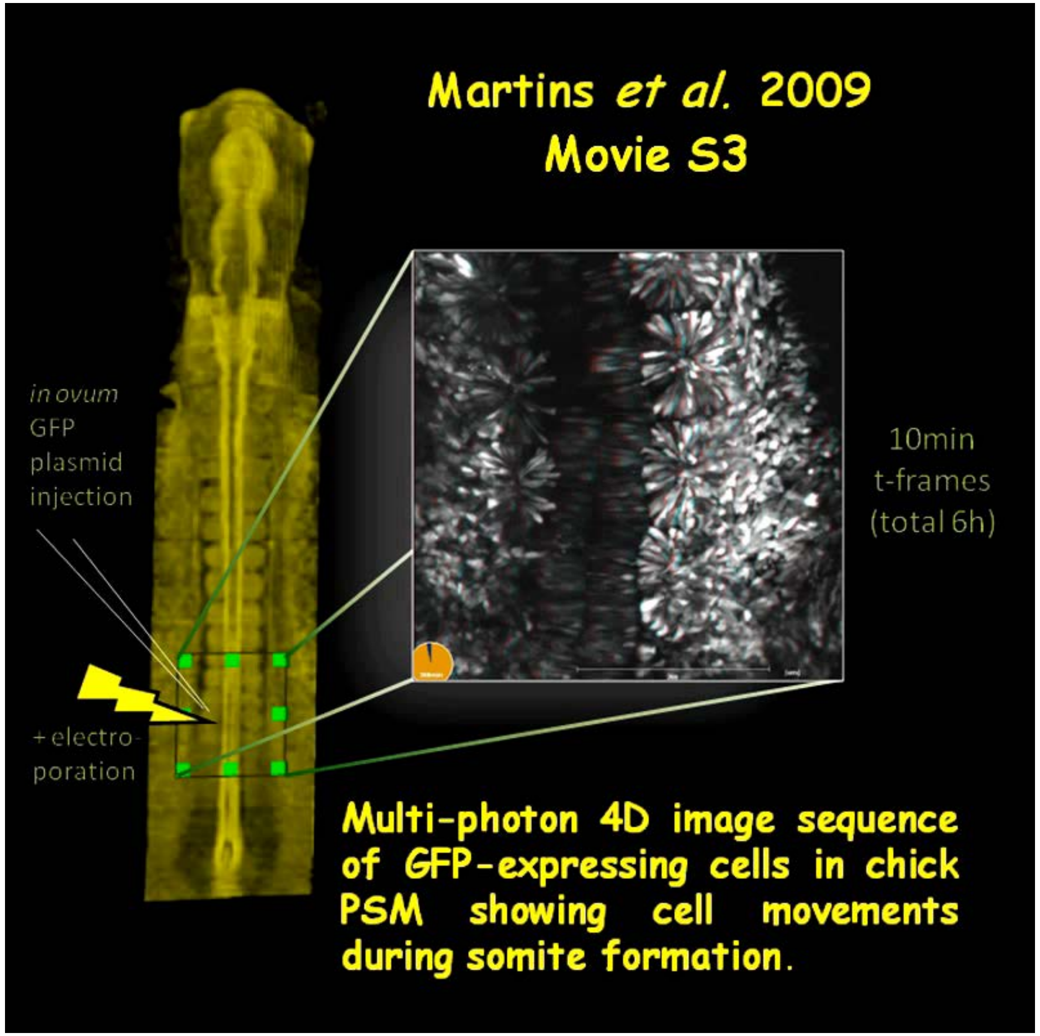




Components of the current neural tube closure model

- Spatial organization based on human physiology
- Apical constriction induced by relevant protein gradients
  - For DLHP and MHP formation
- **Somite formation**

