

Turing pattern prediction in three-dimensional domains: the role of initial conditions and growth

Soha Ben Tahar¹, Jose J Muñoz^{2,3,4}, Sandra J Shefelbine^{1,5,*}, and Ester Comellas^{6,*}

¹Department of Mechanical and Industrial Engineering, Northeastern University, Boston, United States

²Department of Mathematics, Laboratori de Càlcul Numèric (LaCàN), Universitat Politècnica de Catalunya (UPC), Barcelona, Spain

³Centre Internacional de Mètodes Numèrics en Enginyeria (CIMNE), Barcelona, Spain

⁴Institut de Matemàtiques de la UPC-BarcelonaTech (IMTech), Barcelona, Spain

⁵Department of Bioengineering, Northeastern University, Boston, United States

⁶Serra Hùnter Fellow, Department of Physics, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain

* Authors for correspondance (ester.comellas@upc.edu, s.shefelbine@northeastern.edu)

Abstract

Reaction-diffusion systems have been widely used to model pattern formation in biological systems. However, the emergence of Turing patterns in three-dimensional (3D) domains remains relatively unexplored. A few studies on this topic have shown that extending pattern formation from 2D to 3D is not straightforward. Linear stability analysis, which is commonly used to associate admissible wave modes with predicted patterns in 1D and 2D, has yet to be applied in 3D. We have used this approach, together with finite element modelling of a Turing system with Schnakenberg kinetics, to investigate the effects of initial conditions and growing domains on the competition between admissible modes in 3D Turing pattern emergence. Our results reveal that non-random initial conditions on the activator play a stronger role than those of the inhibitor. We also observe a path dependency of the evolving pattern within a growing domain. Our findings shed new light on the mechanisms ensuring reliable pattern formation in 3D domains and have important implications for the development of more robust models of morphogen patterning in developmental processes.

Keywords: pattern formation; reaction-diffusion systems; finite element analysis; mode selection; evolving spatial domain; linear stability analysis

30 1 Introduction

31 The process by which organisms develop their shape and form during embryonic development
32 has fascinated scientists for centuries. Pattern formation is a crucial stage in morphogenesis,
33 as it leads to the emergence of structures that later support function. Alan Turing proposed a
34 mechanism to explain how cell signalling can generate self-organising patterns, which drive cell
35 differentiation and organisation into specific tissues and structures. In his influential paper [1],
36 Turing modelled the behaviour of chemical signals, which he termed morphogens, through a
37 reaction-diffusion system in which a spatial pattern emerges as a result of diffusion-driven in-
38 stabilities. The formation of Turing patterns depends on the delicate balance between diffusion
39 and reaction rates, as well as the nonlinear feedback between chemical species.

40 Turing systems have been extensively used to model patterning in a variety of biological ap-
41 plications [2,3], and the past two decades have brought experimental evidence to support Turing-
42 type computational model predictions [4–9]. Most studies to date have focused on one- and
43 two-dimensional models, with only a handful of papers considering reaction-diffusion systems in
44 three-dimensional (3D) domains to explore patterning in development [10–12].

45 For more than half a century, Turing models have been the focus of research, but questions
46 remain regarding the selection and emergence of specific patterns. Despite a simple and widely
47 applicable mathematical framework, the nonlinearities inherent to the reaction-diffusion system
48 make it challenging to predict pattern evolution. Linear analysis is a common technique to assess
49 the stability of the steady-state system and investigate pattern formation. It has been used to
50 predict patterns in 1D [3] and 2D structures [13–17], albeit with limitations. To account for the
51 effect of the nonlinearities on pattern emergence, more sophisticated mathematical analyses
52 have been used [18–25]. Numerical methods like finite difference and finite element analyses
53 have become the standard tool in the study of Turing pattern formation.

54 To date, a limited number of computational studies have examined the emergence of Turing
55 patterns in 3D domains [19,20,26–33]. The extension from 2D to 3D domains leads to a wider
56 variety of patterns. All these studies have focused on the generation of complex patterns. How-
57 ever, we know from linear stability analysis in 1D and 2D that these patterns are in fact the super-
58 position of simpler patterns (e.g. spheres, cylinders and planes in 3D), which are associated to a
59 specific wave mode. Admissible modes for a specific set of model parameters are obtained from
60 the linear analysis of the governing equations, while the combination of the admissible modes
61 leading to the final pattern is influenced by initial conditions [13,21,29,30,34–36].

62 Through a combination of computational modelling and linear stability analysis, we have in-
63 vestigated how the modes determine the emergence of Turing patterns in 3D domains as well as
64 the effect that initial conditions have on them. A better understanding of mode superposition in
65 3D will lead to insights on how more complex patterns form. Morphogen expression observed in
66 developmental processes like embryonic axis specification or limb formation typically results in
67 relatively simple patterns (e.g. gradients or ellipsoids). With this type of application in mind, we
68 have also explored how growth may affect the evolution of the pattern as the domain grows.

69 2 Theoretical background

70 2.1 A reaction-diffusion model with Schnakenberg kinetics

71 The general dimensionless form of a two-component Turing system is given by the reaction-
72 diffusion equations

$$\begin{aligned}\dot{u} &= \gamma f(u, v) + \Delta u, \\ \dot{v} &= \gamma g(u, v) + d\Delta v,\end{aligned}\tag{1}$$

73 where $u(\mathbf{x}, t)$ and $v(\mathbf{x}, t)$ are the species concentrations. Their time derivatives are indicated by
 74 a superimposed dot, and $\Delta(\bullet) = (\partial_x^2 + \partial_y^2 + \partial_z^2)(\bullet)$ is the standard Laplacian operator. Time
 75 and space dependence will be in general omitted for clarity. The term γ can have multiple inter-
 76 pretations linked to the domain size and to the relative strength of the reaction terms, and d is
 77 the ratio of diffusion coefficients of each species. The functions $f(u, v)$ and $g(u, v)$ will be here
 78 represented by the Schnakenberg kinetics [37], i.e.,

$$\begin{aligned} f(u, v) &= a - u + u^2v, \\ g(u, v) &= b - u^2v, \end{aligned} \quad (2)$$

79 where a and b are the positive parameters of the model. Hence, the reactant u acts as an ac-
 80 tivator by self-activating itself and inhibiting v , while v self-inhibits itself and activates u , which
 81 corresponds to an activator-substrate model.

82 There are several advantages to using the Schnakenberg general nondimensional form. The
 83 first one is that it has a relatively large Turing space in comparison to other models, making
 84 the Schnakenberg model more robust [38]. In addition, other well-known systems, such as the
 85 Gierer-Meinhardt model [39], can be scaled to take this general form. Another advantage is that
 86 the parameters γ and d have a physical and biological interpretation.

87 2.2 Pattern prediction using linear stability analysis

88 Linear stability analysis of the Turing system's steady-state solution is commonly used to study
 89 the conditions necessary for the emergence of patterns [17, 25, 40]. The most unstable mode of
 90 the resulting eigenvalue problem typically determines the wavelength of the pattern. Thus, this
 91 sort of analysis is a useful tool in determining the critical parameter values under which diffusion-
 92 driven instability will occur and Turing patterns will form.

