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3 Benjamin Pfeuty

4 *Univ. Lille, CNRS, UMR 8523 – PhLAM – Physique des Lasers Atomes et Molécules, F-59000 Lille, France*

Email address: benjamin.pfeuty@univ-lille.fr (Benjamin Pfeuty)

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9 **Abstract**

10 The Delta-Notch-Hes signaling pathway is involved in various developmental processes ranging from the
11 formation of somites to the dynamic fine-grained patterns of cell types in developing or regenerating tissues.
12 Such broad patterning capabilities rely in part in the versatile and tunable dynamics of the Notch-Hes
13 feedback circuit eliciting both pulsatile and switching behaviors. This raises the theoretical issue of which
14 specific spatiotemporal features emerges from lateral inhibition between cells that can display and transit
15 between steady, oscillatory and bistable regimes. To address this issue, we consider a discrete cell lattice
16 model where intracellular dynamics is described by a phase-like variable and displays a typical cross-shaped
17 phase diagram. Model analysis identifies how the existence and stability of many spatially-inhomogeneous
18 and temporally-synchronized patterns depends on key intracellular and intercellular parameters, which high-
19 lights an extensive multistability between those diverse spatiotemporal patterns as well as the existence of
20 multiple robust transition scenarios from temporal patterns to spatial patterns. Such broad repertoire and
21 multistability of spatiotemporal patterns is corroborated using a signaling network model of the Notch-Hes
22 pathway.

23 *Keywords:*

24 Multicellular development, Pattern formation, Oscillations, Cell-fate decision, Multistability

25 Introduction

26 The interplay between Notch-mediated intercellular communications and Notch-driven intracellular ac-
27 tivities is an important source of self-organized developmental patterns across metazoan tissues (Andersson
28 et al., 2011; Siebel and Lendahl, 2017; Henrique and Schweisguth, 2019; Boareto, 2020). The interaction
29 between Delta ligands and Notch receptors depends on many cell-specific features including the types and
30 the spatial distribution of ligands and receptors (Sprinzak et al., 2010; Shaya et al., 2017; Nandagopal et al.,
31 2018). In turn, Notch is prone to inhibit the production of Delta ligands through diverse indirect and direct
32 signaling mechanisms involving the Hes family of proteins (Kageyama et al., 2007; Sjöqvist and Andersson,
33 2019). Hes proteins does not only mediate Notch-dependent repression of Delta or fate-inducing proteins,
34 but its autorepression is a source of intracellular oscillations that is prone to occur prior fate commitment
35 in developing and regenerating tissues (Kageyama et al., 2007, 2018). Notch-Hes pathway also contributes
36 to cell-fate decision programs by antagonizing some fate-promoting factors and reciprocally (Roese-Koerner
37 et al., 2016; Wahi et al., 2016; Sagner et al., 2018). This specific ability of Notch signaling pathway to elicit
38 both oscillatory and switching activities is prone to give rise to diverse and complex spatiotemporal patterns
39 of cell fates within tissues (Biga et al., 2021; Uriu et al., 2021), whose repertorie has yet to be fully explored
40 and characterized.

41 From a modeling viewpoint, a primary patterning role of Delta-Notch intercellular coupling is to destabi-
42 lize homogeneous states and promote fine-grained patterning through a spatial symmetry-breaking process
43 triggered by the mutual inhibition between nearest-neighboring cells (Collier et al., 1996). This seminal
44 model has been further refined to illustrate how positive feedback, protrusions, signaling crosstalks or cell
45 division can modulate the relative stability or occurrence of diverse -periodic or aperiodic- spatial patterns
46 (Wearing et al., 2000; Hunter et al., 2016; Hadjivasiliou et al., 2016). In developmental contexts where
47 Notch-Hes signals contribute to cellular oscillations, various models, using a discrete or continuous descrip-
48 tion of tissues and using a phase-like or biochemical description of oscillators, have been used to capture
49 the emergence of patterns such as traveling waves (Murray et al., 2011, 2013; Jörg et al., 2015; Tomka
50 et al., 2018), antiphase synchrony (Lewis, 2003; Wang et al., 2011) or dynamic clusters (Biga et al., 2021).
51 However, a consistent theoretical framework is still lacking to study the coexistence and transition between
52 synchronized patterns of oscillatory cells and spatial patterns of bistable cells in various developmentals
53 contexts. This issue of dynamical routes toward tissue patterning has been nevertheless investigated for
54 some specific developmental contexts and modeling settings (Owen, 2002; Plahte and Øyehaug, 2007; Fujii-
55 moto et al., 2008; Koseska et al., 2010; Suzuki et al., 2011; Murray et al., 2011; Pfeuty and Kaneko, 2014;
56 Stanoev et al., 2021), including cell type-specific regulatory network models (Pfeuty, 2015; Keskin et al.,
57 2018; Tiedemann et al., 2017).

58 In this study, we develop a modeling framework that combines minimal modeling and signaling net-
59 work modeling in order to study developmental transitions between temporal to spatial patterns as those

60 driven by Notch-Hes pathway. First, we introduce an effective model of Notch-Hes intracellular dynamics
61 whose low-dimensional parameter and state spaces eases theoretical analysis of spatiotemporal dynamics
62 of cell population. Under some assumption about intercellular coupling and lattice topology, the stability
63 analysis of several archetypical classes of spatiotemporal patterns reveals the existence of signal-dependent
64 multistability between synchronization and inhomogeneous stationary states states. Biological implications
65 of multistable patterns are investigated at the level of developmental transition scenarios from temporal to
66 spatial patterns or by assessing the validity of the theoretical results in simulations of more realistic systems
67 biology models.

