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# Multistability and transitions between spatiotemporal patterns through versatile Notch-Hes signaling

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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

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## 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; Fuji-  
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  $2\pi$  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  $\theta$  of the sender cells  $j$  must be also  $2\pi$ -periodic and is chosen as  
90 following:

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

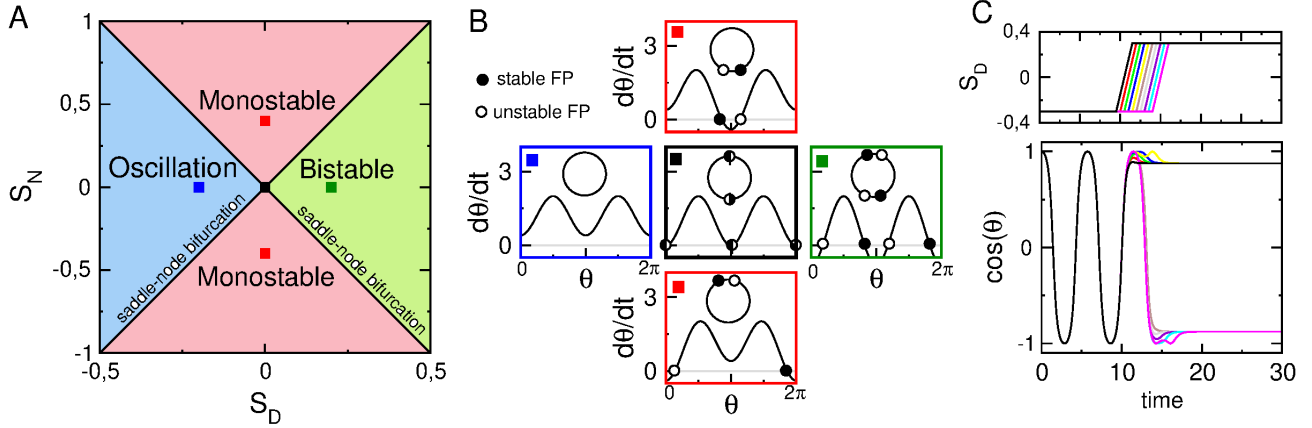


Figure 1: **A low-dimensional model of oscillatory/bistable single-cell dynamics** (A) Phase diagram in the signal parameter space  $S_D$  and  $S_N$ . (B) Vector fields associated with the regime of oscillations (left), bistability (right), monostability (up and down) and the co-dimension 2 saddle-node 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  $\tau$  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  $\Gamma$  and delay  $\tau$ . 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  $S_D$ ,  $\Gamma$  and  $\tau$  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  $\psi$  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  $k_{1/2}$ ,

$\Gamma$  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  $\Gamma$  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



