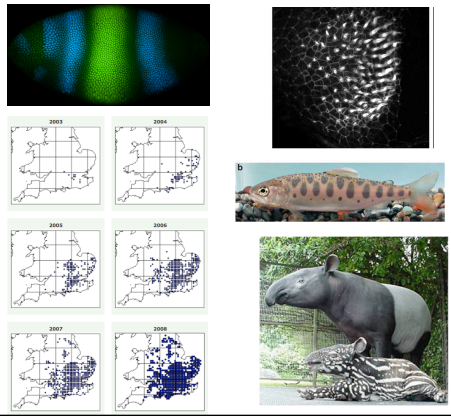
CPIB SUMMER SCHOOL 2011: INTRODUCTION TO BIOLOGICAL MODELLING

Lecture 4.1
Spatial Models

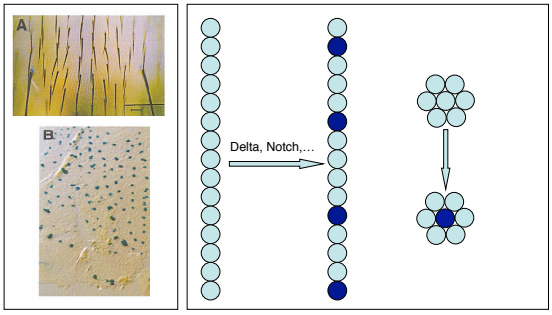
Nick Monk

Spatial Modelling

- The models we have looked at so far have all assumed that our reacting species are distributed uniformly in space.
- While this is sufficient for many processes, there are also many processes that are spatially heterogeneous:
  - Intracellular Ca^{2+} waves
  - Pattern formation in development
  - Spread of infections in a population
  - Population movement

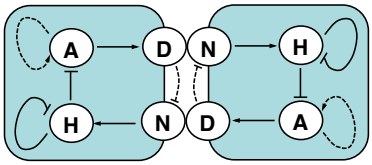


Lateral inhibition



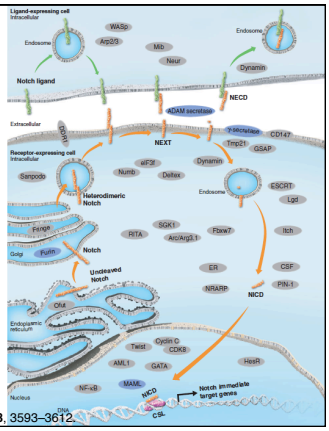
Renaud & Simpson, *Dev. Biol.* **240**, 361–376 (2001).

The Notch intercellular signalling network



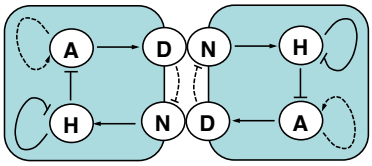
- **D** DSL (Delta–Serrate–Lag-2) family ligand
- **N** Notch family receptor
- **H** Hes/Her basic helix-loop-helix transcriptional repressor
- **A** Proneural basic helix-loop-helix transcriptional activator (Achaete, Scute, Atonal, Neurogenin, …)

Many details glossed over…



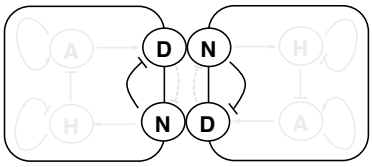
Andersson *et al.* (2011). *Development* **138**, 3593–3612.

The Notch intercellular signalling network



- Multiple feedbacks. What is the core logic of the fate patterning process?
- Use Notch signalling activity as an indicator of cell fate (based on genetic data).
- Assess models of reduced networks.

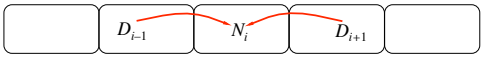
The Notch intercellular toggle switch



- Neglect local (cell autonomous) feedback loops
- Collapse linear pathways
- Signalling-dependent (*directional*) toggle switch via a double-negative feedback loop

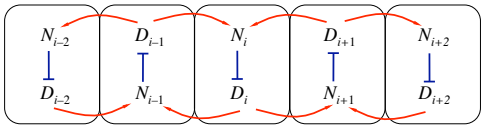
Spatial model of Notch signalling

- Consider a line of cells (index $i = 1, 2, 3, \ldots, M$)
- Each cell has levels of Notch and Delta activities (N_i and D_i)
- Notch activity in cell i is regulated by Delta activity in cells $i - 1$ and $i + 1$



