A multilayer network approach to polarity-driven cell-fate patterning in mammary organoids

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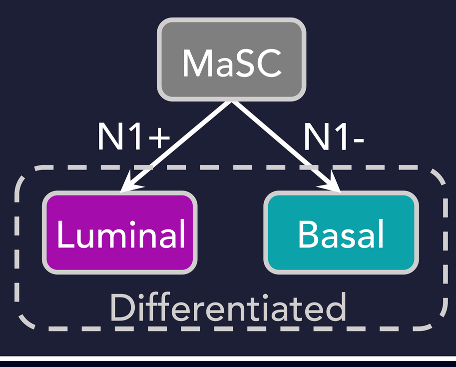
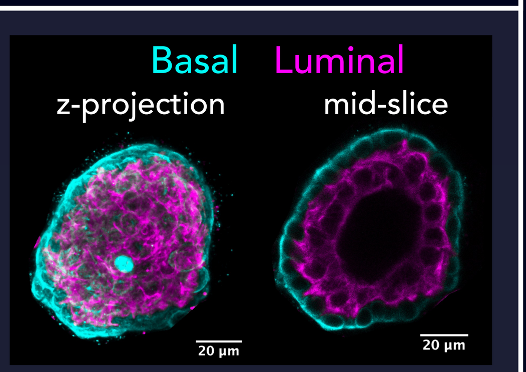
1 Mammary organoids and cell-fate patterning

Mammary organoids are 3D *in vitro* biological models derived from mammary glands that preserve the **bilayer tissue structure** and **cellular functions** [1].

Coordinated control of cell-fate decisions, essential for healthy development, is highly dependent on the cellular microenvironment in mammary organoids [2].

Among many other factors, cell-fate decisions are regulated by Notch1 [3].

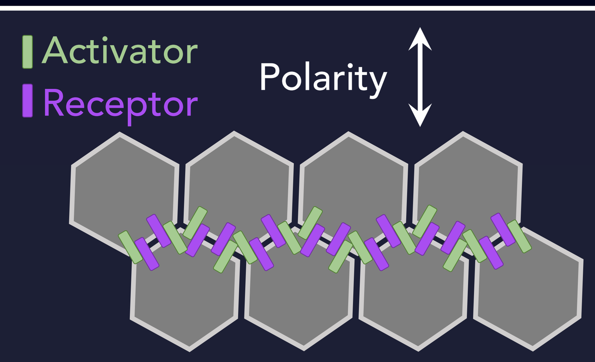




This generates **laminar patterns** of Notch1 in mammary organoids.

However, the mechanisms that robustly generate these patterns are yet to be identified.

2 Modelling cell signalling polarity with weighted networks



Cell signalling polarity is the **coordinated localisation** of pathway signal activators and receptors on the surface of the membrane [4].

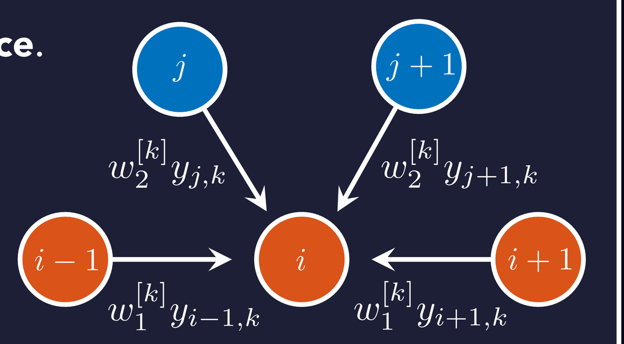
Many cell-fate determinants including Notch have been observed to exhibit polarity characteristics in the developing tissues [5].

A topological (network) approach to cell-cell connectivity allows for **spatial dimension independence**.