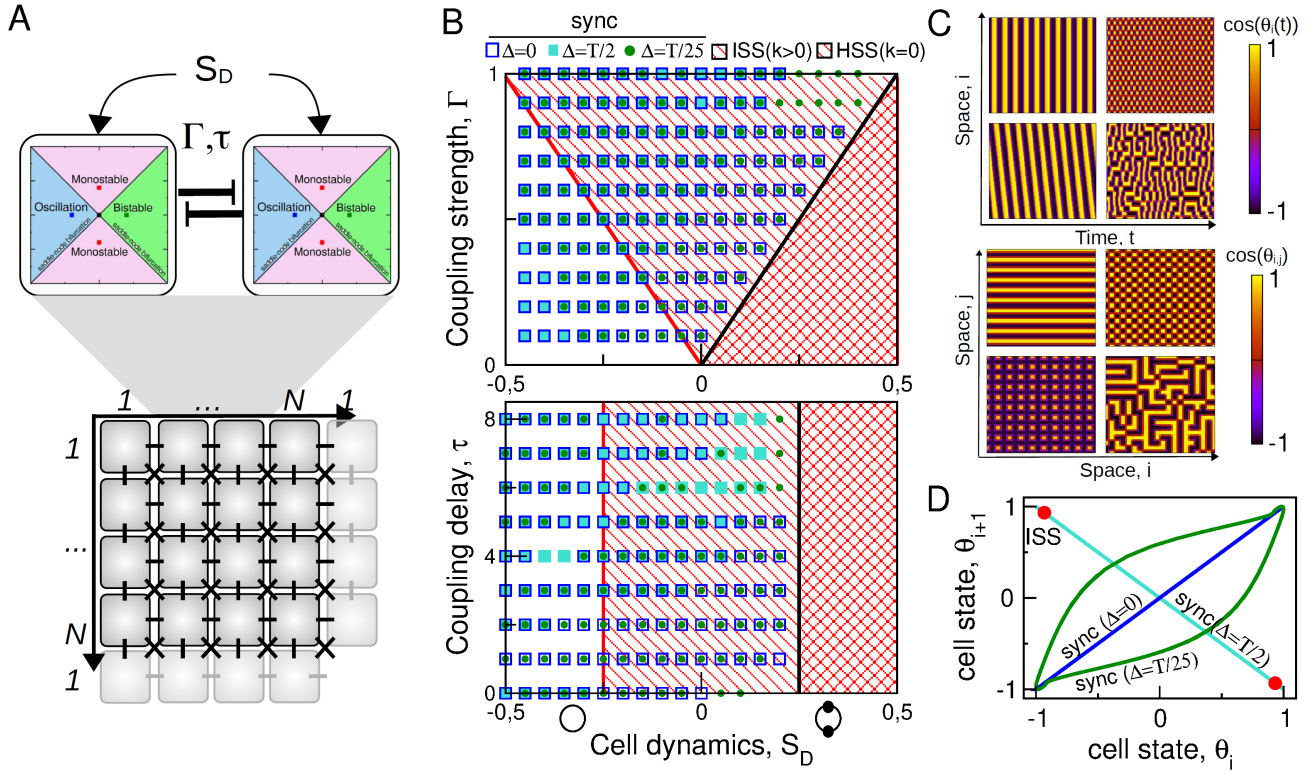


Figure 2: **Spatiotemporal dynamics of inhibitory-coupled oscillatory/bistable cells.** (A) Cell population model organized as a 1D or 2D periodic lattice with first-neighbor inhibitory coupling. (B) Stability domains of typical phase-locked synchronization states and spatial stationary states as function of  $S_D$  and  $\Gamma$  (top:  $\tau = 3$ ), and as function of  $S_D$  and  $\tau$  (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-

