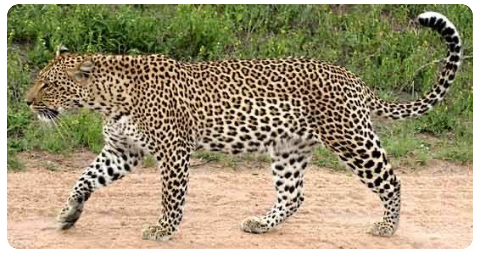
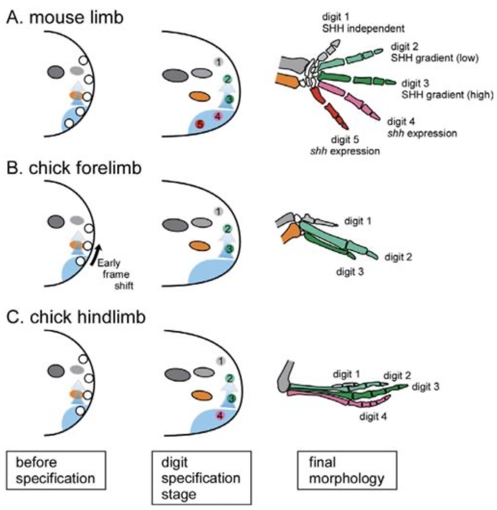
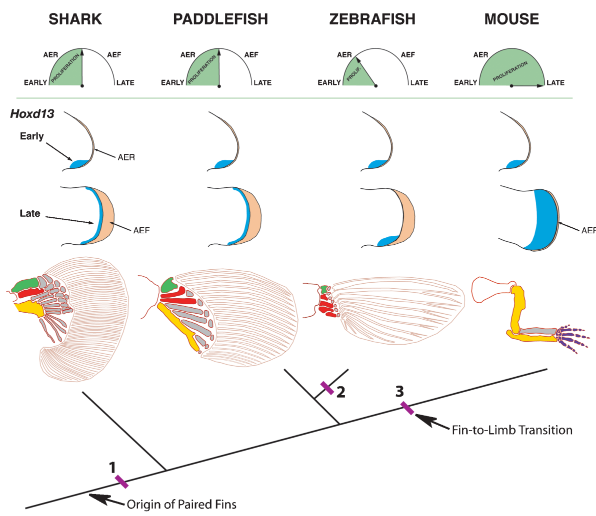
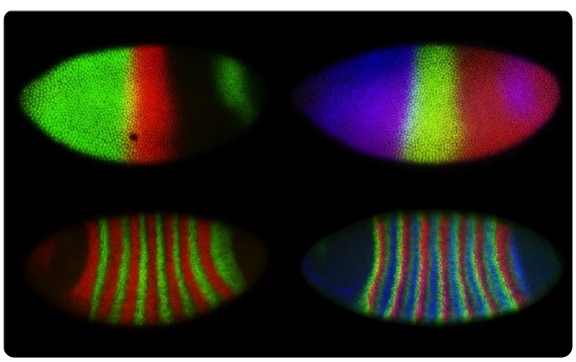
III C. Turing instability + pattern formation

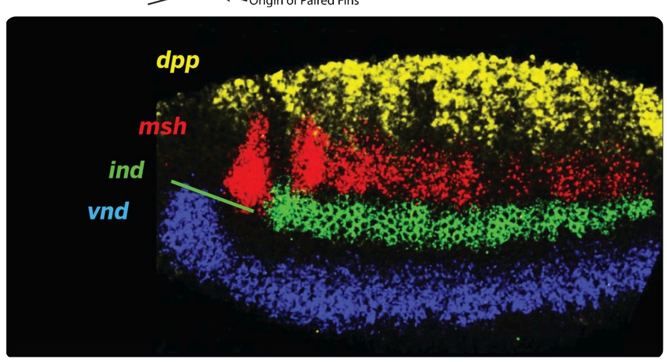
1. Background on biological patterns





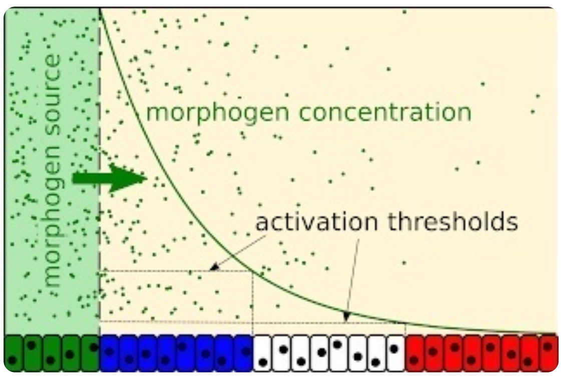


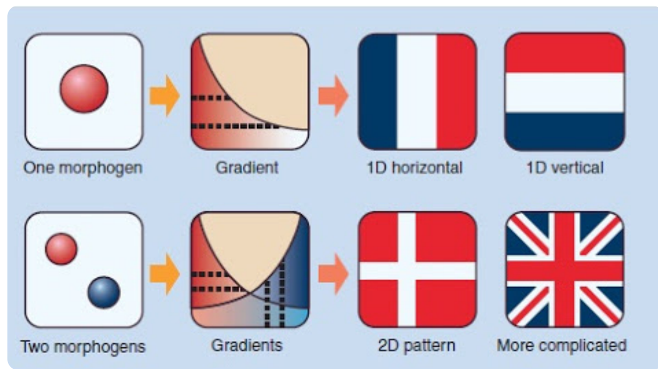




Two general strategies to form biological patterns

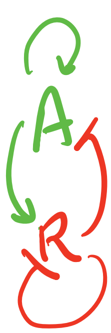
* Morphogen gradient (Lewis Wolpert)
  - positional information laid out externally
  - cells respond passively (gene expression & movement)

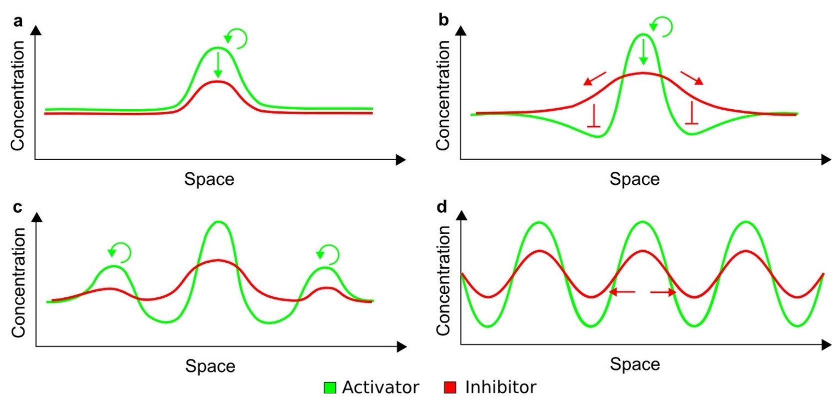




* Reaction-diffusion systems (Alan Turing)
  - pattern formation autonomous (self-organized)
  - typically involve mutual signaling

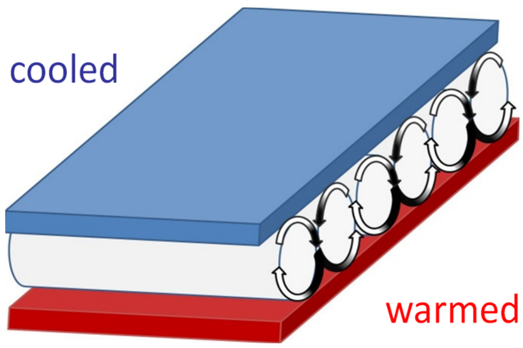
⇒ Turing patterns: 2 diffusing species (A + R)
  - slow diffusion of activator (short-range activation)
  - fast diffusion of inhibitor (long-range inhibition)