68 **Results**

69 *A minimal model of oscillatory-bistable cells coupled through lateral inhibition*

70 Previous models of the intracellular Notch-Hes pathway frequently display both oscillatory and bistable
71 behaviors depending on some key parameters (Agrawal et al., 2009; Goodfellow et al., 2014; Pfeuty, 2015),
72 typically organized as a typical cross-shaped phase diagram where the transition between oscillation to
73 bistability can occur through diverse codimension-2 bifurcation (Boissonade and De Kepper, 1980; Pfeuty
74 and Kaneko, 2009). To further simplify the description of single-cell dynamics featured with oscillation
75 and bistability, we propose an effective one-dimensional model adapted from the so-called *theta* model
76 whose dynamics is described by a single angular variable. Initially introduced as the canonical model for a
77 neuron which undergoes a saddle-node on invariant circle (SNIC) bifurcation as external current increases
78 (Ermentrout, 1996; Laing, 2016), the model can be slightly modified to describe a transition from oscillation
79 to bistability through a two-SNIC bifurcation:

$$\frac{d\theta}{dt} = 1 - \cos(2\theta) - S_D(1 + \cos(2\theta)) + S_N \cos(\theta) \equiv f(\theta, S_D, S_N) \quad (1)$$

80 The phase diagram exhibits monostable, bistable and oscillatory domains which are symmetrically organized
81 as function of S_D and S_N (Fig. 1A). The existence of and transition between these dynamical states are
82 easily explained by the manner how the 2π periodic velocity field changes with S_D and S_N (Fig. 1(B)). Of
83 note, the reduced form $\frac{d\theta}{dt} = 1 - \cos(2\theta)$ for $S_D = S_N = 0$ corresponds to the codimension-2 two-SNIC
84 bifurcation for the transition between oscillations and bistability.

85 In the context of Notch-driven developmental patterning, the phase of the angular variable represents
86 high/low value of Notch and Hes for $\theta \sim \pi/0$. While S_N represents Notch signaling cues, S_D represents
87 other signaling cues (such as FGF or retinoic acid) or epigenetic cues (such as Id), which are known to
88 interfere with intracellular oscillations and eventually promote stable cell-fate choice. The manner how S_N
89 of the receiver cell i depends on the state θ of the sender cells j must be also 2π -periodic and is chosen as
90 following:

$$S_N = S_{N0} + \gamma \cos(\theta_j(t - \tau_j)), \quad (2)$$

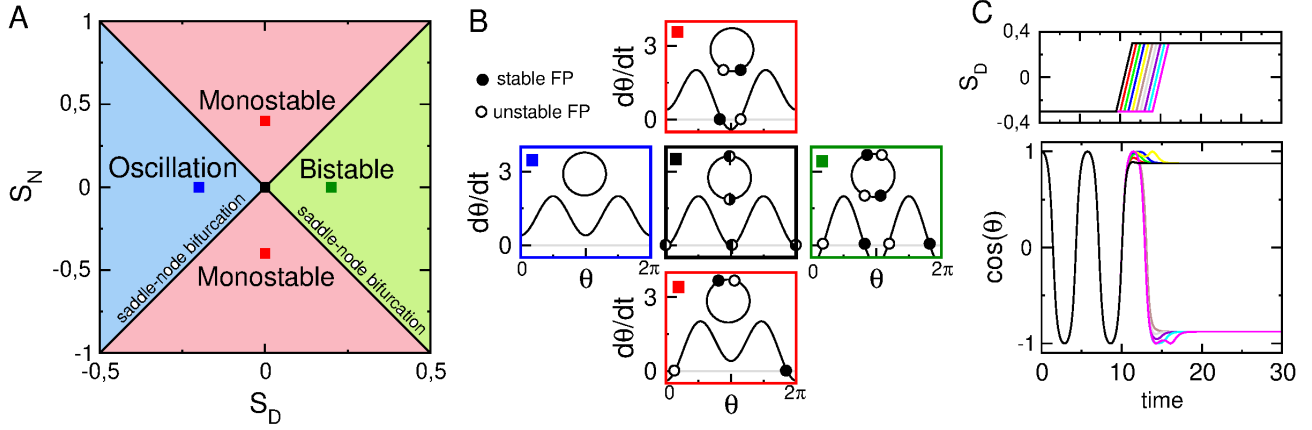


Figure 1: **A low-dimensional model of oscillatory/bistable single-cell dynamics** (A) Phase diagram in the signal parameter space S_D and S_N . (B) Vector fields associated with the regime of oscillations (left), bistability (right), monostability (up and down) and the co-dimension 2 saddle-node bifurcation (center). (C) Signal-driven transition from a single-cell oscillations to distinct steady states depending on signal timing

91 to implement the lateral inhibition property: the coupling term $\gamma \cos(\theta_i) \cos(\theta_j)$ becomes negative and
 92 stabilizing for different cell states ($\theta_j = \theta_i + \pi$), and positive and destabilizing for same cell states ($\theta_j = \theta_i$).
 93 The delay τ represents the signaling delays associated to this lateral inhibition.

94 The population system can thus be written without loss of generality as

$$\frac{d\theta_i}{dt} = f(\theta_i, S_D, S_{N0}) + \Gamma/N \cos(\theta_i) \sum_{j=1, N} J_{ij} \cos(\theta_j(t - \tau)). \quad (3)$$

95 To account for the juxtacrine communication of Delta-Notch, we consider a coupling matrix $J_{ij} = 1$ for
 96 the nearest-neighbor cells and zero otherwise. The global coupling strength $\Gamma = N\gamma$ with a number of
 97 neighboring cells of $N = 2$ for 1D array, $N = 8$ for a square lattice or $N = 6$ for an hexagonal lattice.

