Agent-based Modeling with Embryonic Stem Cells During Gastrulation

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Introduction

Driver: Biologically-inspired models are needed that integrate *in vitro* profiling data with vast knowledge of embryology and translate into an automated system for toxicological prediction.

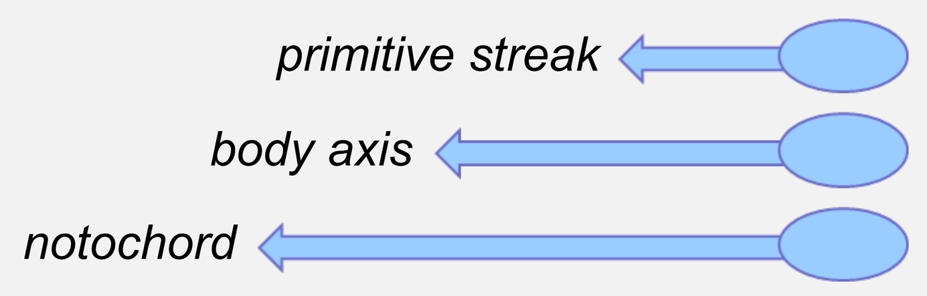
Objective: Engineer a cell-oriented computational agent-based model (ABM) of the epiblast that quantitatively simulates embryonic stem (ES) cell behaviors *in silico* (ES-ABM)

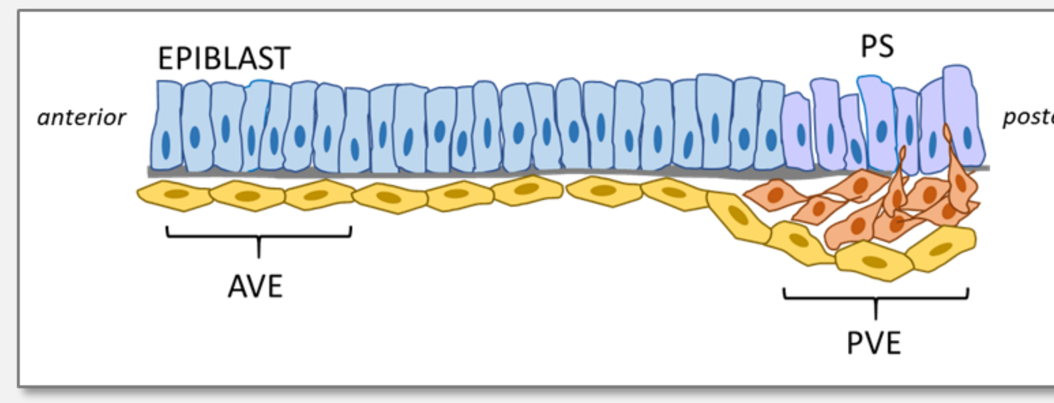
Rationale: The epiblast is the origin for most cell types of the fetus and the tissue most closely resembled by pluripotent embryonic stem cells (hESCs), where a lot of profiling data exists [1].

