Systems Biology: A Personal View IXX. Temporal patterns and Biological oscillators

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Brian C. Goodwin (1931–2009)

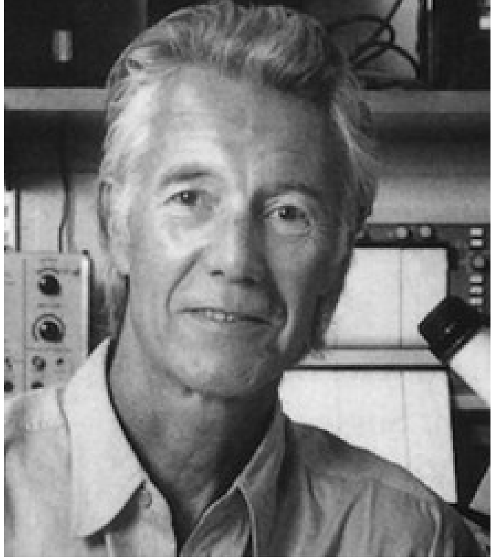
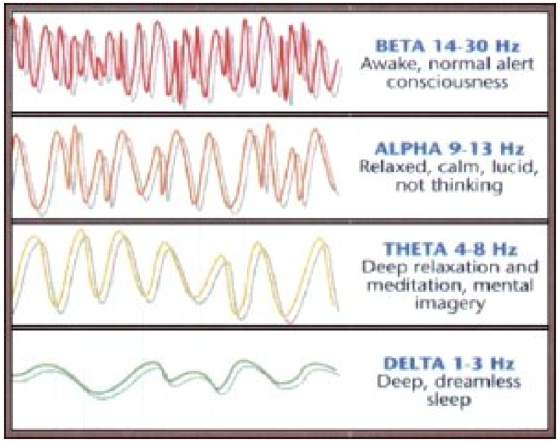


Image source: Wikipedia

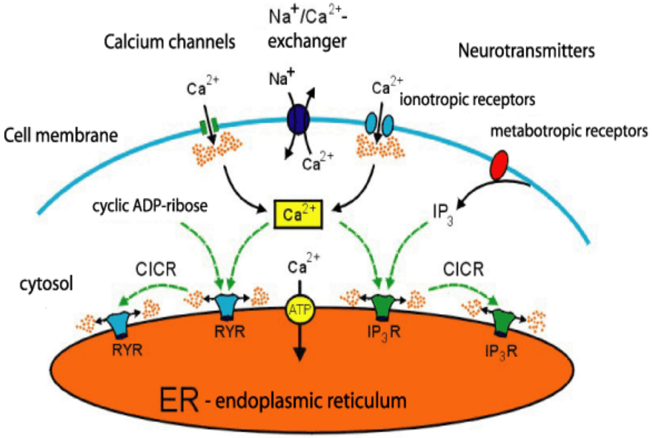
Oscillator Biology

Goodwin: Development of patterns arising from coupled biochemical oscillators

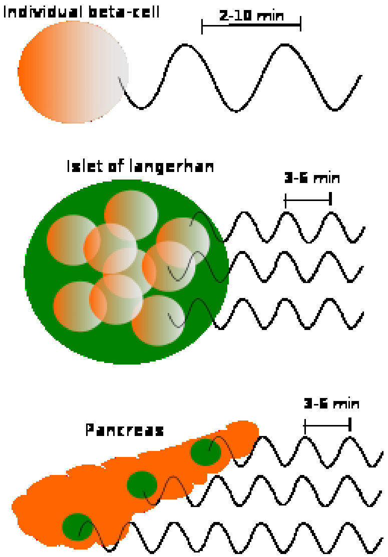
In many biological systems, the individual entities undergo periodic oscillations instead of remaining in a constant state



Neuronal activity oscillations



Intracellular oscillations



Insulin release oscillations

Lotka-Volterra Model (1920-6)

