The Chemical Basis of Morphogenesis

A. M. Turing

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Early Life: The Younger Years

- 1912: Born in London, England

- 1925: Displayed interest in math and science

- 1931: Enrolled at King's College where he proved the Central Limit Theorem

- 1936: Presented the notion of a universal machine

- 1938: Received his Ph.D. from Princeton University

Life During WII: Cryptanalysis & The Bombe
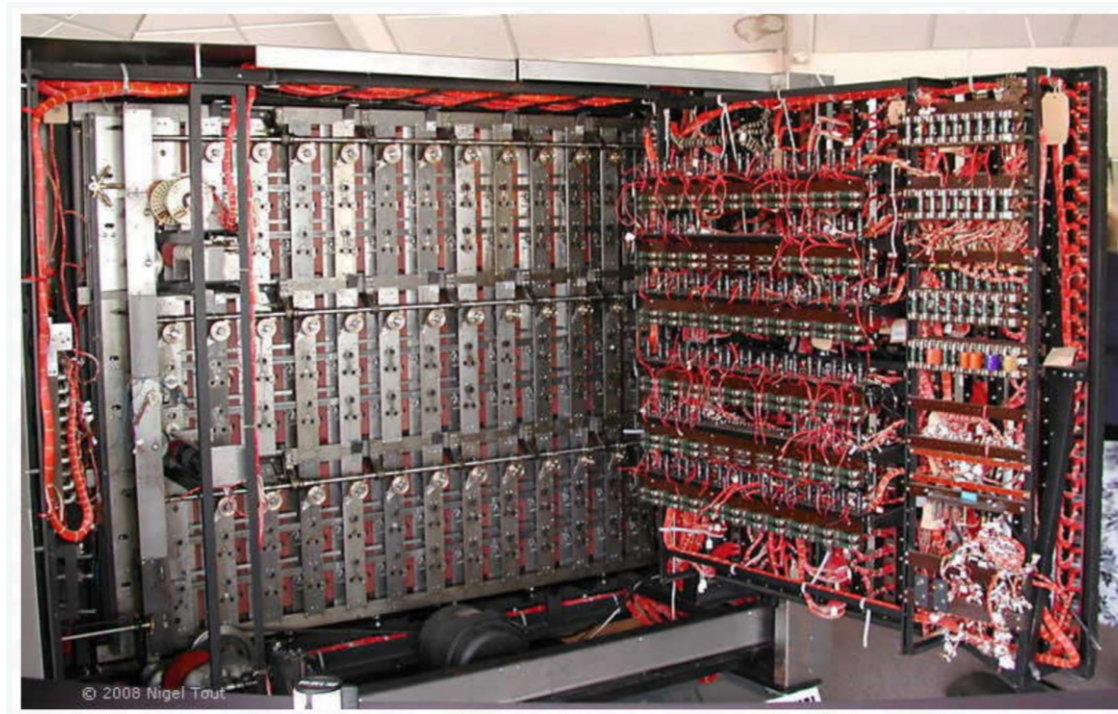
- Worked at Bletchley Park