- Delta activity in cell i is regulated by Notch activity in cell i
- Use a simplified representation of interactions (production and degradation) rather than a detailed representation of the biochemistry

Spatial model of Notch signalling



Rate of change = Production – Degradation

$$\frac{dN_i}{dt} = p_N f\left(\langle D\rangle_i\right) - \delta_N N_i \qquad \langle D\rangle_i = \frac{D_{i-1} + D_{i+1}}{2}$$

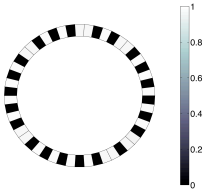
$$\frac{dD_i}{dt} = p_D g\left(N_i\right) - \delta_D D_i \qquad f \text{ increasing}$$

$$g \text{ decreasing}$$

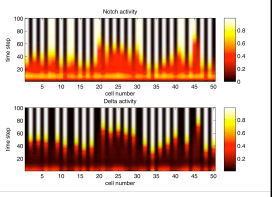
Dynamics of lateral inhibition

The model is just a set of ODEs, so we can use the same tools as before to find time course solutions

Notch activity (steady state)

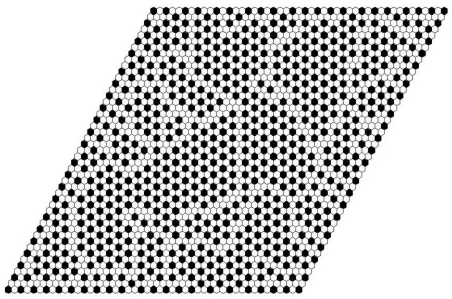


Time course of activities



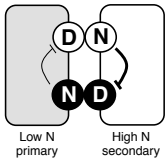
Two-dimensional array (hexagons)

Nearest-neighbour signalling results in fine-grained patterns of Notch activity



Mutual Support of Cell Fates

- Signalling-dependent (*directional*) toggle switch via a double-negative feedback loop.
- Stable one-way "conversations" (Primary fate cells speaking: *lateral inhibition with feedback*).



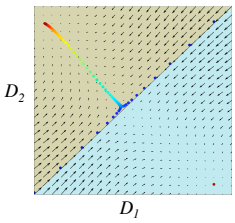
Phase Plane Analysis (toggle switch)

$$\frac{dN_i}{dt} = p_N f\left(\langle D\rangle_i\right) - \delta_N N_i$$

$$\frac{dD_i}{dt} = p_D g\left(N_i\right) - \delta_D D_i$$

Set $0 = p_N f\left(\langle D\rangle_i\right) - \delta_N N_i$ (QSS)

$$\Longrightarrow \frac{dD_i}{dt} = p_D g\left(\frac{p_N f\left(\langle D\rangle_i\right)}{\delta_N}\right) - \delta_D D_i$$

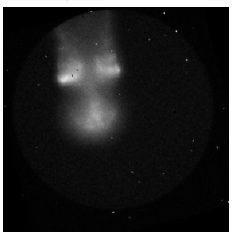


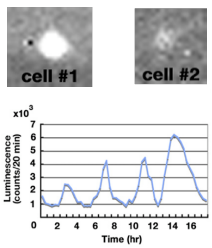
For strict period-2 pattern:

$$\frac{dD_1}{dt} = p_D g\left(\frac{p_N f\left(D_2\right)}{\delta_N}\right) - \delta_D D_1, \quad \frac{dD_2}{dt} = p_D g\left(\frac{p_N f\left(D_1\right)}{\delta_N}\right) - \delta_D D_2$$

Notch network transcriptional oscillations

presomitic mesoderm *Hes1*::Ub1-Luc *neural progenitors*



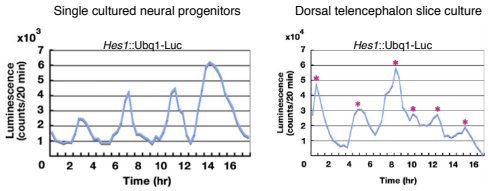


Masamizu *et al., PNAS.* **103**, 1313–1318 (2006).

Shimojo *et al., Neuron* **58**, 52–64(2008).

