Avian somitogenesis as a model for building multi-scale cell-based simulations

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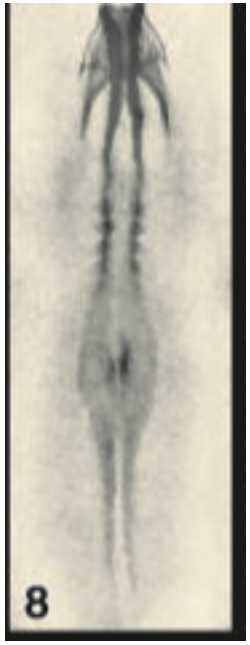
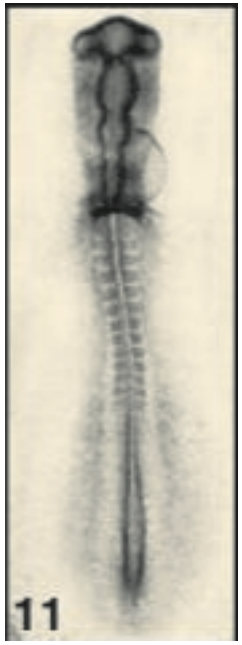
Outline

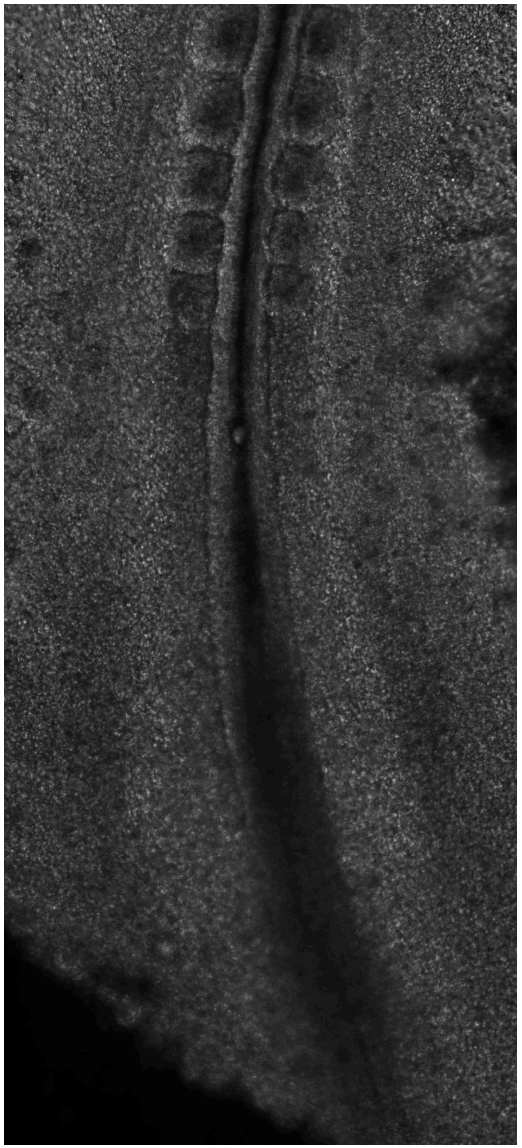
- Somitogenesis
  - A brief description
  - Key features
  - Current understanding
- Our question
- Somitogenesis as a multi-scale problem
- Describing the system for cell-centered modeling
- Initial Results
- Closing remarks

Somitogenesis: a brief description





HH staged chick embryos, fixed
(Wiley)



Recently formed somites and
PSM in living chick embryo
(Hester, Filla, Little)

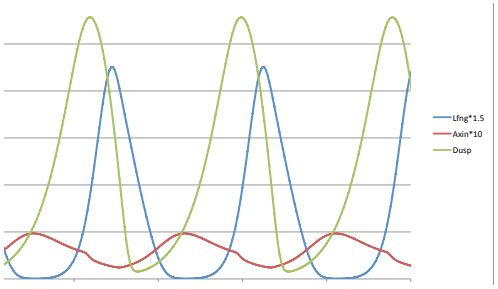
Key features of the system

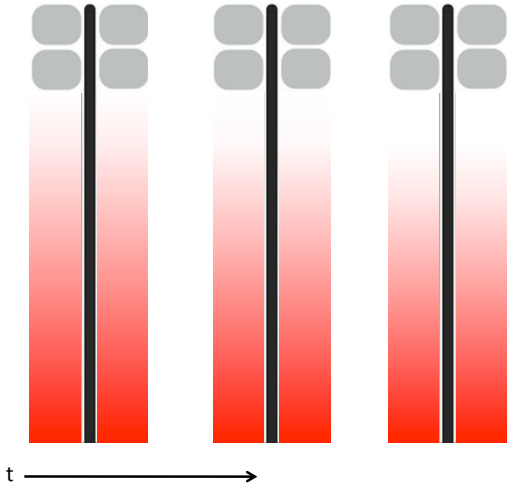
Graded expression of morphogens along AP axis
FGF8, Wnt3a, retinoic acid