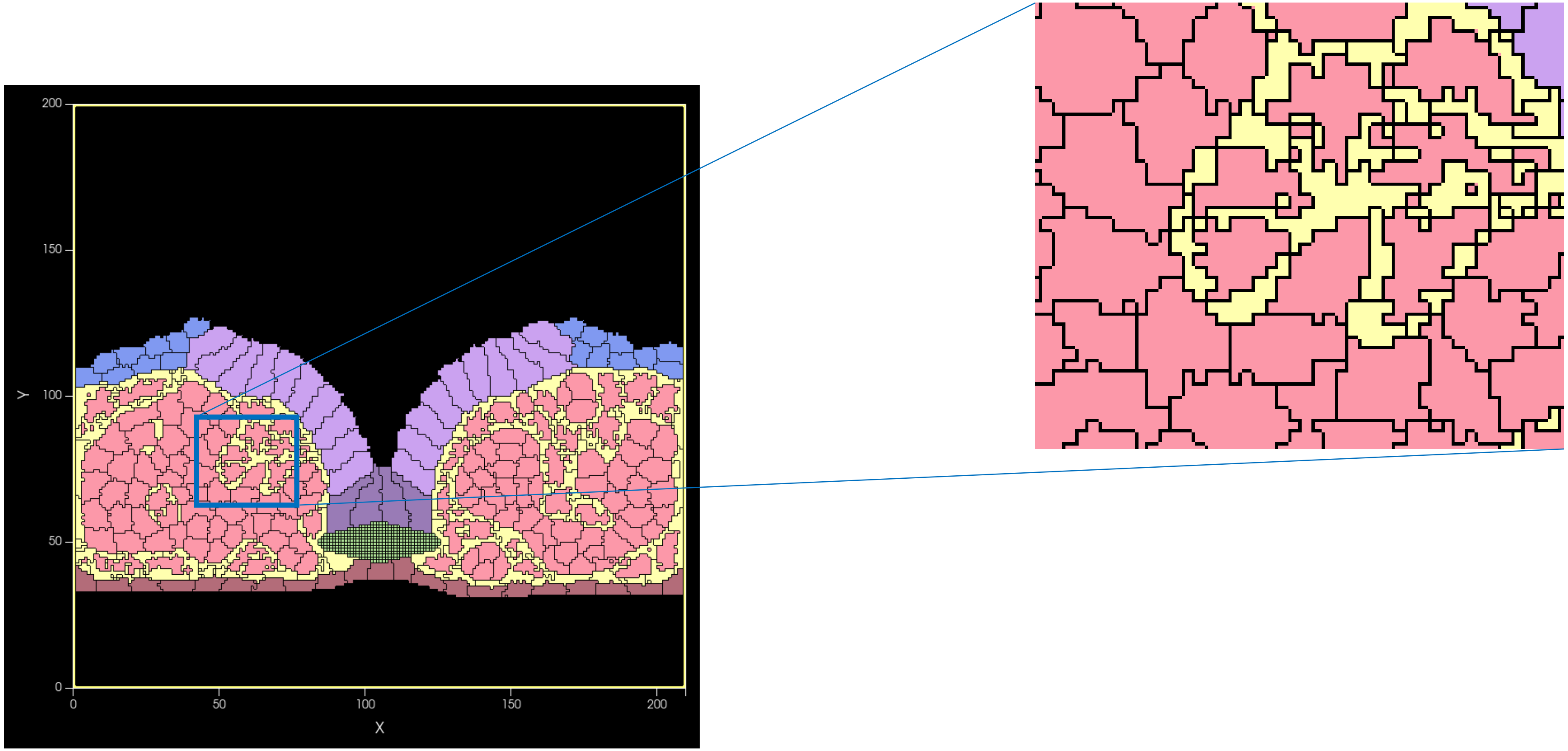
Somite formation



Chick somite formation Martins et al, 2009

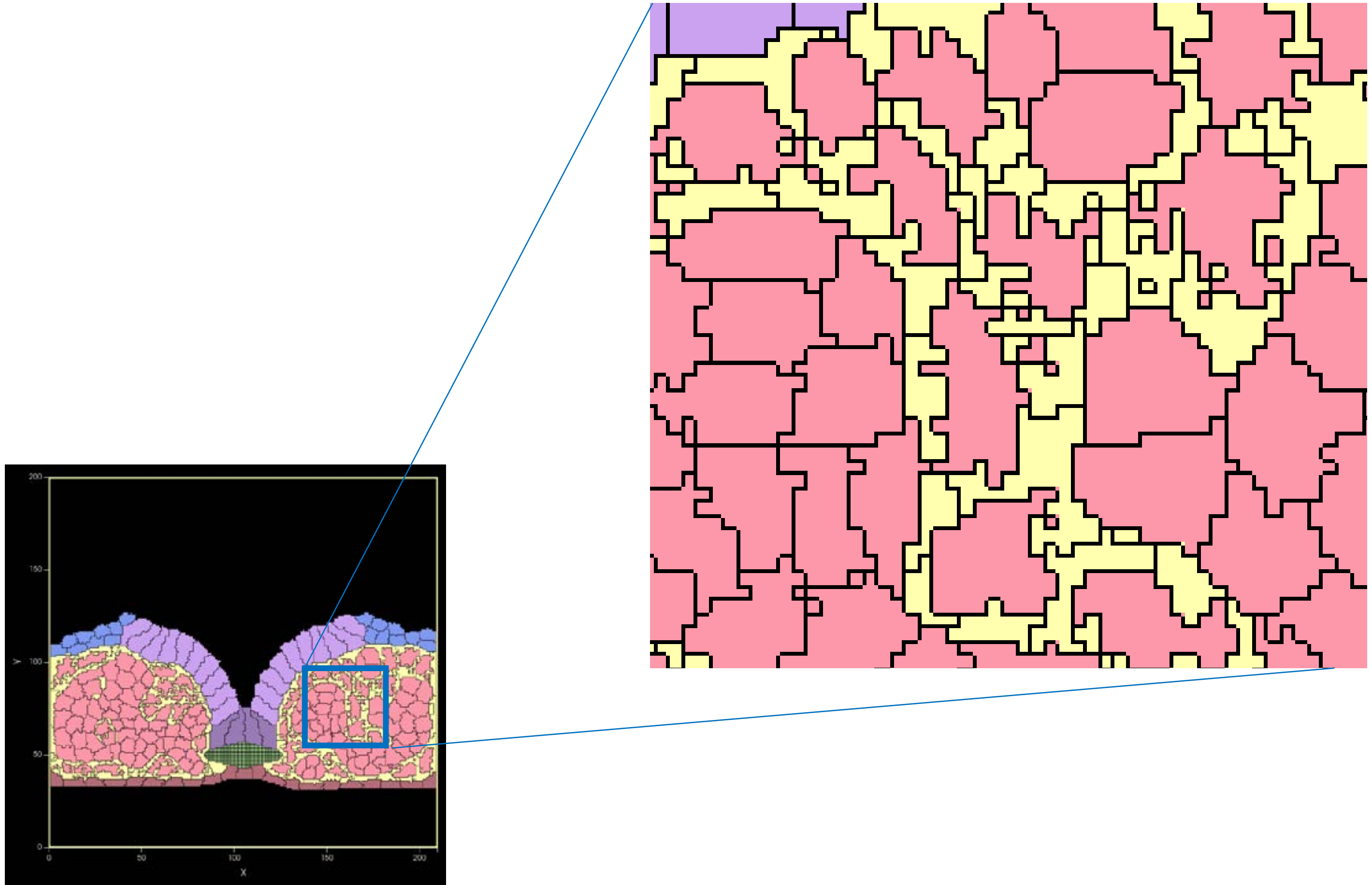
Somite formation

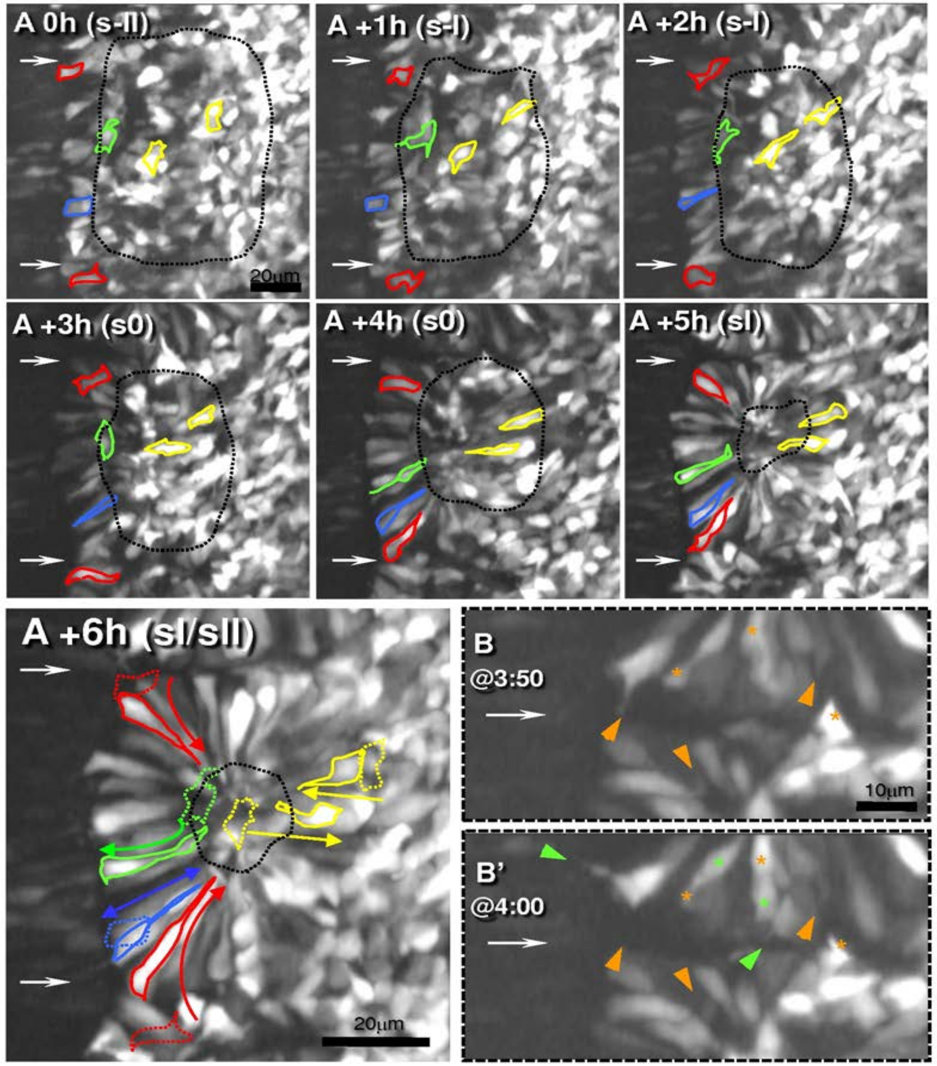
- ECM is formed between mesodermal cells
- Cell differentiation to somite cell