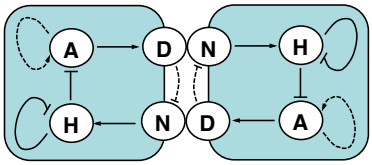
Hes1 oscillations in the developing brain

- Oscillations of Hes1, Ngn2 and Dll1 (all Notch pathway) maintain neural progenitors in the developing mouse brain.
- Notch signalling underlies neural differentiation.



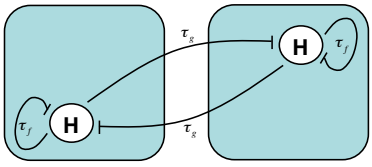
Shimojo *et al. Neuron* **58**, 52–64 (2008).

The Notch intercellular signalling network



- **D** DSL (Delta–Serrate–Lag-2) family ligand
- **N** Notch family receptor
- **H** Hes/Her basic helix-loop-helix transcriptional repressor
- **A** Proneural basic helix-loop-helix transcriptional activator (Achaete, Scute, Atonal, Neurogenin, …)

Coupled Hes oscillators

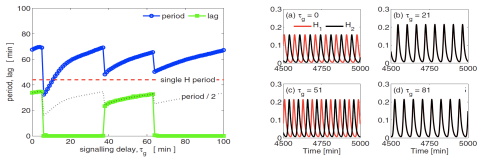


Consider the remainder of the network as intercellular coupling between cell-autonomous oscillators.

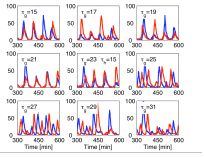
Multiple steps result in signalling delay (in addition to local delay).

Coupled Hes oscillators

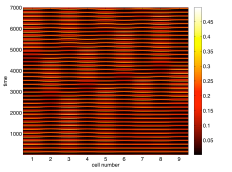
Synchronisation (in-phase or out-of-phase)

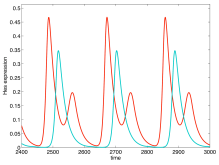


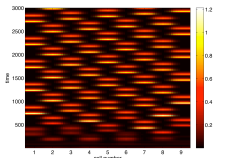
Phase waves (somitogenesis)

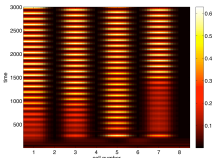


Coupled Hes in rings of cells

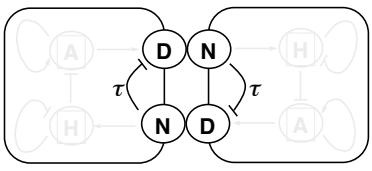






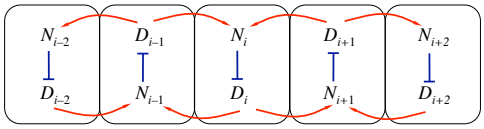


The delayed Notch intercellular toggle switch



- Reduce the Notch response network in a cell to simple down-regulation of Delta activity.
- Hes oscillator models show the importance of incorporating time delays.

Delay model of Notch signalling



Rate of change = Production – Degradation

$$\frac{dN_i}{dt} = p_N f\left(\langle D\rangle_i\right) - \delta_N N_i$$

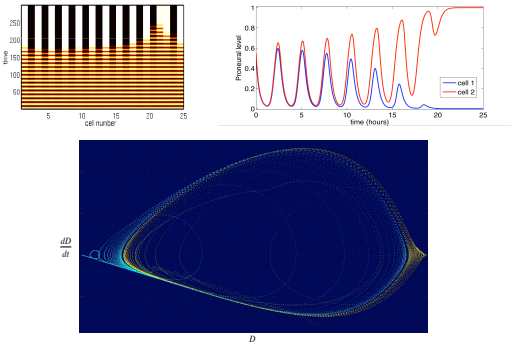
$$\frac{dD_i}{dt} = p_D g\left[N_i(t-\tau)\right] - \delta_D D_i$$