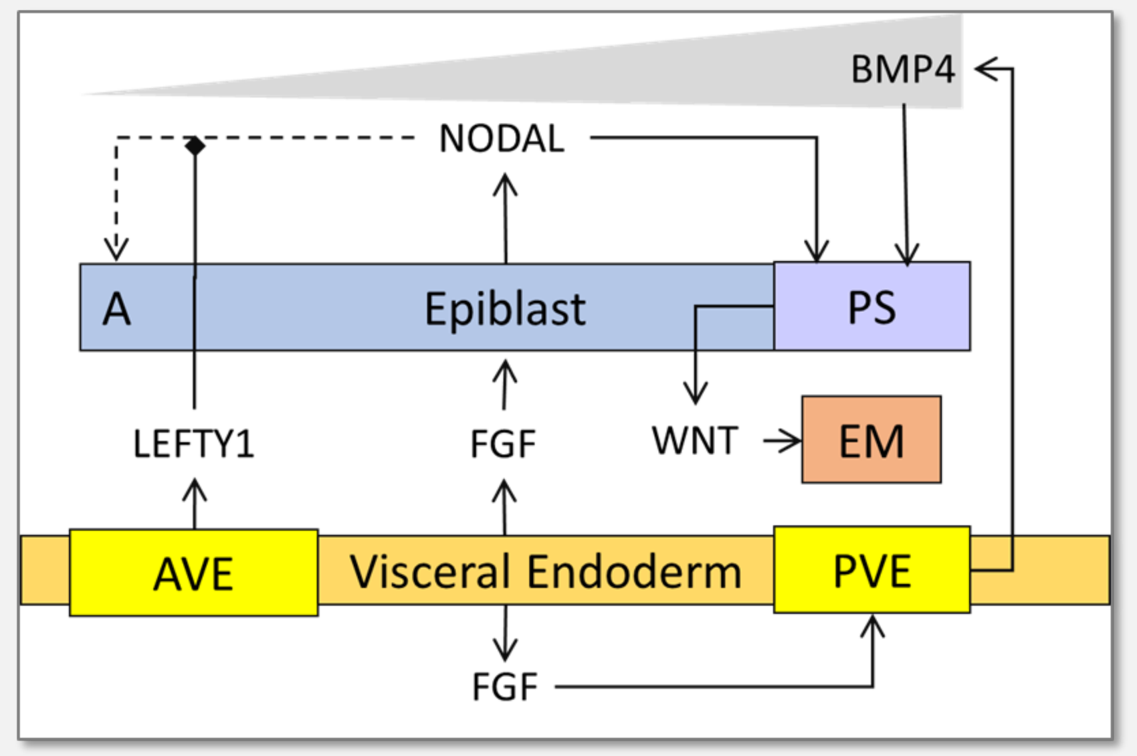
Hypothesis: morphological programming logic of the epiblast puts single cell behavior in motion to quantitatively simulate toxicity on regional specification in a 3Rs-compliant manner.

Epiblast: conceptual systems model

Signaling network: Conserved signaling pathways establish the primary body axis via primitive streak formation, the hallmark of gastrulation [*Takaoka et al (2007) Curr Opin Genet Dev*].