Alfred Lotka

The first model of consecutive chemical reactions giving rise to oscillations in molecular concentrations

$$A + X \rightarrow 2X$$
$$X + Y \rightarrow 2Y$$
$$Y \rightarrow P$$

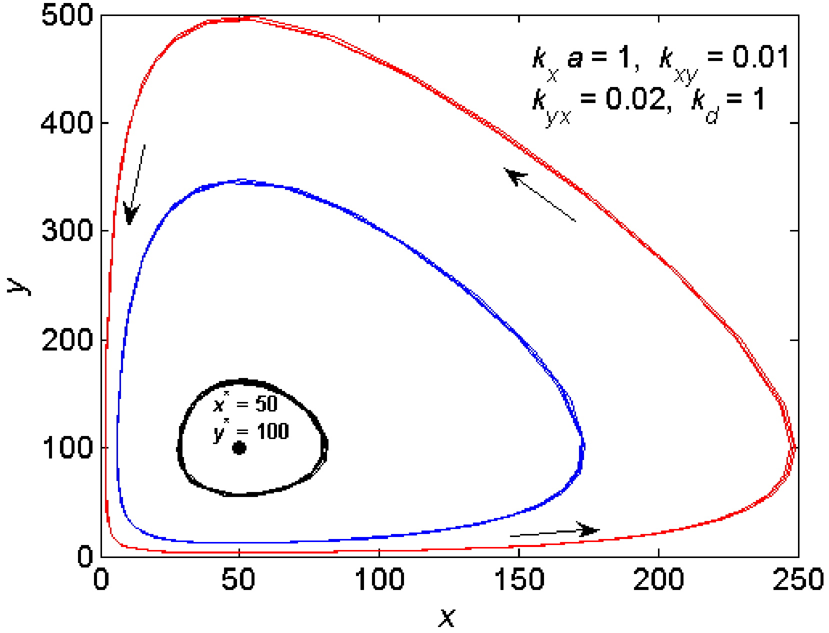
(Autocatalysis: +ve feedback)

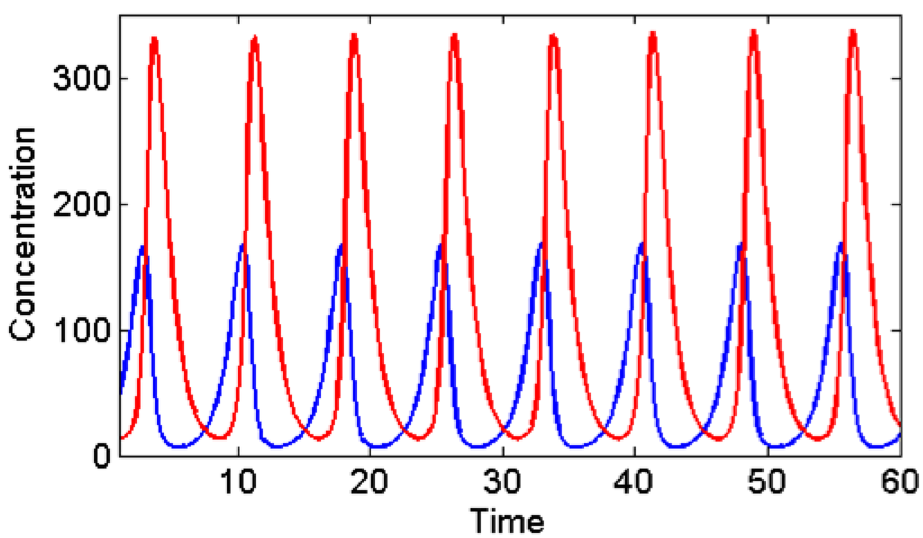
Prey (x) – Predator (y) eqns

More reasonable in the context of ecology

$$dx/dt = k_x\, a\, x - k_{xy}\, x\, y$$
$$dy/dt = k_{yx}\, x\, y - k_d\, y$$

Volterra (1926)

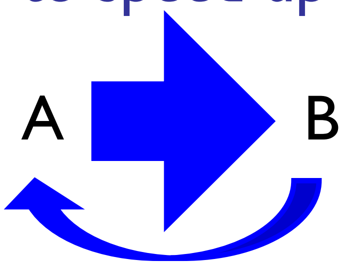




What is Auto-catalysis ?