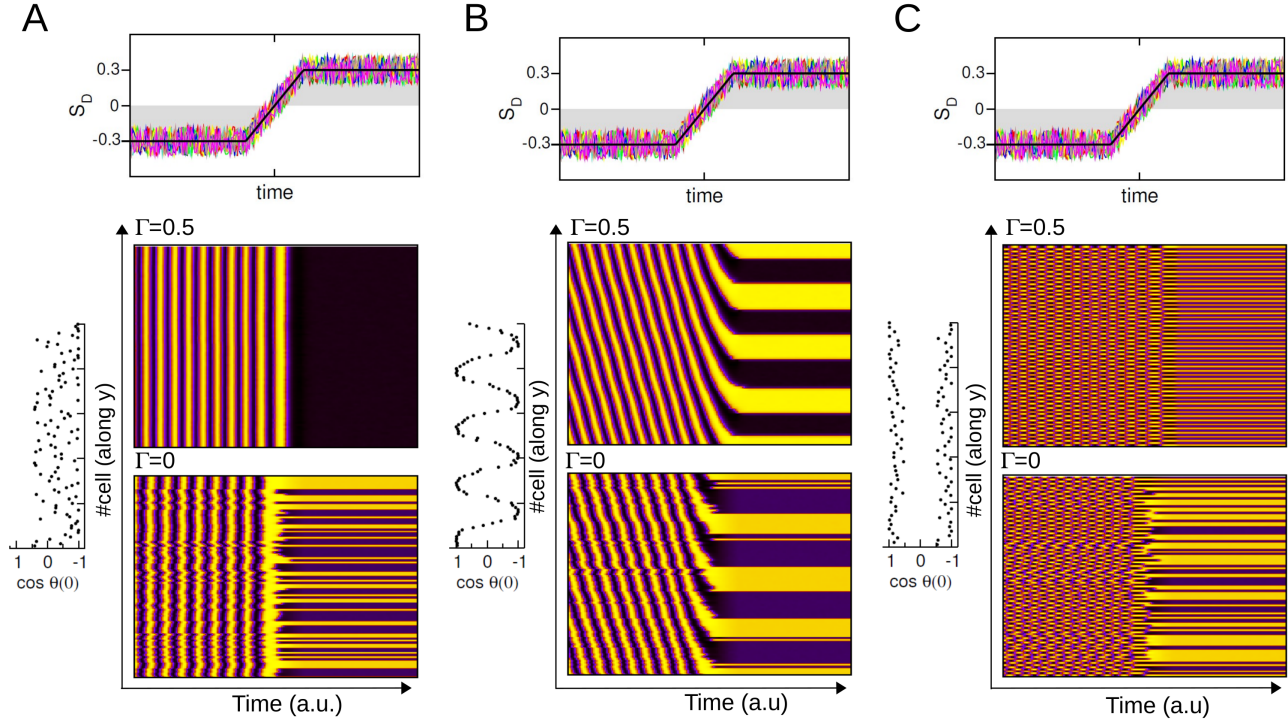


Figure 3: **Robust and tunable transition routes from temporal to spatial patterns.** Transient spatiotemporal dynamics from a noisy initial spatial pattern  $\theta_i(0)$  for  $S_D(t) < 0$  (left panels of A-C) and driven by a noisy temporal pattern  $S_D(t) = S_{D1} + (S_{D2} - S_{D1})\mathcal{H}(t) + \zeta(t)$  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 ( $\tau_i$ ) 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

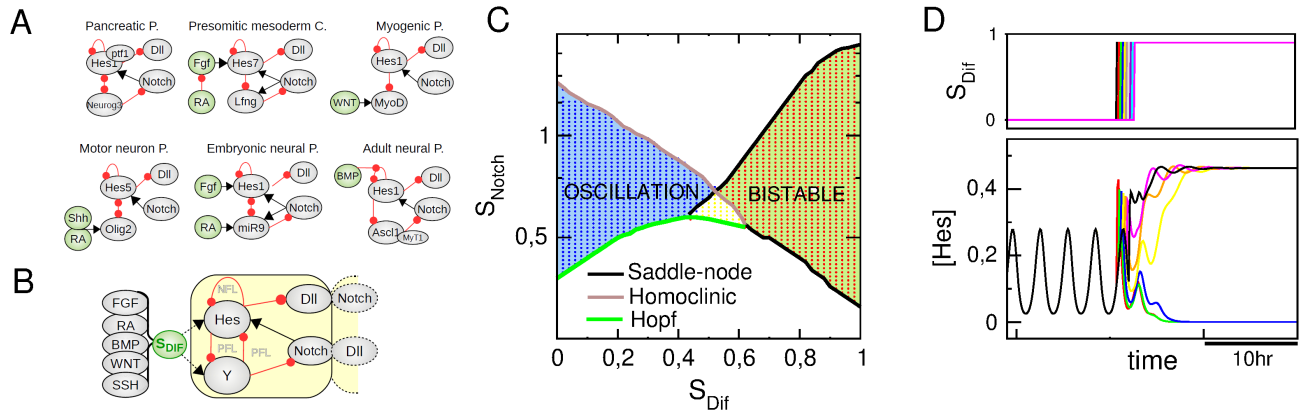


Figure 4: **Oscillation and bistability in a systems-biology model of Notch-Hes signaling.** (A) Feedback regulatory circuits involved in Notch/Hes-driven fate decision in various tissue-specific cell types. (B) Schematic network model of the Notch-Hes-Delta circuit based on the common features of cell 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

