Supplementary Material

A. Deriving dimensionless equation(for single cell)

The dimensionless equation has been derived through several steps. From governing equations we have:

$$\frac{d}{dt}N = \frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + a_N - \alpha_N N \qquad B: BMP4, N: Noggin \tag{1}$$

$$\frac{d}{dt}B = \frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n + (\frac{N}{K_{NB}})^n + (\frac{B.N}{K_1})^n} + a_B - \alpha_B B \tag{2}$$

In above equation each parameter has its own dimension:

$$[B] \equiv concentration, \quad [N] \equiv concentration$$
$$[a_N] \equiv [a_B] \equiv [\beta_N] \equiv [\beta_B] \equiv \frac{concentration}{time}$$
$$[\alpha_N] \equiv [\alpha_B] \equiv \frac{1}{time}$$
$$[K_{NB}] \equiv [K_{BN}] \equiv \ [K_{BB}] \equiv concentration$$
$$[K_1] \equiv concentration^2$$

Next, dimensionless parameters are specified:

$$\begin{gathered}\tilde{t} = \alpha_B t \quad \tilde{N} = \frac{N}{K_{NB}} \quad \tilde{B} = \frac{B}{K_{BB}} \quad \tilde{\beta_N} = \frac{\beta_N}{\alpha_N.K_{NB}} \\ \tilde{\beta_B} = \frac{\beta_B}{\alpha_B.K_{BB}} \quad \lambda = \frac{\alpha_N}{\alpha_B} \quad \tilde{a_N} = \frac{a_N}{\alpha_N.K_{NB}} \quad \tilde{a_B} = \frac{a_B}{\alpha_B.K_{BB}} \\ r_1 = (\frac{K_{BB}.K_{NB}}{K_1})^n \quad r_2 = (\frac{K_{BB}}{K_{BN}})^n\end{gathered} \tag{3}$$

First: dividing both equations by α_B, thus we have:

$$\frac{d}{\alpha_B dt}N = \frac{1}{\alpha_B}\frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}N \tag{4}$$

$$\frac{d}{\alpha_B dt}B = \frac{1}{\alpha_B}\frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n + (\frac{N}{K_{NB}})^n + (\frac{B.N}{K_1})^n} + \frac{a_B}{\alpha_B} - B \tag{5}$$

and considering $\tilde{t} = \alpha_B t$:

$$\frac{d}{d\tilde{t}}N = \frac{1}{\alpha_B}\frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}N \tag{6}$$

$$\frac{d}{d\tilde{t}}B = \frac{1}{\alpha_B}\frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n+(\frac{N}{K_{NB}})^n+(\frac{B.N}{K_1})^n} + \frac{a_B}{\alpha_B} - B \tag{7}$$

Second: Considering $\tilde{N} = \frac{N}{K_{NB}}$ and $\tilde{B} = \frac{B}{K_{BB}}$. Rewriting equations:

$$K_{NB}\frac{d}{d\tilde{t}}\tilde{N} = \frac{1}{\alpha_B}\frac{\beta_N(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}K_{NB}\tilde{N} \tag{8}$$

$$K_{BB}\frac{d}{d\tilde{t}}\tilde{B} = \frac{1}{\alpha_B}\frac{\beta_B(\tilde{B})^n}{1+(\tilde{B})^n+(\tilde{N})^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \frac{a_B}{\alpha_B} - K_{BB}\tilde{B} \tag{9}$$

Again, rewriting both equations lead to:

$$\frac{d}{d\tilde{t}}\tilde{N} = \frac{\beta_N}{K_{NB}.\alpha_B}\frac{(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{a_N}{K_{NB}.\alpha_B} - \frac{\alpha_N}{\alpha_B}\tilde{N} \tag{10}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \frac{\beta_B}{K_{BB}.\alpha_B}\frac{(\tilde{B})^n}{1+(\tilde{B})^n+(\tilde{N})^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \frac{a_B}{K_{BB}.\alpha_B} - \tilde{B} \tag{11}$$

Third: assuming: $\tilde{\beta_B} = \frac{\beta_B}{\alpha_B.K_{BB}}$ $\quad \tilde{\beta_N} = \frac{\beta_N}{\alpha_N.K_{NB}}$ $\quad \tilde{a_N} = \frac{a_N}{\alpha_N.K_{NB}}$ $\quad \tilde{a_B} = \frac{a_B}{\alpha_B.K_{BB}}$

$$\frac{d}{d\tilde{t}}\tilde{N} = \frac{\alpha_N}{\alpha_B}.\tilde{\beta_N}\frac{(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{\alpha_N}{\alpha_B}\tilde{a_N} - \frac{\alpha_N}{\alpha_B}\tilde{N} \tag{12}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \tilde{a_B} - \tilde{B} \tag{13}$$