Catalysis: a chemical compound speeds up the rate (k) of a chemical reaction without itself being changed by the process, e.g., enzymes

In **auto-catalysis**, one of the product molecules acts as a catalyst to speed up the formation of more product molecules



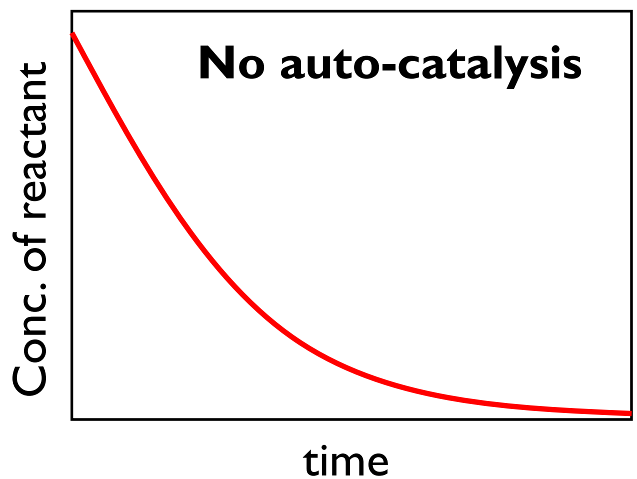
$$\mathbf{A + B \rightarrow 2B}$$

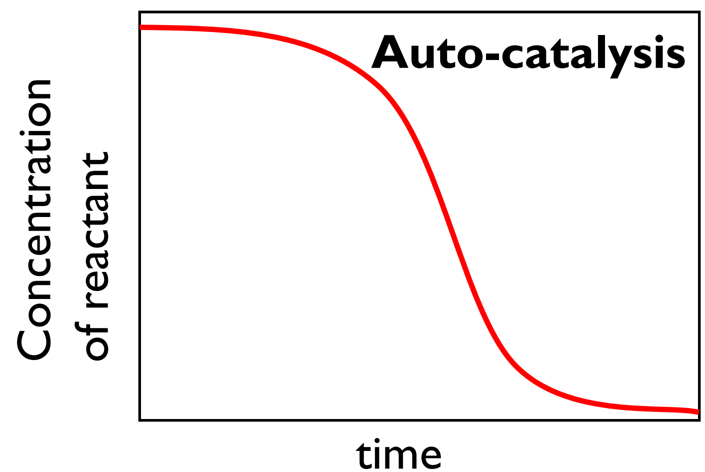
$$v = k[A][B]$$

As product concentration increases, the reaction proceeds faster

Examples:

- Combustion
- Nuclear chain-reaction
- Population growth





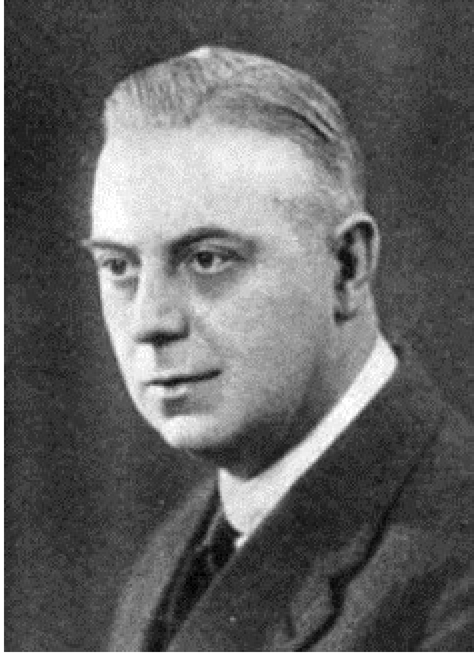
Cross-catalysis: A promotes formation of B, and B of A

$\Rightarrow$ may result in inhibition (-ve feedback) preventing run-away auto-catalysis