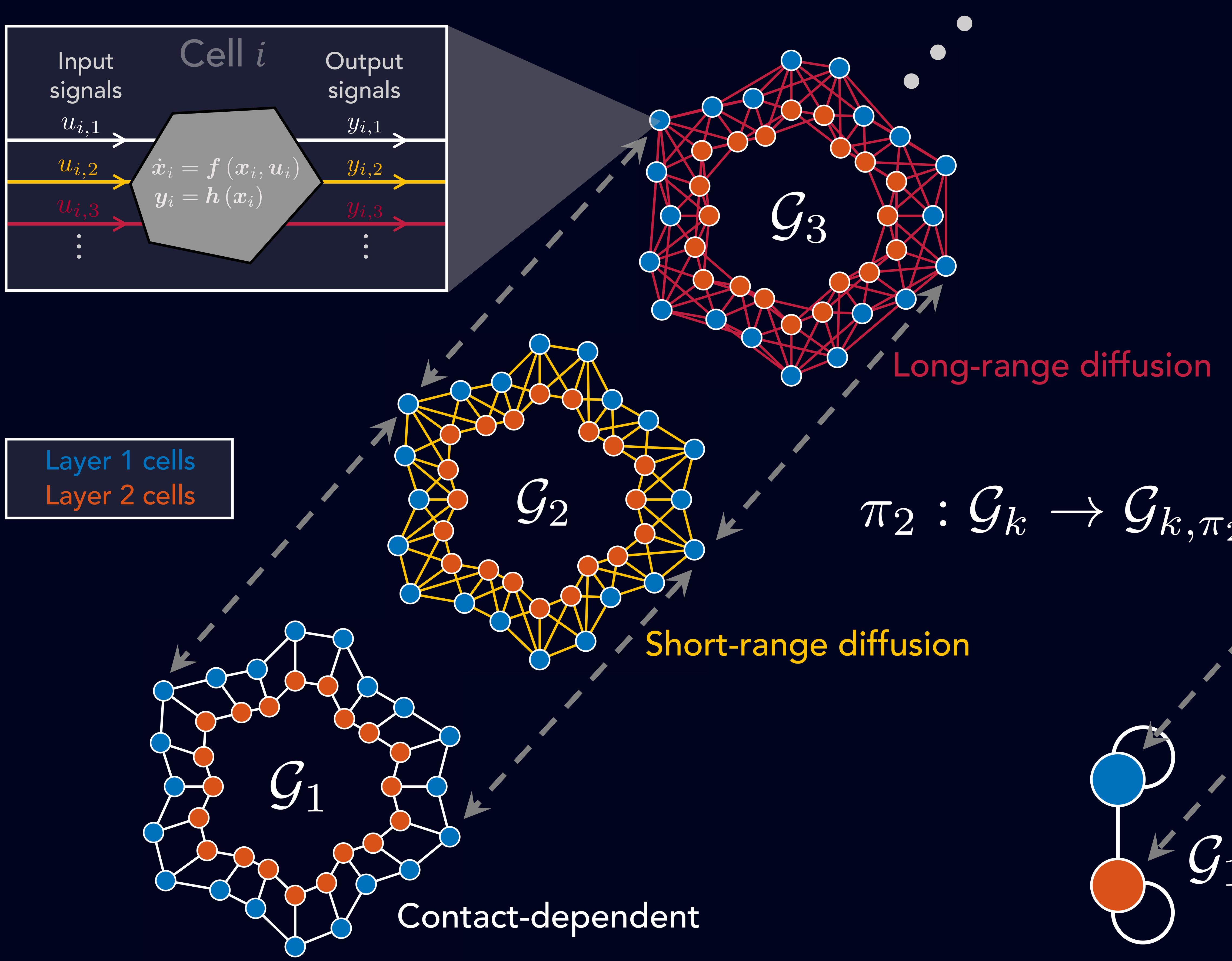
Signal polarity edge weights for $\mathcal{G}_k$

$w_1^{[k]}$ - same layer $w_2^{[k]}$ - different layer

Aim: quantify the relative amount of polarity required to induce laminar patterns of cell-fate determinants.