- Leading participant in wartime code-breaking

- Specified the bombe to help decipher encrypted signals

- Talented long distance runner

Life After WWII: Early Computers

- Worked for the National Physical Laboratory

- Created a blueprint for the world's first personal computer

- Addressed the issue of artificial intelligence
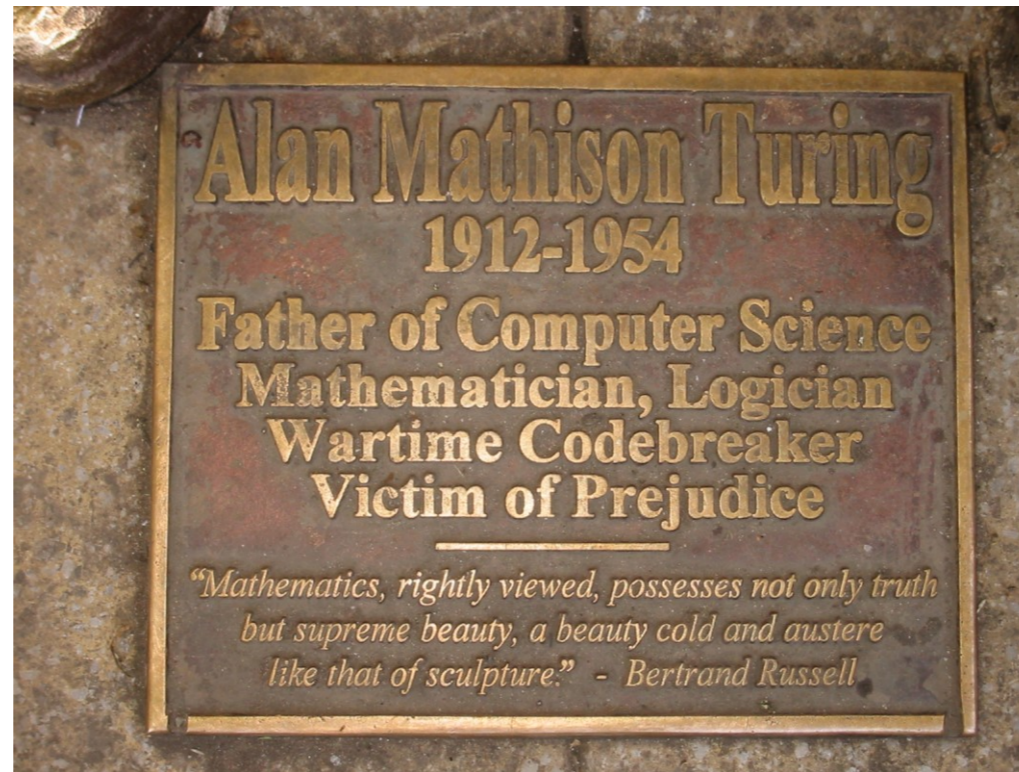
- "Turing Test"
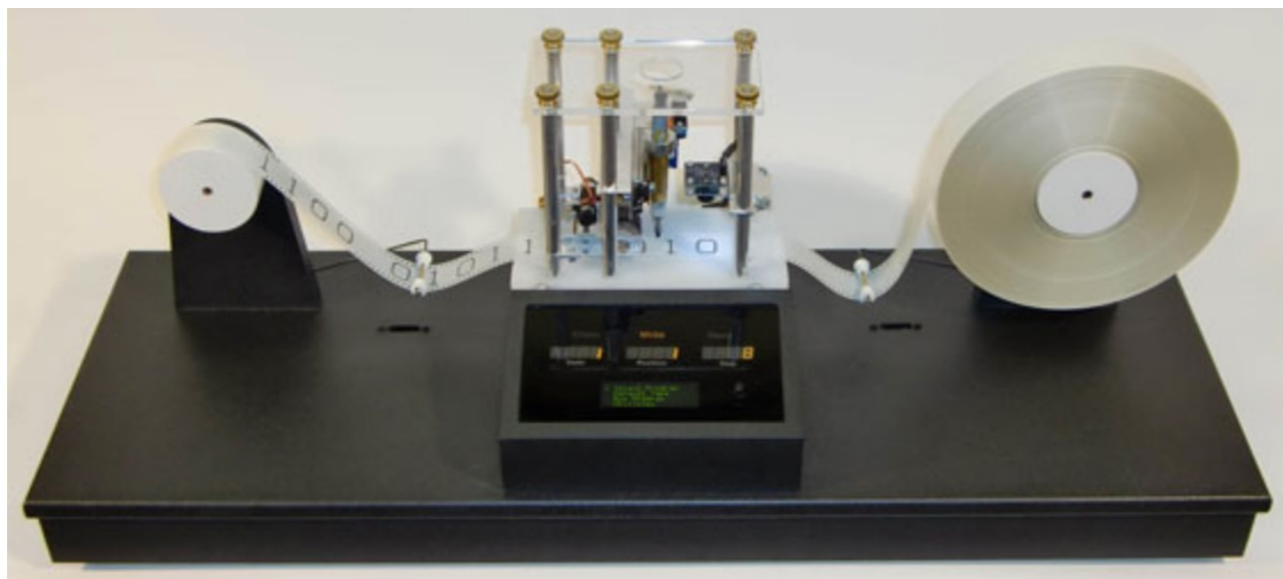
Homosexuality, Conviction and Death

- Convicted for being a homosexual in the early 1950s

- Barred from continuing his work on cryptography at the GCCS

- Died on June 7, 1954 from cyanide poisoning

- Ruled a suicide

Awards, Recognition and Apology

- Honored many different ways - statues, plaques, creation of the "Turing" award

- Time magazine named him one of its "100 Most Important People of the 20th Century"

- 2014: Queen Elizabeth II officially pronounced Turing pardoned

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What is morphogenesis?