$$\langle D\rangle_i = \frac{D_{i-1} + D_{i+1}}{2}$$

f increasing

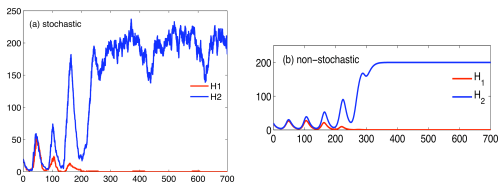
g decreasing

Delay toggle switch: oscillatory transients

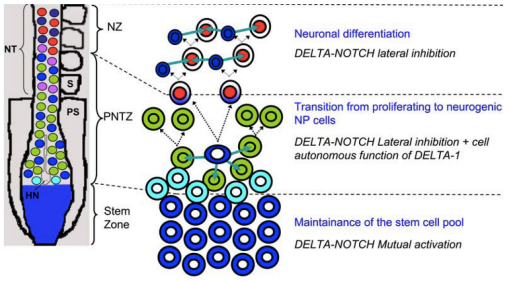


Stochastic switches

Delay stochastic kinetics (DSSA) result in shorter transient oscillations, but qualitative behaviour is not changed.

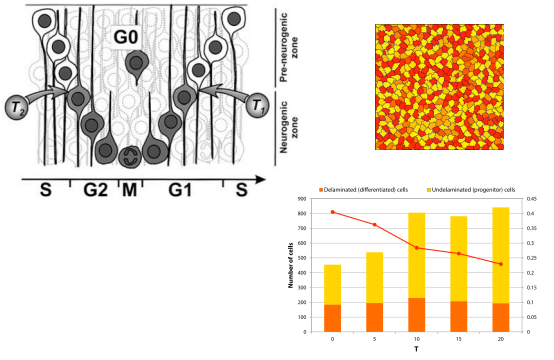


Dynamics of neurogenesis



Hämmerle & Tejedor *PLoS ONE*. **2**, e1169 (2007).

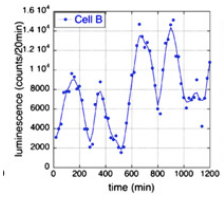
Dynamics of neurogenesis



Stem Cell Heterogeneity

Hes1 also oscillates in mouse ES cells

- Low Hes1 → neural
- High Hes1 → mesodermal



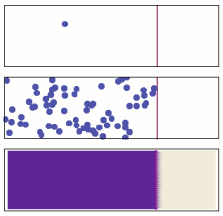
Loss of Hes1 oscillations:

- Premature differentiation
- More homogeneous differentiation

Kobayashi *et al. Genes Dev.* **23**, 1870–1875 (2009).

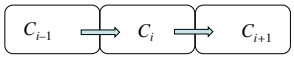
Movement: diffusion

- Particles undergoing Brownian motion will tend to move on average from regions of higher to lower concentration
- Can represent this as a spatially continuous concentration.



Movement: diffusion

- In a spatially discrete model (like the cellular Notch signalling model), we can ask what is the overall flux of molecules between cells.



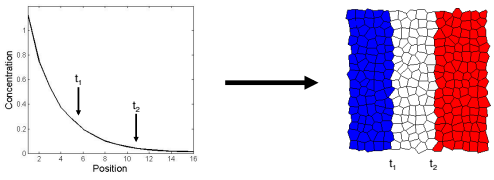
- Net flux from cell $i-1$ to cell i is just $D(C_{i-1} - C_i)$

for some constant D. Thus, a simple rate law is:

$$\frac{dC_i}{dt} = D(C_{i-1} + C_{i+1} - 2C_i) - \delta C_i + \text{source} + \text{reactions}$$

Positional Information: Classical view

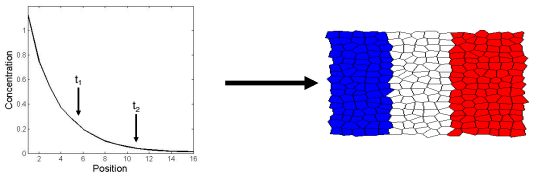
Wolpert (1968): Instructive information from boundaries/sources generates a coordinate system.



Gradient formation → Signalling & patterning

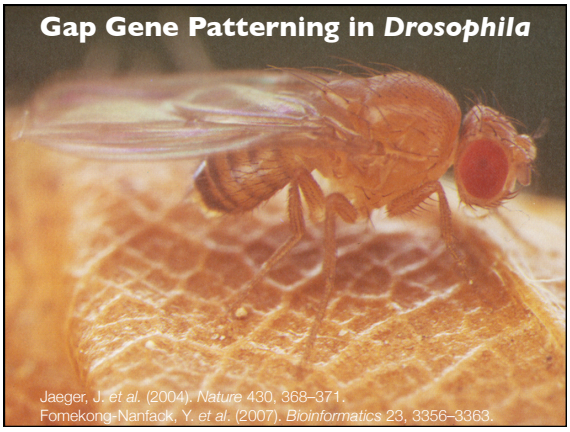
Positional Information: Classical view

Wolpert (1968): Instructive information from boundaries/sources generates a coordinate system.