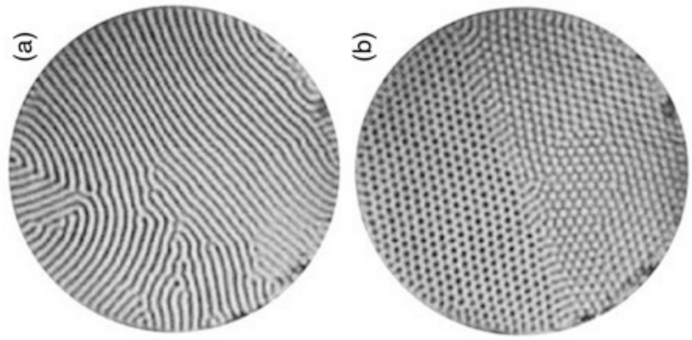




* pattern formation dynamics best studied in exemplary physical & chemical systems

e.g. Rayleigh-Benard convection



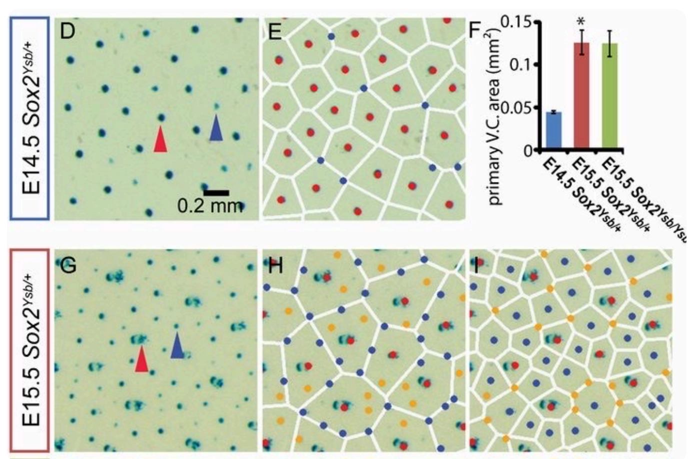


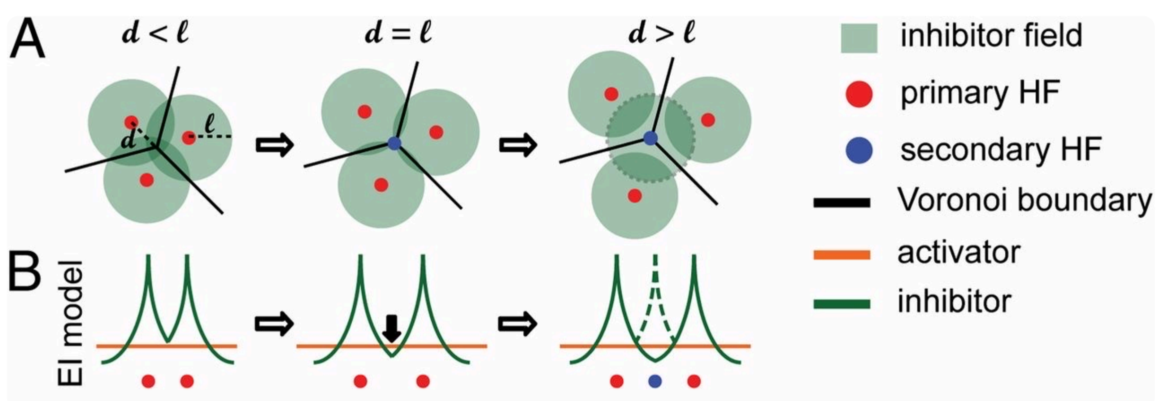
* origins of biological pattern often hard to elucidate

→ early failures

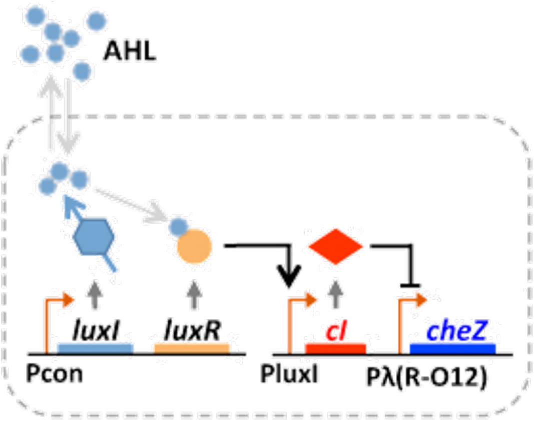
* Some real-life (not-quite-Turing) examples.

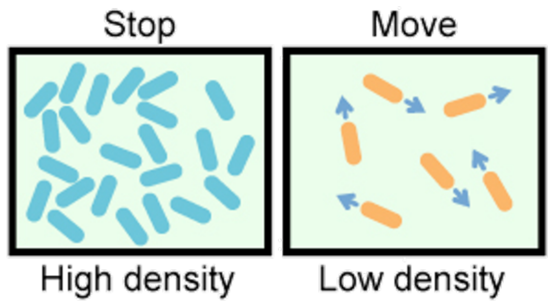
– hair follicles in developing mice (Cheng et al, 2012)





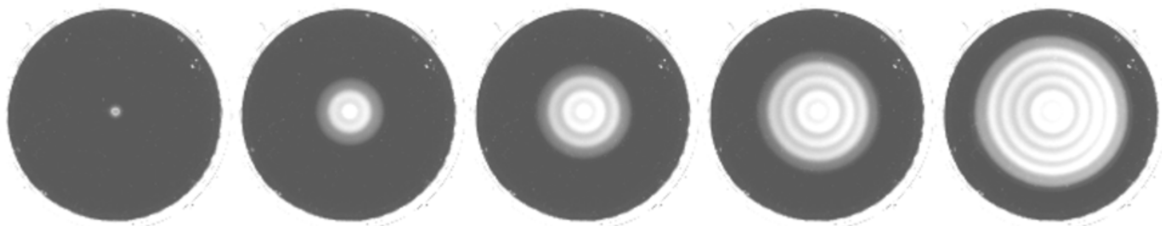
– Synthetic pattern from engineered bacteria (Liu et al, 2011)