The shaping of an organism by embryological processes of differentiation of cells, tissues, and organs and the development of organ systems according to the genetic "blueprint" of the potential organism and environmental conditions.

"Reaction-Diffusion System"

- Possible mechanism by which the genes of a zygote may determine anatomical structure

- Morphogens have the ability to establish chemical gradients through a reaction diffusion system

$$\frac{\partial u}{\partial t} = F(u,v) - d_u v + D_u \Delta u$$

$$\frac{\partial v}{\partial t} = G(u,v) - d_v v + D_v \Delta v$$

Rate of concentration change   Production   Degradation   Diffusion

Reaction

Section 1: A Model of the Embryo. Morphogens.

- Describes a mathematical model of the growing embryo

  - Ring of cells each in contact with its neighbors

  - Continuous ring of tissue

- "The state of the system"

  - 2 or 3 morphogens

  - Initially a stable homogenous condition

  - Slow changes take place in the reaction rates to bring the system out of the stable state

Sections 2-9: Mathematical Background Required.

$$I - \tfrac{1}{2} - 2\sin^2 \frac{\pi s}{N} + \sqrt{\left\{ \left(2\sin^2 \frac{\pi s}{N} + \frac{1}{2} \right)^2 - 1 \right\}}$$

$$\left. \begin{aligned} \xi_r &= \frac{1}{N} \sum_{s=1}^{N} \exp\left[-\frac{2\pi irs}{N} \right] x_s, \\ \eta_r &= \frac{1}{N} \sum_{s=1}^{N} \exp\left[-\frac{2\pi irs}{N} \right] y_s, \end{aligned} \right\}$$

$$\begin{aligned} \frac{d\xi_s}{dt} &= \frac{1}{N} \sum_{s=1}^{N} \exp\left[-\frac{2\pi irs}{N} \right] \left[ax_r + by_r + \mu \left(\exp\left[-\frac{2\pi is}{N} \right] - 2 + \exp\left[\frac{2\pi is}{N} \right] \right) \xi_s \right] \\ &= a\xi_s + b\eta_s + \mu \left(\exp\left[-\frac{2\pi is}{N} \right] - 2 + \exp\left[\frac{2\pi is}{N} \right] \right) \xi_s \\ &= \left(a - 4\mu \sin^2 \frac{\pi s}{N} \right) \xi_s + b\eta_s. \end{aligned}$$

$$\left. \begin{aligned} \frac{dX_r}{dt} &= f(X_r, Y_r) + \mu(X_{r+1} - 2X_r + X_{r-1}) \\ \frac{dY_r}{dt} &= g(X_r, Y_r) + \nu(Y_{r+1} - 2Y_r + Y_{r-1}) \end{aligned} \right\} \quad (r = 1, \ldots, N).$$

$$\left. \begin{aligned} X_r - h &= 2 e^{It} \mathscr{R} \left\{ A_{s_0} \exp\left[\frac{2\pi is_0 r}{N} + i\omega t \right] + A_{N-s_0} \exp\left[-\frac{2\pi is_0 r}{N} - i\omega t \right] \right\}, \\ Y_r - k &= 2 e^{It} \mathscr{R} \left\{ C_{s_0} \exp\left[\frac{2\pi is_0 r}{N} + i\omega t \right] + C_{N-s_0} \exp\left[-\frac{2\pi is_0 r}{N} - i\omega t \right] \right\}. \end{aligned} \right\}$$

Section 4: The Breakdown of Symmetry and Homogeneity.

$$\frac{\partial X}{\partial t} = 5X - 6Y + 1$$

$$\frac{\partial Y}{\partial t} = 6X - 7Y + 1 \ (+ \text{Diffusion})$$

(i) A set of reactions producing the first morphogen at the constant rate 1, and a similar set forming the second morphogen at the same rate.

(ii) A set destroying the second morphogen (Y) at the rate $7Y$.

(iii) A set converting the first morphogen (X) into the second (Y) at the rate $6X$.

(iv) A set producing the first morphogen (X) at the rate $11X$.

(v) A set destroying the first morphogen (X) at the rate $6Y$, so long as any of it is present.

- System can reach various kinds of stable equilibria

- Breaking this symmetry leads from one stable state to another

- 6 equilibrium states

Section 11: Biological Interpretation of the Results.