Gradient formation → Signalling & patterning → Growth/ morphogenesis

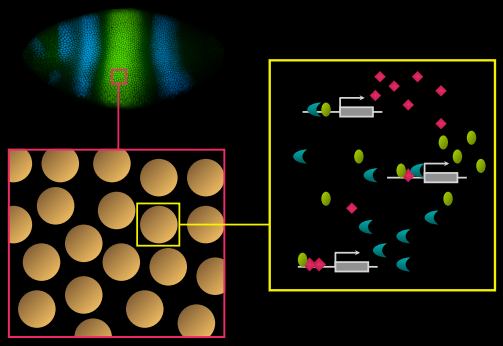
Gap Gene Patterning in *Drosophila*



Jaeger, J. *et al.* (2004). *Nature* 430, 368–371.
Fomekong-Nanfack, Y. *et al.* (2007). *Bioinformatics* 23, 3356–3363.

Maternal Coordinate Genes	Bcd	*bicoid (bcd)* *caudal (cad)* *hunchback (hb)*
Gap Genes	Kr	*hunchback (hb)* *Krüppel (Kr)* *knirps (kni)* *giant (gt)* *tailless (tll)*
Pair Rule Genes	Eve	*even-skipped (eve)* *odd-skipped (odd)* *hairy (h)* *runt (run)* *fushi-tarazu (ftz)* *paired (prd)*
Segment Polarity Genes	En	*engrailed (en)* *wingless (wg)*

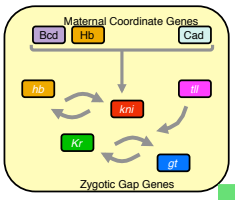
Gap proteins regulate gap genes



Summary

- Transcription delays play a critical role in ultradian transcriptional oscillations.
- It is difficult to generate large amplitude oscillations with short periods. Coupling of distinct oscillators can increase amplitudes.
- Delays can also drive a range of transient oscillations in intercellular toggle switches (*pattern formation*).
- Transient Notch oscillations are a natural feature of fate choices in the presence of delays. No extrinsic factors are necessary to stop oscillations. Can control balance between proliferation and differentiation.

Spatial ODE Model



1. Protein Synthesis
2. Protein Transport
3. Protein Decay

$$\frac{dv_i^a}{dt} = R_a g_a\left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{\mathrm{Bcd}} + h_a\right) + D^a(n)\left[\left(v_{i-1}^a - v_i^a\right) + \left(v_{i+1}^a - v_i^a\right)\right] - \lambda_a v_i^a$$

Synthesis

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{\mathrm{Bcd}} + h_a \right)$$

The Genetic Interconnectivity Matrix (T Matrix)

Gene a \ b	1	2	⋯	N
1	T^{11}	T^{12}	⋯	T^{1N}
2	T^{21}	T^{22}	⋯	T^{2N}
⋮	⋮	⋮		⋮
N	T^{N1}	T^{N2}	⋯	T^{NN}

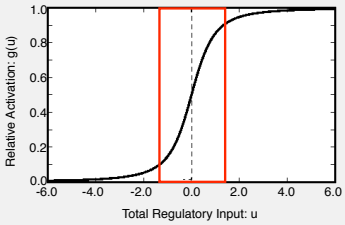
T parameters:

positive: activation
negative: repression
zero: no interaction

Synthesis

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{\mathrm{Bcd}} + h_a \right)$$

The regulation-expression function g(u)



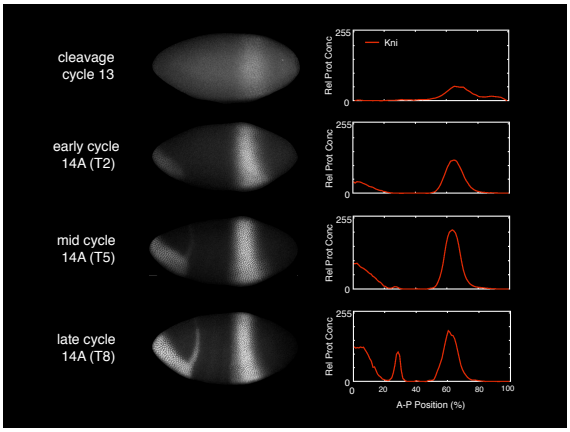
The Gene Circuit has 348 equations with 66 unknown parameters.