93 The emergence and stability of patterns is analysed by assuming solutions of (1) linearised
 94 at $\mathbf{u}_0 = (u_0, v_0) = (a + b, b/(a + b)^2)$ and with the form,

$$\mathbf{u}(\mathbf{x}, t) \simeq \mathbf{u}_0 + \sum_{k_1}^{k_2} \mathbf{c}_k e^{\lambda t} e^{i\mathbf{k} \cdot \mathbf{x}}, \quad (3)$$

95 where \mathbf{k} is the wavevector, and the constants \mathbf{c}_k are determined by a Fourier expansion of the
 96 initial conditions. The sum in (3) runs on a set of plausible values of $k = \|\mathbf{k}\|$, to be specified
 97 below. The stability of the system is determined by the sign of the real part of λ , which can be
 98 written in terms of k . Indeed, after inserting the expression in (3) into the linearisation of (1), the
 99 presence of non-trivial solutions requires that λ depends on k^2 as

$$\lambda = \frac{\gamma}{2} (f_u + g_v) - \frac{k^2}{2} (1 + d) + \frac{1}{2} \sqrt{(\gamma (f_u + g_v) - k^2 (1 + d))^2 - 4 \det_k}, \quad (4)$$

100 where f_u, f_v, g_u and g_v are the derivatives of the Schnakenberg kinetics evaluated at (u_0, v_0)
 101 and function \det_k is the determinant of the matrix in the linearised system. See Supplementary
 102 Information (SI), section S1 for more details.

103 The relation in (4) is the so-called *dispersion relation*, and allows relating the wavelength k
 104 with the (positive) real part of λ . The emergence of plausible (unstable) oscillatory modes requires
 105 that $k^2 \in [k_1^2, k_2^2]$, with the values of the interval given by

$$\begin{aligned} k_1^2 &= \frac{\gamma}{2d} \left((df_u + g_v) - \sqrt{(df_u + g_v)^2 - 4d(f_u g_v - f_v g_u)} \right), \\ k_2^2 &= \frac{\gamma}{2d} \left((df_u + g_v) + \sqrt{(df_u + g_v)^2 - 4d(f_u g_v - f_v g_u)} \right). \end{aligned} \quad (5)$$

106 We will focus our study on parallelepipedic domains of dimensions $L_x \times L_y \times L_z$ and with
107 homogeneous Neumann boundary conditions (BCs). In this case, the wavevectors \mathbf{k} in (3) must
108 take the form

$$\mathbf{k}^T = \pi \left[\frac{m}{L_x}, \frac{n}{L_y}, \frac{p}{L_z} \right], \quad (6)$$

109 where the integers m , n and p represent the number of oscillations along the x , y and z direc-
110 tions, respectively. We have chosen Neumann BCs as they provide a better approximation of the
111 biological environment in morphogenesis than Dirichlet BCs. Note also that in our parallelepipedic
112 domain, adding periodic BCs restricts the set of solutions to even integer numbers in (6), while
113 solutions with homogeneous Neumann BCs can take odd and even integers. In view of (6), the
114 condition $k^2 \in [k_1^2, k_2^2]$ is tantamount to requiring that

$$k_1^2 < k^2 = \pi^2 \left(\frac{m^2}{L_x^2} + \frac{n^2}{L_y^2} + \frac{p^2}{L_z^2} \right) < k_2^2. \quad (7)$$

115 In consequence, there is only a finite and discrete number of integers $\{m, n, p\}$ and values
116 of k for which k^2 is within the interval $[k_1^2, k_2^2]$. Model parameters and domain dimensions may
117 be selected such that only a single wavelength k verifies (7), i.e. there exists a single admissible
118 mode (SI, section S1) and, according to the linear analysis, only this mode will appear in the final
119 pattern. This is referred to as “mode selection” by Murray [3], where the use of linear stability
120 analysis to predict patterns in 1D and 2D domains is explained in detail. We note though that
121 the approximated linearised solution in (3) does not satisfy the nonlinear equations in (1)-(2), and
122 therefore, the steady-state solutions obtained in our simulations cannot be exactly identified with
123 the expression in (3).

124 When several wavelengths are interacting nonlinearly, the wavelength with the maximum λ is
125 expected to grow faster and be the dominant contribution. We denote by (m, n, p) the resulting
126 *pure mode* with $\mathbf{k} = \pi [m/L_x, n/L_y, p/L_z]$ and k^2 satisfying the inequalities in (7). When *multiple*
127 modes are interacting, complex patterns may form, which result from the combination of the
128 patterns corresponding to pure modes.

129 3 Numerical simulations

130 Through computational modelling in 3D domains we examined how the modes predicted by the
131 solution to the linearised system (3) contribute to the final pattern computed with the nonlinear
132 governing equations (1)-(2). We also explored the impact of initial conditions and a growing do-
133 main on Turing pattern emergence.

134 3.1 Methods

135 The governing equations (1)-(2) were discretised in space by applying the finite element method
136 and in time using the implicit mid-point rule. Details of the numerical implementation in Matlab
137 (2022a, The MathWorks Inc.) are provided in SI, section S2. The time step was $\Delta t = 0.1$ and
138 simulations ran for as many increments as required until the pattern reached a steady-state solu-
139 tion. Steady-state was considered to be reached at t_n when the difference of nodal values of
140 u and v where all below 0.5% with respect to values at $t_n - 10\Delta t$. In random initial conditions
141 we considered a perturbation of up to a 10% variation from a constant value corresponding to
142 $\mathbf{u}_0 = (u_0, v_0) = (a + b, b/(a + b)^2)$. Cubic geometries were meshed with $20 \times 20 \times 20$ hexahed-
143 ral elements and homogeneous Neumann BCs were applied. The model parameters a , b and d ,
144 and domain sizes $L_x \times L_y \times L_z$ were adjusted for each simulation. Values are given alongside

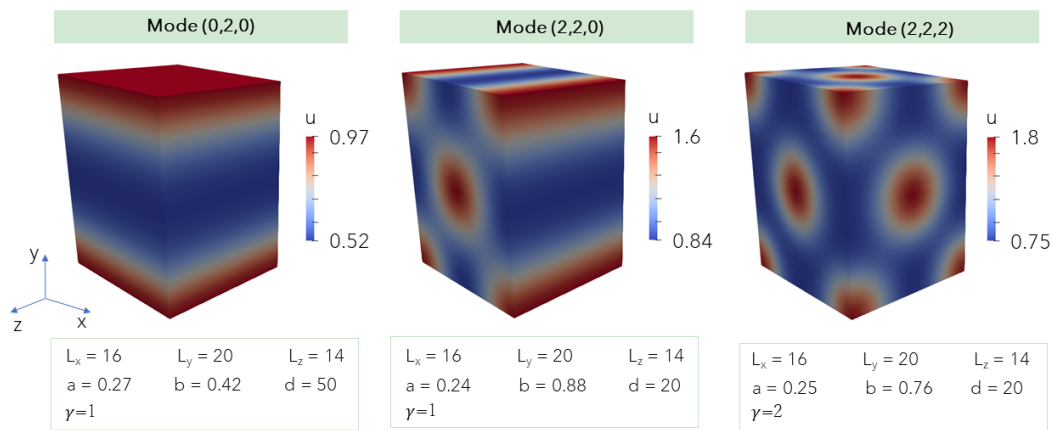


Figure 1: Graphical representation of pure modes in 3D for the reactant u . Applying specific initial conditions, and periodic and homogeneous Neumann boundary conditions allows obtaining a final pattern that corresponds to a pure mode, when selecting a particular geometry and set of model parameters.