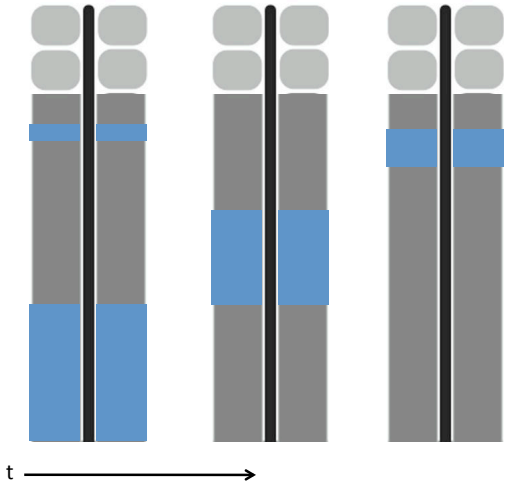
Dynamic stripes of gene expression along tissue

Oscillating gene expression - *segmentation clock*

Patterned expression of adhesion molecules
N-CAM, N-cadherin, EphA4, ephrinB2



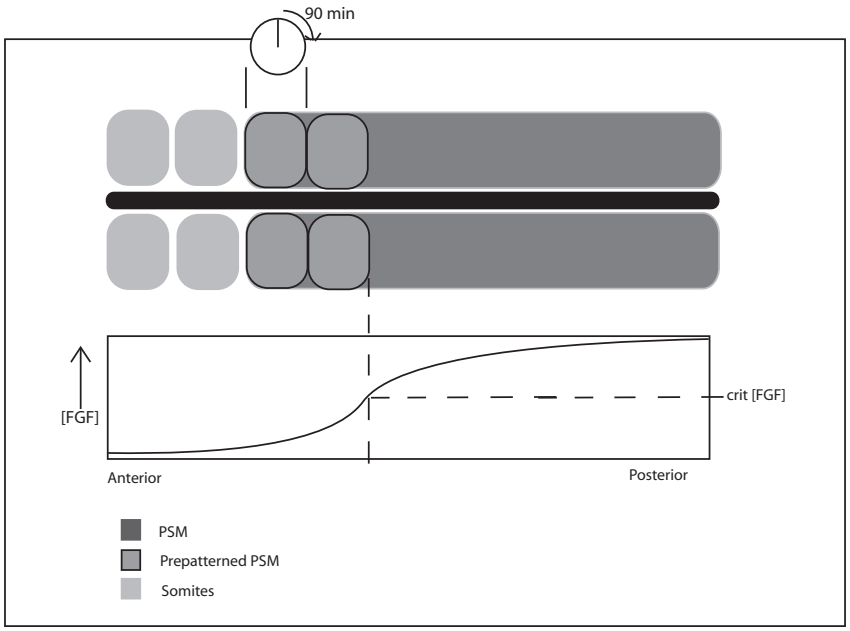


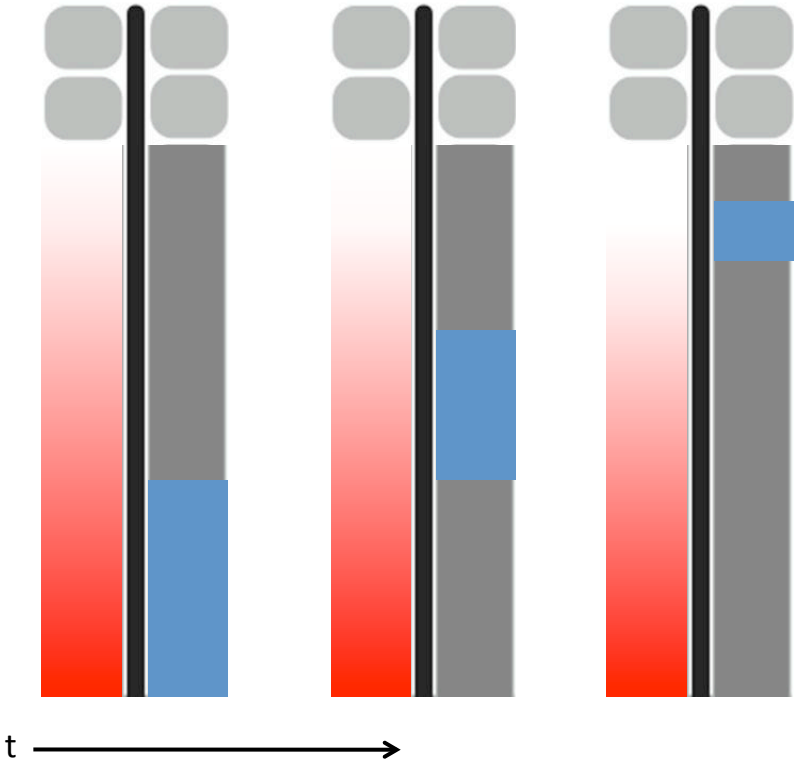