  - Different properties



Somite formation

- Paraxial mesoderm cell shapes comparable to biology
- Somite cells in simplified structure



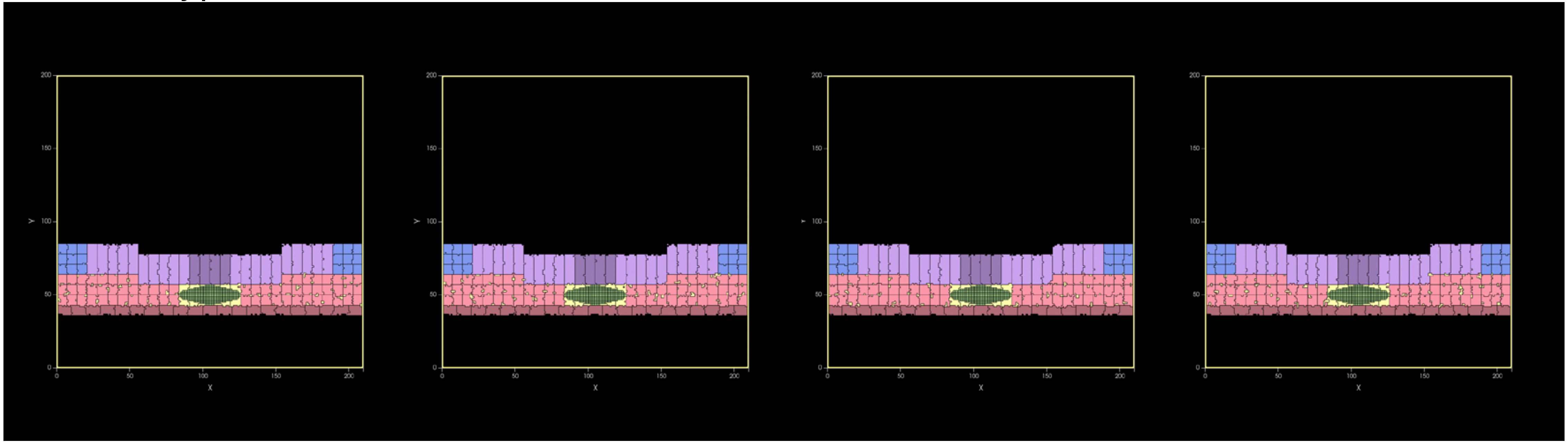


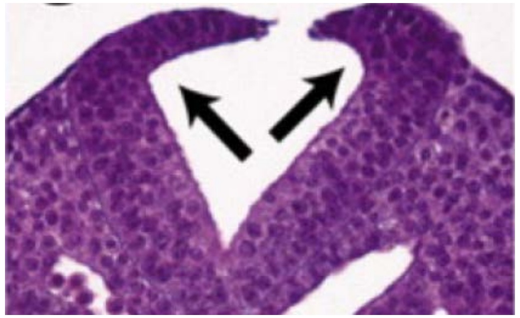
Chick somite formation Martins et al, 2009