145 the results for each case. For simplicity, $\gamma = 1$ was considered in all simulations, unless stated
 146 otherwise.

147 Figure 1 shows three final patterns obtained from a *pure mode* (m, n, p) each. These allow
 148 us to unequivocally associate a mode with its graphical representation (or pattern) in 3D, up to
 149 half-length translations and symmetries. We targeted the mode by choosing specific boundary
 150 conditions, model parameters and domain sizes. To expedite the numerical computation, we con-
 151 sidered an initial distribution of the reactant concentrations close to the targeted mode. In the
 152 results shown in figure 1, we applied periodic and homogeneous Neumann boundary conditions,
 153 which only allow an even number of oscillations, and facilitate the association of the mode to a
 154 pattern.

155 Mode $(0, 2, 0)$ corresponds to a full cosine wave in the y -direction, which results in a pattern
 156 with a plane perpendicular to the y -direction (figure 1, left). Mode $(2, 2, 0)$ corresponds to full
 157 cosine waves in the x - and y -directions, which form central and corner cylinders with their axes
 158 perpendicular to the x - y plane (figure 1, centre). Finally, mode $(2, 2, 2)$ is the product of three full
 159 cosine waves, one in each direction, which result in a set of split spheres (figure 1, right), with a
 160 pattern on each plane similar to the pattern on the x - y plane of mode $(2, 2, 0)$. We note that in all
 161 cases, the central values of u are close to the value $u_0 = a + b$ predicted by the linear analysis.

162 3.2 Mode selection and its influence on the final pattern

163 We performed several simulations in which we chose the parameters and domain size to select
 164 certain admissible modes and, therefore, target specific patterns. We found that the final pattern
 165 sometimes corresponds to the mode associated with the largest eigenvalue of the admissible
 166 wavenumbers, but not always. Figure 2 shows two illustrative cases: when the final pattern is
 167 associated with the largest eigenvalue (C) and when it is not (F). To aid in the identification of
 168 the pattern corresponding to the predominant mode, we ran additional simulations (A, B, D, E) in
 169 which we tailored the model parameters to obtain only one of the possible eigenvalues within the
 170 admissible range of wavenumbers of figure 2C and F. For each simulation (A-F), the positive real
 171 part of the dispersion relation (4) is plotted and the wavelengths verifying (7) are indicated on the
 172 plot.

173 The number of modes interacting depends on the domain dimensions and the model para-
 174 meters a , b and d . Most final patterns are a combination of several admissible modes predicted
 175 by the linear analysis. The multiplicity of modes with a same eigenvalue is typically known as
 176 *mode degeneracy* [26, 29]. For the example in figure 2A, the three modes obtained from the lin-

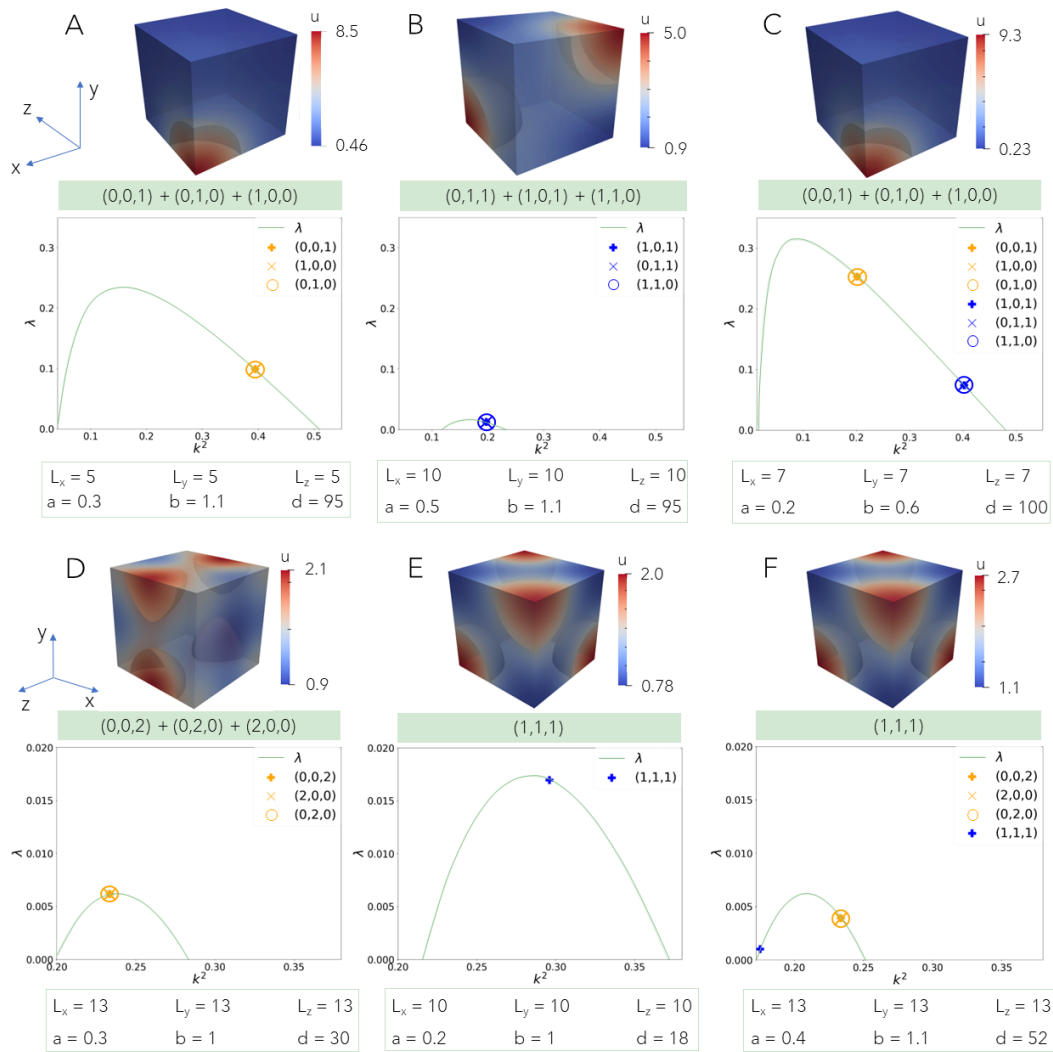


Figure 2: The mode corresponding to the largest eigenvalue is not necessarily the predominant one in the final pattern. For each case (A-F), the plot represents the dispersion relation λ vs the wavenumber k^2 obtained from the linear stability analysis (equations (4)-(7)). We can deduce the admissible modes and their corresponding eigenvalue from it. Below each plot, the domain dimensions and model parameters considered are given. On top of the plot, the steady distribution of u obtained by finite element analysis is shown. The modes participating in the pattern obtained from the non-linear system are specified below each simulation. Each figure shows patterns associated with corresponding admissible modes. The final pattern in C corresponds to the sum of the modes $(0, 0, 1)+ (0, 1, 0)+ (1, 0, 0)$, which have the largest eigenvalue. Conversely, the final pattern in F corresponds to mode $(1, 1, 1)$, which has the lowest eigenvalue.

