Dynamic Switching of Lateral Inhibition Spatial Patterns

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Introduction

Outline

The developing neural tube presents a unique and interesting multicellular spatial pattern - one that switches its peaks and troughs over time [1].

We want to understand the mechanism and function behind this dynamic spatial pattern.

Approach

We use a multicellular HES5 model of lateral inhibition to explore how a stationary pattern can be made dynamic by including differentiation-based perturbations applied to HES5 expression.

Model

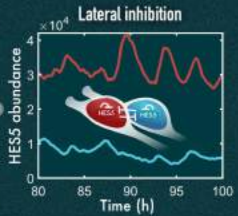
- Stochastic delay differential equations
- Autorepression feedback loop describes single-cell HES5 dynamics [2]
- Hill functions describe Notch-Delta lateral inhibition between cells

Background

Lateral inhibition generates stationary spatial patterns

Notch-Delta is a cell-to-cell, contact-dependent signalling pathway.

Via lateral inhibition it amplifies differences between neighbouring cells.



Nearest neighbour signalling
2-cell periodicity

Lateral inhibition typically results in a stationary spatial pattern of alternating high and low cells, where cells remain stuck in their high and low states.

Nearest neighbour interactions result in a spatial pattern with a 2-cell period.

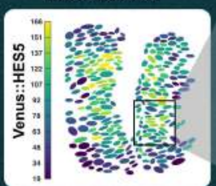
HES5 pattern is dynamic and has a longer spatial period

In the developing neural tube, a downstream target of Notch named HES5 is expressed in a spatial pattern with an average period of 3-4 cells composed of cluster of similarly expressing cells [1].

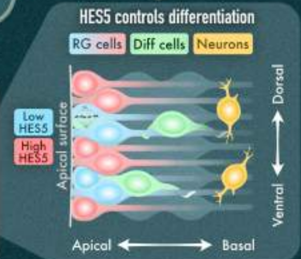
HES5 functions to maintain radial glial (RG) cells in an undifferentiated state.

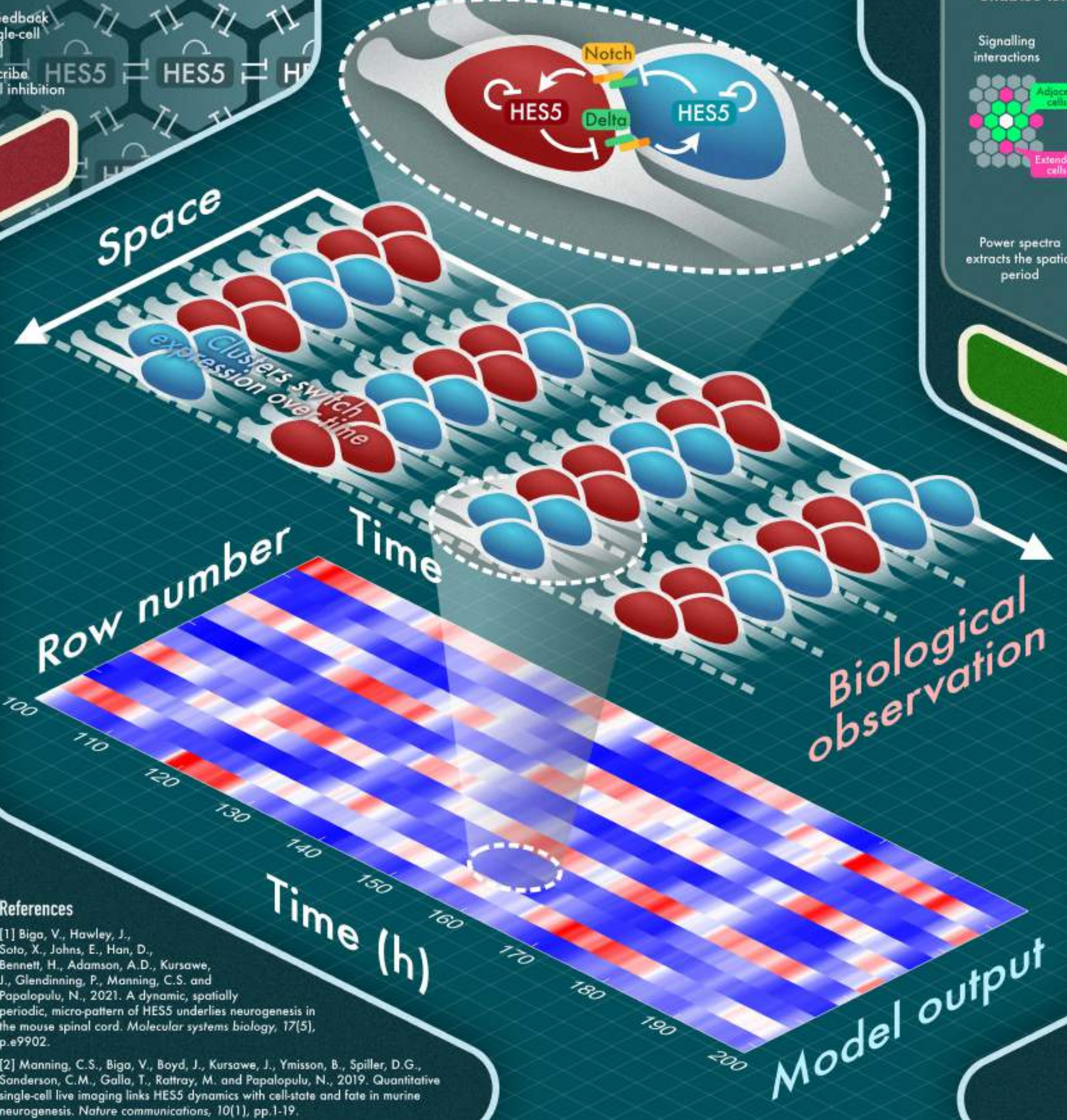
These clusters of cells switch expression between high and low states over time (see central image).