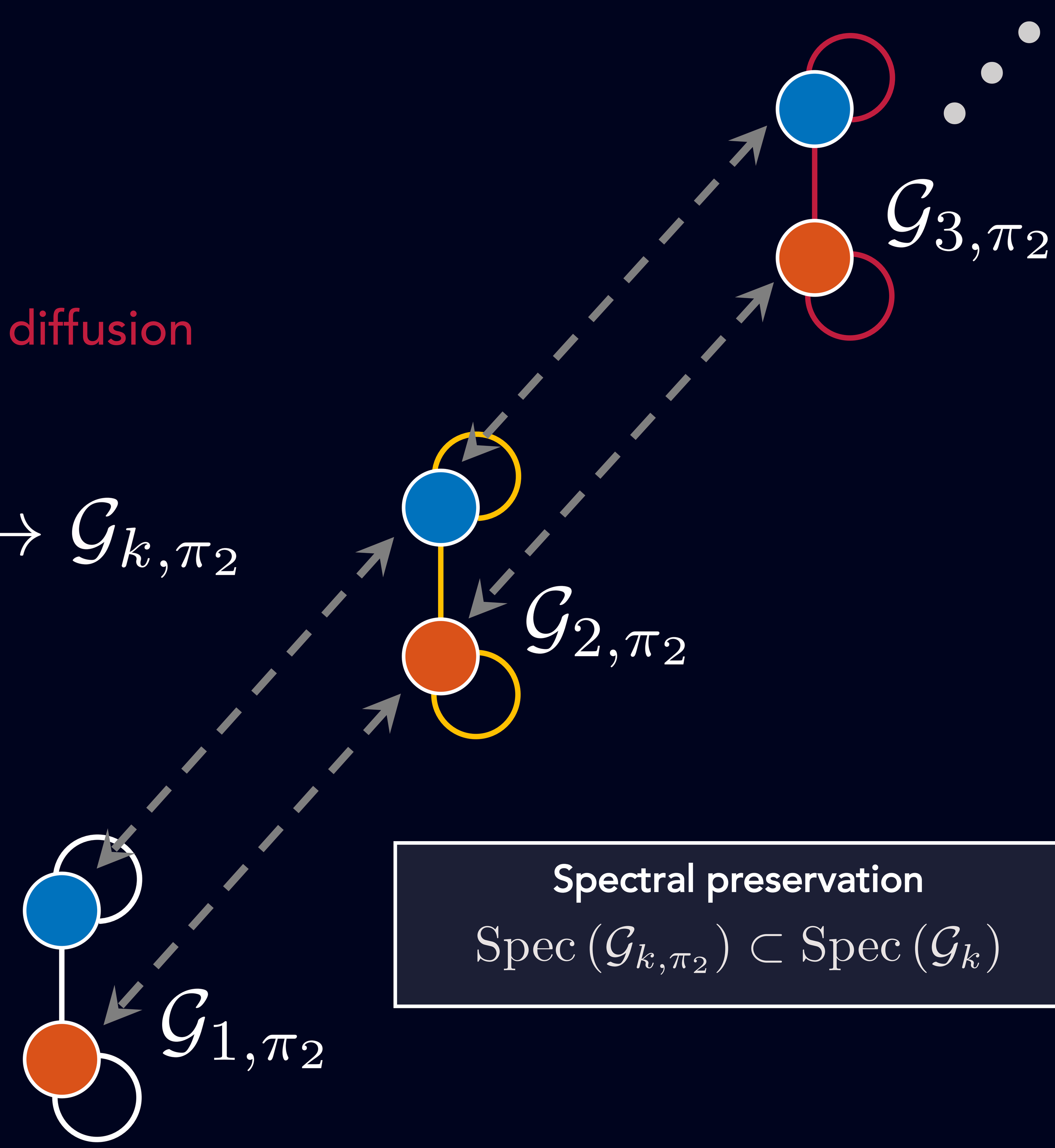


Multilayer networks for multiple channels of intercellular signaling



$$\pi_2 : \mathcal{G}_k \to \mathcal{G}_{k,\pi_2}$$

Quotient networks for laminar pattern templating



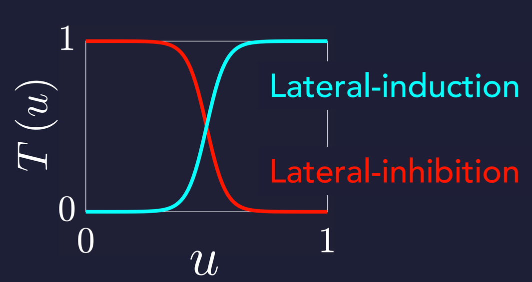
Spectral preservation

$$\mathrm{Spec}(\mathcal{G}_{k,\pi_2}) \subset \mathrm{Spec}(\mathcal{G}_k)$$

3 Monotone IO kinetics generate predictable patterns

A signal input/output (IO) interconnected dynamical system is said to be monotone if the signal transfer function $T : U \to Y$ is monotone.

Bounded and monotonic intercellular signals produce **convergent** and **non-oscillatory** intracellular dynamics that are highly dependent on cell-cell connectivity.



