## Model Development Workflow: Gene Expression Enhances Robust Organization of the Early Mammalian Blastocyst

Holmes WR, Reyes de Mochel NS, Wang Q, Du H, Peng T, Chiang M, et al. (2017) Gene Expression Noise Enhances Robust Organization of the Early Mammalian Blastocyst. PLoS Comput Biol 13(1): e1005320. https://doi.org/10.1371/journal.pcbi.1005320

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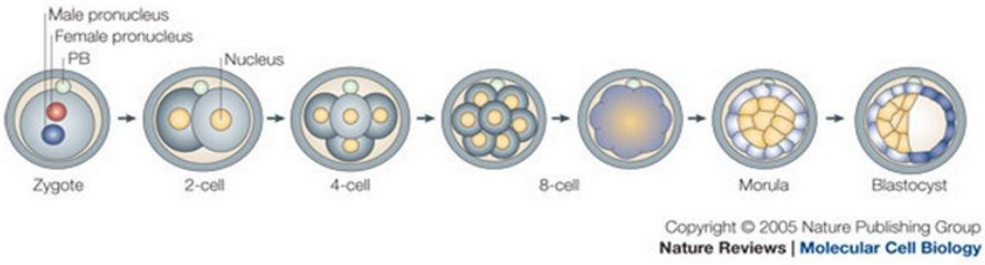
### Biological Observations

Robust pattern of embryonic development: in the transition from the morula to the blastocyst, cells consistently organize and differentiate into inner cells and trophectoderm.

Differential expression of genes Oct4 and Cdx2 associated with specification of blastomeres into inner cell mass and trophectoderm.

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### Initial Questions and Observables

General Questions:

What is responsible for the robust organization observed in the development of mammalian blastocyst?

What is the role of noise in enforcing and correcting developmental patterns?

How differentiating cell respond to changes in their environment?

Observables

Time-lapse microscopy allows to determine the position and shape of cells during the first stages of development.

Quantitative immunofluorescence allows to determine the expression of genes Oct4 and Cdx2 associated with different cell types.

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## Defining Question and Governing Hypotheses

Problem: what is the role of noise in gene expression in correcting and enforcing the patterns of development observed in early mammalian embryos?

Hypotheses:

- Noise enhances cell plasticity and corrects for developmental errors associated with cell movement
- Asymmetry in noise variation ameliorates possible detrimental effects of stochasticity
- Timing of cell specification creates a window for cells to react to changes in their environment

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## Defining Qualitative Verbal Model

Objects

- Cells: blastomeres, inner central mass (ICM), trophectoderm (TE)
- Genes: Cdx2 (associated with TE) and Oct4 (associated with ICM)
- Others: Intracellular fluid, Zona Pellucida (ZP)

Properties:

- Cells: position, volume, orientation (apical /basal)

Behaviours:

- Cells: move, deform, divide, change cell type
- Genes: expressed

Interactions:

- Cells: cell-to-cell contact, adhesion
- Genes: amplify themselves and inhibit other gene

Initial condition:

- Single cell, blastomere type
- Genes not expressed until 8-cells cycle

Boundary conditions:

Cells confined to the circular zona pellucida (ZP) and compressed by intracellular fluid. Cell-to-ZP interactions enhance gene expression.

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## Qualitative Model as Table

| Object | Property | Variable or Constant | Explanation |
|---|---|---|---|
| Universe | X-dimension | Constant | Chosen at convenience of simulation |
| | Y-dimension | Constant | |
| Zona Pellucida | Area | Constant | Radius of simulation |
| Cells | Volume | Variable | Cells divide in half each cycle |
| | Contact Energy | Variable (?) | Cells types have different contact energies |
| | Division | Constant | Determines cell-cycles. All cells divide at the same time |
| | Polarity | Constant (?) | TE cells polarized toward the center |
| Intracellular fluid | Volume | Variable | Increases with time |
| Genes | Expression | Variable | Change according to cell position (contact to ZP)<br>Associated stochasticity |

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## Defining Quantitative Model

Genes dynamics described by non-dimensional ODEs:

$$\frac{dx_i}{dt} = k(b + S_i + \frac{x_i^n}{0.5^n + x_i^n})((1 - I) + I\frac{0.5_i^n}{0.5^n + y_i^n}) - x_i + \sigma_{Cdx2} x_i \cdot \eta$$

$$\frac{dy_i}{dt} = k(b + S_i + \frac{y_i^n}{0.5^n + y_i^n})((1 - I) + I\frac{0.5_i^n}{0.5^n + x_i^n}) - x_i + \sigma_{Oct4} x_i \cdot \eta$$

Cellular dynamics represented:

- Cellular Potts
- Subcellular Element Methods