Hes1 Dynamics: Capturing Oscillations and Fate Decisions via Multiple Modelling Frameworks

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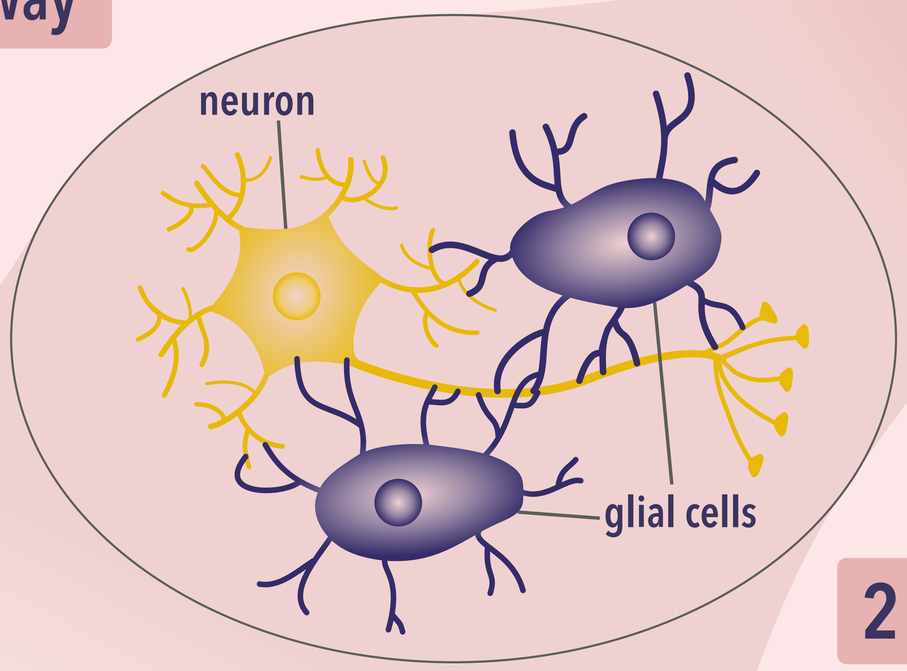
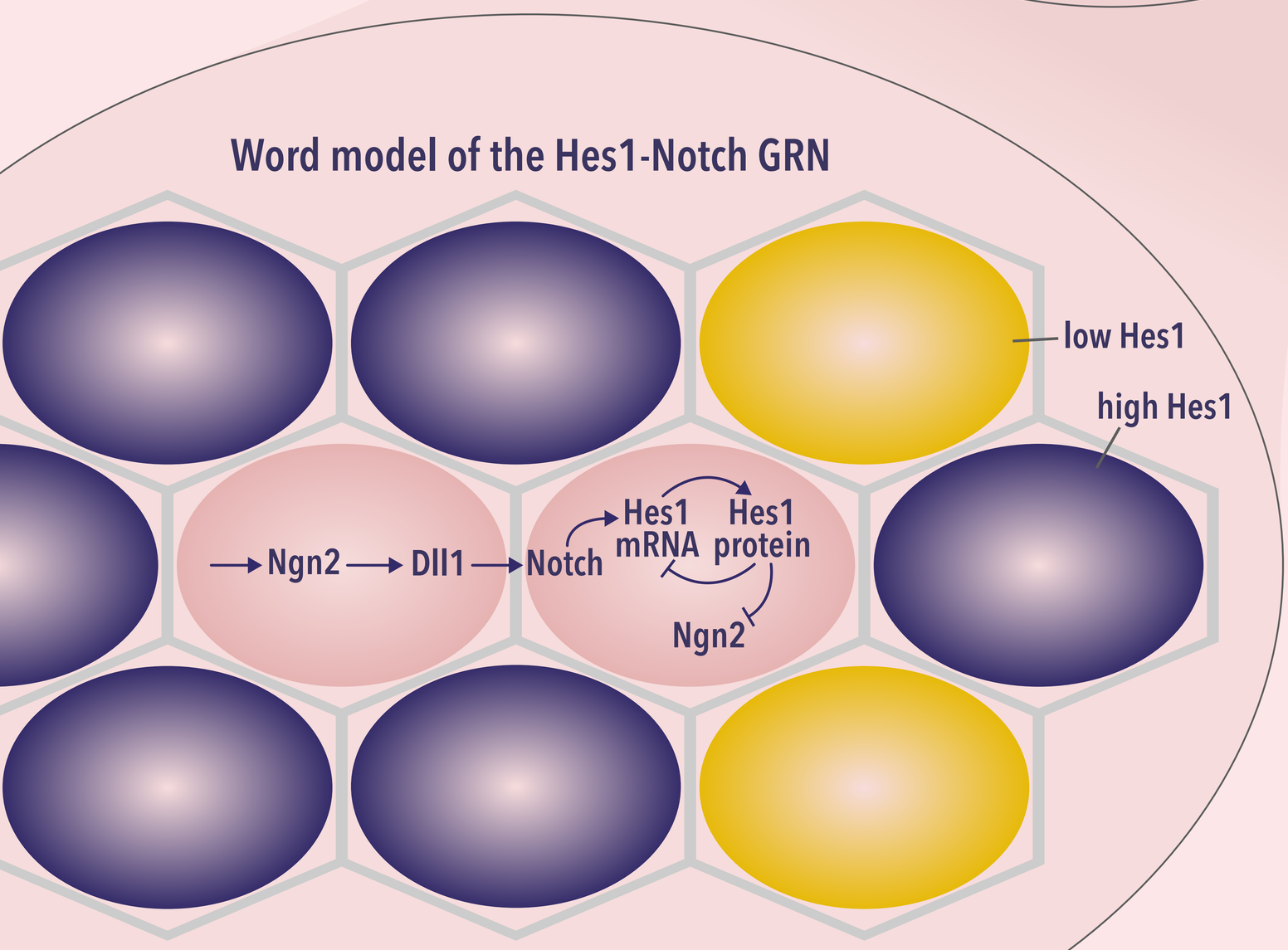
1 Hes1-Notch Signalling Pathway