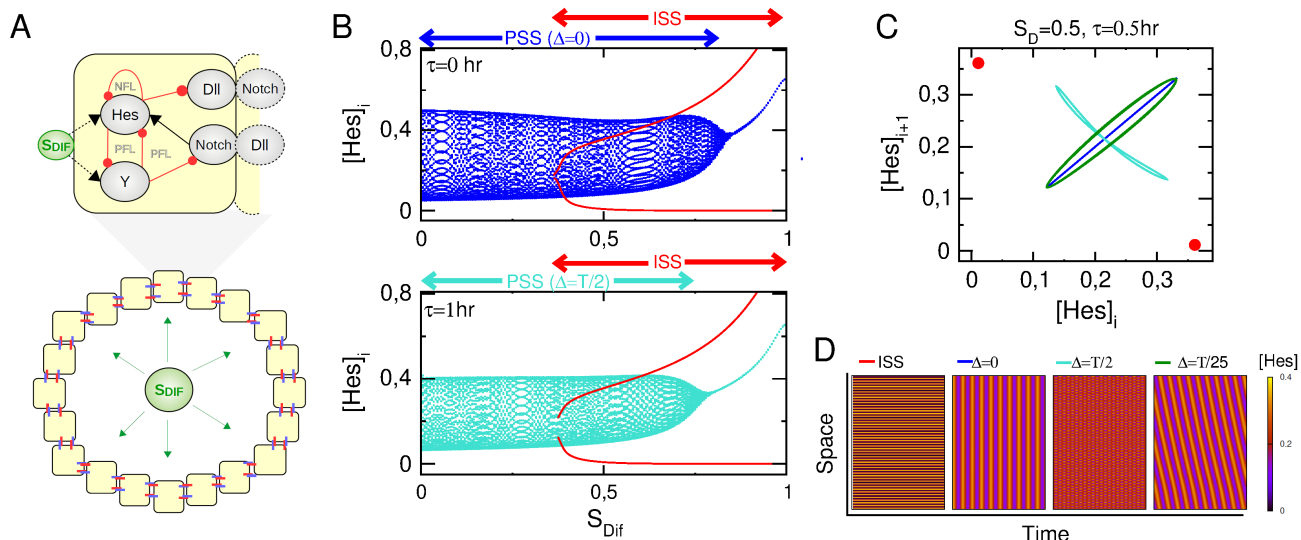


Figure 5: **Multistability between temporally-synchronized and spatially-inhomogeneous states mediated through Delta-Notch-Hes intercellular/intracellular signaling.** (A) One-dimensional ring lattice of Delta-Notch coupled cells. (B) Stability diagram of in-phase (up/blue) or anti-phase (down/turquoise) 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 ( $\tau$ ,  $S_D$ ,  $S_{N0}$ ,  $\Gamma$ ), 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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## 255 **References**

- 256 Agrawal, S., Archer, C., Schaffer, D.V., 2009. Computational models of the Notch network elucidate  
257 mechanisms of context-dependent signaling. *PLoS computational biology* 5.
- 258 Ahnfelt-Rønne, J., Jørgensen, M.C., Klinck, R., Jensen, J.N., Füchtbauer, E.M., Deering, T., MacDonald,  
259 R.J., Wright, C.V., Madsen, O.D., Serup, P., 2012. Ptf1a-mediated control of Dll1 reveals an alternative  
260 to the lateral inhibition mechanism. *Development* 139, 33–45.
- 261 Andersson, E.R., Sandberg, R., Lendahl, U., 2011. Notch signaling: simplicity in design, versatility in  
262 function. *Development* 138, 3593–3612.
- 263 Biga, V., Hawley, J., Soto, X., Johns, E., Han, D., Bennett, H., Adamson, A.D., Kursawe, J., Glendinning,  
264 P., Manning, C.S., et al., 2021. A dynamic, spatially periodic, micro-pattern of *hes5* underlies neurogenesis  
265 in the mouse spinal cord. *Molecular systems biology* 17, e9902.
- 266 Boareto, M., 2020. Patterning via local cell-cell interactions in developing systems. *Developmental biology*  
267 460, 77–85.