ear analysis are $(0, 0, 1)$, $(0, 1, 0)$ and $(1, 0, 0)$. Each of them separately correspond to a plane perpendicular to the z -, y - and x -directions, respectively. Added together, the final pattern forms an eighth of a sphere in one corner of the cubic domain. We note that this is qualitatively different from mode $(1, 1, 1)$ shown in E and F, as illustrated also in SI, figure S1. Therefore, the final pattern in A results from an equal contribution of the three admissible modes.

Similarly, for the example in figure 2B, the final pattern results from the addition of the three modes obtained through the linear analysis. Modes $(0, 1, 1)$, $(1, 0, 1)$ and $(1, 1, 0)$ are individually associated with two quarter cylinders in opposite corners parallel to the x -, y - and z -planes, respectively. Added together, these modes form an eighth of a sphere in two opposite corners of the cubic domain.

Figure 2C shows that the dominant mode of the final pattern corresponds to the largest ei-

188 genvalue (the addition of modes $(0, 0, 1)$, $(0, 1, 0)$ and $(1, 0, 0)$), similar to the pattern observed
 189 in figure 2A. The opposite is true for the example of figure 2F, in which the dominant mode obtained,
 190 $(1, 1, 1)$, corresponds to the smallest eigenvalue. This final pattern is identical to the one
 191 predicted for the example in figure 2E, for which there is a single admissible mode. Note that this
 192 pattern, in contrast to the one in figure 2F, corresponds to what we have termed a pure mode
 193 as it does not result from a combination of modes, and corresponds in fact to one eighth of mode
 194 $(2, 2, 2)$ in figure 1 (right).

195 Figure 2D shows the pattern associated with the sum of modes $(0, 0, 2)$, $(0, 2, 0)$ and $(2, 0, 0)$.
 196 It corresponds to the largest eigenvalue in figure 2F, but for latter parameters and dimensions,
 197 it does not seem to contribute to its final pattern. It appears that when eigenvalues are close
 198 together, as in this case, the nonlinearities of the reaction-diffusion system may result in a smaller
 199 eigenvalue predominating over the largest one, making final pattern prediction based on the linear
 200 analysis unreliable. In these cases, the initial conditions become critical in determining the final
 201 result. This is explored in the next section.

202 3.3 Impact of the initial conditions on the final pattern

203 Initial conditions play a critical role during the mode competition described in the previous section.
 204 A specific initial condition can favour one mode over the other. Leppänen et al. [30] showed that
 205 even random initial conditions can favour one type of pattern over another.

206 To study the impact of initial conditions on the final pattern, we performed a series of simu-
 207 lations considering the same geometry, boundary conditions and model parameters as that of
 208 figure 2C (case 1 in figure 3) and 2F (case 2 in figure 3), but starting from different random initial
 209 conditions with up to a 10% or 20% variation around the constant values (u_0, v_0) .

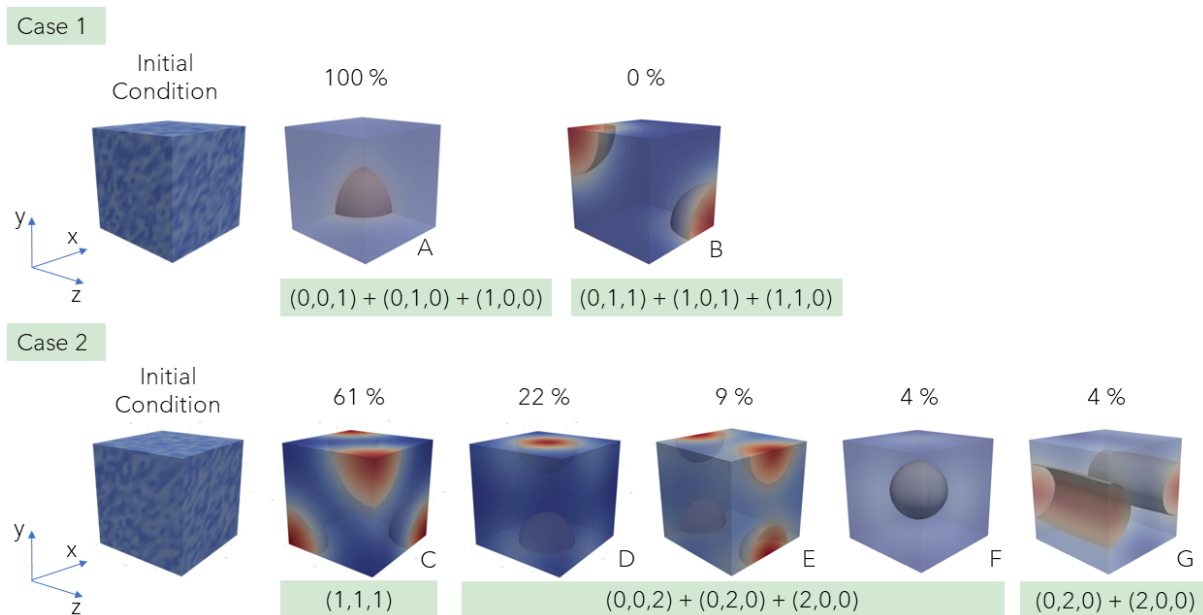


Figure 3: Effect of different random initial conditions on the final pattern of u . The model parameters, boundary conditions and domain size correspond to the ones of figure 2C (case 1) and figure 2F (case 2). The frequency of appearance of each pattern is indicated as a percentage out of the total of 23 simulations performed for each case. The modes that contribute to each final pattern are specified below the patterns. The pattern corresponding to the mode that does not appear in case 1 (B) has been obtained from a different set of model parameters and is shown for illustrative purposes. The highest u values are shown in red, and the lowest in blue. While case 1 always resulted in the same final pattern (A), for case 2 different patterns were obtained depending on the randomness of the initial conditions (C-G).

210 Figure 3 shows that, for particular configurations with the exact same conditions except for
211 different randomness in the initial conditions, different patterns may be obtained. For case 1, we
212 consistently predicted the same final pattern, regardless of the initial conditions (figure 3A). Case
213 2 was very sensitive to initial conditions (figure 3C-G). The difference between the two cases may
214 be explained by the interval between the eigenvalues (see figures 2C and 2F). When eigenvalues
215 are close to each other, the resulting final pattern is more sensitive to the initial conditions and
216 multiple final patterns may emerge. For case 2, mode $(1, 1, 1)$ appeared the most (14 of 23
217 simulations). Note that the patterns observed in figure 3D-F are in fact identical if translated half
218 the length of the domain, and correspond to the combination of modes $(0, 0, 2)$, $(2, 0, 0)$ and
219 $(0, 2, 0)$.