98 *Multistability between synchronization states and inhomogeneous steady states*

99 A comprehensive analysis of the spatiotemporal patterning in the cell population model (Eq. (3)) is
 100 made possible by the relatively low number of control parameters (Fig. 2(A)). The property of intercellular
 101 coupling is monitored at the level of the coupling strength Γ and delay τ . In addition, the symmetric phase
 102 diagram as function of the two parameters S_D and S_N (Fig. 1(A)) provides also the possibility to study
 103 how spatiotemporal patterning depends on qualitative change in single-cell dynamics through continuous
 104 parameter changes. To further simplify the analysis, we consider a ring lattice topology with homogeneous
 105 signaling ($S_{D,i} = S_D$ and $S_{N0,i} = S_{N0} = 0$), which left us with S_D , Γ and τ as the main control parameters
 106 (Fig. 2(A,B)).

107 A basic class of non-stationary pattern are phase-locked synchronization states (PSS) where neighboring
 108 oscillatory cells displays a constant phase shift ψ or time shift $\Delta = \psi \frac{T}{2\pi}$. $\Delta = 0$ and $T/2$ correspond to
 109 in-phase and anti-phase synchronized states while other values can be seen as uniform traveling (or rotating)
 110 waves. With a one-dimensional ring topology, the phase-locked condition reads $\theta_{i+1}(t) = \theta_i(t + \Delta)$ which

111 can be replaced in Eq. (3) to obtain:

$$\frac{d\theta_i}{dt} = f(\theta, S_D, 0) + \Gamma \cos(\theta_i) [\cos(\theta_i(t - \tau - \Delta)) + \cos(\theta_i(t - \tau + \Delta))] / 2. \quad (4)$$

112 Defining the T -periodic delay function $H_u(\theta(t)) = \theta(t) - \theta(t - u)$ (that satisfies $H_0 = 0$ or $H_{u+v} = H_u + H_v$),
 113 trigonometric relations can then be used to obtain:

$$\frac{d\theta_i}{dt} = f(\theta_i, S_D, 0) + \Gamma \cos(\theta_i) \cos(H_\tau(\theta_i)) (\cos(\theta_i) \cos(H_\Delta) + \sin(\theta_i) \sin(H_\Delta)). \quad (5)$$

114 In the particular cases of in-phase synchronized solution with no coupling delay ($\Delta = \tau = 0$) and anti-phase
 115 synchronized solution with half-period delay ($\tau_\Delta = \tau = T/2$), Eq.(5) reduces to $\dot{\theta} = f(\theta, S_D - \Gamma/2, 0)$ for
 116 which a periodic solution exists only for $S_D < \Gamma/2$ (Fig. 1(A)) defining a maximal bound for the existence
 117 of PSS (Fig. 2(B)).

118 Stability analysis of phase-locked solutions $\theta_{i+1}(t) = \theta_i(t + \Delta)$ of identical oscillators could be done by
 119 linearizing around the periodic solution manifold and compute Floquet multipliers or exponents. We use
 120 a more heuristic approach that is to simulate the response of the full system to small spatially-periodic
 121 transverse perturbation $\delta\theta$ ($\delta\theta_i(0) = -\delta\theta_{i+1}(0) = \delta\theta_{i+2}(0)$) and evaluate whether such perturbation is
 122 relaxed or amplified after one period. Phase diagram shows that relative stability of different phase-locked
 123 solutions (e.g., $\Delta = 0, T/2$ and $T/25$) essentially depends on coupling delays such that phase multistability
 124 can naturally occur for some values of coupling strength and delays (Fig. 2(B)). Besides synchronization
 125 states, incoherent state attractors are also observed (lower left panel of Fig. 2(C)) but are beyond the scope
 126 of this study.

127 This system also displays stationary spatial patterns such as spatially periodic patterns in which cells
 128 settle in two states $\theta_{i=1,2}$ with a fixed proportion $k_{i=1,2}$ (i.e., order parameters) of neighbors in different
 129 states. In case of a square lattice, $k_{1,2} = 0.75$ for a 1-cell stripe pattern, $k_{1,2} = 0.5$ for a 1-cell or 2-cell
 130 checkerboard pattern, $k_{1,2} = \{0.125, 1\}$ for the spot/gap pattern and $k_{1,2} = \{0.375, 0.75\}$ for the 2-cell/1-cell
 131 stripe pattern. In case of a hexagonal lattice, $k_{1,2} = 2/3$ for a 1-cell stripe pattern and $k_{1,2} = \{1/3, 1\}$ for
 132 the spot/gap pattern. For a one-dimensional lattice, $k_{1,2} = 1$ for the 1-cell stripe pattern. For any of these
 133 patterns, steady-state solution of Eq. (3) can be casted into two equations associated to $d\theta_{1/2}/dt = 0$ as,

$$F(\theta_{1/2}, S_D, S_{N0}) + \Gamma \cos(\theta_{1/2}) ((1 - k_{1/2}) \cos(\theta_{1/2}) + k_{1/2} \cos(\theta_{2/1})) = 0. \quad (6)$$

A particular steady-state solution corresponds to a saddle-node instability for each cell type, which coincides
 with the appearance or disappearance of an inhomogeneous stationary state. Such instability necessarily
 occurs for $\theta_1 = 0$ and $\theta_2 = \pi$ which are replaced in Eq. (6) to finally obtain a set of relation between $k_{1/2}$,