268 Boareto, M., Jolly, M.K., Lu, M., Onuchic, J.N., Clementi, C., Ben-Jacob, E., 2015. Jagged–delta asymmetry  
269 in notch signaling can give rise to a sender/receiver hybrid phenotype. *Proceedings of the National*  
270 *Academy of Sciences* 112, E402–E409.

271 Boissonade, J., De Kepper, P., 1980. Transitions from bistability to limit cycle oscillations. Theoretical  
272 analysis and experimental evidence in an open chemical system. *J. Phys. Chem.* 84, 501–506. doi:10.  
273 1021/j100442a009.

274 Collier, J.R., Monk, N.A., Maini, P.K., Lewis, J.H., 1996. Pattern formation by lateral inhibition with  
275 feedback: a mathematical model of delta-notch intercellular signalling. *Journal of theoretical Biology* 183,  
276 429–446.

277 Crowley, M.F., Epstein, I.R., 1989. Experimental and theoretical studies of a coupled chemical oscillator:  
278 phase death, multistability and in-phase and out-of-phase entrainment. *The Journal of Physical Chemistry*  
279 93, 2496–2502.

280 Ermentrout, B., 1996. Type i membranes, phase resetting curves, and synchrony. *Neural computation* 8,  
281 979–1001.

282 Formosa-Jordan, P., Ibañes, M., 2014. Competition in notch signaling with cis enriches cell fate decisions.  
283 *PloS one* 9, e95744.

284 Fujimoto, K., Ishihara, S., Kaneko, K., 2008. Network evolution of body plans. *PloS one* 3, e2772.

285 Goodfellow, M., Phillips, N.E., Manning, C., Galla, T., Papalopulu, N., 2014. microRNA input into a neural  
286 ultradian oscillator controls emergence and timing of alternative cell states. *Nature communications* 5,  
287 3399.

288 Hadjivasiliou, Z., Hunter, G.L., Baum, B., 2016. A new mechanism for spatial pattern formation via lateral  
289 and protrusion-mediated lateral signalling. *Journal of the Royal Society Interface* 13, 20160484.

290 Henrique, D., Schweisguth, F., 2019. Mechanisms of Notch signaling: a simple logic deployed in time and  
291 space. *Development* 146, dev172148.

292 Hunter, G.L., Hadjivasiliou, Z., Bonin, H., He, L., Perrimon, N., Charras, G., Baum, B., 2016. Coordi-  
293 nated control of Notch/Delta signalling and cell cycle progression drives lateral inhibition-mediated tissue  
294 patterning. *Development* 143, 2305–2310.

295 Jörg, D.J., Morelli, L.G., Soroldoni, D., Oates, A.C., Jülicher, F., 2015. Continuum theory of gene expression  
296 waves during vertebrate segmentation. *New journal of physics* 17, 093042.

297 Kageyama, R., Ohtsuka, T., Kobayashi, T., 2007. The hes gene family: repressors and oscillators that  
298 orchestrate embryogenesis. *Development* 134, 1243–1251.

299 Kageyama, R., Shimojo, H., Isomura, A., 2018. Oscillatory control of notch signaling in development.  
300 *Molecular Mechanisms of Notch Signaling* , 265–277.

301 Keskin, S., Devakanmalai, G.S., Kwon, S.B., Vu, H.T., Hong, Q., Lee, Y.Y., Soltani, M., Singh, A., Ay, A.,  
302 Özbudak, E.M., 2018. Noise in the vertebrate segmentation clock is boosted by time delays but tamed  
303 by notch signaling. *Cell reports* 23, 2175–2185.

304 Koseska, A., Ullner, E., Volkov, E., Kurths, J., García-Ojalvo, J., 2010. Cooperative differentiation through  
305 clustering in multicellular populations. *Journal of theoretical biology* 263, 189–202.

306 Lahmann, I., Bröhl, D., Zyrianova, T., Isomura, A., Czajkowski, M.T., Kapoor, V., Griger, J., Ruffault,  
307 P.L., Mademtzoglou, D., Zammit, P.S., et al., 2019. Oscillations of myod and hes1 proteins regulate the  
308 maintenance of activated muscle stem cells. *Genes & development* 33, 524–535.