- important in **neural development** in embryos and tumour development
- regulates **differentiation of cells into neurons or glial cells**
- **Hes1 oscillates** throughout development to keep cells undifferentiated long enough to develop enough cells overall
- **fate decision at the end**: cells low in Hes1 become neurons, cells with high Hes1 levels become glial cells





2 Models

- use mathematical modelling to investigate details of molecular mechanisms
- find a relatively simple mathematical model that **captures both oscillations and fate decision** as well as allows for some mathematical analysis
- **deterministic and stochastic modelling** to determine analysability and resistance to noisy environments

ODE Model

$$\dot{D} = \alpha_D n - \mu_D D$$
$$\dot{N} = \alpha_N D_{\text{in}} - \mu_N N$$
$$\dot{M} = \frac{\alpha_M N}{1+(P/K_M)^k} - \mu_M M$$
$$\dot{P} = \alpha_P M - \mu_P P$$
$$\dot{n} = \frac{\alpha_n}{1+(P/K_n)^h} - \mu_n n$$

repression modelled by Hill function

analysis of reduced form gives insight on patterning

D turns into in-signal which then induces Notch in neighbour cell

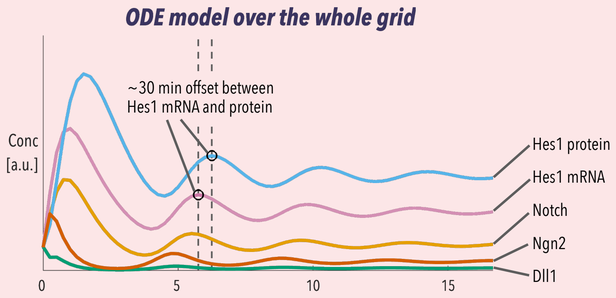
RDME model

n	$\xrightarrow{\alpha_D n}$	$n + D$
D	$\xrightarrow{2\alpha_N D}$	$D + D_{\text{in}}$
$D_{k_{\text{in}}}$	$\xrightarrow{2\alpha_N D_{k_{\text{in}}}}$	N_l
N	$\xrightarrow{\alpha_M N/(1+(P/K_M)^k)}$	$N + M$
M	$\xrightarrow{\alpha_P M}$	$M + P$
$\varnothing$	$\xrightarrow{\alpha_n/(1+(P/K_n)^h)}$	n
all	$\xrightarrow{\mu_i}$	$\varnothing$