Γ and $S_{D/N0}$ as:

$$-2(S_D - \Gamma(1 - k_1)/2) - \Gamma k_1 + S_{N0} = 0 \quad (7a)$$

$$-2(S_D - \Gamma(1 - k_2)/2) - \Gamma k_2 - S_{N0} = 0 \quad (7b)$$

Summing these equations cancels out S_{N0} to finally derive the critical coupling strength for which the inhomogeneous state is destabilized:

$$\Gamma = \frac{2S_D}{1 - k_1 - k_2} \equiv \Gamma_c \quad (8a)$$

$$S_D = \frac{\Gamma}{2}(1 - k_1 - k_2)/2. \quad (8b)$$

134 The above condition for saddle-node instability boundary thus delimits the stability domain of an inhomogeneous steady state (ISS) defined by the order parameter $k_1 + k_2$. On the one hand, spatial patterns for which neighboring cells are in average more similar than different ($k_1 + k_2 < 1$) are destabilized above some inhibitory coupling strength $\Gamma > \Gamma_c > 0$ when cells are bistable $S_D > 0$, such as the fully homogeneous state ($k_{1/2} = 0$) destabilized for $\Gamma > 2S_D$ (Fig. 2(B)). On the other hand, spatial patterns for which neighboring cells are in average more different than similar (i.e., $k_1 + k_2 > 1$) are always stable for $S_D > 0$ ($\Gamma_c < 0$) and are stabilized above some inhibitory coupling strength $\Gamma > \Gamma_c = \frac{2S_D}{1 - k_1 - k_2}$ for oscillatory cells ($S_D < 0$), supporting a scenario of oscillation amplitude death. Numerical simulations show that lateral inhibition can stabilize non-periodic spatial patterns for which neighboring cells are more different than similar, such as labyrinthin pattern for which $k_i = 5/8$ or $6/8$ (lower right panel of Fig. 2(C)).

144 These stability properties of phase-locked synchronized states (PSS) and inhomogeneous steady states (ISS) reveal two key complementary features of the spatiotemporal dynamics of oscillatory/bistable cells coupled through delayed inhibition between nearest neighbors. Lateral inhibitory coupling stabilizes ISS even when uncoupled cells oscillate and PSS even when uncoupled cells are in steady states. As a result, the multicellular system exhibits a robust multistability between PSS and ISS especially when uncoupled cells are operating close enough to the transition between oscillation and bistability (i.e., $|S_D| < \Gamma$). Accordingly, multiple stationary or non-stationary attractors can coexist such as those satisfying spatial periodicity $\theta_{i+2}(t) = \theta_i(t)$ (Fig. 2(D)), such that attractor selection would depend on the initial conditions. It is important to note that this extensive multistability property does not occur for negative value of Γ and is therefore mediated by the lateral inhibitory coupling.

154 *Pattern selection through transition from temporal to spatial patterns*

155 The class of biological phenomena that motivates the present theoretical study concerns the developmental transition whereby a given population of oscillatory cells gives rise to two subpopulations of well-distinct cell states. In particular, a pending question is the ability of Notch pathways to underlie very diverse