220 This example illustrates how the symmetries of homogeneous Neumann BCs may span the
221 possible patterns arising from the simulation, suggesting that boundary conditions play a strong
222 role during mode competition and the frequency of their appearance. In case 2, the equivalent
223 patterns in figures 3D-F corresponding to combinations of modes with the smallest eigenvalue,
224 were obtained in 61% of the simulations while those corresponding to the largest value were
225 obtained in 39% of the simulations. The pattern in figure 3G corresponds to the sum of modes
226 $(2, 0, 0)$ and $(0, 2, 0)$, and further illustrates how modes may combine in unexpected ways to form
227 different final patterns.

228 Results in figures 2 and 3 were computed using a random perturbation about an homogene-
229 ous initial condition. However, as Turing stated, “Most of an organism, most of the time, is de-
230 veloping from one pattern into another, rather than from homogeneity into a pattern” [1]. To gain
231 insights in biological development and morphogenesis, it may be useful to study Turing systems
232 with different patterns as initial conditions. Morphogen gradients have been observed during early
233 embryonic pattern formation in multiple studies [41, 42], suggesting a gradient in one or both
234 morphogens might be a sensible initial pattern to consider.

235 A gradient was imposed along a direction with values ranging from 0 to the value (u_0, v_0)
236 using the model parameters of figure 2F. Initial gradients were prescribed for either v (figure 4A,
237 top row), u (figure 4B, top row) or for both (figure 4C, top row). The initial conditions on u have a
238 stronger impact than initial conditions on v . When an initial gradient was imposed for v , the final
239 pattern was similar to the pattern obtained for random initial conditions, which corresponds to
240 mode $(1, 1, 1)$ (figure 4A, bottom row). However, an initial gradient on u , regardless of the initial
241 values considered for v , resulted in a final pattern associated with mode $(0, 0, 2)$ (figure 4B and C,
242 bottom row). This stronger effect of the reactant u may be explained by its higher exponent in the
243 term u^2v with respect to v in the nonlinear reaction term (see equation (2)). Imposing a specific
244 pattern as initial condition allows in this case targeting a particular mode.

245 3.4 Influence of a growing domain on the final patterns

246 Results in the previous sections reveal the influence of domain size on the admissible modes, in
247 addition to the significant role of initial conditions in mode competition. Thus, emerging patterns
248 are dependant on domain dimensions and possibly existing pre-patterning. Since template size
249 increases during most developmental events such as gastrulation or limb formation, it follows that
250 morphogen pattern evolution will likely be determined, in part, by the growth of the domain.

251 We conducted numerical simulations to examine the effect of a growing domain on the res-
252 ulting patterns. To model domain growth, we took the converged pattern of a first simulation in a
253 cubic domain starting from random initial conditions (figure 2F) and imposed this pattern as initial
254 conditions in an elongated geometry, where the mesh size was increased by 10% along a direc-
255 tion (represented by a dotted arrow in figure 5). Next, we ran the simulation with this new domain
256 size and the prescribed initial conditions until the pattern converged once again (represented by
257 a solid arrow in figure 5). This process was repeated three more times, increasing the domain

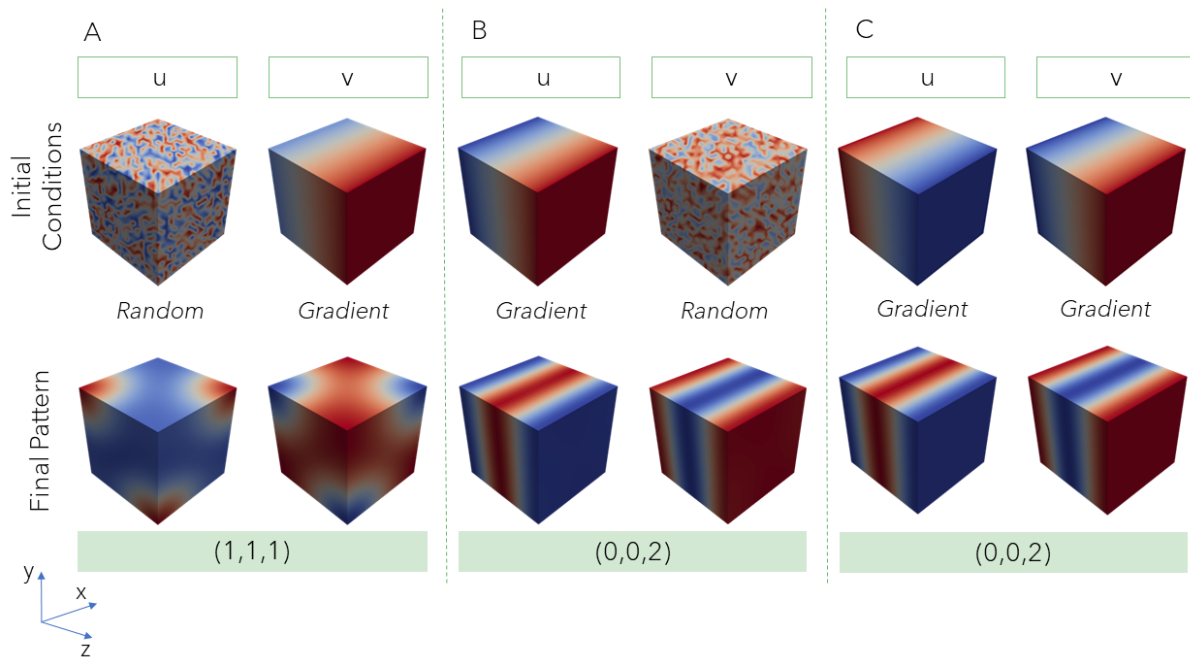


Figure 4: Effect of imposing gradients as initial conditions on the final pattern. The same parameters and dimensions as in figure 2F are used. Red represents the highest values of the reactant concentration while blue corresponds to the lowest ones. The initial conditions considered are shown in the top row while final patterns are shown in the bottom row. Note that Schnakenberg kinetics result in the two reactants being out of phase. An initial gradient for v and random values for u (A) result in the same final pattern (corresponding to mode $(1, 1, 1)$) as having both u and v with random initial values (figure 2F). However, an initial gradient for u results in a final pattern corresponding to mode $(0, 0, 2)$ for both initial random values (B) and an initial gradient (C) in v .

258 size along the same direction by 10% each time, until we reached a total elongation of 40%. The
 259 top rows of figure 5 show the initial conditions considered and the converged patterns obtained
 260 for each step in this growth process. For comparison, a pattern obtained for the same domain
 261 size in each step of the process, but considering random initial conditions, is shown in the bottom
 262 rows of figure 5. Note the difference in converged patterns obtained at each step of the growth
 263 process with respect to the equivalent domain size with random initial conditions.