1. Instability for an isolated cell leading to a uni-directional drift away from equilibrium.

2. Similar to Case #1. Departure from equilibrium is oscillatory.

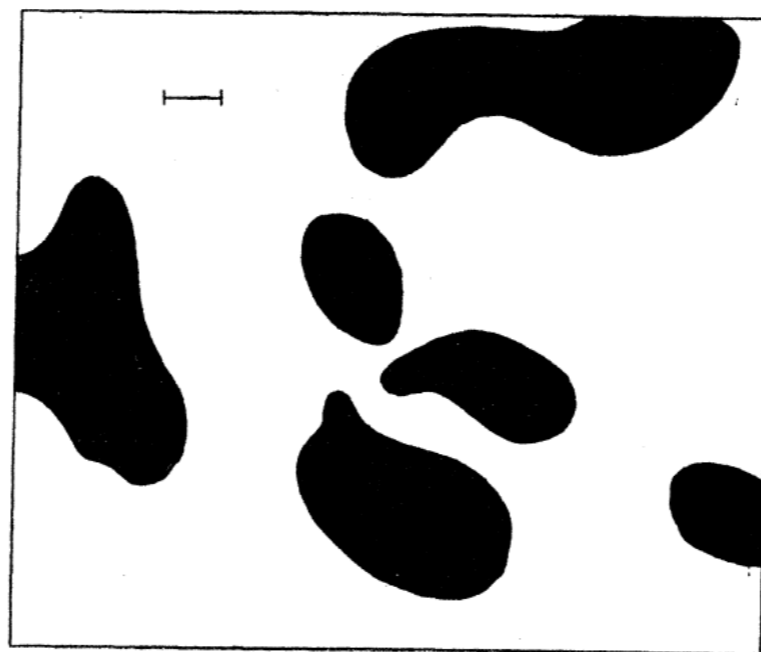3. Drift from equilibrium is in opposite directions.

FIGURE 2. An example of a 'dappled' pattern as resulting from a type (a) morphogen system. A marker of unit length is shown. See text, §9, 11.

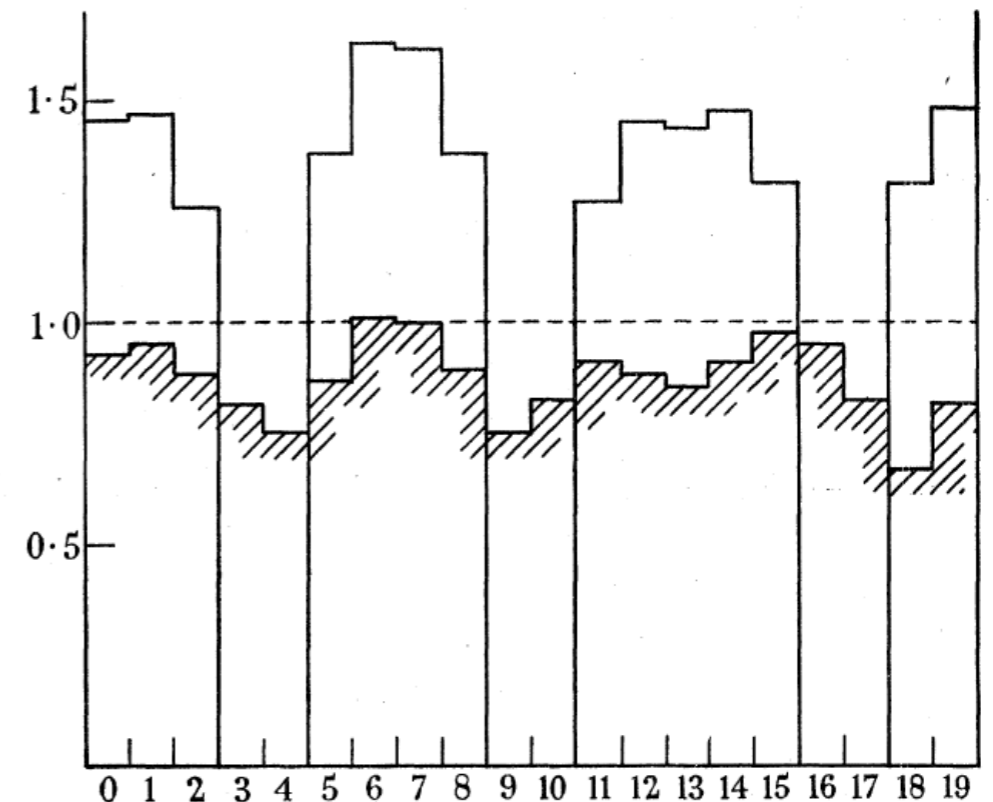# Section 11: Biological Interpretation of the Results.