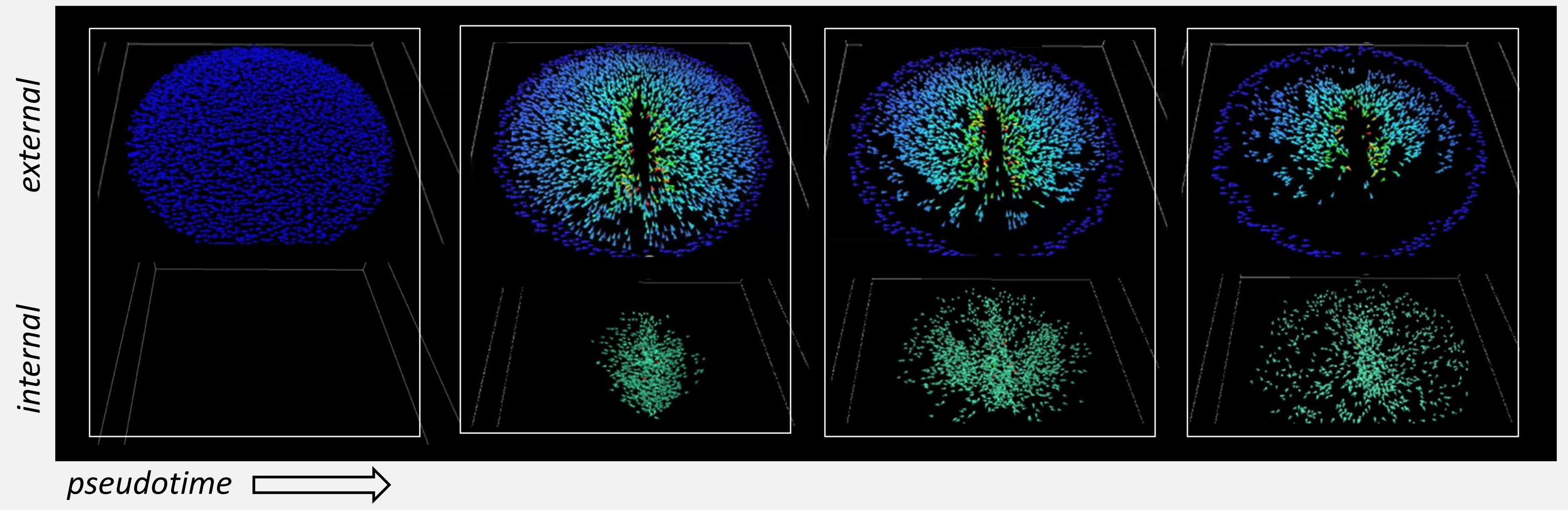




- Primitive streak (PS) appears gestation day 6 in the mouse and days 14-17 in humans;
- midline feature in the epiblast appearing posteriorly and extending anteriorly;
- positioned by NODAL from the epiblast and BMP4 from posterior visceral endoderm (PVE)
- extends by circular cell movements driven by FGF and WNT signaling;
- WNT3a is a biomarker of endo-mesoderm formation (EM);
- anterior visceral endoderm (AVE) is a major organizing center via LEFTY1;
- LEFTY1 antagonizes NODAL signaling to confine it posteriorly;
- results in anterior-posterior patterning of the embryo and left-right asymmetry.

Quasi-gastrulation: dynamical systems model

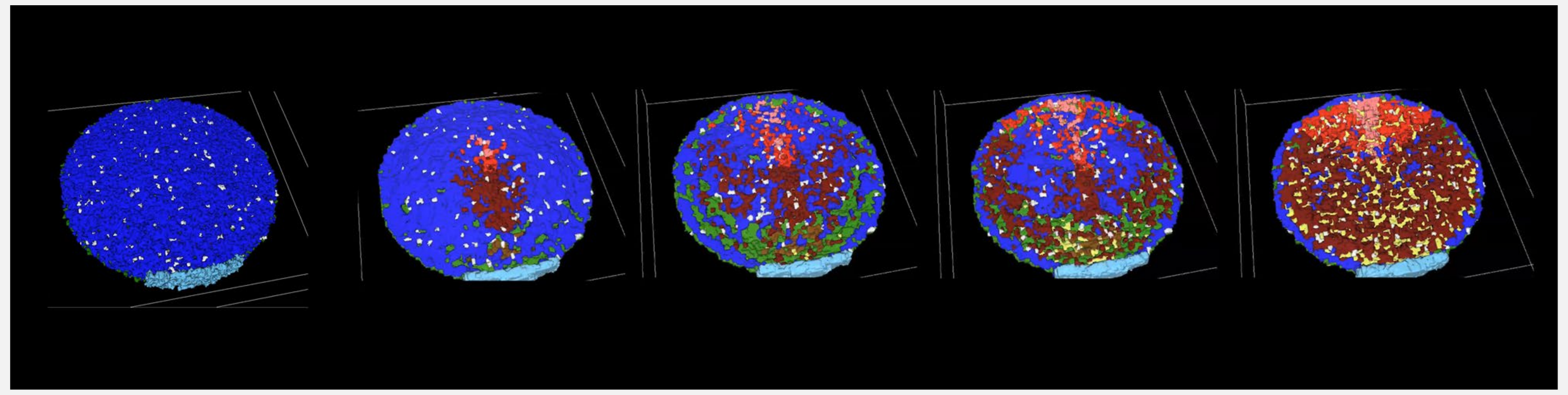
ES-ABM: prototype simulating the control network in the human epiblast built in the compucell3d.org modeling environment; epiblast viewed from above (top) during PS formation:

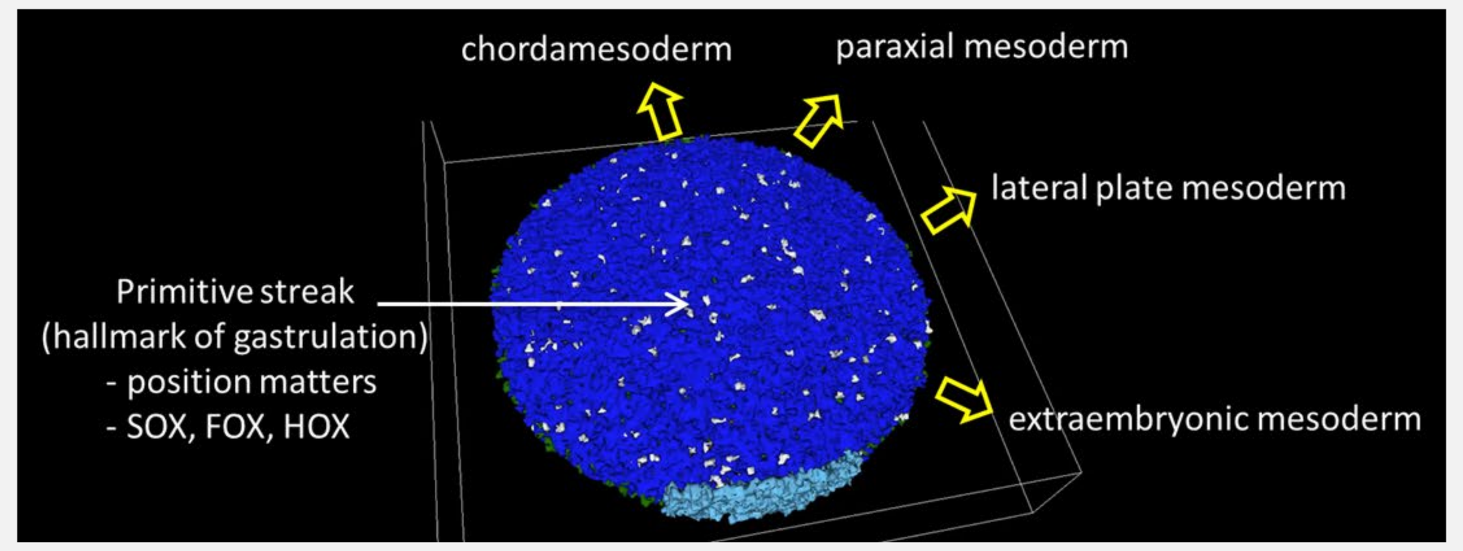


- individual cells represented by vectors that point to their direction of migration;
- cells meet at the midline and undergo epithelial-mesenchymal transformation;
- PS appears as EM cells sink-in and migrate beneath the epiblast.

***In silico* specification of mesoderm:** spatio-temporal distribution of regional mesodermal subpopulations as they are formed during gastrulation; orientation anterior (top) to posterior (bottom).

- cell fate (HOX code) is locked-in as they migrate through the PS;
- essentially decodes the genomic body plan (HOX clock not yet implemented in this version);
- position and timing determines which structures the mesoderm will populate.