Fourth: after substituting $r_1 = (\frac{K_{BB}.K_{NB}}{K_1})^n, \quad r_2 = (\frac{K_{BB}}{K_{BN}})^n, \quad \lambda = \frac{\alpha_N}{\alpha_B}$ we have:

$$\frac{d}{d\tilde{t}}\tilde{N} = \lambda.\tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \lambda\tilde{a_N} - \lambda\tilde{N} \tag{14}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{A}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} \tag{15}$$

and eventually final equation obtained:

$$\boxed{\begin{aligned} \lambda^{-1}\frac{d}{d\tilde{t}}\tilde{N} &= \tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \tilde{a_N} - \tilde{N} \\ \frac{d}{d\tilde{t}}\tilde{B} &= \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{A}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} \end{aligned}} \tag{16}$$

B. Deriving dimensionless equation(by considering interaction via diffusion)

For cell population simulation first equation changes as follows:

$$\frac{d}{dt}N = \frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + a_N - \alpha_N N + D_N(\frac{\partial^2 N}{\partial x^2} + \frac{\partial^2 N}{\partial y^2}) \qquad B: BMP4, N: Noggin \tag{17}$$

$$\frac{d}{dt}B = \frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n+(\frac{N}{K_{NB}})^n+(\frac{B.N}{K_1})^n} + a_B - \alpha_B B + D_B(\frac{\partial^2 B}{\partial x^2}+\frac{\partial^2 B}{\partial y^2}) \tag{18}$$

Which

$$[D_N] \equiv [D_B] \equiv \frac{length^2}{time}$$
$$[(\frac{\partial^2 *}{\partial x^2}+\frac{\partial^2 *}{\partial y^2})] \equiv \frac{concentration}{time}$$

Same as previous section we have:

$$\frac{d}{\alpha_B dt}N = \frac{1}{\alpha_B}\frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}N + \frac{D_N}{\alpha_B}(\frac{\partial^2 N}{\partial x^2}+\frac{\partial^2 N}{\partial y^2}) \tag{19}$$

$$\frac{d}{\alpha_B dt}B = \frac{1}{\alpha_B}\frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n+(\frac{N}{K_{NB}})^n+(\frac{B.N}{K_1})^n} + \frac{a_B}{\alpha_B} - B + \frac{D_B}{\alpha_B}(\frac{\partial^2 B}{\partial x^2}+\frac{\partial^2 B}{\partial y^2}) \tag{20}$$

and considering $\tilde{t} = \alpha_B t$:

$$\frac{d}{d\tilde{t}}N = \frac{1}{\alpha_B}\frac{\beta_N(\frac{B}{K_{BN}})^n}{1+(\frac{B}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}N + \frac{D_N}{\alpha_B}(\frac{\partial^2 N}{\partial x^2}+\frac{\partial^2 N}{\partial y^2}) \tag{21}$$

$$\frac{d}{d\tilde{t}}B = \frac{1}{\alpha_B}\frac{\beta_B(\frac{B}{K_{BB}})^n}{1+(\frac{B}{K_{BB}})^n+(\frac{N}{K_{NB}})^n+(\frac{B.N}{K_1})^n} + \frac{a_B}{\alpha_B} - B + \frac{D_B}{\alpha_B}(\frac{\partial^2 B}{\partial x^2}+\frac{\partial^2 B}{\partial y^2}) \tag{22}$$

Considering $\tilde{N} = \frac{N}{K_{NB}}$ and $\tilde{B} = \frac{B}{K_{BB}}$. Rewriting equations:

$$K_{NB}\frac{d}{d\tilde{t}}\tilde{N} = \frac{1}{\alpha_B}\frac{\beta_N(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{a_N}{\alpha_B} - \frac{\alpha_N}{\alpha_B}K_{NB}\tilde{N} + \frac{D_N}{\alpha_B K_{AB}}(\frac{\partial^2 \tilde{N}}{\partial x^2}+\frac{\partial^2 \tilde{N}}{\partial y^2}) \tag{23}$$

$$K_{BB}\frac{d}{d\tilde{t}}\tilde{B} = \frac{1}{\alpha_B}\frac{\beta_B(\tilde{B})^n}{1+(\tilde{B})^n+(\tilde{N})^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \frac{a_B}{\alpha_B} - K_{BB}\tilde{B} + \frac{D_B}{\alpha_B K_{BB}}(\frac{\partial^2 \tilde{B}}{\partial x^2}+\frac{\partial^2 \tilde{B}}{\partial y^2}) \tag{24}$$