4. Stationary wave pattern on the ring, with no time variation, apart from a slow increase in amplitude.

   (I) Pattern is slowly becoming more marked.
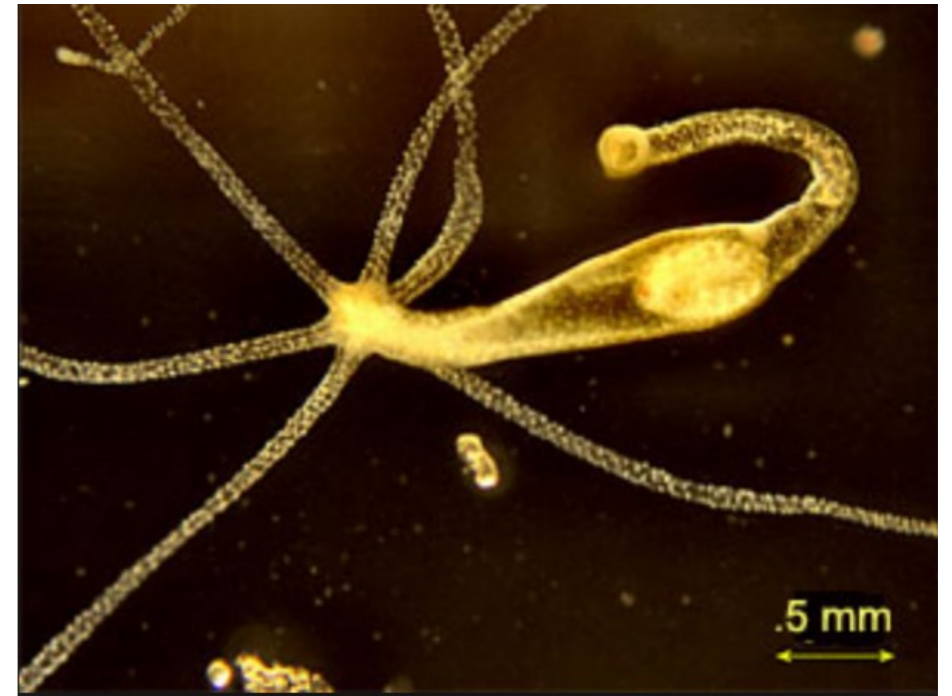
5. Traveling waves.

6. Metabolic oscillation with neighboring cells in opposite phases.

Main Points

- Coined the term "morphogen"

- Instability can arise solely due to the interactions between a number of stabilizing components

  - Pattern formation can be accomplished by the interaction of two substances that spread with different rates