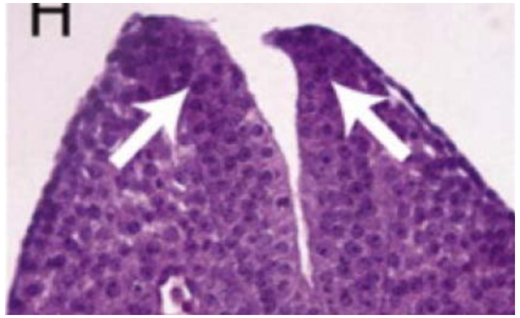
In silico prediction of Neural tube closure defects

Synthetic dose-response BMP inhibition/activation

BMP Hypoactivation | Normal | BMP upregulation | BMP Hyperactivation

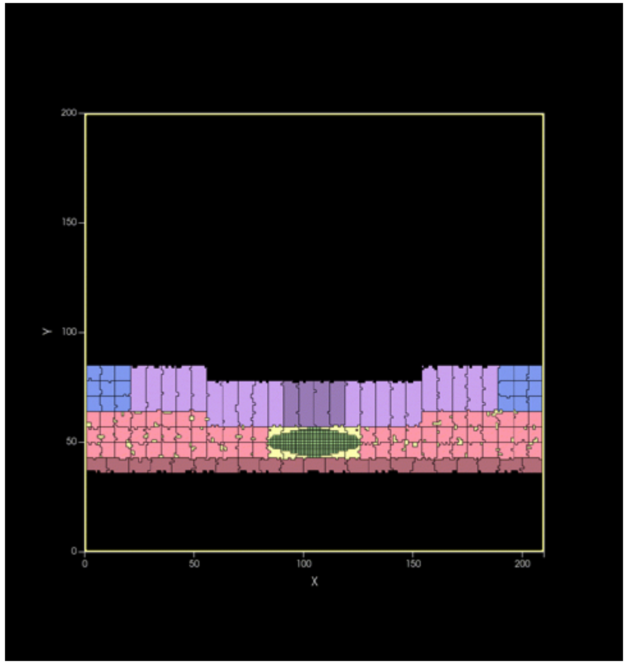




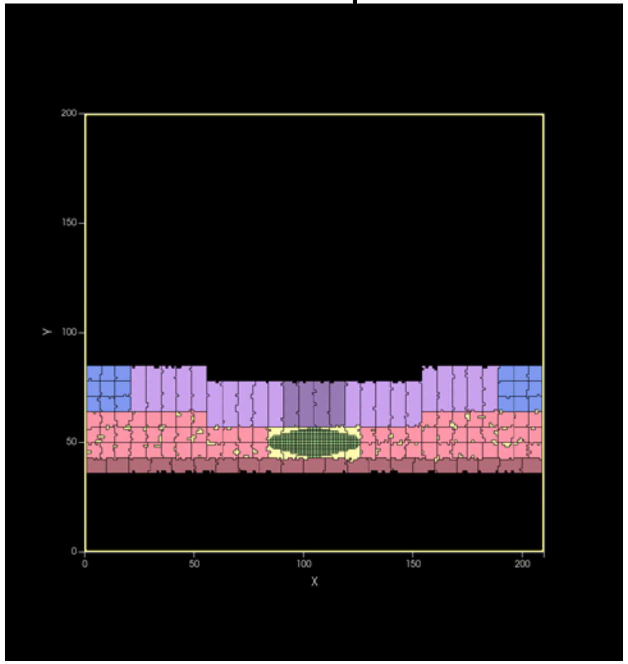


Disruption floor plate formation

Normal



Disrupted



To conclude

- Introduced ontologies
- The first steps towards a biologically relevant computational model of human neural tube closure
- The Computational model showed adverse outcomes comparable to in vivo studies

Acknowledgements

My Promotion team:

- Dr. Harm Heusinkveld
- Prof. Aldert Piersma
- Prof. Juliette Legler

External advisors:

- Dr. Tom Knudsen
- Dr. Richard Spencer
- Prof James Glazier
- Dr. Julio Belmonte

The ONTOX team

Universiteit Utrecht

Funded by the Horizon 2020 Framework Programme of the European Union

The end

Contact me if you want to know more

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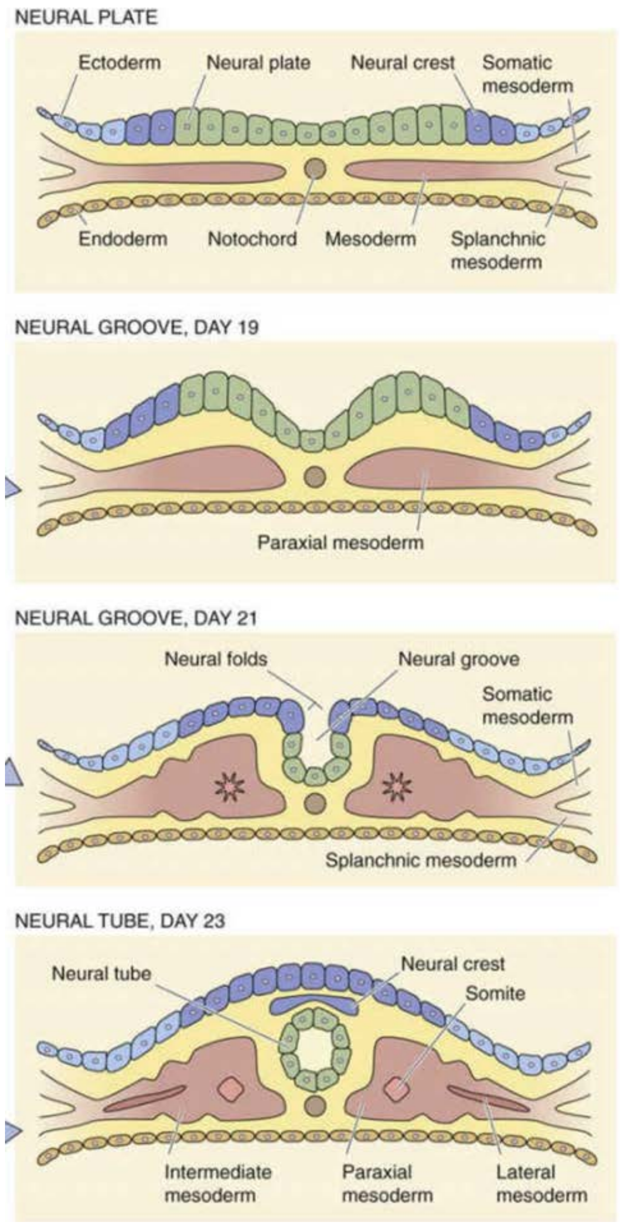
An ontology for neural tube closure