Rewriting both equations lead to:

$$\frac{d}{d\tilde{t}}\tilde{N} = \frac{\beta_N}{K_{NB}.\alpha_B}\frac{(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{a_N}{K_{NB}.\alpha_B} - \frac{\alpha_N}{\alpha_B}\tilde{N} + \frac{D_N}{\alpha_B}(\frac{\partial^2 \tilde{N}}{\partial x^2}+\frac{\partial^2 \tilde{N}}{\partial y^2}) \tag{25}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \frac{\beta_B}{K_{BB}.\alpha_B}\frac{(\tilde{B})^n}{1+(\tilde{B})^n+(\tilde{N})^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \frac{a_B}{K_{BB}.\alpha_B} - \tilde{B} + \frac{D_B}{\alpha_B}(\frac{\partial^2 \tilde{B}}{\partial x^2}+\frac{\partial^2 \tilde{B}}{\partial y^2}) \tag{26}$$

Now $\frac{D_N}{\alpha_B}(\frac{\partial^2 \tilde{N}}{\partial x^2}+\frac{\partial^2 \tilde{N}}{\partial y^2})$ and $\frac{D_B}{\alpha_B}(\frac{\partial^2 \tilde{B}}{\partial x^2}+\frac{\partial^2 \tilde{B}}{\partial y^2})$ are dimensionless. Now it is possible to rewrite the equations as following:

$$\frac{d}{d\tilde{t}}\tilde{N} = \frac{\beta_N}{K_{NB}.\alpha_B}\frac{(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{a_N}{K_{NB}.\alpha_B} - \frac{\alpha_N}{\alpha_B}\tilde{N} + \frac{\alpha_N}{\alpha_B}\tilde{D}_N(\frac{\partial^2 \tilde{N}}{\partial x^2}+\frac{\partial^2 \tilde{N}}{\partial y^2}) \tag{27}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \frac{\beta_B}{K_{BB}.\alpha_B}\frac{(\tilde{B})^n}{1+(\tilde{B})^n+(\tilde{N})^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \frac{a_B}{K_{BB}.\alpha_B} - \tilde{B} + \tilde{D}_B(\frac{\partial^2\tilde{B}}{\partial x^2} + \frac{\partial^2\tilde{B}}{\partial y^2}) \tag{28}$$

Where:

$$\tilde{D}_N = \frac{D_N}{\alpha_N} \quad and \quad \tilde{D}_B = \frac{D_B}{\alpha_B}$$

Assuming: $\tilde{\beta_B} = \frac{\beta_B}{\alpha_B.K_{BB}}$ $\quad \tilde{\beta_N} = \frac{\beta_N}{\alpha_N.K_{NB}}$ $\quad \tilde{a_N} = \frac{a_N}{\alpha_N.K_{NB}}$ $\quad \tilde{a_B} = \frac{a_B}{\alpha_B.K_{BB}}$

$$\frac{d}{d\tilde{t}}\tilde{N} = \frac{\alpha_N}{\alpha_B}.\tilde{\beta_N}\frac{(\frac{K_{BB}\tilde{B}}{K_{BN}})^n}{1+(\frac{K_{BB}\tilde{B}}{K_{BN}})^n} + \frac{\alpha_N}{\alpha_B}\tilde{a_N} - \frac{\alpha_N}{\alpha_B}\tilde{N} + \frac{\alpha_N}{\alpha_B}\tilde{D}_N(\frac{\partial^2\tilde{N}}{\partial x^2} + \frac{\partial^2\tilde{N}}{\partial y^2}) \tag{29}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+(\frac{K_{NB}.\tilde{N}.K_{BB}.\tilde{B}}{K_1})^n} + \tilde{a_B} - \tilde{B} + \tilde{D}_B(\frac{\partial^2\tilde{B}}{\partial x^2} + \frac{\partial^2\tilde{B}}{\partial y^2}) \tag{30}$$