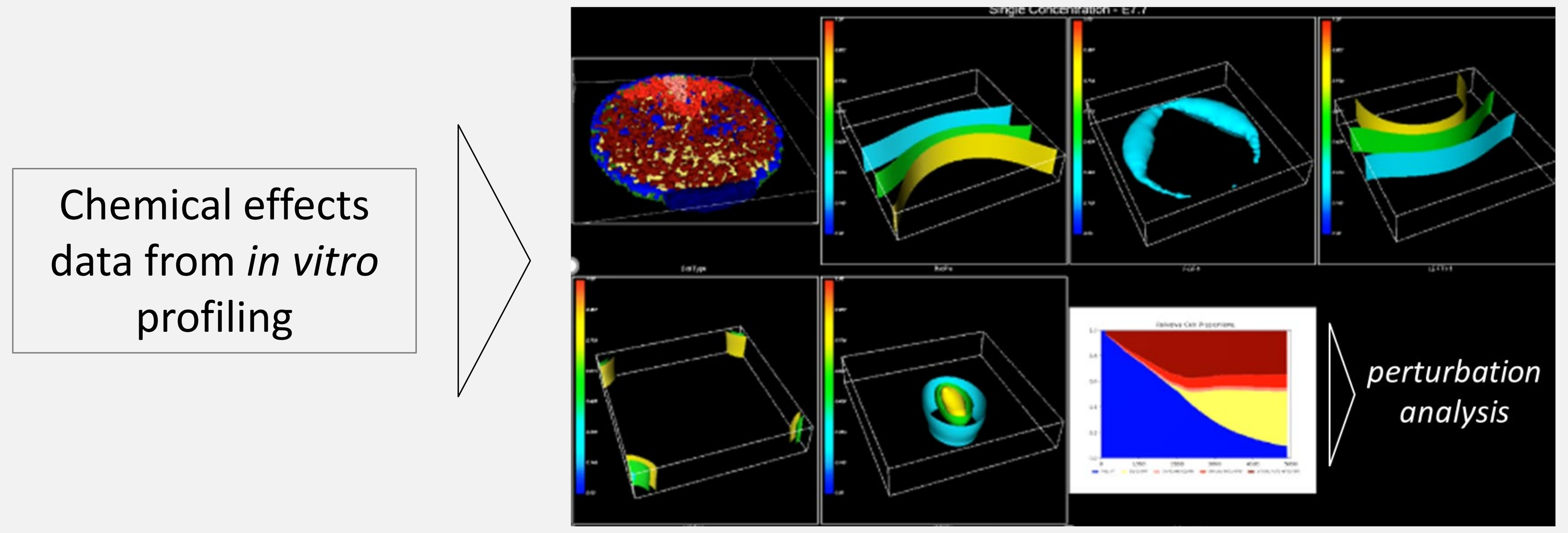




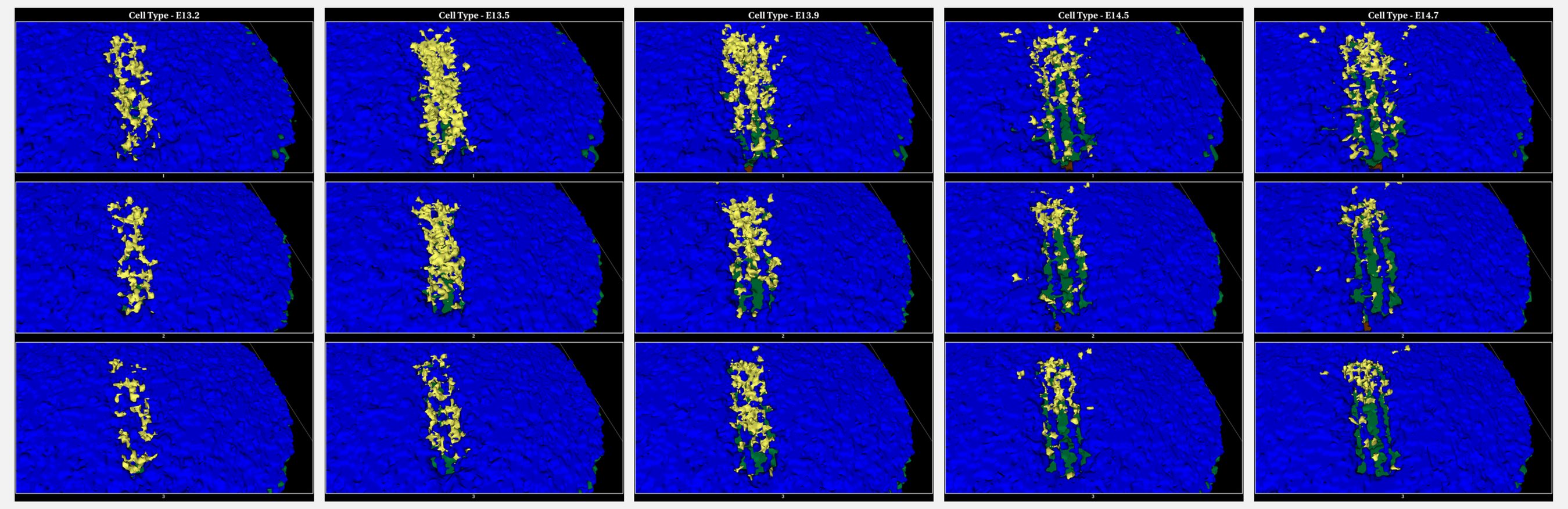
- chordo-mesoderm (notochord)
- paraxial mesoderm (presomites)
- lateral plate mesoderm (limbs, body wall)
- extraembryonic mesoderm (hematopoietic)
- definitive endoderm
- extraembryonic ectoderm

Perturbation analysis: cybermorphs

Quantitation: Metrics for individual cells and signals can be computed over time, to track the impact of various perturbations introduced from *in vitro* chemical profiling data.



Example: FGF signaling has a critical role in PS formation (FGF → BMP4 → WNT) and the number of WNT-positive cells (yellow) is a proxy measurement of FGF signaling.



100% strength
(405 cells ingress)
25% strength
(260 cells ingress)
10% strength
(207 cells ingress)

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Applications: *in silico* toxicodynamics

Now: With computer simulations that are closer to biological reality (e.g., *in vivo* embryogeny), we can use them in predictive toxicology to:

- put in motion *in vitro* profiling data;
- add positional information to embryonic stem cell platforms;
- infer regional specification for data-driven models;
- quantitatively simulate what chemical exposures would do in an automated system;
- provide inferences on developmental effects in a 3Rs-compliant manner.

Future: cell-oriented agent-based models can provide quantitative support for accurate profiling of individual cell behavior *in situ*, and a smarter way to predict developmental toxicity.