309 Laing, C.R., 2016. Travelling waves in arrays of delay-coupled phase oscillators. *Chaos: An Interdisciplinary*  
310 *Journal of Nonlinear Science* 26, 094802.

311 Lewis, J., 2003. Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitoge-  
312 nesis oscillator. *Curr. Biol.* 13, 1398–1408.

313 Liao, B.K., Oates, A.C., 2017. Delta-Notch signalling in segmentation. *Arthropod structure & development*  
314 46, 429–447.

315 Luna-Escalante, J.C., Formosa-Jordan, P., Ibañes, M., 2018. Redundancy and cooperation in Notch inter-  
316 cellular signaling. *Development* 145, dev154807.

317 Morelli, L.G., Ares, S., Herrgen, L., Schröter, C., Jülicher, F., Oates, A.C., 2009. Delayed coupling theory  
318 of vertebrate segmentation. *HFSP journal* 3, 55–66.

319 Murray, P.J., Maini, P.K., Baker, R.E., 2011. The clock and wavefront model revisited. *Journal of theoretical*  
320 *biology* 283, 227–238.

321 Murray, P.J., Maini, P.K., Baker, R.E., 2013. Modelling delta-Notch perturbations during zebrafish somi-  
322 togenesis. *Developmental biology* 373, 407–421.

323 Nandagopal, N., Santat, L.A., LeBon, L., Sprinzak, D., Bronner, M.E., Elowitz, M.B., 2018. Dynamic ligand  
324 discrimination in the Notch signaling pathway. *Cell* 172, 869–880.

325 Owen, M.R., 2002. Waves and propagation failure in discrete space models with nonlinear coupling and  
326 feedback. *Physica D: Nonlinear Phenomena* 173, 59–76.

327 Owen, M.R., Sherratt, J.A., Wearing, H.J., 2000. Lateral induction by juxtacrine signaling is a new mech-  
328 anism for pattern formation. *Developmental biology* 217, 54–61.



329 Palau-Ortin, D., Formosa-Jordan, P., Sancho, J.M., Ibañes, M., 2015. Pattern selection by dynamical  
330 biochemical signals. *Biophysical journal* 108, 1555–1565.

331 Pfeuty, B., 2015. A computational model for the coordination of neural progenitor self-renewal and differ-  
332 entiation through Hes1 dynamics. *Development* 142, 477–485. doi:10.1242/dev.112649.

333 Pfeuty, B., Kaneko, K., 2009. The combination of positive and negative feedback loops confers exquisite  
334 flexibility to biochemical switches. *Physical Biology* 6, 046013.

335 Pfeuty, B., Kaneko, K., 2014. Reliable binary cell-fate decisions based on oscillations. *Phys. Rev. E* 89,  
336 022707. doi:10.1103/PhysRevE.89.022707.

337 Pfeuty, B., Kaneko, K., 2016. Requirements for efficient cell-type proportioning: regulatory timescales,  
338 stochasticity and lateral inhibition. *Physical Biology* 13, 026007.

339 Plahte, E., Øyehaug, L., 2007. Pattern-generating travelling waves in a discrete multicellular system with  
340 lateral inhibition. *Physica D: Nonlinear Phenomena* 226, 117–128.

341 Roese-Koerner, B., Stappert, L., Berger, T., Braun, N.C., Veltel, M., Jungverdorben, J., Evert, B.O.,  
342 Peitz, M., Borghese, L., Brüstle, O., 2016. Reciprocal regulation between bifunctional miR-9 and its  
343 transcriptional modulator notch in human neural stem cell self-renewal and differentiation. *Stem cell*  
344 *reports* 7, 207–219.

345 Sagner, A., Gaber, Z.B., Delile, J., Kong, J.H., Rousso, D.L., Pearson, C.A., Weicksel, S.E., Melchionda,  
346 M., Gharavy, S.N.M., Briscoe, J., et al., 2018. Olig2 and Hes regulatory dynamics during motor neuron  
347 differentiation revealed by single cell transcriptomics. *PLoS biology* 16, e2003127.