Step-by step

- Charting physiology
- Determining key phenotypes
- Build computational model
- In vitro/in silico test strategy



Adopted from H. Heusinkveld

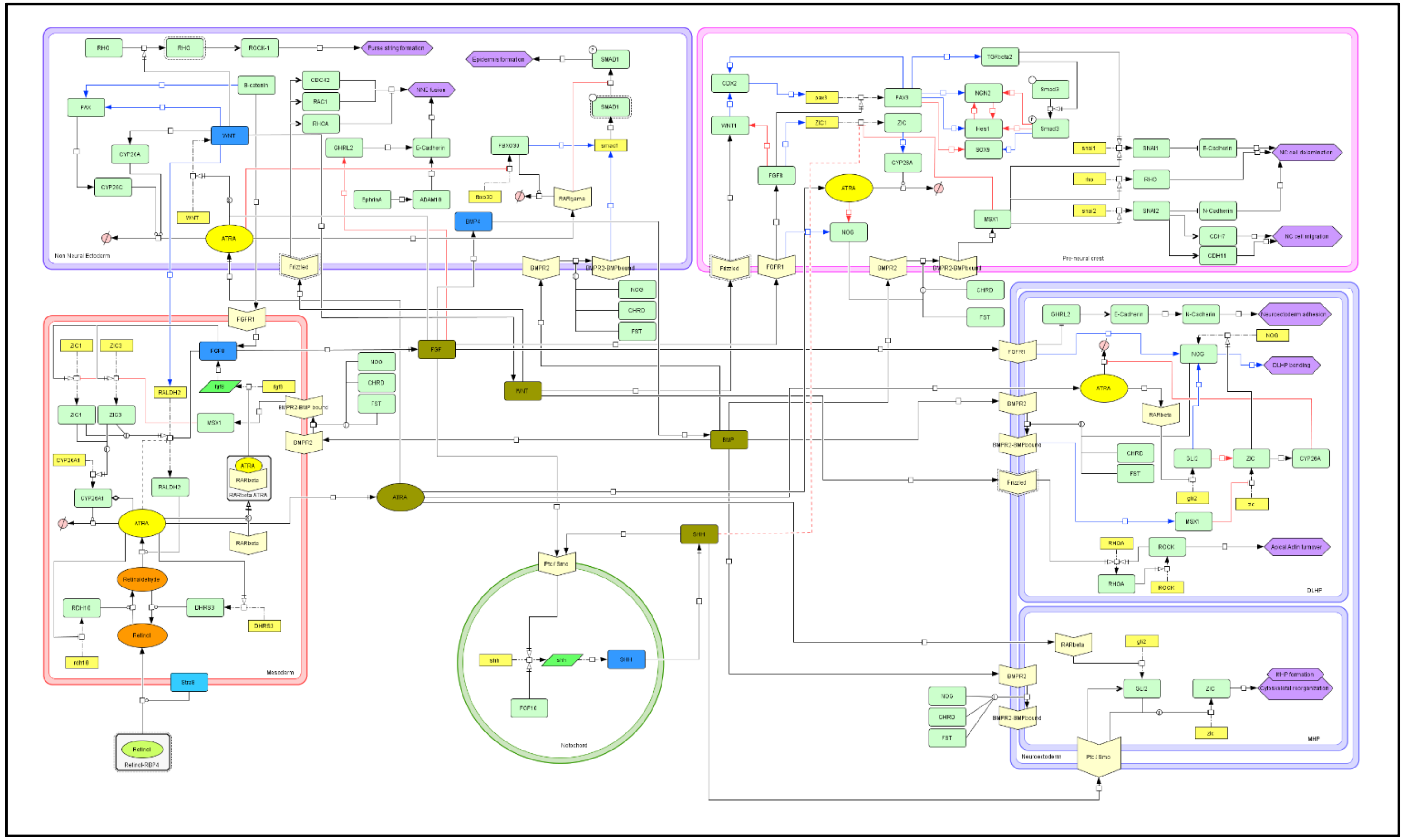
Charting physiology

CellDesigner

Systems Biology Markup Language (SBML)