Substituting $r_1 = (\frac{K_{BB}.K_{NB}}{K_1})^n$, $\quad r_2 = (\frac{K_{BB}}{K_{BN}})^n$, $\quad \lambda = \frac{\alpha_N}{\alpha_B}$ we have:

$$\boxed{\begin{aligned} \frac{d}{d\tilde{t}}\tilde{N} &= \lambda.\tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \lambda\tilde{a_N} - \lambda\tilde{N} + \lambda\tilde{D}_N(\frac{\partial^2\tilde{N}}{\partial x^2} + \frac{\partial^2\tilde{N}}{\partial y^2}) \\ \frac{d}{d\tilde{t}}\tilde{B} &= \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{N}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} + \tilde{D}_B(\frac{\partial^2\tilde{B}}{\partial x^2} + \frac{\partial^2\tilde{B}}{\partial y^2}) \end{aligned}} \tag{31}$$

We can go even further in non-dimensionalization by considering three more dimensionless parameters:

$$\tilde{x} = \frac{x}{\sqrt{\tilde{D}_N}} \quad \tilde{y} = \frac{y}{\sqrt{\tilde{D}_N}} \quad d = \frac{\tilde{D}_B}{\tilde{D}_N}$$

And rewriting the equations:

$$\frac{d}{d\tilde{t}}\tilde{N} = \lambda.\tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \lambda\tilde{a_N} - \lambda\tilde{N} + \lambda(\frac{\partial^2\tilde{N}}{\partial \tilde{x}^2} + \frac{\partial^2\tilde{N}}{\partial \tilde{y}^2}) \tag{32}$$

$$\frac{d}{d\tilde{t}}\tilde{B} = \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{N}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} + d(\frac{\partial^2\tilde{B}}{\partial \tilde{x}^2} + \frac{\partial^2\tilde{B}}{\partial \tilde{y}^2}) \tag{33}$$

This equation shows that only ratio of diffusion of Noggin and BMP4 is important in pattern formation and this non-dimension parameter is what matters for pattern formation. because in our simulations x and y are not "dimensionless-able" we use Eq. 31 as our base equation.

Final equation obtained as follows:

$$\boxed{\begin{aligned} \lambda^{-1}\frac{d}{d\tilde{t}}\tilde{N} &= \tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \tilde{a_N} - \tilde{N} + (\frac{\partial^2\tilde{N}}{\partial \tilde{x}^2} + \frac{\partial^2\tilde{N}}{\partial \tilde{y}^2}) \\ \frac{d}{d\tilde{t}}\tilde{B} &= \tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{N}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} + d(\frac{\partial^2\tilde{B}}{\partial \tilde{x}^2} + \frac{\partial^2\tilde{B}}{\partial \tilde{y}^2}) \end{aligned}} \tag{34}$$

C. Implementation details

Simulations have been performed with Morpheus software. In order to perform analysis and run simulation, initial condition, boundary condition and numerical solver for solving partial differential equation must be specified. In the following, a detailed description of these conditions will be explained precisely.

Equations 10,11 in the main text, are executed within each cell in the population. Production rate is non-zero within each cell and in the extracellular space only degradation and diffusion occurs. In order to consider this effect in the Morpheus, we have assumed a variable which is called "*is_Cell*"; this variable distinguishes the regions where the cell is present and not present. Furthermore, according to the model assumptions described in the previous section, degradation rate outside and inside of the cell is different from each other. So the final model is executed in Morpheus as follows:

$$\begin{aligned}\frac{d}{d\tilde{t}}\tilde{N} = {} & is\_Cell * (\lambda.\tilde{\beta_N}\frac{r_2\tilde{B}^n}{1+r_2\tilde{B}^n} + \lambda\tilde{a_N} - \lambda\tilde{N} \\ & + \lambda\tilde{D}_N(\frac{\partial^2\tilde{N}}{\partial x^2} + \frac{\partial^2\tilde{N}}{\partial y^2})) \\ & - (1.0 - is\_Cell) * (deg_1 * \tilde{N} + \lambda\tilde{D}_N(\frac{\partial^2\tilde{N}}{\partial x^2} + \frac{\partial^2\tilde{N}}{\partial y^2}))\end{aligned} \tag{35}$$

$$\begin{aligned}\frac{d}{d\tilde{t}}\tilde{B} = {} & is\_Cell * (\tilde{\beta_B}\frac{\tilde{B}^n}{1+\tilde{B}^n+\tilde{N}^n+r_1\tilde{A}^n\tilde{B}^n} + \tilde{a_B} - \tilde{B} \\ & + \tilde{D}_B(\frac{\partial^2\tilde{B}}{\partial x^2} + \frac{\partial^2\tilde{B}}{\partial y^2})) \\ & - (1.0 - is\_Cell) * (deg_2 * \tilde{B} + \tilde{D}_B(\frac{\partial^2\tilde{B}}{\partial x^2} + \frac{\partial^2\tilde{B}}{\partial y^2}))\end{aligned} \tag{36}$$

where deg_1 and deg_2 are the degradation rate of BMP4 and Noggin respectively outside of the cell (their ratio remains the same as inside the cell).