264 4 Discussion

265 The few groups that have explored Turing patterns in 3D domains to date [19, 20, 26–32] have
 266 focused on predicting and classifying the complex patterns arising due to the added dimension.
 267 In contrast, our study shows that the pattern predicted by a Turing system is an addition of pure
 268 patterns associated with the admissible modes computed from the linearised equations. We have
 269 demonstrated that the contribution of these modes to the final pattern depends on their associ-
 270 ated eigenvalues and the initial conditions considered. We have also explored the effect of a
 271 growing domain on pattern emergence.

272 4.1 The largest eigenvalue does not always determine the final pattern

273 Turing patterns can help us understand how and why certain patterns emerge in Nature. Lin-
 274 ear stability analysis provides a tool to predict the emerging patterns through the study of the
 275 admissible modes and how they interact together. The power of this technique resides on its

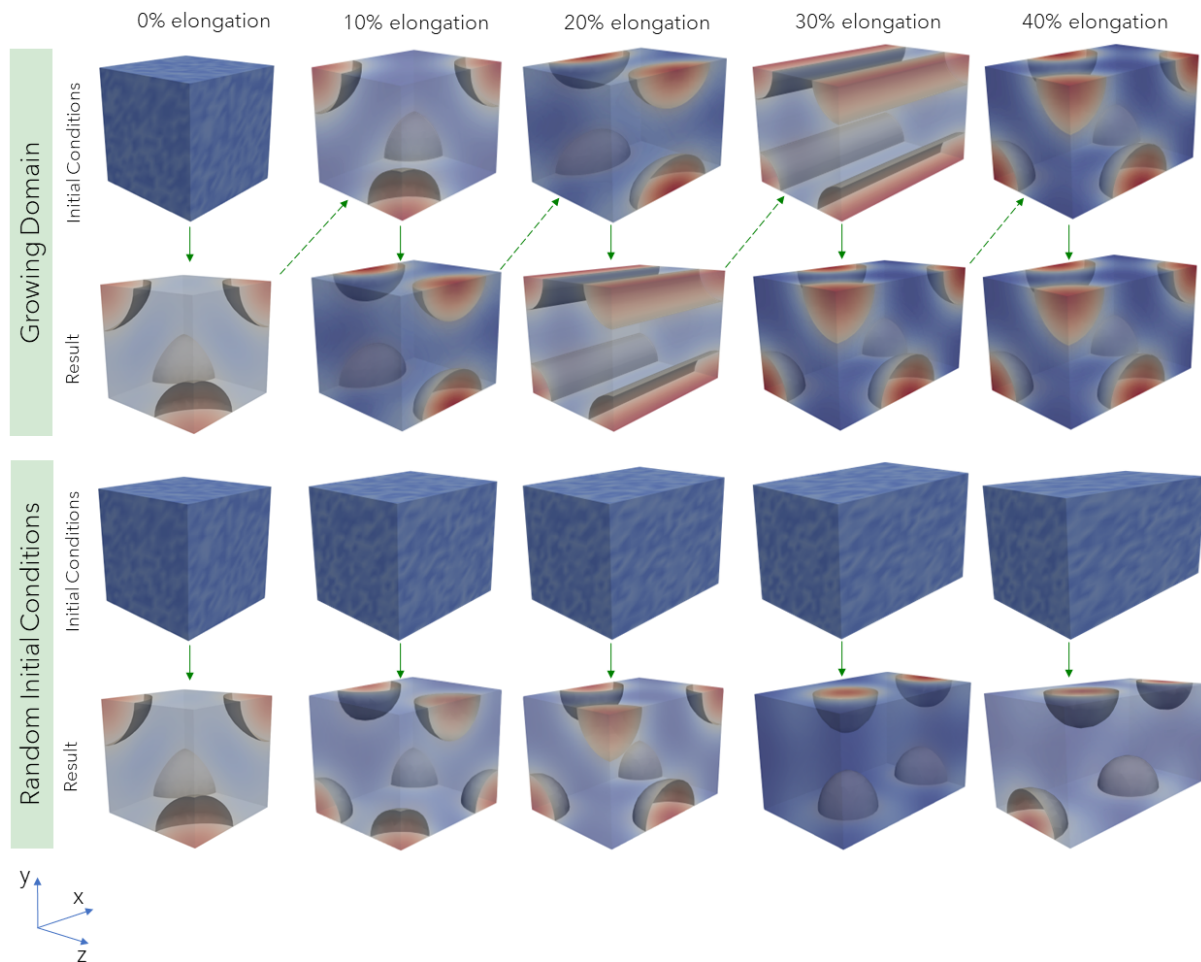


Figure 5: Effect of a growing domain on the final pattern of u . Red represents the highest activator values and blue the lowest ones. The initial conditions are shown above the final patterns for all simulations. For the growing domain, initial conditions correspond to the final pattern of the previous step, stretched by 10% along a direction (top two rows). In the other cases, each simulation is computed considering a random perturbation of up to 10% about the linearised steady-state solution as initial conditions at each corresponding domain size. The vertical arrows represent the simulation process and the dotted arrows represent the stretching of the domain. The patterns obtained at each step of a growing domain are different from the ones obtained for the same domain size but starting from random initial conditions.

276 simplicity in both formulation and computation. However, as we have seen in this and past stud-
 277 ies [13, 18, 19, 25], it is limited due to the nonlinearities of the reaction-diffusion system, which can
 278 play a strong role during mode competition.

279 Mode contribution is determined, in part, by the eigenvalue corresponding to each admissible
 280 mode. It is often assumed that the largest eigenvalue will have the largest growth factor, and thus,
 281 will determine the dominant pattern for small random initial conditions [3]. We have shown that,
 282 even in this case, associating the largest eigenvalue and the dominant mode in the final pattern
 283 is not straightforward, especially when the eigenvalues corresponding to competing modes are
 284 close together (figure 2).

285 To unequivocally predict the final pattern using only linear stability analysis, we would have
 286 to select the model parameters to target only one admissible mode, which will result in what we
 287 call a pure mode, e.g., the example in figure 2E. The linear combination of patterns, as assumed
 288 in the linear analysis, is altered by nonlinear effects. Indeed, two steady solutions (u_1, v_1) and
 289 (u_2, v_2) of the Schnakenberg system in (1)-(2), if added, would yield a transient solution where

$$\dot{u}_1 + \dot{u}_2 + \dot{v}_1 + \dot{v}_2 = -(a + b) < 0,$$

290 so that the system would necessary evolve and reach a different steady-state solution. Nonethe-
291 less, linear analysis has allowed us to sufficiently predict and explain most of the results simulated
292 here numerically.