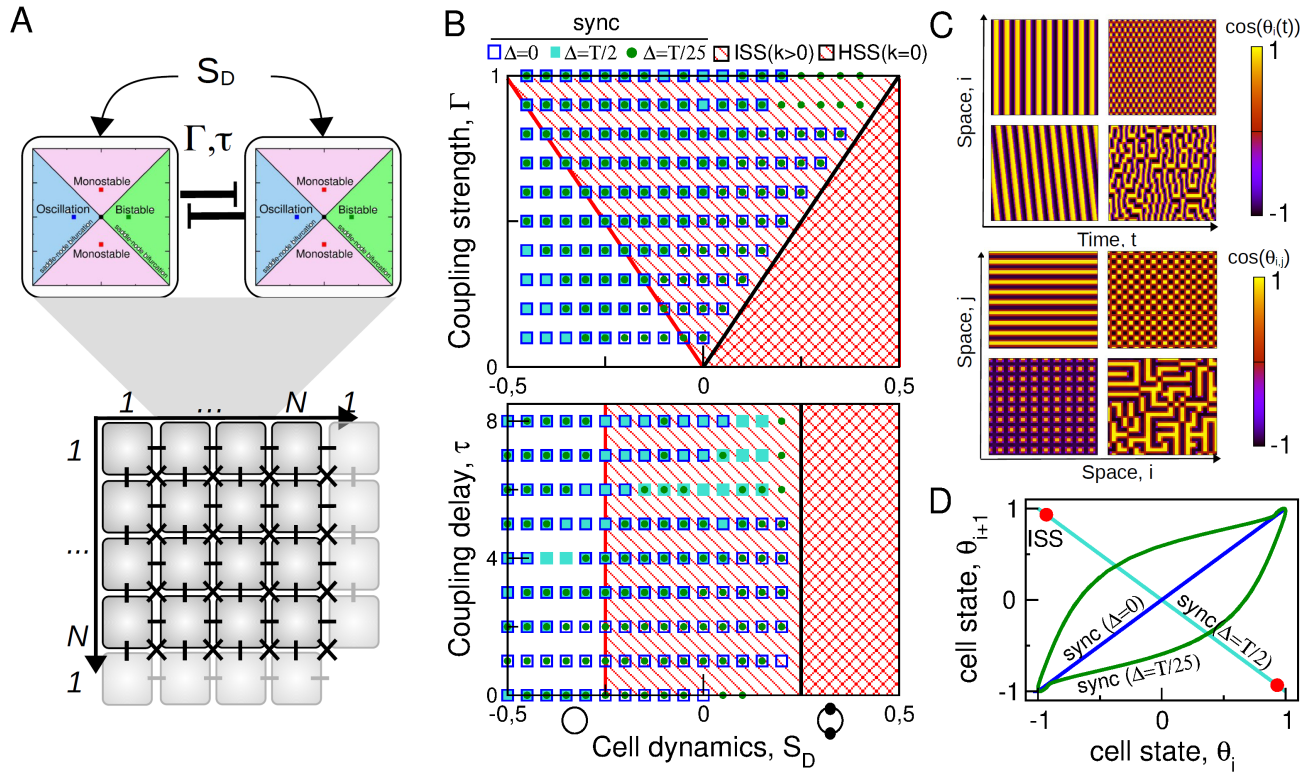


Figure 2: **Spatiotemporal dynamics of inhibitory-coupled oscillatory/bistable cells.** (A) Cell population model organized as a 1D or 2D periodic lattice with first-neighbor inhibitory coupling. (B) Stability domains of typical phase-locked synchronization states and spatial stationary states as function of S_D and Γ (top: $\tau = 3$), and as function of S_D and τ (bottom: $\Gamma = 0.5$). (C) Example of stable temporal patterns for a 1D lattice with $\Gamma = 0.5$, $\tau = 3$ and $S_D = 0$ (up panels) and of stable spatial patterns for a 2D lattice with $\Gamma = 0.5$ and $S_D = 0$ (Down panels). (D) Example of multistability between phase-locked synchronization states (PSS) and inhomogeneous spatial states (ISS) in the 1D lattice plotted in the phase plane $\{\theta_i, \theta_{i+1}\}$ for $S_D = -0.1$, $\Gamma = 0.5$ and $\tau = 3$.

158 symmetry-breaking scenarios from temporal to spatial patterns, involving stripe patterns as during somito-
 159 genesis or salt-and-pepper patterns as during neurogenesis. This issue is addressed in the population model
 160 (Eq. (3)) by simulating the spatiotemporal dynamics in response to a temporal increase S_D corresponding
 161 to a slow developmental change of signaling or epigenetic cues. According to the repertoire and stability
 162 domains of states identified in Fig. 2, the population can be prepared and settled for $S_D(t = 0) = S_{D1} < 0$
 163 into diverse spatiotemporal states such as in-phase synchronization, traveling waves and antiphase synchrono-
 164 zation (Fig. 3). By stabilizing these states, intercellular coupling provides robustness to diverse sources
 165 of noise, here in the initial conditions and in the signal dynamics $S_D(t)$. Following an increase of S_D , each
 166 temporal pattern gives rise to a specific stationary pattern depending on the spatial pattern at the time of
 167 the differentiation signal increase and the profile of such increase. First, a synchronous oscillatory pattern
 168 translates into a homogeneous stationary pattern as far as $S_{D2} > \Gamma/2$ (Fig. 3(A)). Second, a traveling wave
 169 pattern translates into a regular stripes (Fig. 3(B)) produces stripes of tunable size as far as $S_D(t = t_f)$
 170 is sufficiently high to stabilize these stripe patterns. Last, an antisynchronous pattern translates into an
 171 inhomogeneous stationary pattern stripe pattern of one-cell width in 1D (Fig. 3(C)). In these transition
 172 processes, the role of lateral inhibition in stabilizing phase shifts between neighboring cells is very effec-