Furthermore, initial conditions should be described clearly. Different initial conditions can lead to different behaviors in dynamical system. In our proposed model, we have considered that BMP4 has been distributed homogeneously in the field and Noggin is not present in the field at the beginning (except negligible amount inside the cells) which is in agreement with Warmflash14 et al. paper.

$$BMP4_{init} : 5 + Normal(0,1) \tag{37}$$

$$Noggin_{init} : is\_Cell * (0.1 + Normal(0, 0.0005)) \tag{38}$$

The response of the system is robust with respect to the noise level. 40% deviation in noise standard deviation does not have any effect on the response and behavior of the system.

D. Effects of parameters

In this section, we will go through assessing the effect of each parameter in final pattern and giving some intuition and analysis about it as well as analyzing of the dynamical system have been proposed in this paper. We have run grid search over parameter space and observed the effect of each parameter on emerging pattern. These simulations have consolidated our understanding of how the pattern changes with respect to each parameter and it gives us a better insight into our proposed model. In each simulation, all the parameters have been set based on Table. 2 (in original paper) and we are only manipulating one variable in logarithmic scale to see its influence on the behavior.

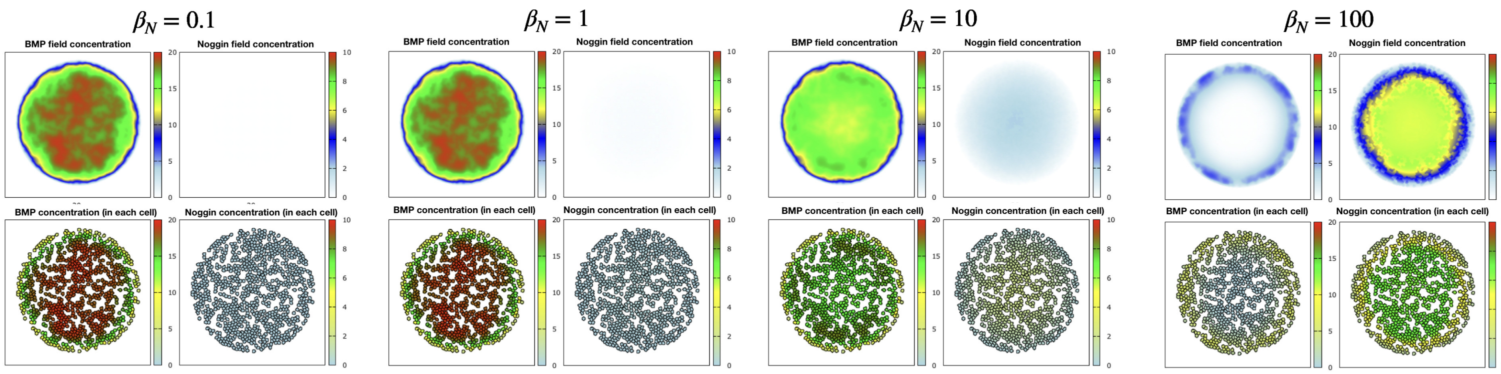

Figure S1: Effect of β_N on pattern formation and cell fate decision. Increasing β_N can increase Noggin production and consequently reduce BMP4 production.

The first parameter we are considering is β_N. The pattern changes in a very intuitive way with respect to β_N. β_N is production rate of Noggin and increasing it can cause the increase of Noggin production, which consequently reduce the amount of BMP4. We see behavior is completely consistent with our intuitive analysis.