  - Diffusion driven instability
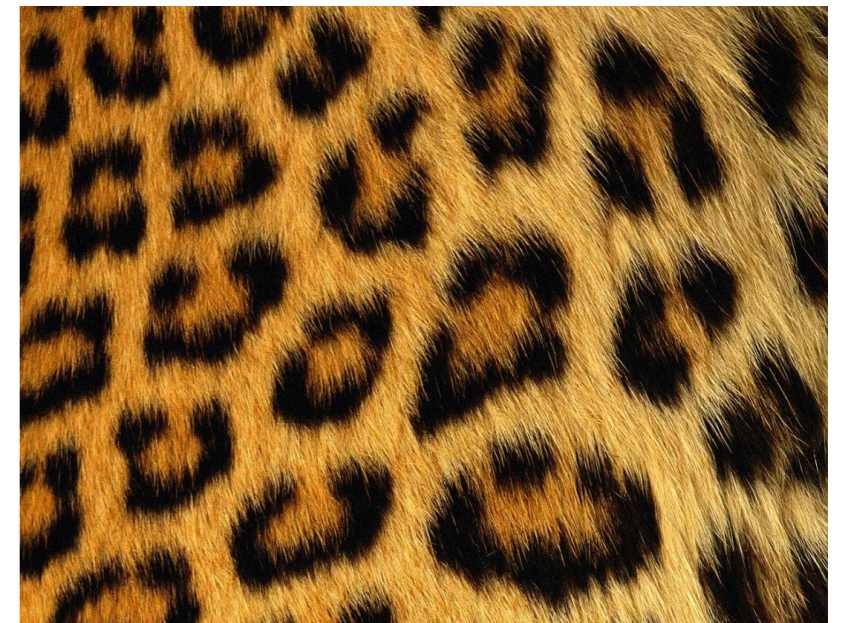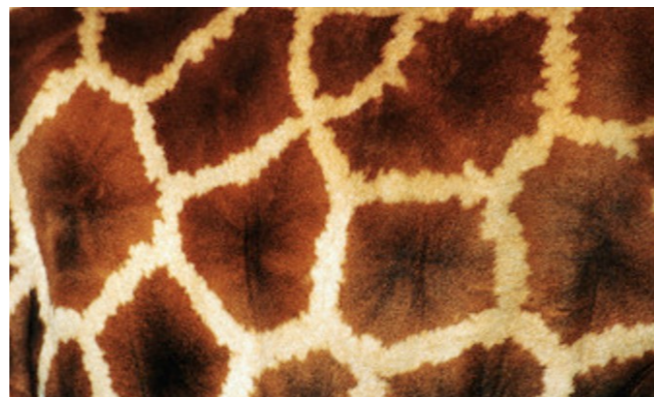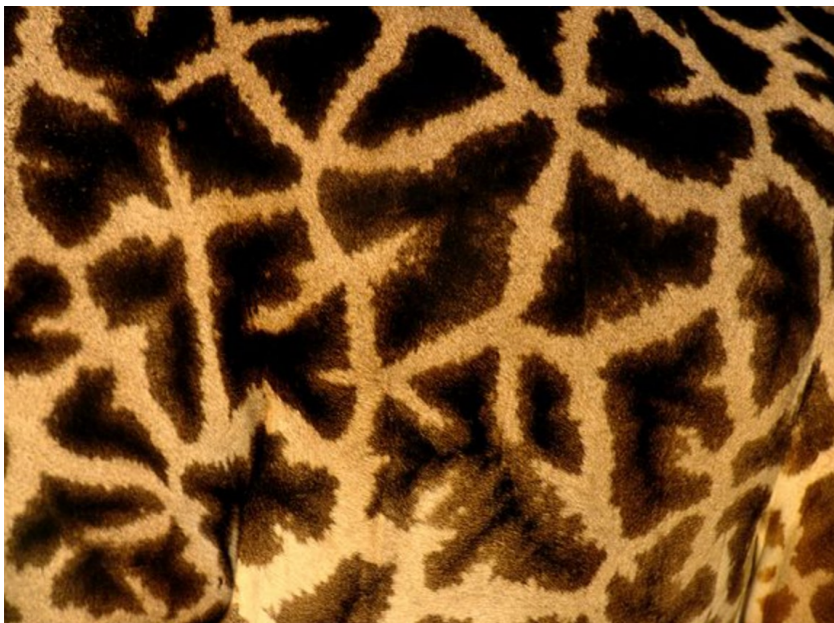
Criticisms of Turing's Work

"…While the math and models are beautiful, none of this theory has been borne out by the discoveries of the last twenty years. The mathematicians never envisioned that modular genetic switches held the key to pattern formation, or that the periodic patterns we see are actually the composition of numerous individual elements…"

Mathematically elegant but biologically irrelevant

Alternative Views of Morphogenesis?

Alternative Views of Morphogenesis

- Mechanochemical theory of morphogenesis

  - Cell density undergoes instability

  - Oster and Murray, 2003

- Neuronal firing patterns

- All have the same underlying pattern generating mechanism

Turing's Theory of Morphogenesis Validated 60 Years After His Death

Pitt mathematics and biology professor G. Bard Ermentrout part of team showing how identical cells differentiate

Testing Turing's theory of morphogenesis in chemical cells

Nathan Tompkins[a], Ning Li[a], Camille Girabawe[a], Michael Heymann[a,b], G. Bard Ermentrout[c], Irving R. Epstein[d], and Seth Fraden[a,1]

Departments of [a]Physics, [b]Biochemistry, and [d]Chemistry, Brandeis University, Waltham, MA 02454; and [c]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260

The Chemical Basis of Morphogenesis…Verified

- Exploited an experimental system of emulation drops

- Created rings of synthetic cell-like structures

- Verified Turing's thesis of the chemical basis of morphogenesis