3 Results

- we implement all models on a hexagonal grid
- assumption: one cell per hexagon

Mean behaviour of the full ODE model over the whole grid

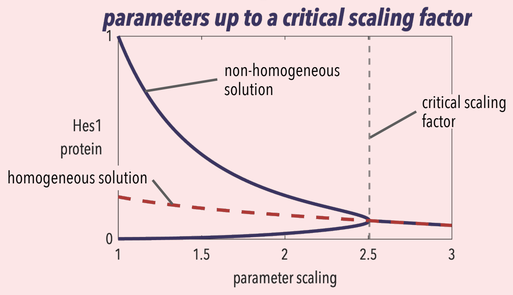


- all constituents oscillate in ODE model
- dampened oscillations
- expected: phase difference between constituents

4 Conclusion

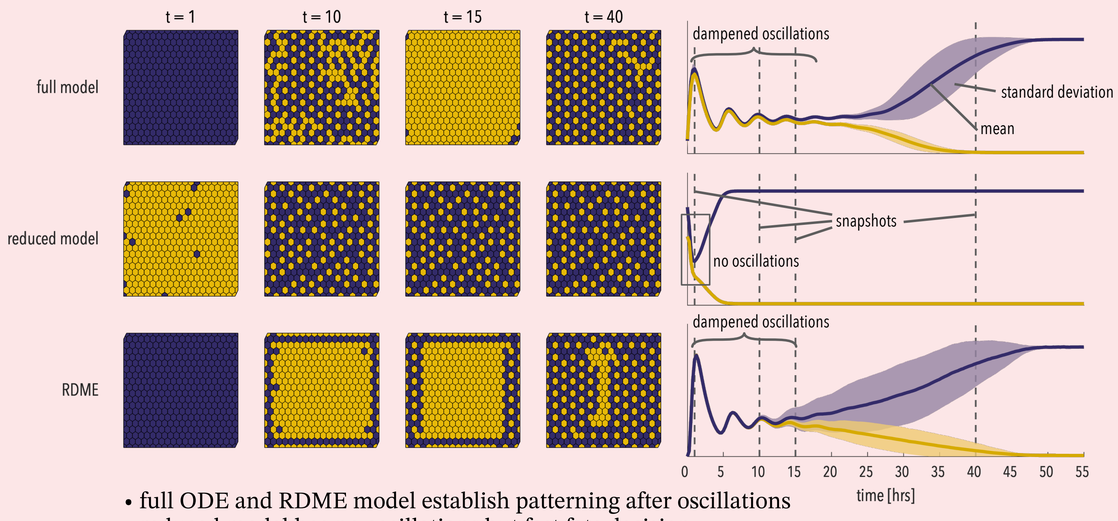
1. we can capture both oscillations and fate decision
2. oscillations are slightly longer and not as pronounced as found experimentally - we might be missing interactions with other pathways
3. possible to **analyse the fate decision** behaviour
4. time scales differ between deterministic and stochastic setting but **overall behaviour is quite similar**
5. stochastic behaviour **stable for high noise** levels

Patterning occurs for our parameters up to a critical scaling factor



- we can see a bifurcation if we scale all parameters
- above the critical scaling factor, there are only homogeneous solutions, i.e. no patterning
- below the critical scaling factor patterning occurs

Behaviour of Hes1 mRNA in all models over time with snapshots at specific times



- full ODE and RDME model establish patterning after oscillations
- reduced model has no oscillations but fast fate decision
- all oscillations are dampened
- shorter oscillations for RDME than for ODE model due to noise

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