Laminar pattern existence

Spatially-driven homogenous steady state instability in the quotient system:

$$\prod_{i=1}^{r} (1 - \mu_i) < 0$$

$\mu_i \in \mathrm{Spec}(\boldsymbol{\Lambda}_{min} \partial_u \boldsymbol{T}(u^*))$

$\boldsymbol{\Lambda}_{min} = \mathrm{diag}(\min(\mathrm{Spec}(\mathcal{G}_{1,\pi_2})), \ldots, \min(\mathrm{Spec}(\mathcal{G}_{r,\pi_2})))$

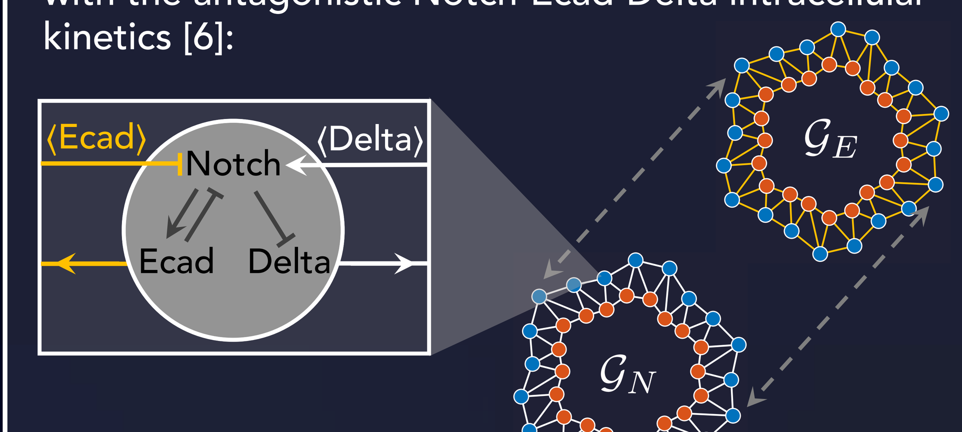
Global laminar pattern convergence

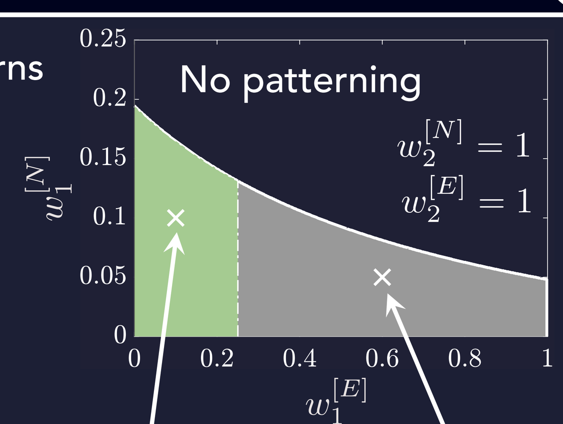
A sufficient condition for quotient patterns to be preserved in the large-scale system:

$$\min(\mathrm{Spec}(\mathcal{G}_{k,\pi_2})) = \min(\mathrm{Spec}(\mathcal{G}_k))$$

4 Notch-Ecad crosstalk laminar pattern analysis in bilayers

We study the polarity required for Notch laminar patterns with the antagonistic Notch-Ecad-Delta intracellular kinetics [6]:

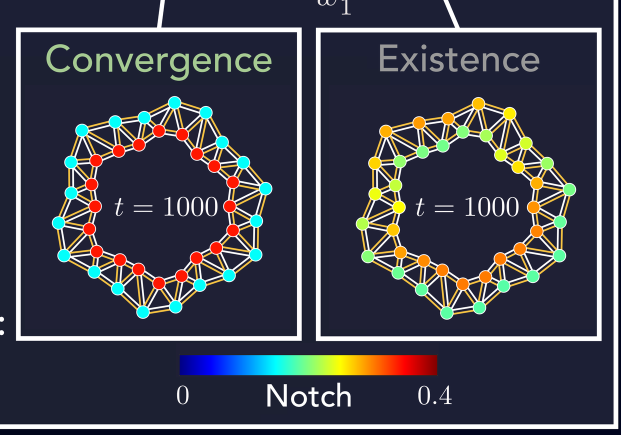




Analytical insights:

- Delta-Notch localisation on the basal-luminal interface initiates pattern existence;
- Ecad localisation is required for pattern convergence:

$$w_1^{[k]} < 4 w_2^{[k]} \quad (k \in \{N, E\})$$



Supported by

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Cronfa Gymdeithasol Ewrop European Social Fund

References