How can these be determined?

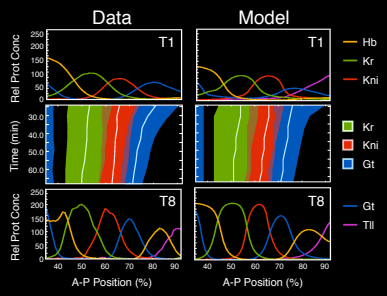
— Inference of optimal parameters.

— Generate time-course protein expression data (antibody-stained embryos; sorted into nine time classes; data averaged in each time class.

flyex.uchicago.edu/flyex/ urchin.spbcas.ru/flyex



Gap Domains Shift Anteriorly



Constraints on the *T* Matrix

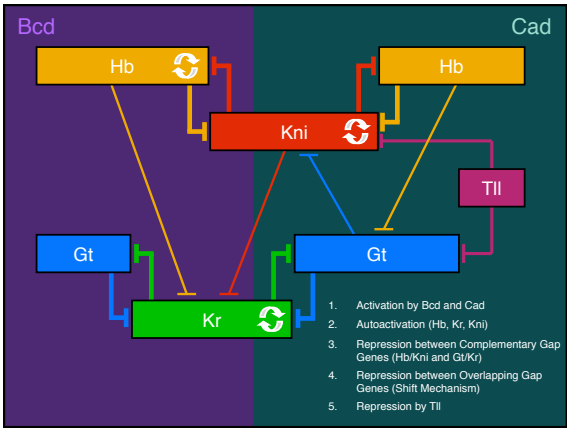
Inferred parameters give regulatory interactions in good qualitative accord with genetic data.

	bcd	*cad*	*hb*	*Kr*	*gt*	*kni*	*tll*
hb	0/0/10	0/0/10	0/0/10	0/10/0	0/2/8	10/0/0	1/8/1
Kr	0/0/10	0/0/10	9/1/0	0/0/10	10/0/0	9/1/0	10/0/0
gt	0/0/10	0/0/10	9/0/1	10/0/0	0/3/7	1/9/0	10/0/0
kni	3/0/7	0/0/10	10/0/0	6/4/0	9/1/0	0/0/10	10/0/0

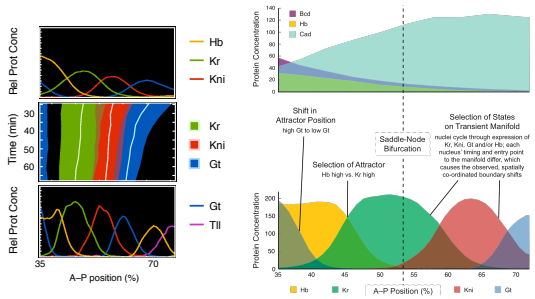
Triplets represent numbers of gene circuits which show repression/no interaction/activation.

Repression | No Interaction (cutoff = 0.005) | Activation

N = 10



Spatio-temporal dynamical system



Turing patterns

- If we consider space to be continuous, then the diffusive movement term becomes a derivative:

$$\frac{dC_i}{dt} = D(C_{i-1} + C_{i+1} - 2C_i) - \delta C_i + \text{source} + \text{reactions}$$

becomes

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} - \delta C(x,t) + \text{source} + \text{reactions}$$

- This type of equation is known as a **partial differential equation** (it is a reaction-diffusion equation).

Turing patterns (reaction-diffusion)

- We saw before that diffusion tends to smooth out spatial inhomogeneities in concentration.
- However, Alan Turing showed in 1952 that for two (or more) interacting diffusible chemicals, under certain conditions diffusion can destabilise spatially uniform distributions, and spontaneously generate pattern: diffusion-driven instability.
- e.g. activator-inhibitor kinetics:

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + a - u + u^2 v$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + b - u^2 v$$

Turing patterns: practical

Can you suggest how these different patterns might arise?