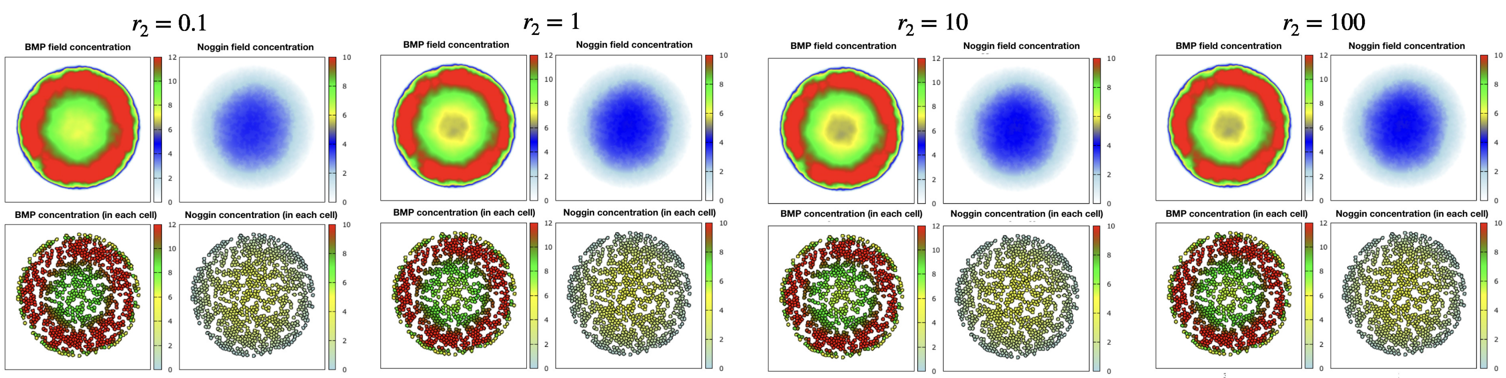

Figure S2: how pattern changes by increasing r_2. The pattern is completely independent of r_2 and we see no difference in the images.

r_2 does not have huge impact on the behavior. It is obvious that the pattern is robust to r_2. By inspecting dynamical systems equations carefully, we can deduce that r_2 can only influence the transient behavior of the system and the steady-state response is completely independent of r_2.

r_1 has very great importance in cell fate decision. r_1 indicates how Noggin and BMP4 cooperate for binding to BMP4 promoter and whether their binding is independent or not. For example, $r_1 = 1$ implies that binding of BMP4 and Noggin to BMP4 promoter is completely independent, $r_1 = 0$ implies that their interaction has no effect on the final pattern and each value other than these two represents some sorts of dependency in binding. The system is not acting in a very intuitive way with respect to r_1 and the system is very sensitive to the variation of this parameter. For example, in our model, $r_1 = 0.1$ can lead to proper behavior. So, for the system has right behavior, it must be set to a certain value and we can hypothesize that evolution has tuned this parameter.

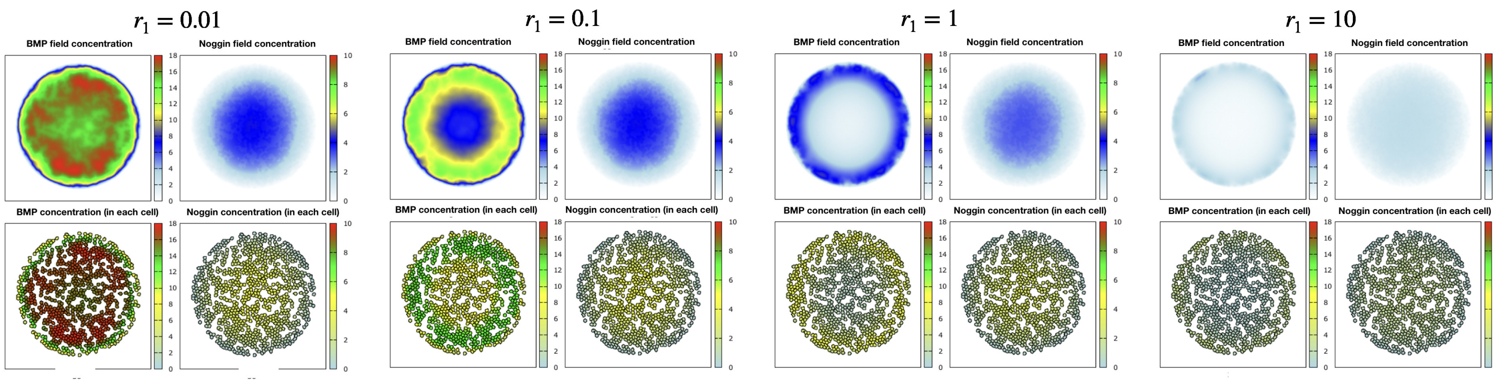

Figure S3: How increasing r_1 can influence pattern formation. r_1 indicate the level of interaction between BMP4 and Noggin for binding to BMP4 promoter and the system is very sensitive to this variable.

λ is a dimensionless parameter and represents the ratio of Noggin degradation rate to BMP4 degradation rate. During running different simulations, we have observed that the value of λ should be less than one in order the right pattern emerges. As we increase λ gradually, BMP4 disappears from the environment. Moreover, when the value of λ is greater than one, we can't see the appearance of oscillatory behavior by increasing colony diameter, which is another evidence that reveals the value of this parameter must be less than one.