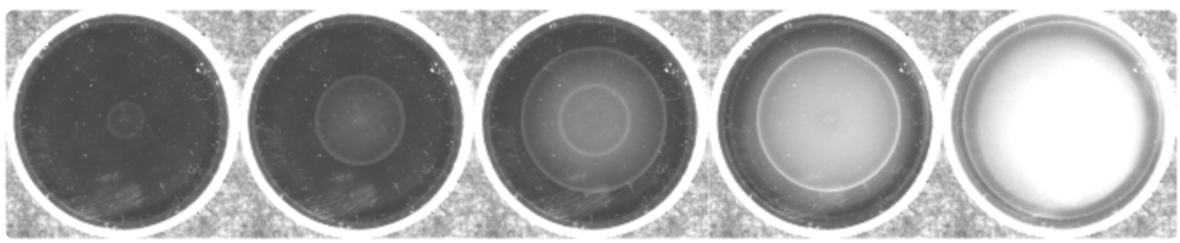


→ time

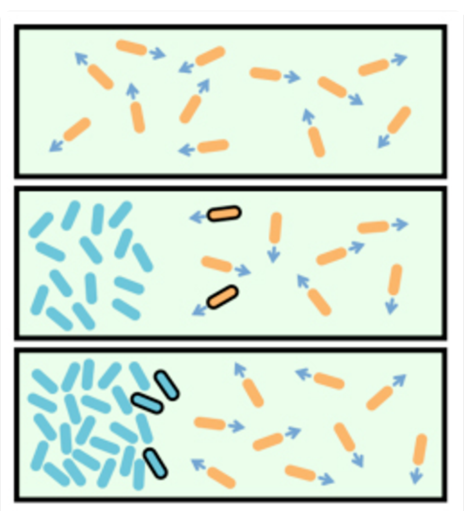
engr strain



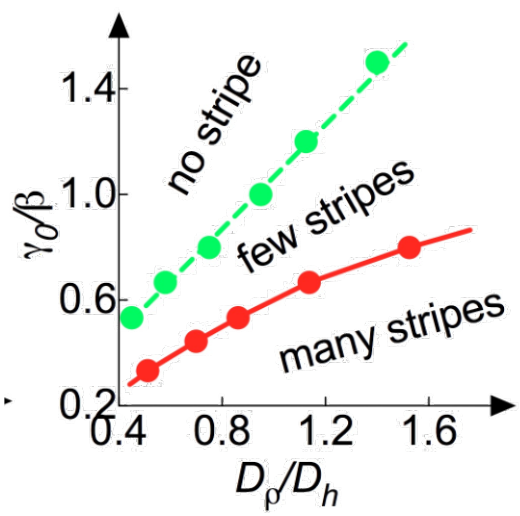
WT



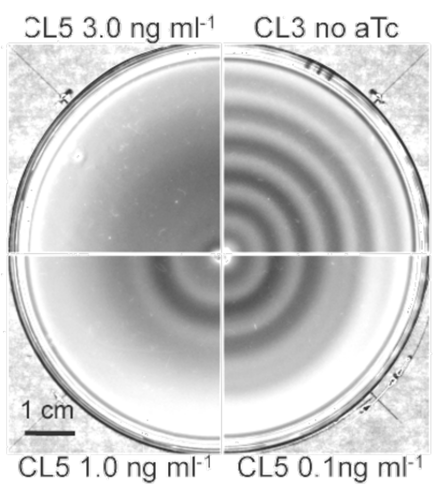
Mechanism:



Phase diagram:

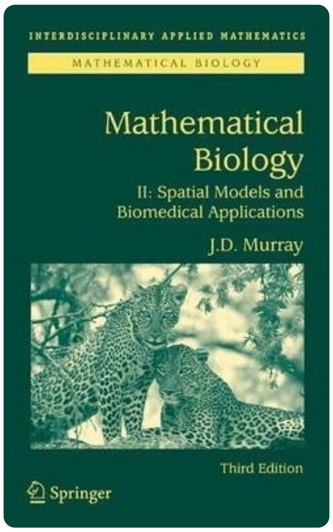


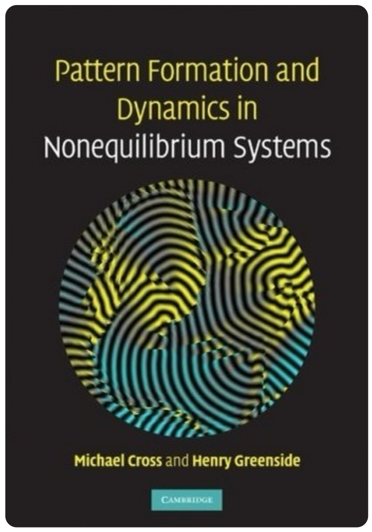
vary D_ρ



Outline for this section:

- describe the math of Turing instability
- pattern formation for simple dynamical system
- Turing space: mode selection
  and system size dependence





- Amplitude eqn: Stripe vs spots
  secondary instability

⇒ bio applications (team projects)

2. Turing instability

Recall $N=2$ dynamical system

$$\begin{cases}\dot u = f(u,v)\\ \dot v = g(u,v)\end{cases} \xrightarrow[v=v^*+\delta v]{u=u^*+\delta u} \begin{pmatrix}\delta\dot u\\ \delta\dot v\end{pmatrix} = M\begin{pmatrix}\delta u\\ \delta v\end{pmatrix}$$

Community matrix M:

$$M = \begin{pmatrix} f_u & f_v\\ g_u & g_v\end{pmatrix};$$

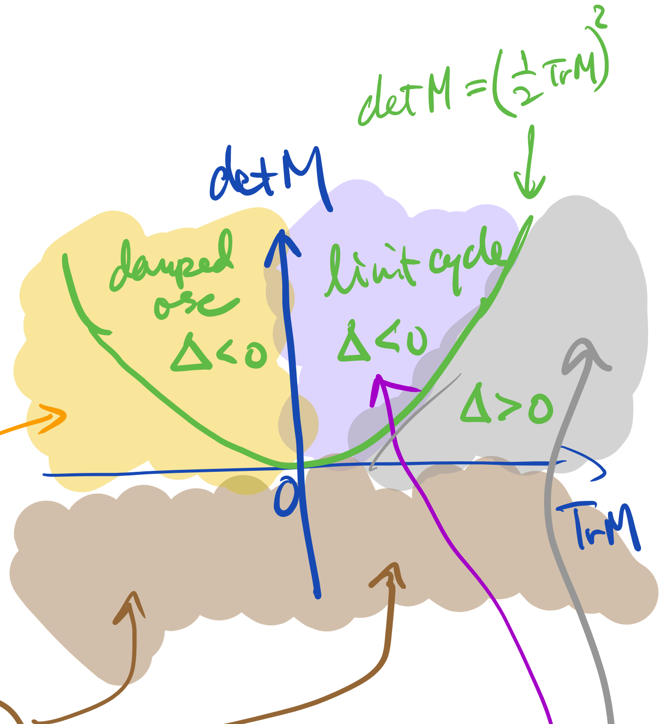
$\det(M-\lambda I)=0$

$\to (f_u-\lambda)(g_v-\lambda) - f_v g_u = 0$

(Note derivatives evaluated at u^*, v^*)

$$\lambda^2 - \lambda\underbrace{(f_u+g_v)}_{\mathrm{Tr}M} + \underbrace{f_u g_v - f_v g_u}_{\det M} = 0$$

$$\lambda = \frac{1}{2}\mathrm{Tr}M \pm \sqrt{\underbrace{\left(\tfrac{1}{2}\mathrm{Tr}M\right)^2 - \det M}_{\Delta}}$$



→ Condition for stability:

$\left.\begin{array}{l}\mathrm{Tr}M<0\\ \det M>0\end{array}\right\}$ $\lambda_\pm < 0$

→ bistability (saddle pt)

$\det M<0$: $\lambda_+>0,\ \lambda_-<0$

→ unstable spiral: $\mathrm{Tr}M>0,\ \det M > \left(\frac{1}{2}\mathrm{Tr}M\right)^2$

→ unstable node: $\left.\begin{array}{l}\mathrm{Tr}M>0\\ \det M < \left(\frac{1}{2}\mathrm{Tr}M\right)^2\end{array}\right\}$ $\lambda_\pm > 0$

from the stable state ($\mathrm{Tr}\,M<0$, $\det M>0$)

- transition across $\mathrm{Tr}\,M=0$: Hopf bifurcation
- transition across $\det M=0$ (for finite k):

Turing instability (1952)

* Consider diffusive spatial coupling:

(1912 - 1954)

$$\partial_t u = f(u,v) + D_u \partial_x^2 u$$
$$\partial_t v = g(u,v) + D_v \partial_x^2 v.$$

Finite wavelength perturbation (k = wave #)

let $u(x,t) = u^* + \delta u(t)\, e^{ikx}$

$v(x,t) = v^* + \delta v(t)\, e^{ikx}$

$$\frac{\partial}{\partial t}\begin{pmatrix}\delta u\\ \delta v\end{pmatrix} = \begin{pmatrix} f_u & f_v\\ g_u & g_v\end{pmatrix}\begin{pmatrix}\delta u\\ \delta v\end{pmatrix} + \begin{pmatrix}-D_u k^2 \delta u\\ -D_v k^2 \delta v\end{pmatrix}$$

$$\Rightarrow \underbrace{\begin{pmatrix} f_u - D_u k^2 & f_v\\ g_u & g_v - D_v k^2\end{pmatrix}}_{M(k)} - \lambda I = 0$$

Stability at k: $\det\left[M(k) - \lambda I\right] = 0$

$$\rightarrow \lambda^2 - \lambda \underbrace{\mathrm{Tr}(M(k))}_{T(k)} + \underbrace{\mathrm{Det}(M(k))}_{\Delta(k)} = 0$$

$$\lambda(k) = \frac{T(k)}{2} \pm \sqrt{\left(\frac{T(k)}{2}\right)^2 - D(k)}$$ (dispersion relation)

* Express $T(k)$ and $D(k)$ in terms of $T(0)$, $D(0)$

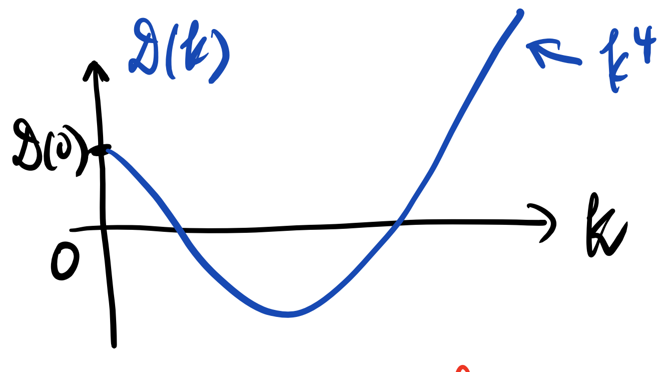
$$T(k) = f_u - D_u k^2 + g_v - D_v k^2$$
$$= T(0) - D_u k^2 - D_v k^2$$

→ since $k=0$ state stable, $T(0) < 0$, → $T(k) < 0 \ \forall k$.

$$D(k) = f_u g_v - f_v g_u + D_u D_v k^4$$
$$- (g_v D_u k^2 + f_u D_v k^2)$$
$$= D(0) - (g_v D_u + f_u D_v) k^2 + D_u D_v k^4$$

Since $k=0$ state stable, then $D(0) > 0$.

→ possible for $D(k)$ to be -ve for some k.



– requires $g_v D_u + f_u D_v > 0$

but since $f_u + g_v = T(0) < 0$,

→ must have $D_u \neq D_v$

and f_u, g_v have opposite sign.

Without loss of generality, take $f_u > 0 > g_v$

i.e., v is auto-inhibiting,

u is auto-activating

Since $f_u + g_v < 0 \to |g_v| > |f_u|$

for $f_u D_v + g_v D_u > 0$,

must have $D_v > D_u$

$\Rightarrow$ Inhibitor diffuses more rapidly than activator!

Note: Since $\Delta(0) = f_u g_v - f_v g_u > 0$.

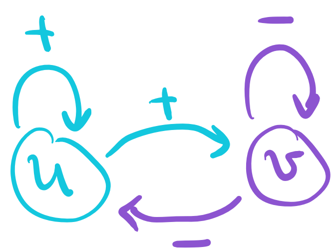
and $f_u g_v < 0$

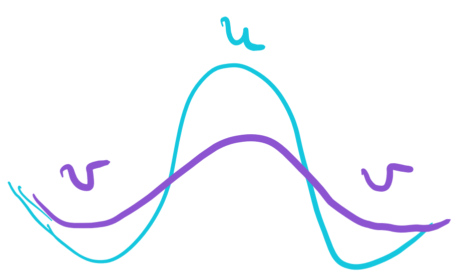
we must also have $f_v g_u < 0$

two scenarios:

i) $f_v < 0$, $g_u > 0$.

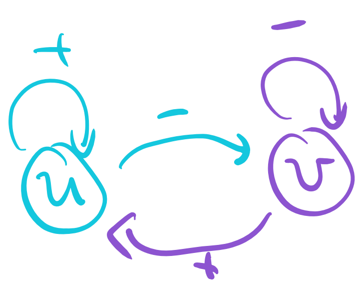
$$M = \begin{pmatrix} + & - \\ + & - \end{pmatrix}$$

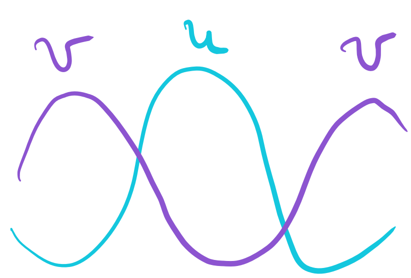




ii) $f_v > 0$ $g_u < 0$

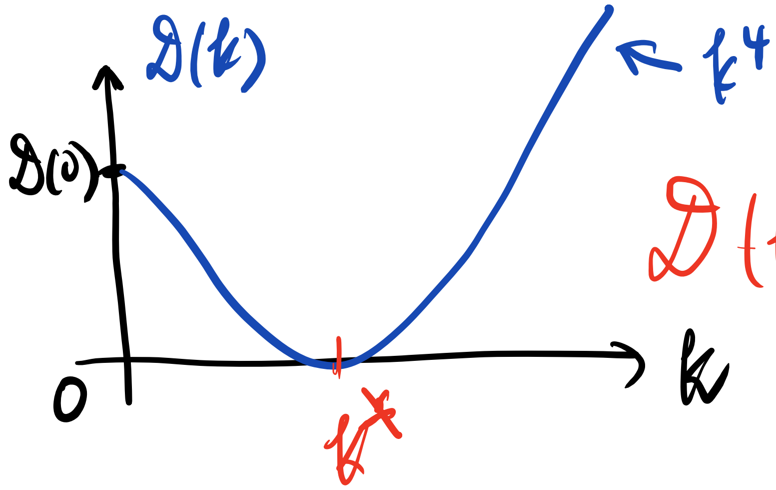
$$M = \begin{pmatrix} + & + \\ - & - \end{pmatrix}$$





* quantitative criterion for Turing instability:

$$\mathcal{D}(k) = \mathcal{D}(0) - (g_v D_u + f_u D_v)\,k^2 + D_u D_v\, k^4$$



$\mathcal{D}(k^*) \leq 0$

minimum: $\displaystyle \frac{d}{dk}\mathcal{D}(k)\Big|_{k^*} = 0 = -2k^*(g_v D_u + f_u D_v) + 4(k^*)^3 D_u D_v$

$$(k^*)^2 = \frac{g_v D_u + f_u D_v}{2 D_u D_v}.$$

$$\mathcal{D}(k^*) = \mathcal{D}(0) - \frac{(g_v D_u + f_u D_v)^2}{2 D_u D_v} + \cancel{D_u D_v}\,\frac{(g_v D_u + f_u D_v)^2}{4 D_u^{\cancel{2}} D_v^{\cancel{2}}}$$

$$= \mathcal{D}(0) - \frac{(g_v D_u + f_u D_v)^2}{4 D_u D_v}$$

$\Rightarrow$ quantitative criterion for Turing instability:

$\mathcal{D}(k^*) \leq 0$: $\quad f_u D_v + g_v D_u \geq 2\sqrt{\mathcal{D}(0)\, D_u \cdot D_v}$

at threshold, unstable mode is

$$(k^*)^2 = \frac{g_v D_u + f_u D_v}{2 D_u D_v} = \frac{\cancel{2}\sqrt{\mathcal{D}(0) D_u D_v}}{\cancel{2} D_u D_v} = \sqrt{\frac{\mathcal{D}(0)}{D_u D_v}}$$

3. Turing Space:

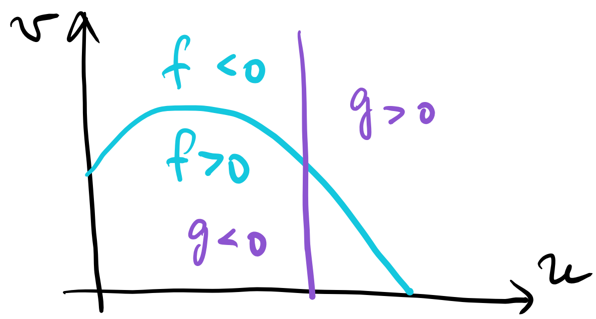
parameter space where Turing instability occurs

$$\partial_t u = f(u,v) + D_u \partial_x^2 u$$
$$\partial_t v = g(u,v) + D_v \partial_x^2 v.$$

Specific examples: requirement $f_u > 0 > g_v$

- predator-prey systems insufficient ($g_v = 0$)

$$f(u,v) = u(1-u) - \frac{uv}{1+u/K}$$
$$g(u,v) = \left(\frac{1}{\gamma}\frac{u}{1+u/K} - 1\right)\cdot v$$

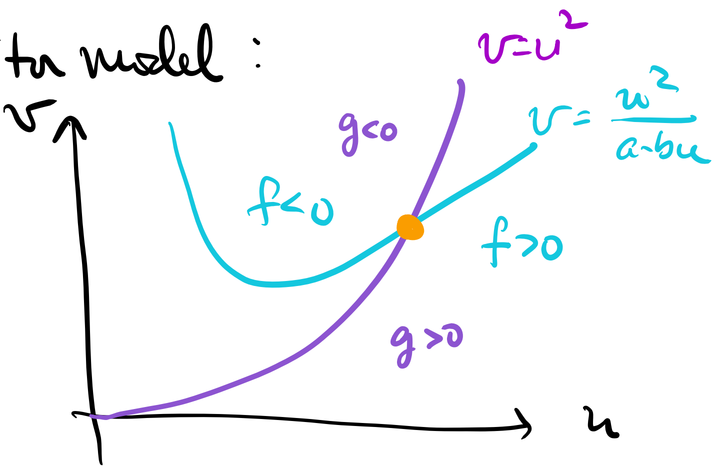


- Meinhardt's activator-inhibitor model:

$$f(u,v) = a - bu + u^2/v$$
$$g(u,v) = u^2 - v$$

$f_u > 0$, $f_v < 0$

$g_u > 0$, $g_v < 0$ ok



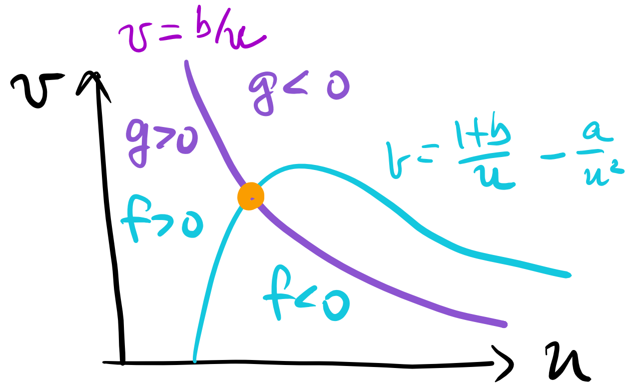
but mathematically cumbersome to analyze.

→ will use the "Brusselator" model: $\begin{cases} A \to B \\ 2A + B \to 3A \end{cases}$

$$f(u,v) = a - (1+b)u + u^2 v$$
$$g(u,v) = bu - u^2 v$$

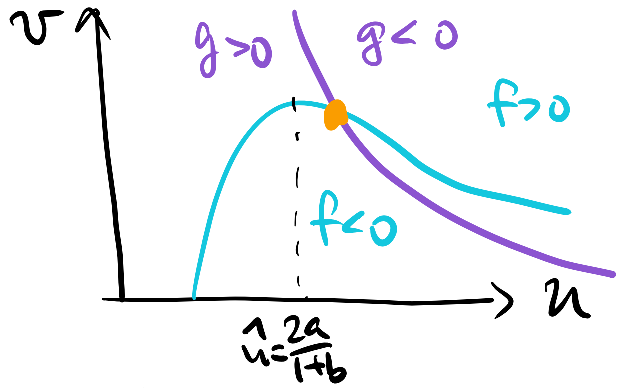
$f_u < 0 \quad f_v > 0$
$g_u < 0 \quad g_v < 0$

no Turing Instability



$f_u > 0, \quad f_v > 0$
$g_u < 0, \quad g_v < 0$

$\rightarrow$ Turing Instab.



(requires $u^* > \hat{u}$)

Explicitly compute:

$g = 0 \rightarrow v^* = b/u^* = b/a$

$f = 0 \rightarrow u^* = a$

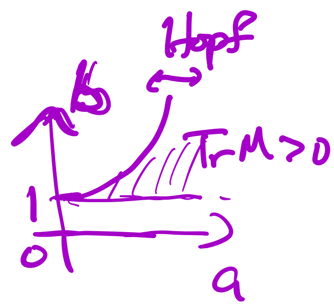
$f_u^* = -(1+b) + 2u^*v^* = b-1, \quad f_v^* = (u^*)^2 = a^2$

$g_u^* = b - 2uv = -b, \quad g_v^* = -u^2 = -a^2$

Note: Turing instability requires $\underline{f_u > 0} > g_v$
(or $b > 1$)

also, $\mathrm{Tr}M < 0$: $f_u + g_v < 0 \rightarrow b - 1 - a^2 < 0$

$\Rightarrow \boxed{1 < b < 1 + a^2}$



Next, look at spatio temporal perturbation:

$u(x,t) = u^* + \delta u \, e^{\lambda t} e^{ikx}$

$v(x,t) = v^* + \delta u \, e^{\lambda t} e^{ikx}$

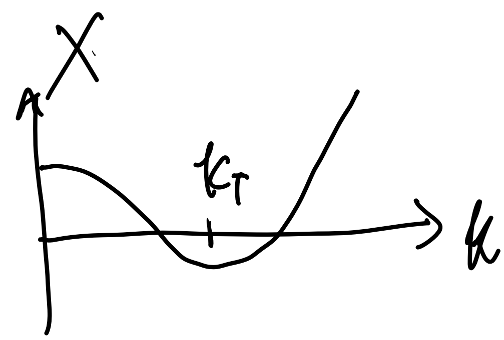
$$\lambda \begin{pmatrix} \delta u \\ \delta v \end{pmatrix} = \begin{pmatrix} b-1 & a^2 \\ -b & -a^2 \end{pmatrix} \begin{pmatrix} \delta u \\ \delta v \end{pmatrix} + \begin{pmatrix} -D_u k^2 \delta u \\ -D_v k^2 \delta v \end{pmatrix}$$

$$\left[b-1-D_u k^2-\lambda\right]\cdot\left[-a^2-D_v k^2-\lambda\right]+a^2 b=0$$

$$\lambda^2+\lambda\left((D_u+D_v)k^2+a^2-(b-1)\right)+D_uD_v k^4-\left(D_v(b-1)-D_u a^2\right)k^2+a^2=0$$

$$\lambda=-\frac{1}{2}\left[(D_u+D_v)k^2+(a^2+1-b)\right]\cdot\left(1\pm\sqrt{1-X}\right)$$

$$X=\frac{D_uD_v k^4-\left(D_v(b-1)-D_u a^2\right)k^2+a^2}{\frac{1}{4}\left[(D_u+D_v)k^2+(a^2+1-b)\right]^2}$$