Current understanding

Clock and wavefront models

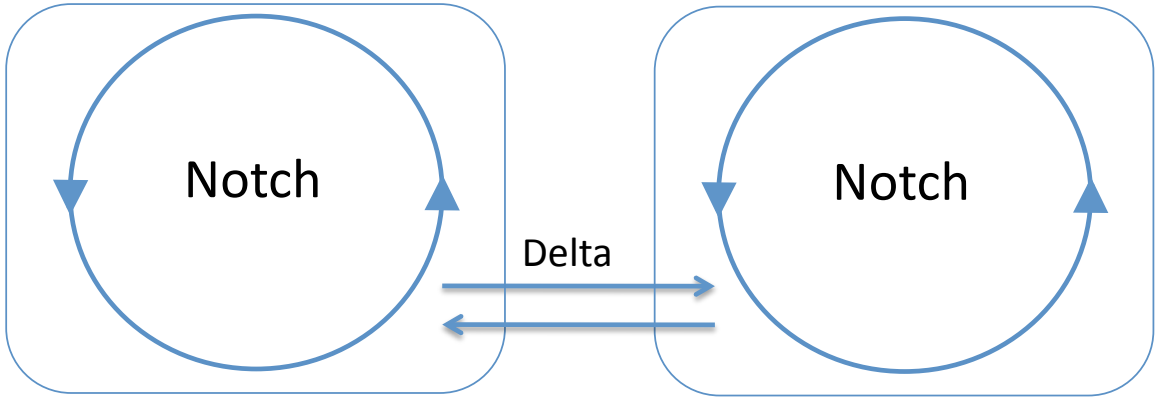
Cooke and Zeeman, 1976
Baker and Schnell, 2006
Aulehla et al., 2008



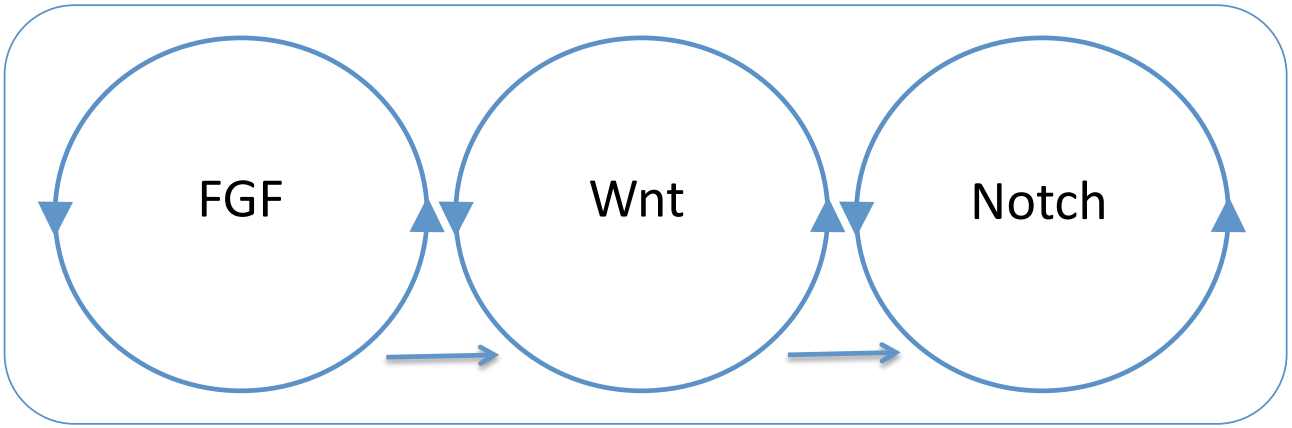


Current understanding

Segmentation clock networks



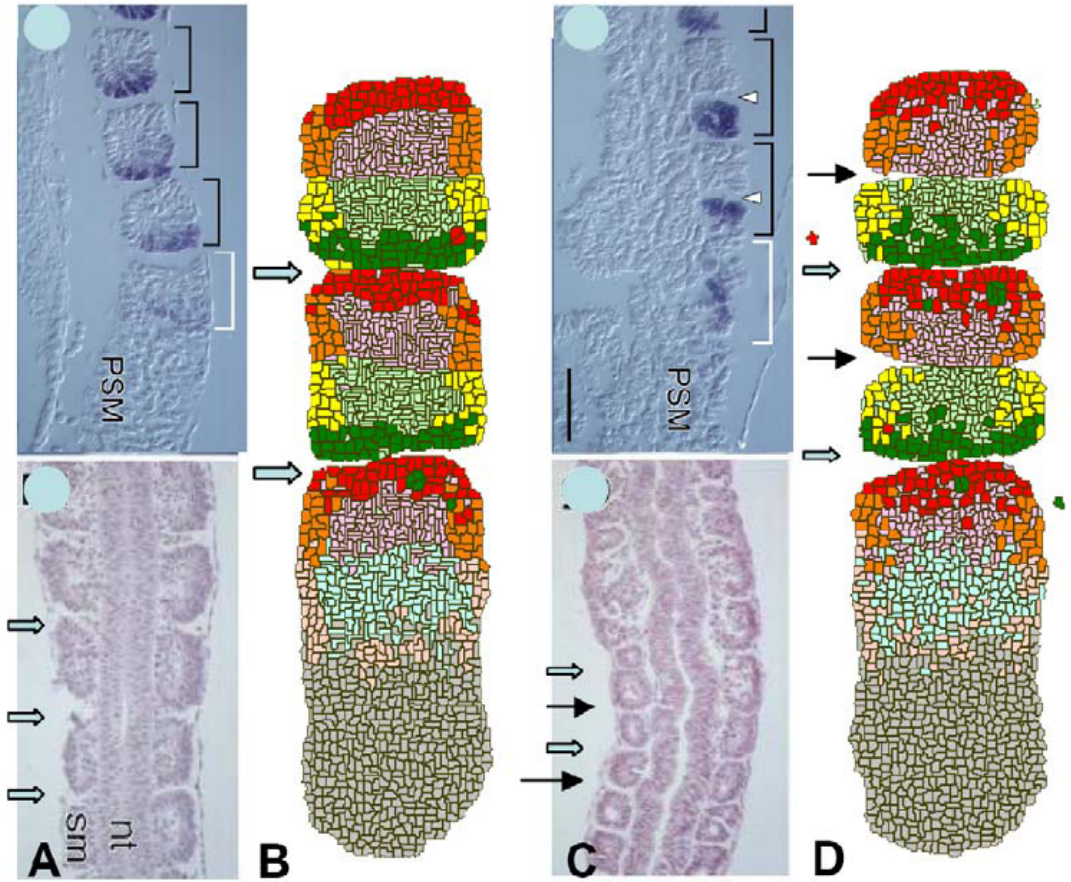
Lewis (2000, 2003)