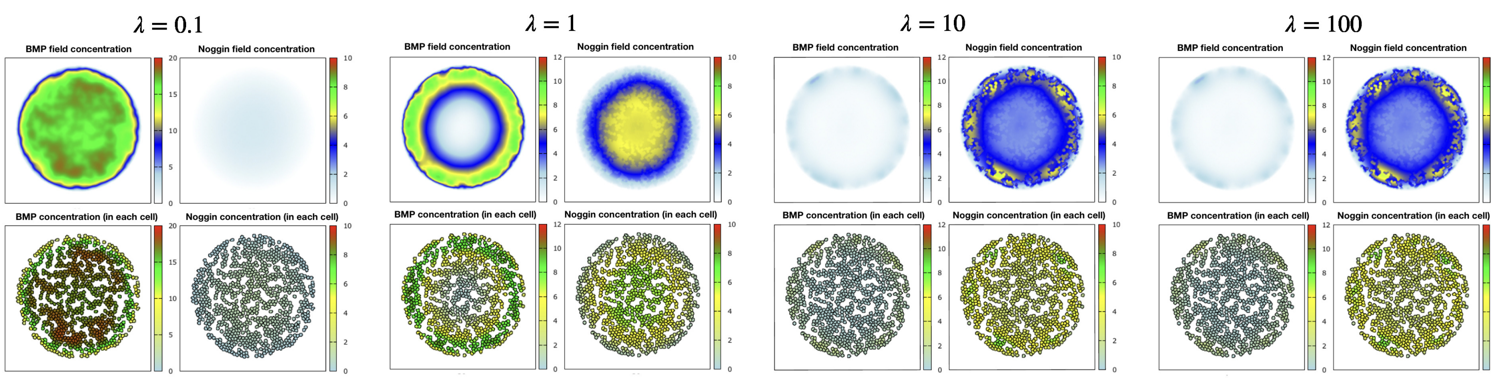

Figure S4: λ has the significant effect on behavior. If it exceeds one, it will disrupt the pattern. It depends on the half-life of BMP4 and Noging and its value can be tuned under evolution.

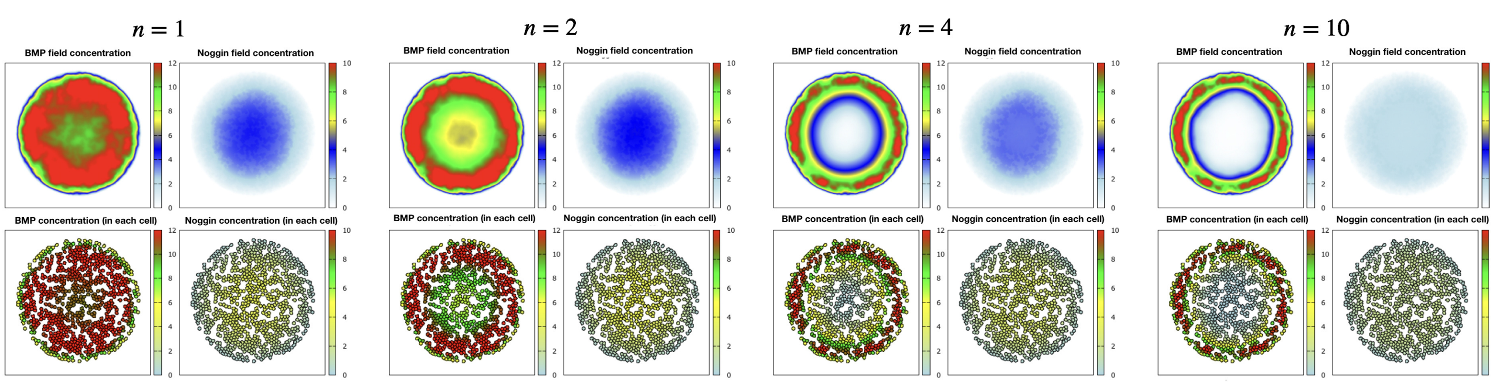

Figure S5: Effect of n parameter on the final cell fate differentiation. Increasing n causes sharper decreasing in BMP radial pattern but smoother increasing in Noggin pattern structure.

As the order of sigmoidal function in the dynamical system equation goes up, the derivative of each element in equation behaves in shaper manner. Based on diffusion rates and the interaction between BMP and Noggin, this changing may affect the final pattern. We expect that this alteration has more effect on BMP due to its lower diffusion rate and the result in S5 confirm this intuition.