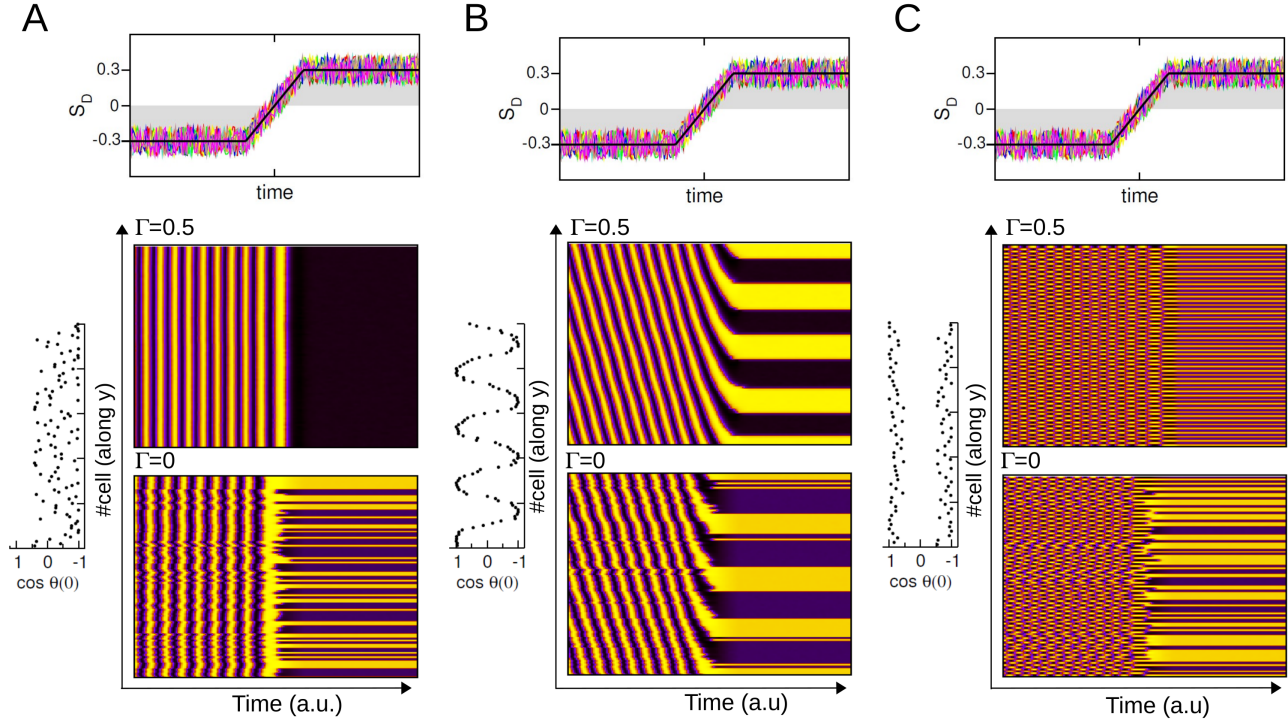


Figure 3: **Robust and tunable transition routes from temporal to spatial patterns.** Transient spatiotemporal dynamics from a noisy initial spatial pattern $\theta_i(0)$ for $S_D(t) < 0$ (left panels of A-C) and driven by a noisy temporal pattern $S_D(t) = S_{D1} + (S_{D2} - S_{D1})\mathcal{H}(t) + \zeta(t)$ where $S_{D1} = -0.3$ and $S_{D2} = 0.2$ (uppest panel of A-C). The spatiotemporal dynamics $\cos(\theta_i(t))$ is compared with and without coupling ($\Gamma = 0.5$ for the upper-right panel and $\Gamma = 0$ for the lower-right panel). (A) From a noisy initial conditions, lateral inhibition promotes a robust transition from synchronous oscillations to an homogeneous spatial pattern. (B) From a noisy and spatially-periodic initial conditions, lateral inhibition promotes a robust transition from a traveling wave pattern to a regular stripe pattern. (C) From noisy checkerboard noisy initial conditions, lateral inhibition promotes a robust transition from antisynchronous oscillations to a checkerboard spatial patterns.

173 tive to obtain regular and defect-free spatial patterns (compare dynamics with and without coupling in
 174 Fig. 3(A,B,C)).

175 *Multistable spatiotemporal patterns in a systems biology model of Delta-Notch-Hes circuit*

To assess the biological relevance of results obtained with effective low-dimensional intracellular dynamics, we develop a systems biology model of Delta-Notch-Hes pathways whose feedback architecture enables a cross-shaped diagram similar to Fig.1(A). Previous single-cell models have first focused on the core autorepression of Hes1 protein (Lewis, 2003) before to incorporate additional set of factors mutually interacting with Notch or Hes, such as Rbpj (Agrawal et al., 2009), miR9 (Goodfellow et al., 2014), Cyclins-Cdks (Pfeuty, 2015) or Neurog (Tiedemann et al., 2017). Such interlocking between a core negative feedback mediated by Hes autorepression, and positive feedback mediated by mutual inhibition between Notch or Hes and other cell fate-specific factors is indeed a common feature in various tissues and cell types (Fig. 4(A)). For instance, members of Hes family proteins mutually antagonize with transcription factors including miR9 or Ascl1 in neural progenitors (Roese-Koerner et al., 2016; Vasconcelos et al., 2016), Olig2 in motoneuron progenitors (Sagner et al., 2018), Neurog3 in multipotent pancreatic progenitor cells (Ahnfelt-Rønne et al., 2012), Myod in myoblast (Lahmann et al., 2019) and Lfng or Mesp2 in presomitic stem cells (Wahi et al.,

2016). Although the detailed set of regulatory mechanisms can differ depending on cell type, we can nevertheless develop a generic model where Notch, Hes and Delta concentration variables are supplemented with an antagonistic factor, named Y (Fig. 4(B)), based on the model of Delta-Notch-Hes-miR9 circuit developed in (Pfeuty, 2015):

$$\tau_N \frac{dN}{dt} = \frac{S_N}{1 + \mathbf{S}_N + k_{YN}Y^2} - N \quad (9a)$$

$$\tau_{H_m} \frac{dH_m}{dt} = \frac{k_{NH}N^2}{1 + k_{HH}(1 + k_{FH}S_{Dif})H(t - \tau_1)^n + k_{NH}Y^2} - H_m \quad (9b)$$

$$\tau_H \frac{dH}{dt} = H_m(t - \tau_2) - d_H H \quad (9c)$$

$$\tau_Y \frac{dY}{dt} = \frac{1}{1 + k_{FY}S_{Dif}^2 + k_{HY}H^2} - Y \quad (9d)$$

$$\tau_D \frac{dD}{dt} = \frac{1}{1 + k_{HD}H^2} - D \quad (9e)$$

$$S_{N,i} = S_{N0,i} + \gamma \sum_j D_j(t - \tau) \quad (9f)$$

176 where N represents Notch activity, H_m and H represent concentrations of Hes mRNA and proteins, D
 177 represents Delta ligand and Y represents a fate-specific factor antagonizing with Notch and/or Hes proteins.
 178 Regarding signaling cues, S_N represents the extracellular juxtacrine signals associated with Delta-dependent
 179 activation of Notch receptor while S_{Dif} represents an extracellular morphogenetic fields associated with
 180 relative concentrations of extracellular signals (such as FGF and RA) assumed to promote expression of Y
 181 and inhibiting autorepression of H .

182 Degradation and time-delay parameters of the model (τ_i) are set with agreement with experimental
 183 measurements and the approximate 2-hour period of Hes oscillation (Pfeuty, 2015). In the case where
 184 the species Y is weakly expressed associated to S_{Dif} low (e.g., low RA and high FGF), the Notch-Hes
 185 regulatory module displays oscillations for intermediate Notch signal S_N . In the case where the species
 186 Y is highly expressed associated to S_{Dif} high (e.g., high RA and low FGF), the concomittant decrease
 187 of Hes autorepression leads to a robust bistability due to mutual inhibition between Notch-Hes and Y .
 188 Given these two archetypical oscillation and bistable behaviors obtained for low and high S_{Dif} level, the
 189 parameters for mutual inhibition between Hes and Y are then adjusted to obtain a phase diagram similar
 190 with the low-dimensional model for the sake of comparison (Fig. 4(C) as compared to Figure 1(A)). Although
 191 biochemical and low-dimensional models share a similar cross-shaped phase diagram, it is to mention that
 192 the detailed model shows a more complex bifurcation scenario where the transition between oscillation and
 193 bistability occurs typically through a concomittant Hopf and saddle-node bifurcation (instead of a two-
 194 SNIC bifurcation). These fine-grained dissimilarities do not impact the coarse-grained transition behavior
 195 whereby increase of S_{Dif} leads to a cellular transition from an oscillatory state toward diverging steady states
 196 depending on the relative timing between signal course and oscillatory phase (Figure 4(D) as compared to