Turing instability: $X(k\neq 0)<0$

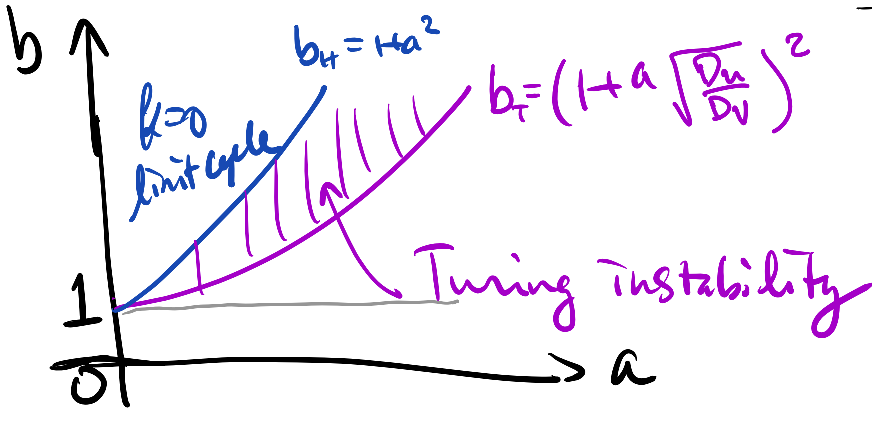
$$\left.\frac{dX}{dk}\right|_{k_T}=0 \rightarrow 4D_uD_v k_T^3-2k_T\left(D_v(b-1)-D_u a^2\right)=0$$

$$k_T^2=\frac{D_v(b-1)-D_u a^2}{2D_uD_v}\ ; \quad k_T^2>0 \rightarrow b>1+\frac{D_u}{D_v}a^2$$

$$X(k_T)\leq 0 \rightarrow \frac{\left[D_v(b-1)-D_u a^2\right]^2}{4D_uD_v}\geq a^2$$

$$D_v(b-1)-D_u a^2 \geq 2a\sqrt{D_uD_v} \rightarrow \boxed{b\geq\left(1+a\sqrt{\frac{D_u}{D_v}}\right)^2}>1+\frac{D_u}{D_v}a^2$$

$$\text{or,}\ D_v(b-1)-D_u a^2 \leq -2a\sqrt{D_uD_v} \rightarrow b\leq\left(1-a\sqrt{\frac{D_u}{D_v}}\right)^2<1$$



for $D_v>D_u$

→ work in system size L explicitly into dynamics (since change in L commonly encountered in development)

let $\xi=x/L$, $\tau=D_u t/L^2$; $\gamma\equiv\frac{L^2}{D_u}$, $D=\frac{D_v}{D_u}$

then $\partial_\tau u=\gamma f(u,v)+\partial_\xi^2 u$

$\partial_\tau v=\gamma g(u,v)+D\partial_\xi^2 v$

(will call ξ by x, τ by t)

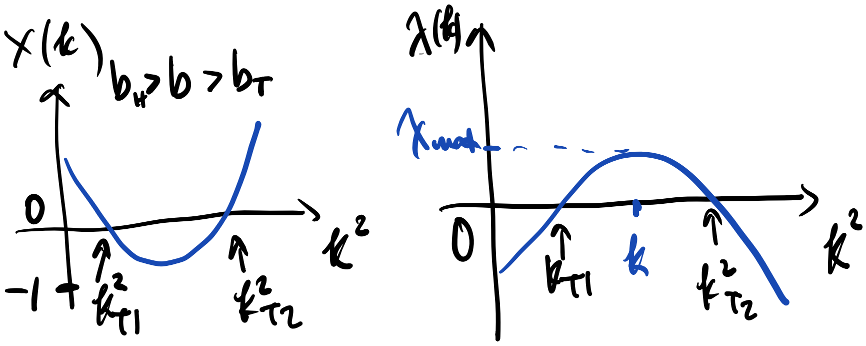
4. Mode Selection:

At the threshold of Turing instability,

$$k_T^2 = \frac{D_v(b-1) - D_u a^2}{2D_u D_v} \overset{b=b_T}{=} \frac{a}{\sqrt{D_u D_v}}$$

- for $b_H > b > b_T$, $\lambda(k) > 0$ for a range $k_{T_1} < k < k_{T_2}$

from $\lambda = -\frac{1}{2}\left[(D_u+D_v)k^2 + (a^2+1-b)\right]\cdot\left(1 \pm \sqrt{1-X}\right)$



$$X(k) = 0 \rightarrow D_u D_v k^4 - \left(D_v(b-1) - D_u a^2\right)k^2 + a^2$$

$$k^2 = \frac{D_v(b-1) - D_u a^2}{2D_u D_v} \pm \sqrt{\left(\frac{D_v(b-1)-D_u a^2}{2D_u D_v}\right)^2 - \frac{a^2}{D_u D_v}}$$

$$\sqrt{\cdots} = \sqrt{\left[\frac{1}{2D_u}\left(b - b_T + 2a\sqrt{\frac{D_u}{D_v}}\right)\right]^2 - \frac{a^2}{D_u D_v}}$$

$$= \frac{1}{2D_u}\sqrt{(b-b_T)^2 + 4a\sqrt{\frac{D_u}{D_v}}(b-b_T)}$$

since $b_T = \left(1 + a\sqrt{\frac{D_u}{D_v}}\right)^2 = 1 + a^2\frac{D_u}{D_v} + 2a\sqrt{\frac{D_u}{D_v}}$

$$k^2 = \frac{1}{2D_u}\left(\left(b - b_T + 2a\sqrt{\frac{D_u}{D_v}}\right) \pm \sqrt{4a\sqrt{\frac{D_u}{D_v}}(b-b_T) + (b-b_T)^2}\right)$$

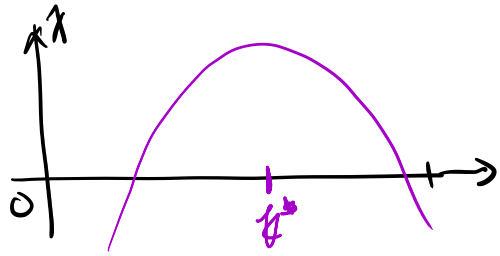
$$\simeq \frac{a}{\sqrt{D_u D_v}} \pm \sqrt{4a\sqrt{\frac{D_u}{D_v}}(b-b_T)} \quad \text{for } b \gtrsim b_T.$$

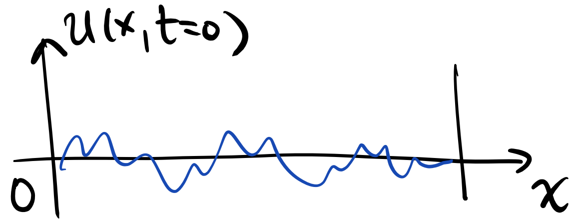
refer to the two roots as $k_\pm$, then $k_{T_1} = k_-$, $k_{T_2} = k_+$

$k_+ - k_- = \Delta k \propto \sqrt{b - b_T}$ close to threshold.