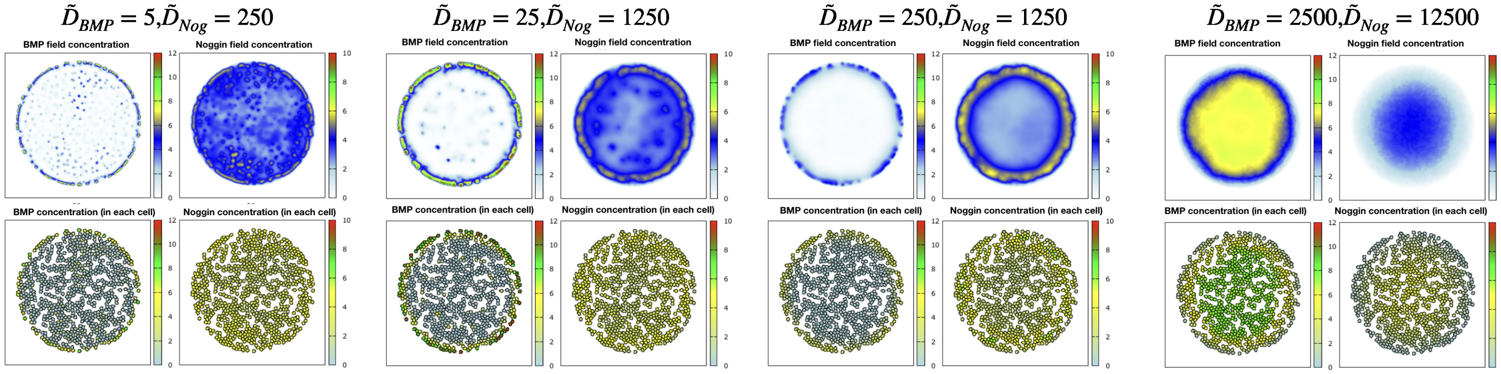

Figure S6: Effect of different diffusion rate on pattern formation as well as cell fate decision.

Diffusion plays an important role in pattern formation and for the appearance of oscillatory behavior, the diffusion rate of inhibitor (Noggin) should be greater than BMP4. In order to examine how diffusion can change pattern formation and determining the effect of diffusion, we designed different simulations with different diffusion coefficient. We observed that diffusion plays a central role in pattern formation and its variation can have a dramatic effect on the pattern and consequently on the fate determination.

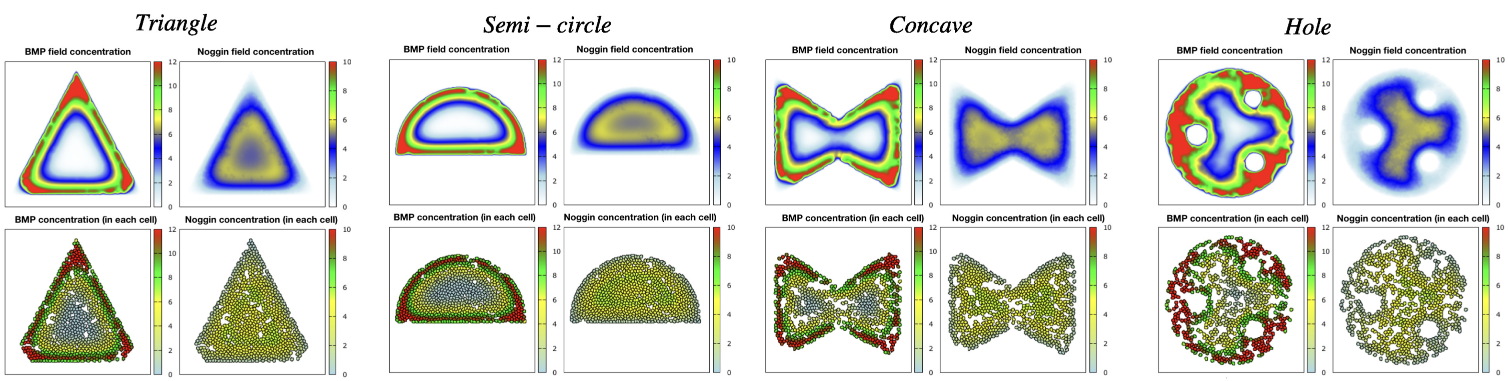

Figure S7: Effect of different geometric confinements on pattern formation and cell fate decision.

We were curious to see how the pattern changes with respect to geometry. Most of the in vitro experiments have been done on circular micropattern; but, in the real situation, cells confront with situations where the boundary is not circular. Moreover, we can observe that the pattern formation is initiated from the boundary and gradually spread towards the center. But the situation becomes more interesting when the cells have put on concave or perforated geometry.