348 Sato, M., Yasugi, T., Minami, Y., Miura, T., Nagayama, M., 2016. Notch-mediated lateral inhibition  
349 regulates proneural wave propagation when combined with egf-mediated reaction diffusion. *Proceedings*  
350 *of the National Academy of Sciences* 113, E5153–E5162.

351 Shaya, O., Binshtok, U., Hersch, M., Rivkin, D., Weinreb, S., Amir-Zilberstein, L., Khamaisi, B., Oppen-  
352 heim, O., Desai, R.A., Goodyear, R.J., et al., 2017. Cell-cell contact area affects notch signaling and  
353 notch-dependent patterning. *Developmental cell* 40, 505–511.

354 Siebel, C., Lendahl, U., 2017. Notch signaling in development, tissue homeostasis, and disease. *Physiological*  
355 *reviews* 97, 1235–1294.

356 Sjöqvist, M., Andersson, E.R., 2019. Do as i say, not (ch) as i do: Lateral control of cell fate. *Developmental*  
357 *biology* 447, 58–70.

358 Sprinzak, D., Lakhanpal, A., LeBon, L., Santat, L.A., Fontes, M.E., Anderson, G.A., Garcia-Ojalvo, J.,  
359 Elowitz, M.B., 2010. Cis-interactions between Notch and Delta generate mutually exclusive signalling  
360 states. *Nature* 465, 86–90.

361 Stanoev, A., Schröter, C., Koseska, A., 2021. Robustness and timing of cellular differentiation through  
362 population-based symmetry breaking. *Development* 148, dev197608.

363 Suzuki, N., Furusawa, C., Kaneko, K., 2011. Oscillatory protein expression dynamics endows stem cells with  
364 robust differentiation potential. *PloS one* 6, e27232.

365 Tiedemann, H.B., Schneltzer, E., Beckers, J., Przemeck, G.K., de Angelis, M.H., 2017. Modeling coexistence  
366 of oscillation and Delta/Notch-mediated lateral inhibition in pancreas development and neurogenesis.  
367 *Journal of theoretical biology* 430, 32–44.

368 Tomka, T., Iber, D., Boareto, M., 2018. Travelling waves in somitogenesis: collective cellular properties  
369 emerge from time-delayed juxtacrine oscillation coupling. *Progress in biophysics and molecular biology*  
370 137, 76–87.

371 Ullner, E., Koseska, A., Kurths, J., Volkov, E., Kantz, H., García-Ojalvo, J., 2008. Multistability of synthetic  
372 genetic networks with repressive cell-to-cell communication. *Physical Review E* 78, 031904.

373 Uriu, K., Liao, B.K., Oates, A.C., Morelli, L.G., 2021. From local resynchronization to global pattern  
374 recovery in the zebrafish segmentation clock. *Elife* 10, e61358.

375 Vasconcelos, F.F., Sessa, A., Laranjeira, C., Raposo, A.A., Teixeira, V., Hagey, D.W., Tomaz, D.M., Muhr,  
376 J., Broccoli, V., Castro, D.S., 2016. Myt1 counteracts the neural progenitor program to promote vertebrate  
377 neurogenesis. *Cell reports* 17, 469–483.

378 Wahi, K., Bochter, M.S., Cole, S.E., 2016. The many roles of notch signaling during vertebrate somitogenesis,  
379 in: *Seminars in cell & developmental biology*, Elsevier. pp. 68–75.

380 Wang, R., Liu, K., Chen, L., Aihara, K., 2011. Neural fate decisions mediated by trans-activation and  
381 cis-inhibition in notch signaling. *Bioinformatics* 27, 3158–3165.

382 Wearing, H., Owen, M., Sherratt, J., 2000. Mathematical modelling of juxtacrine patterning. *Bulletin of*  
383 *mathematical biology* 62, 293–320.

384 Williams, C.R., Sorrentino, F., Murphy, T.E., Roy, R., 2013. Synchronization states and multistability in a  
385 ring of periodic oscillators: Experimentally variable coupling delays. *Chaos: An Interdisciplinary Journal*  
386 *of Nonlinear Science* 23, 043117.