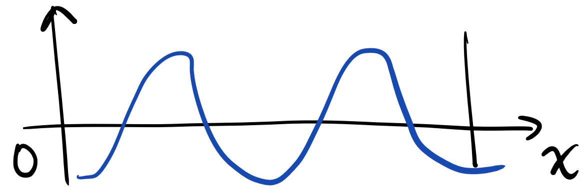
⟹ for large Δt, most unstable mode k^* (where $\lambda(k^*)$ is maximum) dominates

since $u(x,t) = e^{\lambda(k)t} \cos kx$





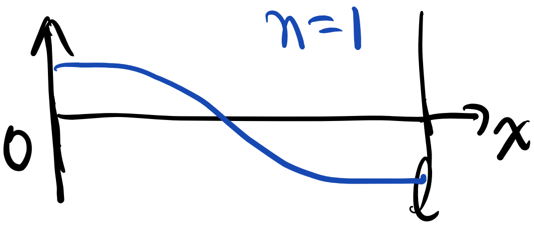
⟹



→ stabilized by higher order nonlinearity (later)

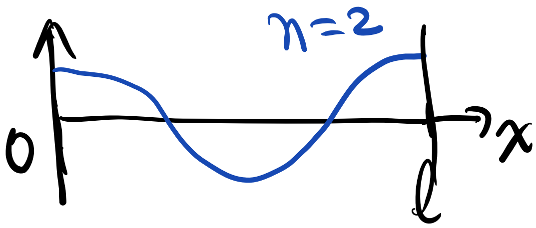
▷ discreteness important for small systems or $b \gtrsim b_T$

<u>allowed</u> k over interval ℓ (in 1d)



suppose $\frac{\partial u}{\partial x} = 0$ at both boundary

then $u(x,t) = \delta u \, e^{\lambda t} \cdot \cos \frac{n\pi x}{\ell}$

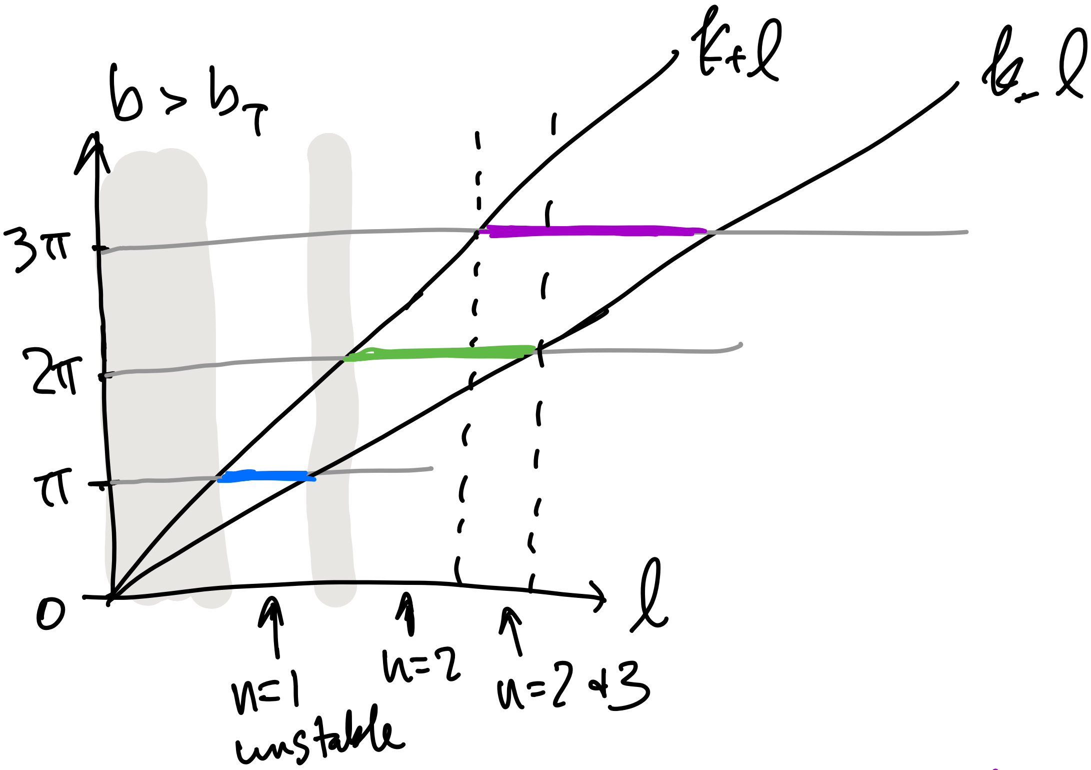


$k = \frac{n\pi}{\ell}$, $n = \pm 1, \pm 2, \dots$

unstable modes: $k_{T1} \le k \le k_{T2}$

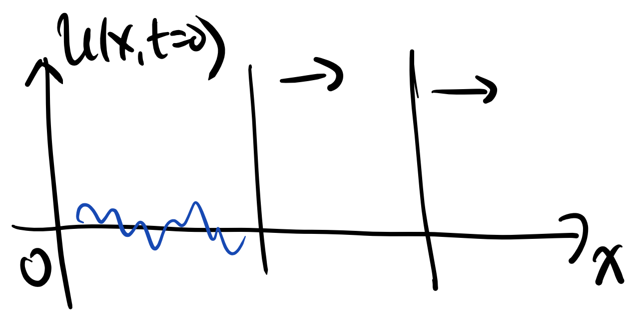
→ $\ell \cdot k_- \le n\pi \le \ell \cdot k_+$

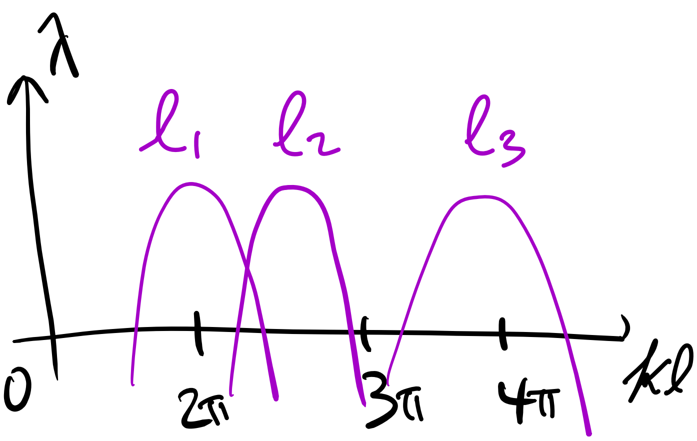
$$k_\pm^2 = \frac{1}{2D_u}\left(\left(b - b_T + 2a\sqrt{\frac{D_u}{D_v}}\right) \pm \sqrt{4a\sqrt{\frac{D_u}{D_v}}(b-b_T) + (b-b_T)^2} \right)$$