Goldbeter and Pourquié (2008)

Current understanding

Adhesion-mediated evolution of morphology



Experimental image from Horikawa *et al.* 1999.

Glazier et al. (2008)

Can the current models of somitogenesis at different scales be combined into a single, multi-scale simulation that gives rise to observed phenomena?

Somitogenesis as a multi-scale problem

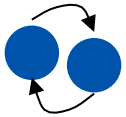
Cellular/Subcellular scale

Gene networks (e.g., clock)

Protein expression (e.g., adhesion proteins, excreted morphogens)

Intercellular scale

Cell-cell signaling



Mechanical cell-cell interactions

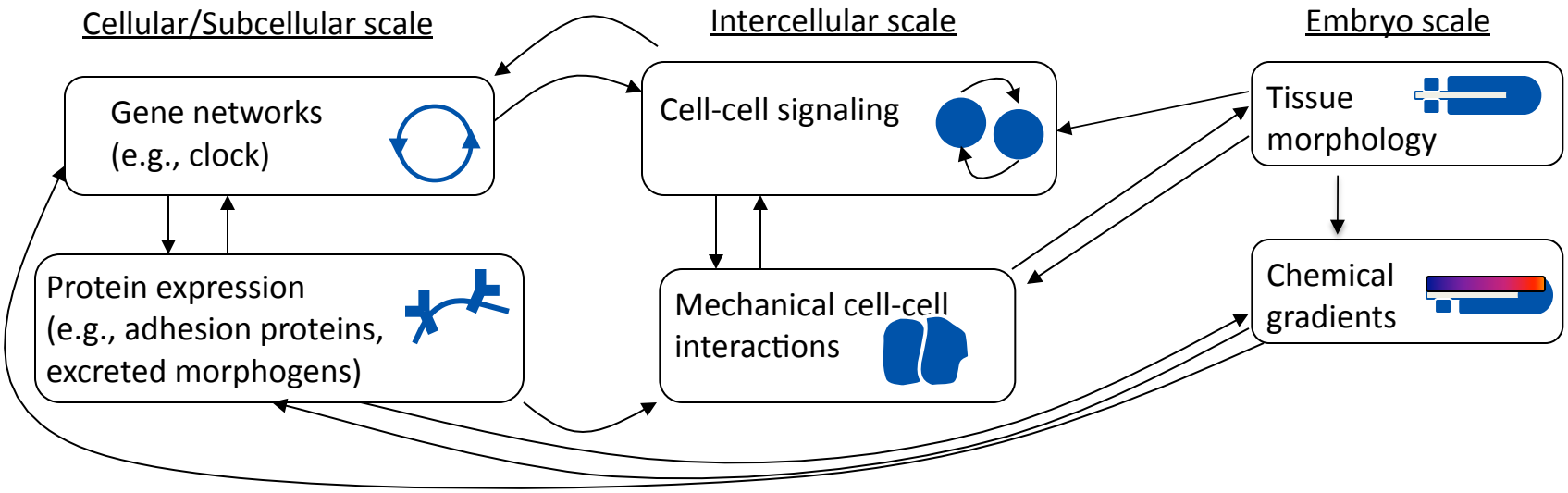
Embryo scale

Tissue morphology

Chemical gradients

- Phenomena of somitogenesis (and developmental processes in general) occur at multiple scales. To date, models have focused on handling a single scale (e.g., *segmentation clock* models at the subcellular scale) or the interface between two scales (e.g., *clock and wavefront* models connecting subcellular and embryo scales).