First version: manual

CellDesigner™
Ver. 4.0



Adopted from H. Heusinkveld

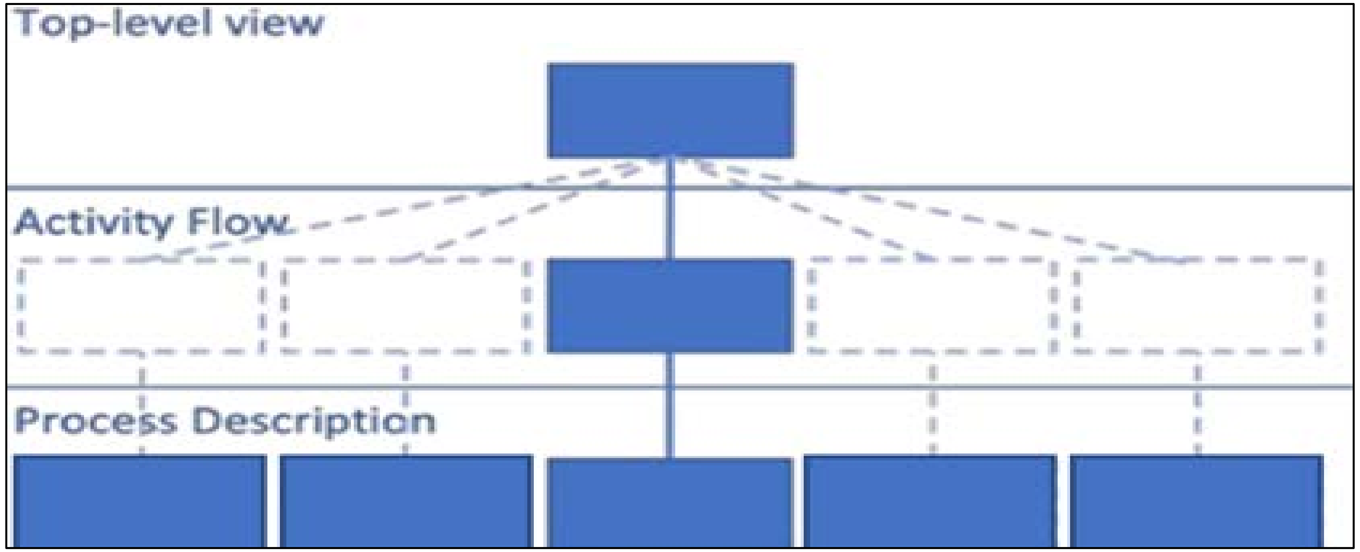
Heusinkveld et al., 2021 Reproductive Toxicology

Physiological maps 2.0

- University of Liège
  - Genes, proteins, and RNA node names were standardized using the HGNC-approved symbol.
  - Chemicals (compounds) were annotated with the respective ChEBI ID.
  - Phenotypes with the Gene Ontology (GO) ID.

Switch to Minerva

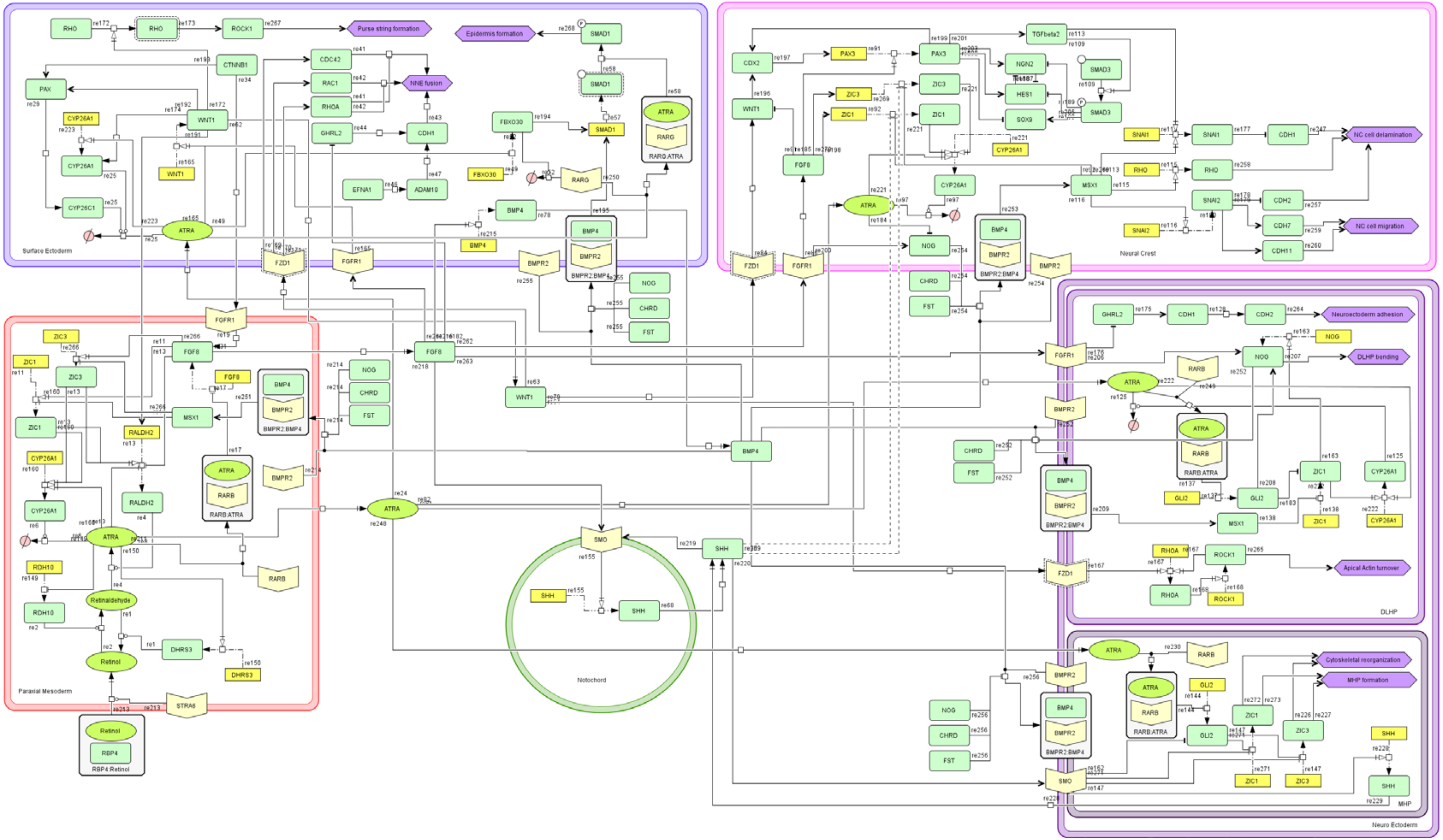
- Online tool
- Editable -> ease of correction