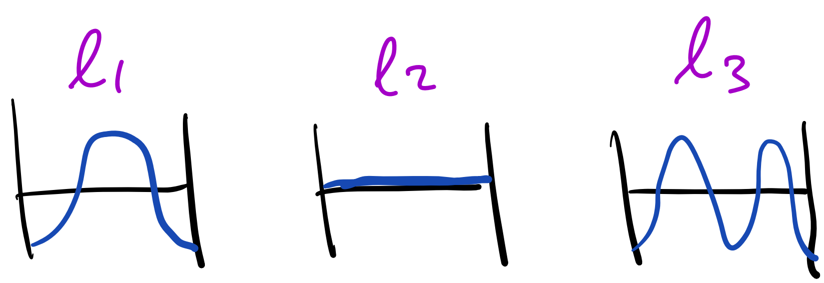


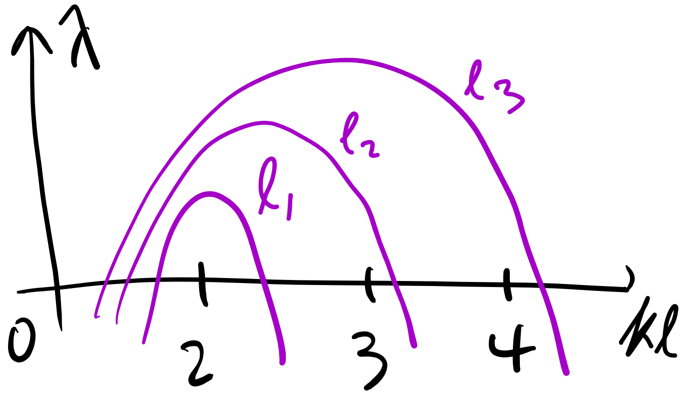
Close to the threshold: $b \gtrsim b_T$, $\Delta k = k_+ - k_- \to 0$
→ the two slopes are similar; unstable modes allowed only for narrow range of l

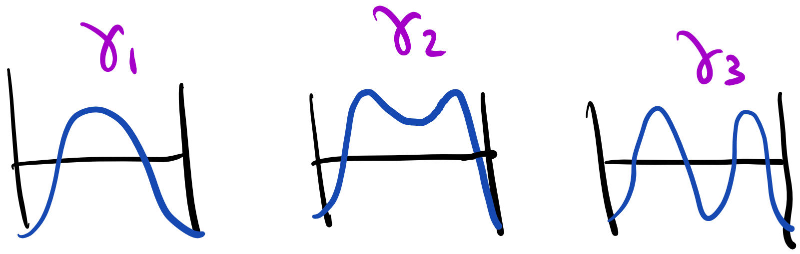
Domain growth:











Many biological applications

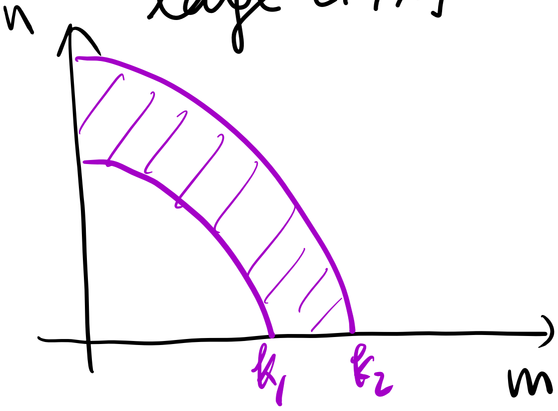
* 2d patterns:

Same condition for instability: $k_-^2 < k^2 < k_+^2$

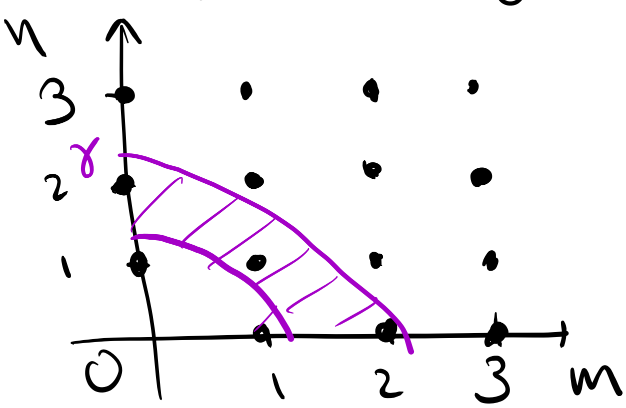
but for $u(x,y) \sim \cos\frac{m\pi x}{l_x} \cdot \cos\frac{n\pi y}{l_y}$

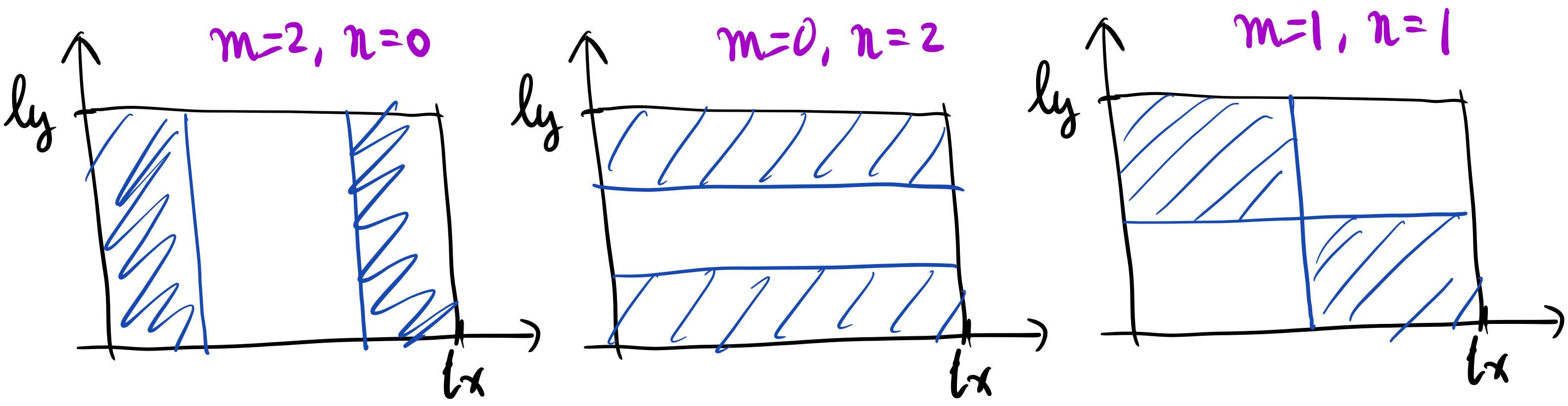
$$k^2 = \left(\frac{m\pi}{l_x}\right)^2 + \left(\frac{n\pi}{l_y}\right)^2$$

large l_x, l_y



Small l_x, l_y





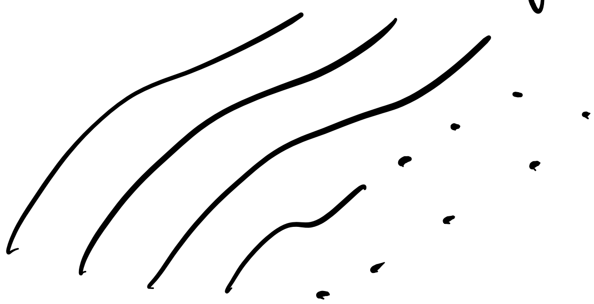
other tesselation pattern, e.g. hexagonal.

$$u(x,y) \sim \cos kx + \cos k\left(\frac{x}{2}+\frac{\sqrt{3}}{2}y\right) + \cos k\left(\frac{\sqrt{3}}{2}y-\frac{x}{2}\right)$$

$\Rightarrow$ regular array of spots

(e.g. hair follicles, spot coating, ...)

or combination of stripes and spots.



$\Rightarrow$ pattern selection depends on nonlinear terms which stabilizes linear instability