Somitogenesis as a multi-scale problem



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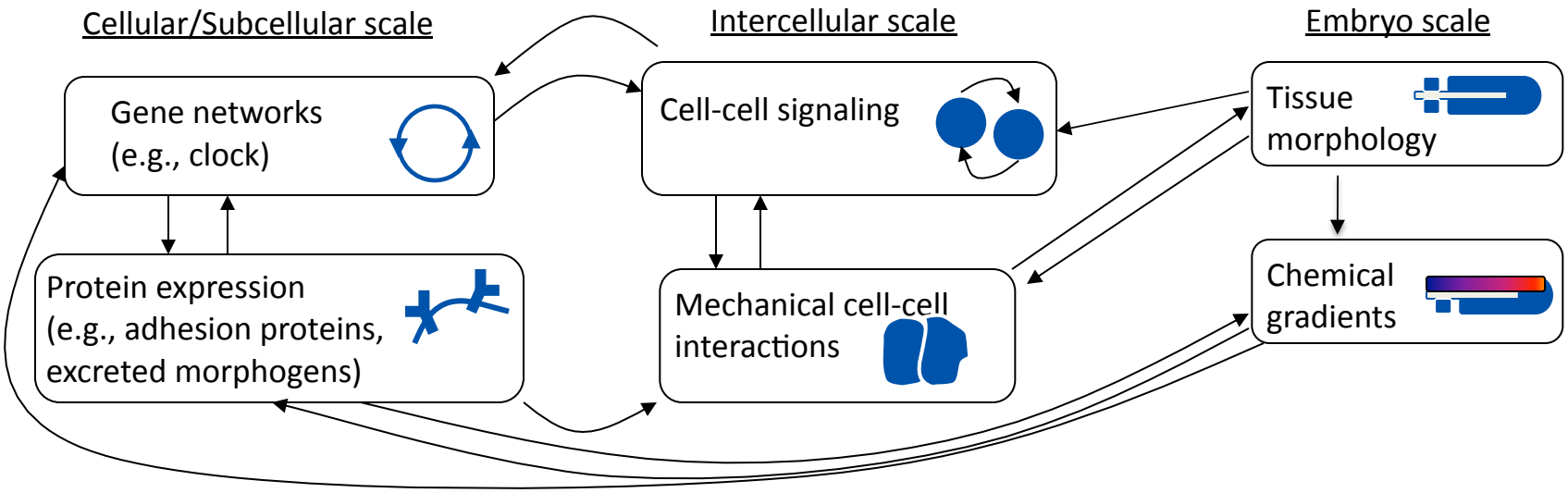

Choose the cell as the “agent of integration.”

Describing the system for cell-centered modeling

Cell properties
- Cell-cell adhesion
- Motility
- Growth
- Division
- Cell-cell signaling
- Access of local extracellular signals
- Secretion of extracellular signals
- Differentiation criteria

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Cells of a given *simulation type* share a common set of rules governing these properties.

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Cell types:

- PSM cell
- Somite cell

Describing the system for cell-centered modeling

Cells of a given *simulation type* share a common set of rules governing cell properties.

Cell types:

- PSM cell
  - Immature
  - Differentiation-competent
- Somite cell
  - Anterior
  - Posterior
  - Interior

Describing the system for cell-centered modeling

Cell Type: **Immature PSM**

Cell properties

- Cell-cell adhesion
  - N-CAM
- Motility
  - ERK/MAPK (FGF8 signaling)
  - β-catenin (Wnt3a signaling)
- Growth
  - FGF8 signaling
- Division
  - FGF8 signaling
- Cell-cell signaling
  - Delta/Notch
- Access of local extracellular signals
  - FGF8
  - Wnt3a
- Secretion of extracellular signals
  - FGF8
  - Wnt3a

Differentiation criteria

→ Differentiation-competent PSM

- FGF8 threshold

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Differentiation criteria

→ Anterior somite segmentation clock phase

→ Posterior somite segmentation clock phase

→ Interior somite segmentation clock phase

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Differentiation criteria

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  - segmentation clock phase
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Describing the system for cell-centered modeling

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  - FGF8
  - Wnt3a

Differentiation criteria

→ Anterior somite segmentation clock phase

→ Posterior somite segmentation clock phase

→ Interior somite segmentation clock phase

Need experimental data!

Describing the system for cell-centered modeling

Cell Type: **Anterior Somite**

Cell properties

- Cell-cell adhesion
  - EphA4
    - adheres to EphA4
    - repels ephrinB2
  - N-CAM
    - adheres to N-CAM
- Motility
  - Low motility
- Growth
  - None
- Division
  - None
- Cell-cell signaling
  - None
- Access of local extracellular signals
  - None
- Secretion of extracellular signals
  - None

Differentiation Criteria

- None

Describing the system for cell-centered modeling

Cell Type: **Posterior Somite**

Cell properties

- Cell-cell adhesion
  - ephrinB2
    - adheres to ephrinB2
    - repels EphA4
  - N-CAM
    - adheres to N-CAM
- Motility
  - Low motility
- Growth
  - None
- Division
  - None
- Cell-cell signaling
  - None
- Access of local extracellular signals
  - None
- Secretion of extracellular signals
  - None

Differentiation Criteria

- None

Describing the system for cell-centered modeling

Cell Type: **Interior Somite**

Cell properties

- Cell-cell adhesion
  - N-CAM
    - adheres to N-CAM
- Motility
  - Low motility
- Growth
  - None
- Division
  - None
- Cell-cell signaling
  - None
- Access of local extracellular signals
  - None
- Secretion of extracellular signals
  - None