293 Past studies in 3D domains have shown intricate patterns arising for random initial condi-
294 tions [20, 27, 29–32]. Complex patterns result from the combination of pure modes as illustrated
295 in SI, figure S2. When several admissible modes coexist, the dominant modes cannot always be
296 consistently predicted. We believe the reliability of the emerging pattern is associated to the prox-
297 imity between the eigenvalues of the different admissible modes. When the largest eigenvalue
298 was far from the other eigenvalues, only one pattern corresponding to the mode of the largest
299 eigenvalue was observed for all simulations (figure 3A). However, we obtained different patterns
300 as we repeated simulations when the eigenvalues were close together (figure 3B-F). In the latter
301 case, the different randomness in each simulation was enough to also generate translations of
302 a same pattern (figure 3D-F) as well as produce a pattern in which only two of the three modes
303 sharing a same eigenvalue contributed (figure 3E).

304 The coexistence of multiple patterns for a same set of parameters and general conditions
305 has been one of the main criticisms of the Turing system as a model for pattern emergence in
306 morphogenesis [6, 43]. However, we have shown that with suitable set of parameters, leading to
307 one eigenvalue far from the others, the final pattern is consistent and predictable when consider-
308 ing different random initial conditions (figure 3A).

309 **4.2 Initial conditions on u have a stronger impact on pattern prediction** 310 **than initial conditions on v**

311 Initial conditions are known to play a crucial role in mode competition and, therefore, the final
312 pattern [3, 36]. When initial conditions are similar to one of the admissible modes, this mode
313 typically dominates in the final pattern. This is the case in figure 4C, in which the final pattern
314 associated to mode $(0, 0, 2)$ is the closest pattern to the gradient imposed as initial conditions
315 in the simulation. Interestingly, due to the non-symmetric roles of activator and inhibitor in the
316 reaction terms, initial conditions have different effects on each reactant: when an initial gradient
317 is imposed only on the activator u (figure 4B) the same result is observed, while equivalent initial
318 conditions only on v (figure 4A) do not seem to affect the final pattern. Turing patterns arise when
319 a local self-enhancing reaction is coupled to a longer range antagonistic process. This may be
320 accomplished in several ways, as described by Meinhardt [6], but always requires v to diffuse
321 faster than u .

322 For the Schnakenberg kinetics (2) used in the present study, the activator u fulfils the role of
323 self-activation through a nonlinear positive feedback on itself, but also inhibits the production of
324 v . In turn, v is self-inhibiting but with a linear feedback on itself and acts as an activator of u .
325 Then, the concentration of v decreases in response to high concentrations of u . The quadratic
326 term u^2 amplifies the effect of the activator, likely making it more sensitive to changes in its
327 concentration. In contrast, the effect of v is linear, which means that its influence is proportional
328 to its concentration. Altogether, it seems reasonable that initial conditions on u have a strong
329 influence on the final pattern while initial conditions on v do not.

330 A similar dependence on the initial concentration of u has been reported for the Gierer-
331 Meinhardt [39] model. A small baseline production of activator u initiates patterning even at low
332 concentrations, whereas a small baseline production of inhibitor v can maintain a stable inactive
333 state until activated by an external trigger like an influx of activator from a neighbouring zone [6].
334 Hence, it is plausible to assume that similar behaviours will be observed for all models in which
335 the reactant u promotes pattern emergence. Nonetheless, whether imposing specific initial con-
336 ditions on either reactant for different kinetic models affects the resulting pattern merits further
337 study. Future work will also include testing alternative patterns as initial conditions, such as a local

338 source of reactant, to verify whether such asymmetry in pattern emergence is still observed.

339 4.3 Bifurcations and path dependence in a growing domain

340 The Turing system provides a useful model for understanding how patterns arise during a variety
 341 of morphogenetic processes, which generally involve a growing structure. Morphogen expres-
 342 sion driving these processes evolves in the expanding tissue over time. Hence, studying the
 343 emergence of Turing patterns in 3D growing domains may provide insights into the factors and
 344 conditions involved in morphogenesis.

345 As discussed in the previous section, initial conditions can enhance certain admissible modes
 346 when they are close to the pattern associated with one of these modes. However, the admissible
 347 modes may change within a growing domain, such that some modes might appear and others
 348 disappear as the domain increases in size, giving rise to bifurcation events in the configuration
 349 space. This may condition how the observed pattern evolves, which could explain the predictions
 350 at different stages of the growing domain in figure 5. The admissible modes associated to each
 351 domain size in this example are given in figure 6.

352 We observe that for the domain size corresponding to 20% elongation, the final pattern for
 353 the growing domain corresponds to a combination of modes $(0, 2, 0)$ and $(2, 0, 0)$. Here, initial
 354 conditions were the pattern associated with the sum of modes $(0, 0, 2)$, $(0, 2, 0)$ and $(2, 0, 0)$, but
 355 only the former two are admissible modes for this domain size. It seems that the resulting pat-
 356 tern “keeps” the admissible modes of the initial conditions, namely, $(0, 0, 2) + (0, 2, 0)$, instead of
 357 “switching” to the new modes which have the largest eigenvalue. However, when starting from
 358 random initial conditions (figure 5), the new admissible modes $(0, 1, 2)$ and $(1, 0, 2)$ may be more
 359 likely to be favoured. Our simulations (SI, figure S3) show that different combinations of the ad-
 360 missible modes form various final patterns when starting from random initial conditions. Similar
 361 analyses can be made for the other steps in the growing domain.

362 A recent study already showed that domain growth in curved surfaces affects pattern selec-
 363 tion [44]. A previous study in 1D had discussed the history dependence of pattern evolution, and

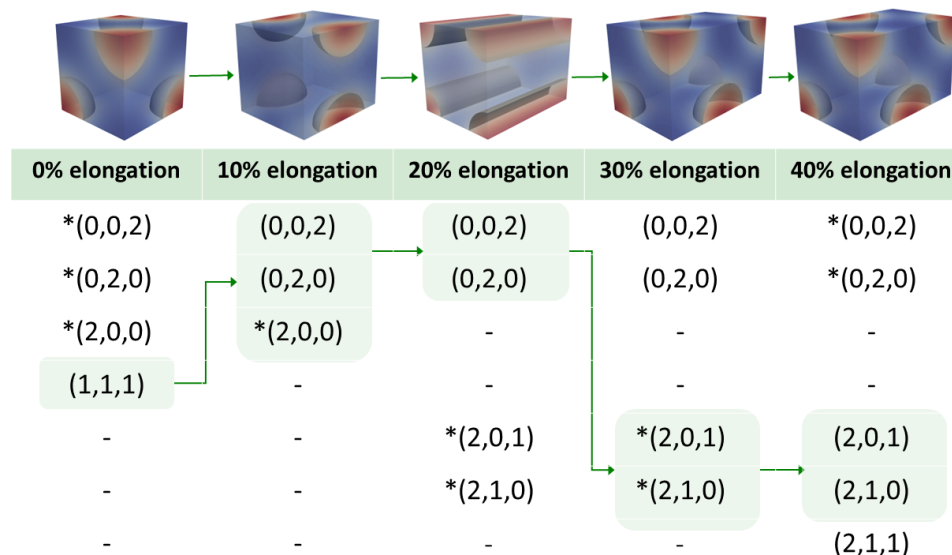


Figure 6: Admissible modes change as the domain grows, forcing the pattern evolution as seen in figure 5. The admissible modes identified for each domain size are listed in each column. Asterisks (*) indicate the modes with the largest eigenvalues. The header indicates the percentage of elongation of the domain. The modes associated with the pattern observed at each domain size increment have been highlighted, showing the path the pattern followed during its evolution with the growing domain.