Neural tube HES5



HES5 controls differentiation





References

[1] Biga, V., Hawley, J., Soto, X., Johns, E., Han, D., Bennett, H., Adamson, A.D., Kursawe, J., Glendinning, P., Manning, C.S. and Papalopulu, N., 2021. A dynamic, spatially periodic, micro-pattern of HES5 underlies neurogenesis in the mouse spinal cord. *Molecular systems biology*, 17(5), p.e9902.

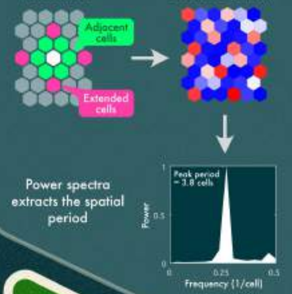
[2] Manning, C.S., Biga, V., Boyd, J., Kursawe, J., Ymisson, B., Spiller, D.G., Sanderson, C.M., Galla, T., Rattray, M. and Papalopulu, N., 2019. Quantitative single-cell live imaging links HES5 dynamics with cell-state and fate in murine neurogenesis. *Nature communications*, 10(1), pp.1-19.

Methods

Extended signalling distance enables longer spatial period

Signalling interactions

Resulting clustered pattern

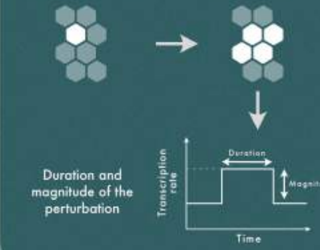


Power spectra extracts the spatial period

Perturbation algorithm reflects signalling strength changes during differentiation

Expression-dependent selection of a differentiation event

Selection of cells for the perturbation to be applied to

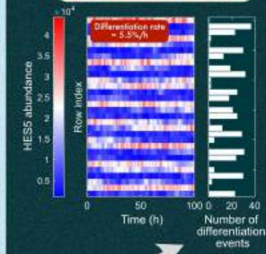


Duration and magnitude of the perturbation

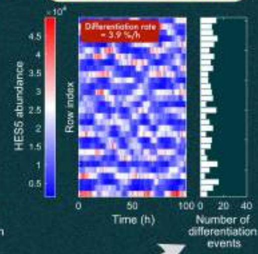
Results

Perturbation enables dynamic switching of peak and trough locations over time

No perturbation



With perturbation



Stationary patterning generates differentiated cells in specific locations in space

Dynamic patterning spreads out differentiation events spatially while maintaining a high differentiation rate