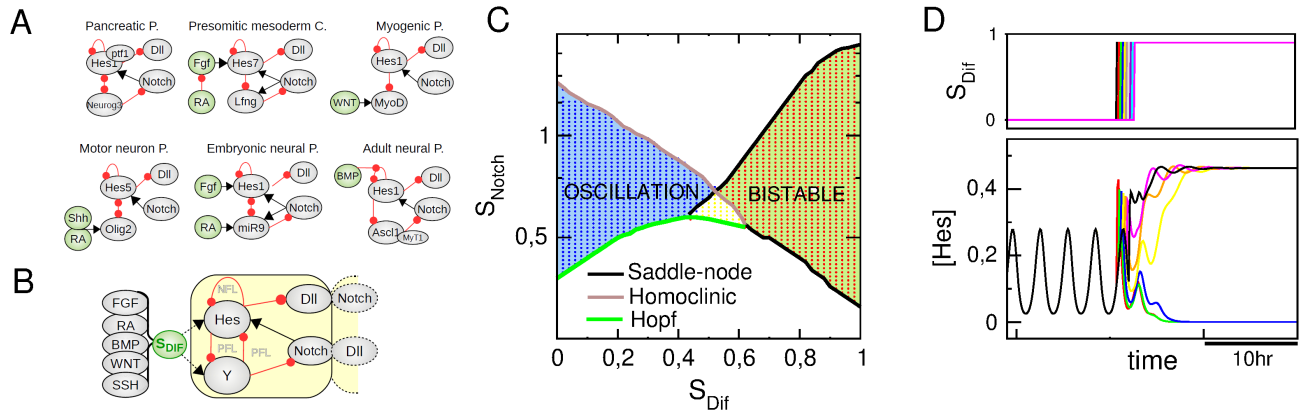


Figure 4: **Oscillation and bistability in a systems-biology model of Notch-Hes signaling.** (A) Feedback regulatory circuits involved in Notch/Hes-driven fate decision in various tissue-specific cell types. (B) Schematic network model of the Notch-Hes-Delta circuit based on the common features of cell type-specific circuits in (A). (C) Phase diagram with a transition from oscillation to bistability obtained for the following parameter set: $d_N = 1$, $d_H = d_Y = 2$, $d_{mH} = 10$, $k_{NH} = 10$, $k_{HY} = 17$, $k_{YH} = 7$, $k_{YN} = 7$, $k_{FY} = 0.25$; $\tau_{1,2} = 0.5h$. (D) Example of a transition from single-cell oscillations to distinct steady states as function of the timing of S_{Dif} increase.

197 Figure 1(C)).

198 To address again the spatiotemporal dynamics of oscillatory/bistable cells coupled through Delta-Notch,
 199 we consider a periodic 1D lattice with homogeneous signaling field, in order to define the same setting used
 200 for the theoretical analysis of the simple model (Fig.5(A)). Multistability between diverse spatiotemporal
 201 patterns are investigated through adiabatic increase of S_{Dif} starting from stable inphase or antiphase syn-
 202 chronization states for small S_{Dif} values and through adiabatic decrease of S_{Dif} starting from a typical
 203 inhomogeneous stationary states of 1-cell period (Fig.5(B)) Simulation shows that Delta-Notch intercellular
 204 communications can stabilize (i) inhomogeneous steady states (ISS) even for cells oscillating without cou-
 205 pling ($S_{Dif} < 0.5$) and (ii) phase-locked synchronized states (PSS), both synchronous and antisynchronous
 206 depending on coupling delay, even for stationary cells without coupling ($S_{Dif} > 0.5$), indicating a robust
 207 multistability between PSS and ISS. for intermediate differentiation signals. Such extensive multistability
 208 between stationary and nonstationary patterns is exemplified for some intermediate value of coupling delay
 209 $\tau = 0.5$ showing the phase-plane attractors associated with inhomogeneous stationary state and phase-locked
 210 synchronization states of various phase shifts (Fig4(C,D)).

211 Discussion

212 The present modeling study investigates the transition properties between temporally-synchronized and
 213 spatially-inhomogeneous patterns driven by the Delta-Notch-Hes signaling axis. To address this issue, we
 214 introduced a particular class of discrete cell lattice model where single-cell dynamical repertoire comprises
 215 both autonomous oscillatory and switching behaviors. The model could recapitulate a wide spectrum of
 216 spatiotemporal behaviors that has been reported over last decades using distinct classes of theoretical models
 217 of lateral inhibition. Lateral inhibition itself is a notorious mechanism to generate diverse, and eventually