364 the transiency of certain modes in growing domains [45]. Here, we have made similar observa-
365 tions in 3D and associated pattern evolution to the corresponding (transient) admissible modes.
366 Although we were not exhaustive in the study of pattern repeatability for each domain size (SI,
367 figure S3), and we are neglecting convective terms and growth rate effects [46], our example
368 illustrates how changes in admissible modes may drive pattern evolution as the domain grows.
369 In fact, our results appear to be consistent with the recent conjecture by Van Gorder et al. [46],
370 stating that how long a given mode remains admissible within a growing domain is more determ-
371 inant in pattern selection than the magnitude of its associated eigenvalue. Given that growth has
372 been suggested as a mechanism for endowing robustness to emerging Turing patterns [34, 35],
373 further investigations on the influence of growth rate would be of interest. Especially, because
374 robustness of the solution has been seen to break down when growth is too fast or too slow [46].
375 Overall, exploring the impact of these factors as well as the effect of growth type (e.g. stretching
376 the domain versus adding domain in an apical manner) on the reliability of final pattern prediction
377 is especially relevant in the study of morphogenetic processes.

378 **4.4 Challenges and opportunities for 3D Turing models in morphogenesis**

379 We have begun to explore the effect of initial conditions and growth on simple 3D Turing patterns
380 with the ultimate goal of modelling more complex patterns of morphogen expression observed
381 in development. We explored a gradient as initial conditions because it is a morphogenic pattern
382 frequently identified in early embryogenesis and they have been associated with the polar-axial
383 organisation of cells [6]. For example, a gradient of retinoic acid signalling appears to coordinate
384 the proximo-distal patterning in vertebrate limb formation [47]. Following positional information
385 theory [48], such a concentration gradient is believed to inform cells of their relative position in
386 space, and these then differentiate accordingly. Yet, in the past years, it has become apparent that
387 Turing-like self-organising mechanisms may work in conjunction with cell-fate informing gradient
388 establishment [43].

389 Incorporating additional components into the reaction-diffusion model has allowed investiga-
390 tion of biological mechanisms driving digit patterning [49, 50], embryonic axis specification [50]
391 and frog embryo gastrulation [51], among others. Coupling reaction-diffusion systems with tissue
392 growth [52, 53] provides additional means to explore the factors regulating these processes. The
393 role of physical interactions between cells and how they respond to their mechanical environment
394 have also been considered in mechanochemical models of pattern formation [10, 12]. All these
395 mechanisms work together to generate the complex spatial patterns that define the tissues and
396 organs of the developing organism and they are now starting to be integrated together into a
397 more comprehensive understanding of the processes involved.

398 One of the main concerns in using Turing-based systems to model morphogenesis is their ro-
399 bustness or lack thereof. As mentioned in the previous section, domain growth under specific con-
400 ditions may make pattern emergence more robust. The use of different boundary conditions for
401 each reactant has also been shown to reduce the sensitivity of patterns to domain changes [54].
402 We considered homogeneous Neumann BCs, i.e. no flux conditions at the domain boundary,
403 because we believe that, in general, it adequately represents biological conditions. However, the
404 use of Dirichlet or mixed boundary conditions could be a closer approximation in specific morpho-
405 genetic events, which is worth exploring. Remarkably, boundary conditions do affect the number
406 of potential symmetries in the resulting solutions, and the probability of the emerging patterns.
407 Only through a better understanding of the fundamental elements driving the patterning in Turing
408 models, can we successfully use them to elucidate the biophysical mechanisms in morphogen-
409 esis.

410 Finally, extension from 1D and 2D patterns to 3D is not trivial, and we must study 3D domains
411 to fully capture the characteristics of certain developmental processes such as limb structure

412 asymmetries. Predicting the type of pattern that will arise in these domains, and relating it to
413 the model parameters and initial conditions as we have done in this study is an additional step
414 towards developing useful models to interrogate biological hypotheses. All in all, the use of Turing-
415 like reaction-diffusion systems to model the spatial-temporal expression of morphogens in 3D will
416 enable us to probe the factors and conditions that affect the emergence of patterns at the organ
417 level, which then drive cell fate, throughout the complete morphogenetic process.

418 5 Conclusions

419 The use of Turing patterns as a means to explore morphogen expression is widespread in devel-
420 opmental biology applications. However, a full understanding of the factors that lead to a specific
421 pattern forming in three-dimensional (3D) domains is still lacking. Through linear stability analysis
422 and finite element modelling, we have associated the admissible modes of the linearised Turing
423 system with the emerging patterns, and studied the effects of initial conditions and domain growth
424 in 3D.

425 Our results reveal that nonlinearities play a strong role when the eigenvalues of the linearised
426 system are close to each other. This can lead to less robust predictions, with different patterns
427 emerging for repeated simulations in which random perturbations around the linearised steady-
428 state solution are considered as initial conditions. We also demonstrate that the effect of initial
429 conditions is asymmetric between the reactants u and v , with initial conditions on u having a
430 greater influence than the initial conditions on v . Therefore, carefully selecting the model para-
431 meters that determine the system's eigenvalues and the initial conditions are crucial factors in
432 accurately predicting 3D Turing patterns. Finally, the bifurcations in admissible modes that we
433 have seen within a growing domain have the potential to improve the reliability of predictions,
434 which supports the use of Turing patterns as a model for morphogenesis.

435 Further research on Schnakenberg and other alternative kinetic models is necessary to gain
436 a complete understanding of how 3D Turing patterns evolve in growing domains, as this particular
437 field of research has been relatively overlooked. Exploring the emergence of patterns, and their
438 dependence on the evolution of domain size is particularly relevant to the study of developmental
439 processes such as limb formation. By combining computational modelling of Turing patterns with
440 experimental analyses of morphogen expression, we will improve our understanding of morpho-
441 gen patterning and gain further insights into the mechanisms that underlie these processes.

442 **Data Accessibility** The code used to generate the finite element results in this study can be accessed
443 at <https://gitlab.com/turing-embryogenesis-group/TuringPattern>. All other data required for
444 reproducing the results in this study are included in the article and/or supporting information.

445 **Acknowledgements** This work was completed using the Discovery cluster, supported by Northeastern
446 University's Research Computing team.

447 **Funding Statement** This project has received funding from the European Union's Horizon 2020 re-
448 search and innovation programme under the Marie Skłodowska-Curie grant agreement No 841047 and
449 the National Science Foundation under grant number 1727518. JJM has also been funded by the Span-
450 ish Ministry of Science and Innovation under grants PID2020-116141GB-I00 and CEX2018-000797-S,
451 and the local government Generalitat de Catalunya with grant 2021 SGR 01049. SBT is a Department of
452 Mechanical and Industrial Engineering Chair's Fellow at Northeastern University.

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