Overview model > Main map > Submaps

Adopted from H. Heusinkveld

Physiological map 2.0



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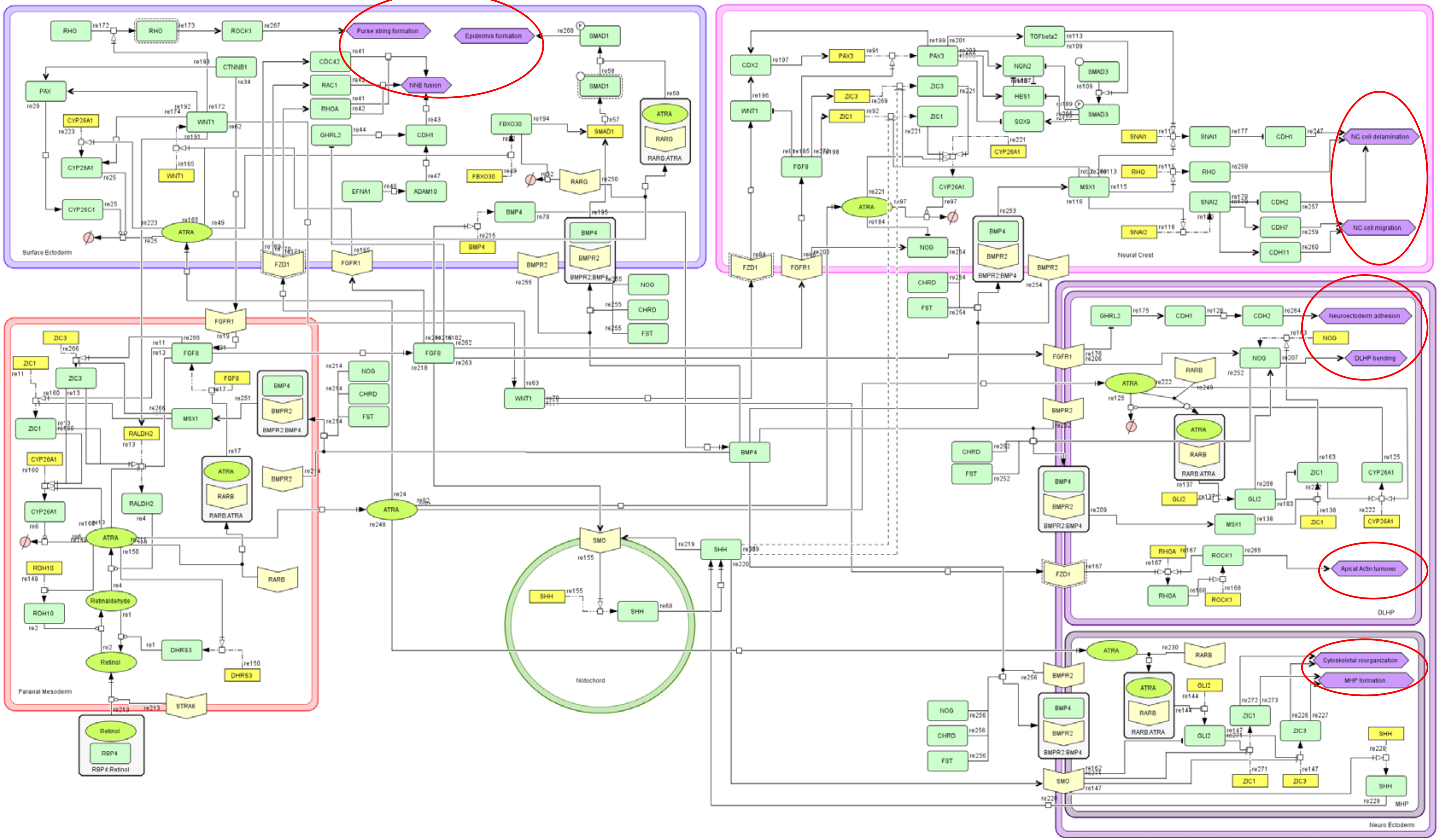
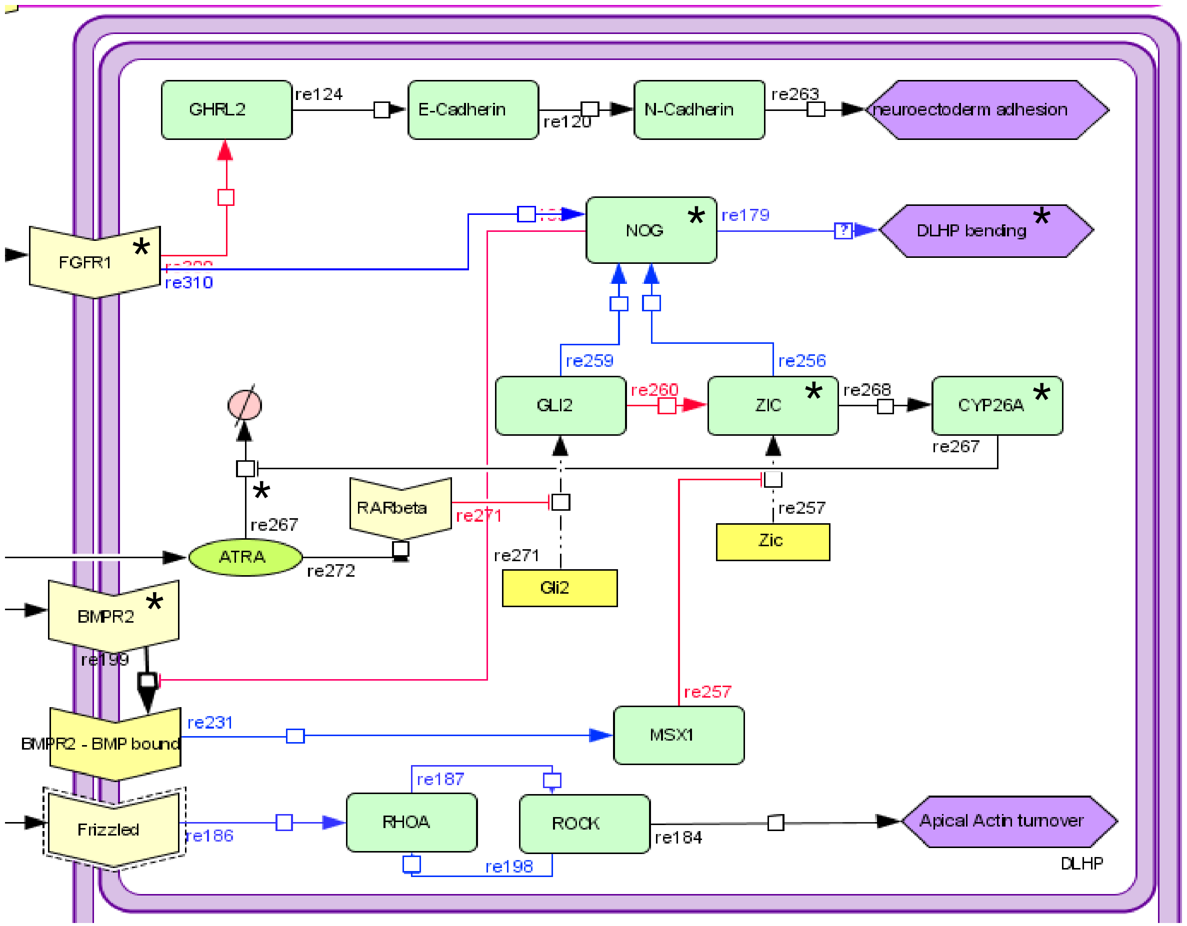
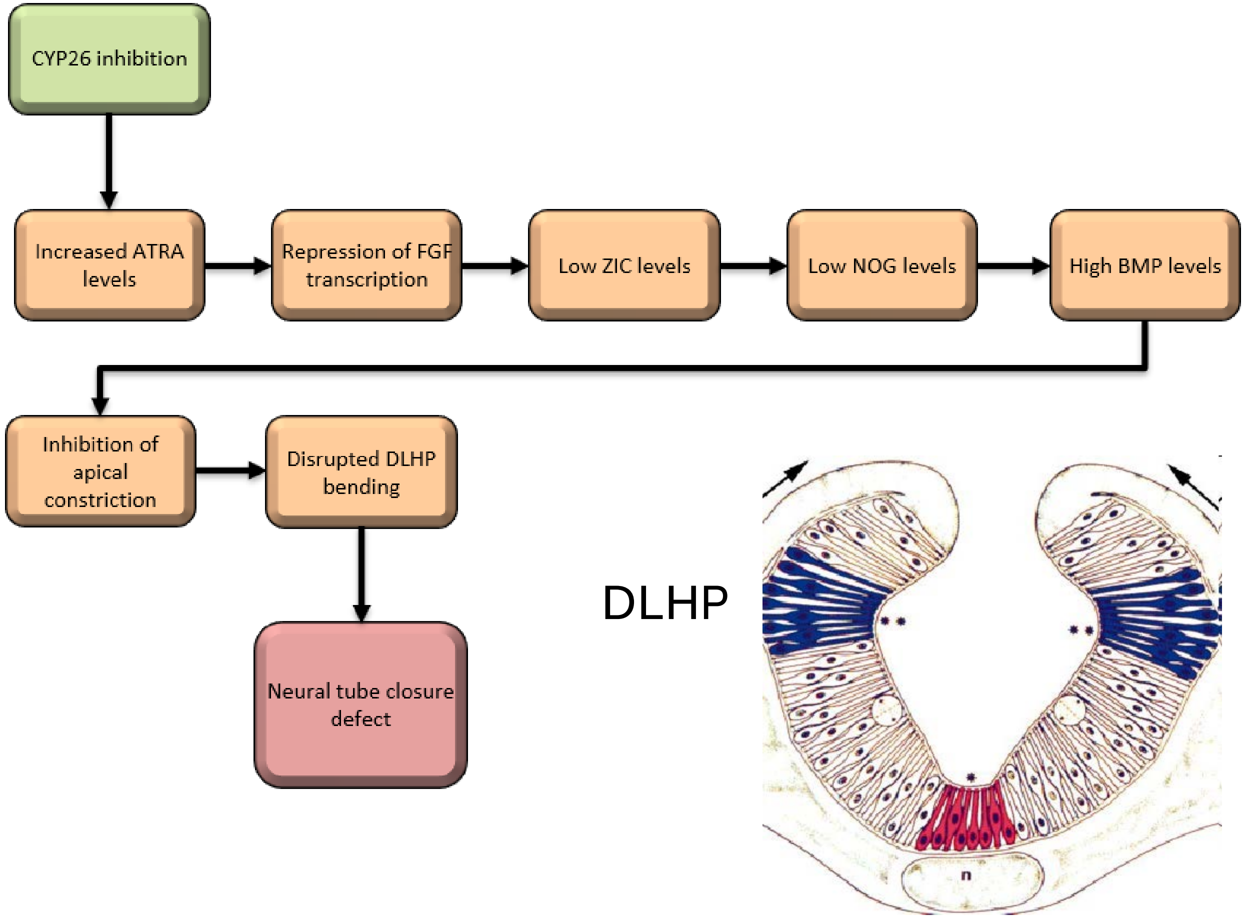


Intermediate BMP is needed for DLHP formation





Apical constriction in the NTC CC3D model MHP

- Reduce apical cell volume, increase basal cell volume
- Reduce apical fpp link target distance
  - increase basal link target distance to a lesser extend
- Anchor multiple points to prevent basal cell elongation