Differentiation Criteria

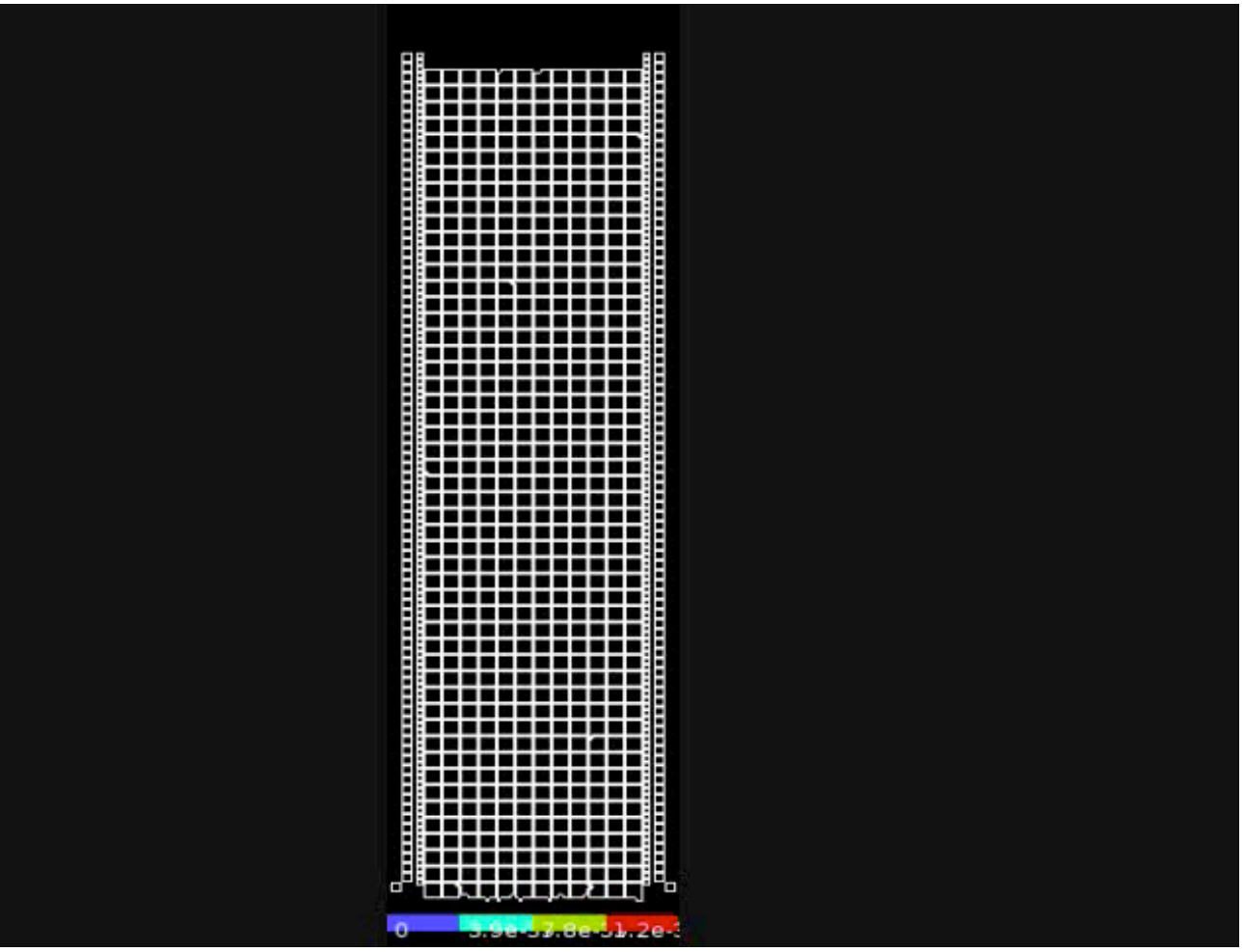
- None

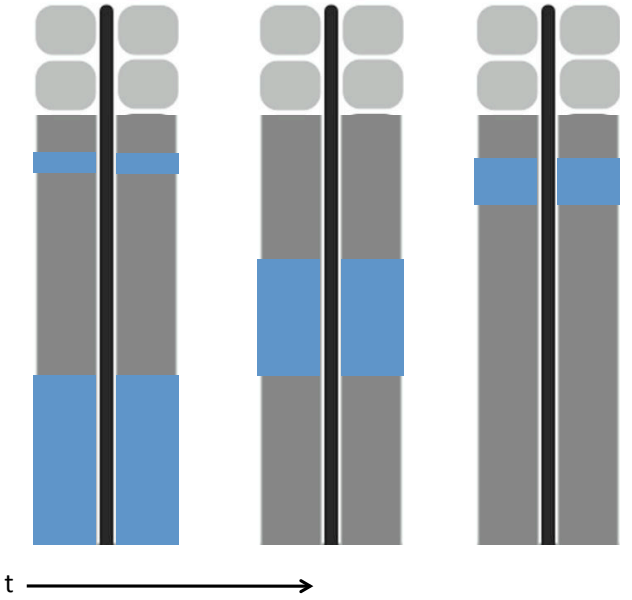
Results: Pattern formation

Wave formation in Lfng (Notch target) and Axin2 (Wnt target) expression

An array of frozen cells initialized with identical segmentation clock networks in the same phase in the presence of linear Wnt and FGF gradients:

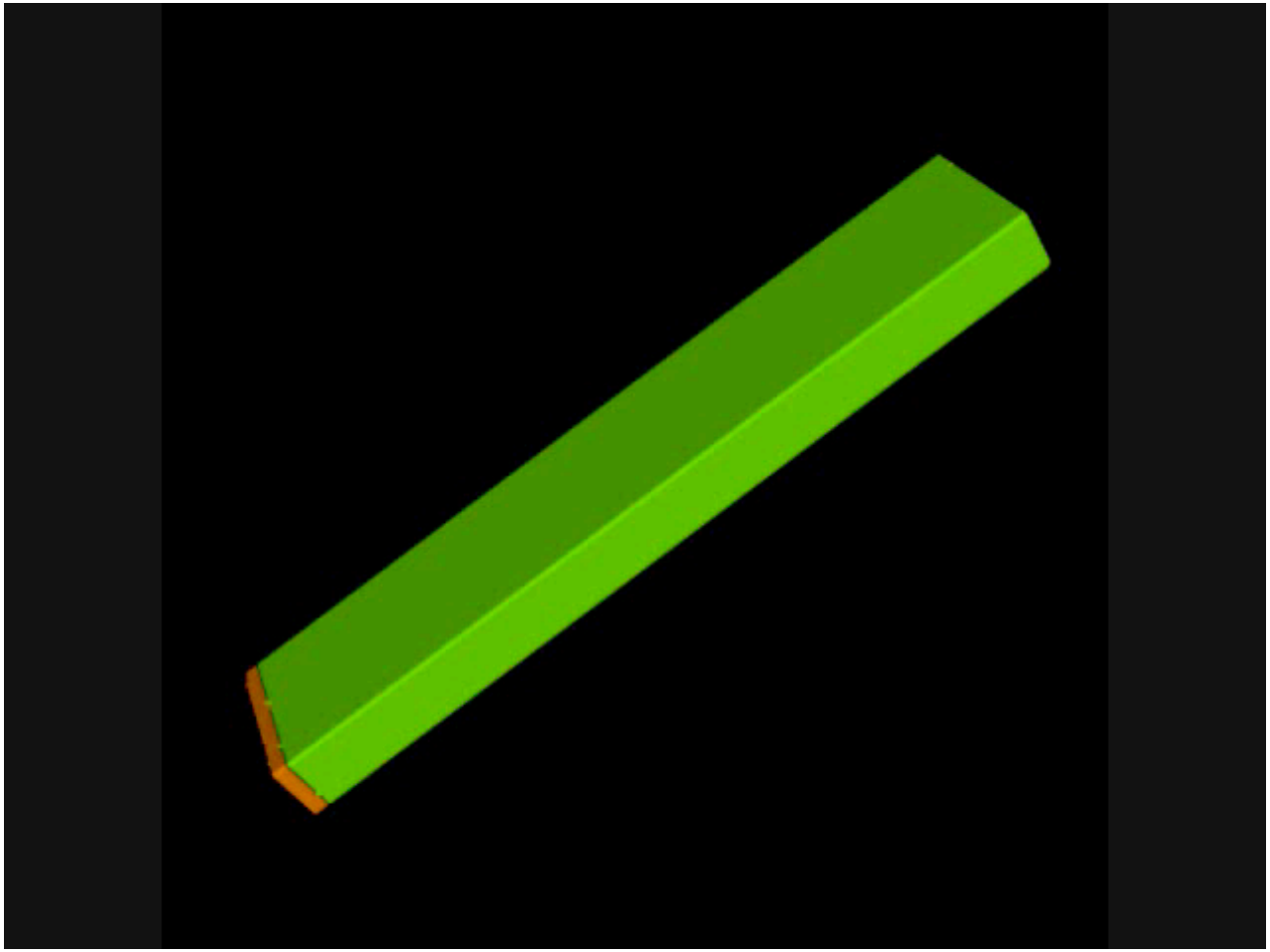
Lfng and Axin2





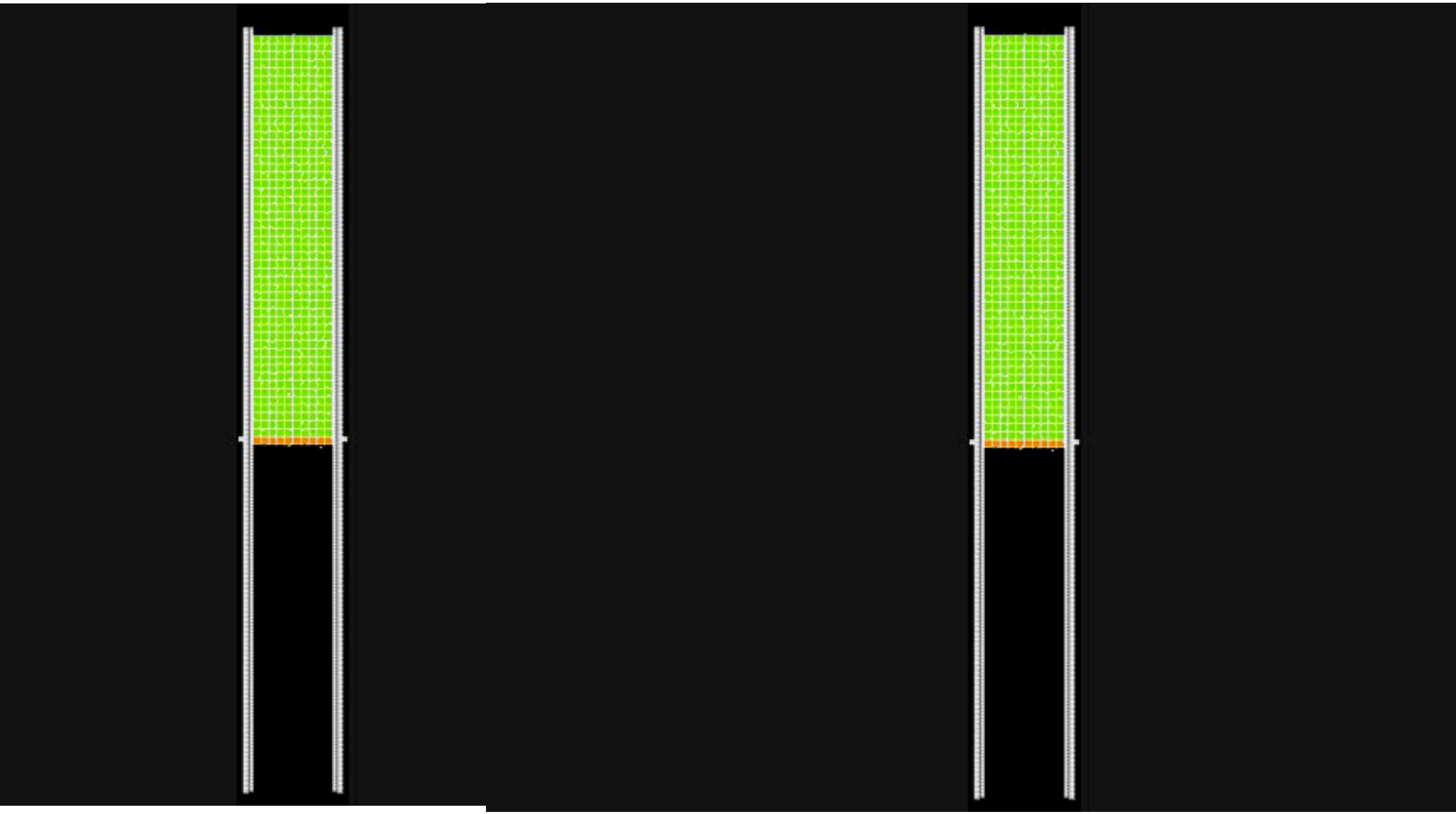
Results:

Somite formation

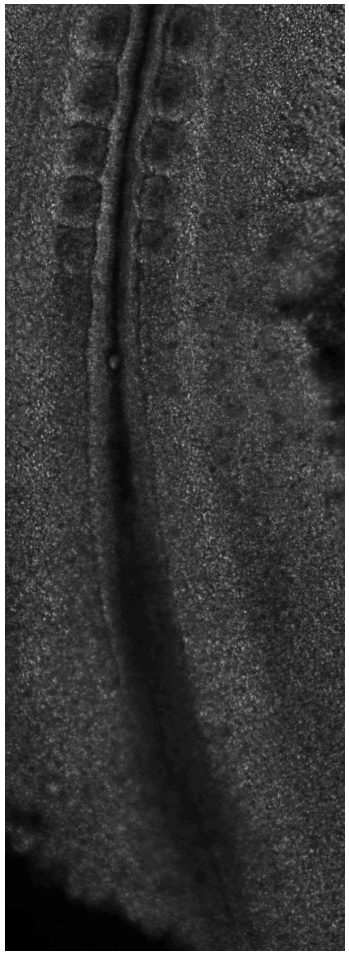


Results:

Variation of motility

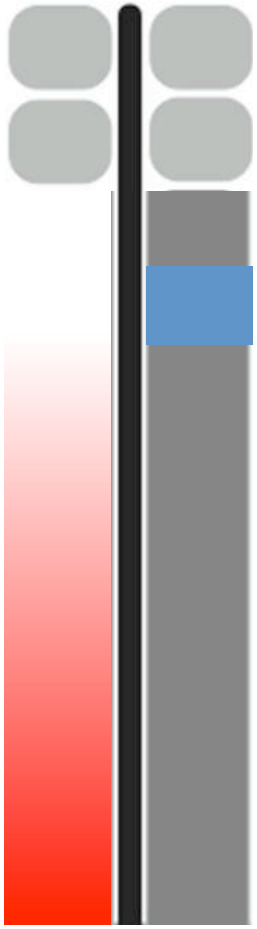


Closing Remarks



Important experimental data for simulation development include

- protein localization – FGF8, Wnt3a, membrane-bound signaling and adhesion proteins
- segmentation "readout" pathways translating clock and wavefront expression patterns into cell differentiation (although we are in a position to make predictions about likely characteristics of these pathways)



We are ready to run more sophisticated simulations exploring the ways in which, e.g., motility and cell adhesivity affect somitogenesis and the mechanisms by which perturbations disturb development. These future simulations will require experimental validation.

Acknowledgments

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