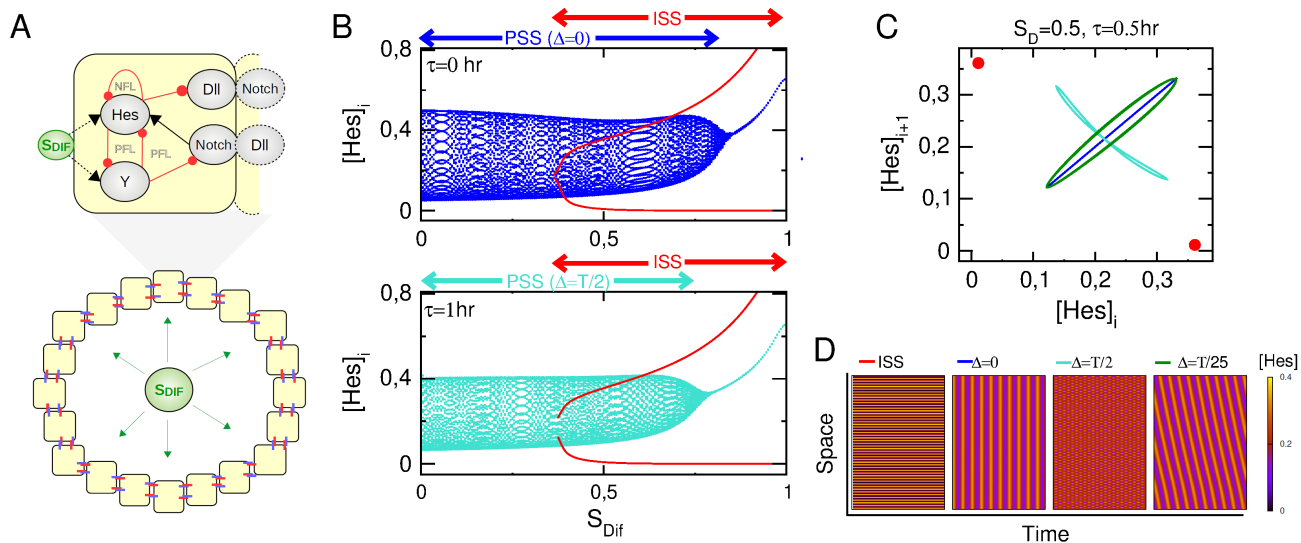


Figure 5: **Multistability between temporally-synchronized and spatially-inhomogeneous states mediated through Delta-Notch-Hes intercellular/intracellular signaling.** (A) One-dimensional ring lattice of Delta-Notch coupled cells. (B) Stability diagram of in-phase (up/blue) or anti-phase (down/turquoise) synchronization state and inhomogeneous stationary state (red) as function of S_{Dif} where $S_{N0,i} = 0.2$, $\Gamma = 1$ and $\tau = 0$ or $1h$ (i.e., $T/2$). (C) Multistability and coexistence of multiple archetypical (i.e., 2-cell periodic) attractors represented in a relevant section of the state space. Parameters are $S_{N0,i} = 0.2$, $S_{Dif} = 0.5$, $\Gamma = 1$ and $\tau = 0.5h$. (D) Space-time representation of attractors in (C).

218 multistable, inhomogeneous fine-grained patterns (Collier et al., 1996; Owen et al., 2000; Hadjivasiliou et al.,
 219 2016; Hunter et al., 2016), but can also give rise to diverse coherent and synchronization states through time-
 220 delayed juxtacrine coupling between oscillatory cells (Lewis, 2003; Morelli et al., 2009; Murray et al., 2011;
 221 Wang et al., 2011; Jörg et al., 2015; Tomka et al., 2018). Furthermore, repulsive coupling between synthetic
 222 oscillators has been shown to generate a wide range of collective regimes including synchronization states and
 223 inhomogeneous stationary states (Ullner et al., 2008; Koseska et al., 2010). By capturing those very diverse
 224 collective behaviors as function of a very few parameters (τ , S_D , S_{N0} , Γ), the proposed low-dimensional
 225 model proves well-suited to qualitatively study a wide range of developmental processes based on versatile
 226 single-cell dynamics, in support or in parallel to more detailed signaling network models.

227 The extensive multistability reported in the present study builds on several mechanisms and has some
 228 implications, notably for pattern selection in different contexts or between functional and spurious ones
 229 (Morelli et al., 2009; Palau-Ortin et al., 2015; Pfeuty and Kaneko, 2016; Uriu et al., 2021). Multistationarity
 230 between spatial patterns typically arise from the combination of intrinsic bistability of cells and the in-
 231 tercellular positive feedback through Delta/Notch-mediated lateral inhibition (Collier et al., 1996; Wearing
 232 et al., 2000). Multistability between synchronization states is also frequently observed in coupled oscillator
 233 systems (Crowley and Epstein, 1989; Morelli et al., 2009; Williams et al., 2013). Less common is the here-
 234 characterized multistability between diverse temporally-synchronized and spatially-inhomogeneous states,
 235 which entails the existence of many transition paths from a particular temporal pattern to a particular
 236 spatial pattern. In addition, signal-driven transition from a stable spatiotemporal pattern toward a given
 237 spatial pattern can operate as a both robust and flexible canalization process to the desired multicellular

238 outcome. This mechanism is complementary to pattern selection and fine-tuning mechanisms mediated
239 by the developmental modulation of Delta-Notch interactions and/or Notch-Delta intracellular signaling
240 (Formosa-Jordan and Ibañes, 2014; Palau-Ortin et al., 2015; Boareto et al., 2015; Sato et al., 2016; Luna-
241 Escalante et al., 2018). This issue of pattern selection is illustrated by the differences observed during
242 neurogenesis and somitogenesis where a similar circuit gives rise either to dynamic salt-and-pepper patterns
243 or traveling waves (Liao and Oates, 2017; Kageyama et al., 2018). It is possible that the desynchronizing
244 action of asymmetric division in the neurogenic case and the synchronizing action of Wnt and Fringe in the
245 somitogenic case could explain diverging spatiotemporal trajectories and outcomes. Another set of differ-
246 ential constraints would relate to the existence of pre-existing boundaries, axis and gradients, for instance
247 related to the layered structure of the developing neural systems or the antero-posterior axis in the somites.
248 In any case, the effective phase-like model could easily incorporate additional constraints at the levels of
249 intercellular coupling or tissue topology to investigate more specific developmental dynamics and reveals
250 how a similar signaling circuitry could give rise to such diversity of developmental patterning processes.

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