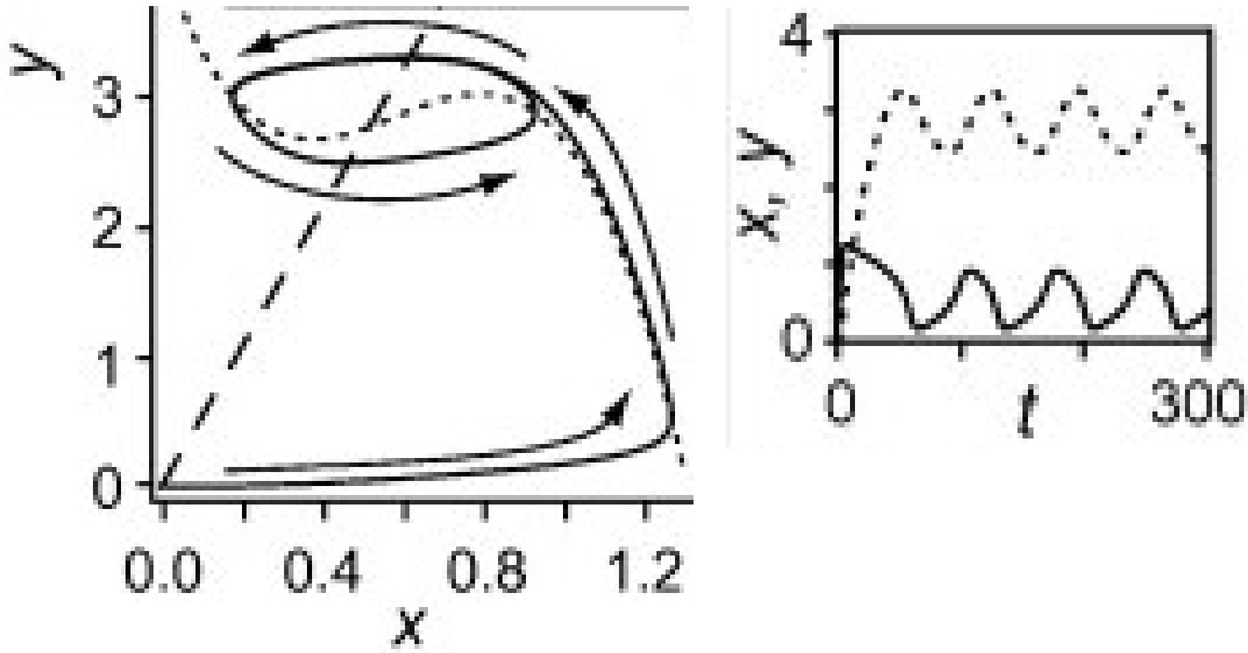
Van der Pol oscillator (1927)

originally proposed by Dutch electrical engineer (at Philips) Balthasar van der Pol to describe stable oscillations (relaxation oscillations) in electrical circuits comprising vacuum tubes.

$$\dot{x} = \mu\left(x - \frac{1}{3}x^3 - y\right) \qquad \dot{y} = \frac{1}{\mu}x.$$



Balthasar Van der Pol
1889-1959



Source: NYTimes

Belousov-Zhabotinskii reaction (1950s-1960s)

A family of oscillating <u>homogeneous</u> chemical reactions

Boris P. Belousov

B P Belousov (1951) Investigated a solution of bromate, citric acid (the reductant) and ceric ions (the catalyst)

$$2Ce^{3+} + BrO_3^- + 3H^+ \longrightarrow 2Ce^{4+} + 2HBrO_2 + H_2O$$

Instead of monotonic conversion of yellow Ce^{4+} (reduced) to colorless Ce^{3+} (oxidized), saw **periodic oscillations** of the color

A M Zhabotinskii (1961+) Established the validity of Belousov's results – showed the phenomenon to be robust

A. M. Zhabotinskii

1 : $Br^- + HOBr + H^+ \rightarrow Br_2 + H_2O$

2 : $HBrO_2 + Br^- + H^+ \rightarrow 2\,HOBr$

3 : $BrO_3^- + Br^- + 2\,H^+ \rightarrow HBrO_2 + HOBr$

4 : $2\,HBrO_2 \rightarrow BrO_3^- + HOBr + H^+$

5 : $BrO_3^- + HBrO_2 + H^+ \rightarrow 2\,BrO_2\bullet + H_2O$

6 : $BrO_2\bullet + Ce(III) + H^+ \rightarrow HBrO_2 + Ce(IV)$

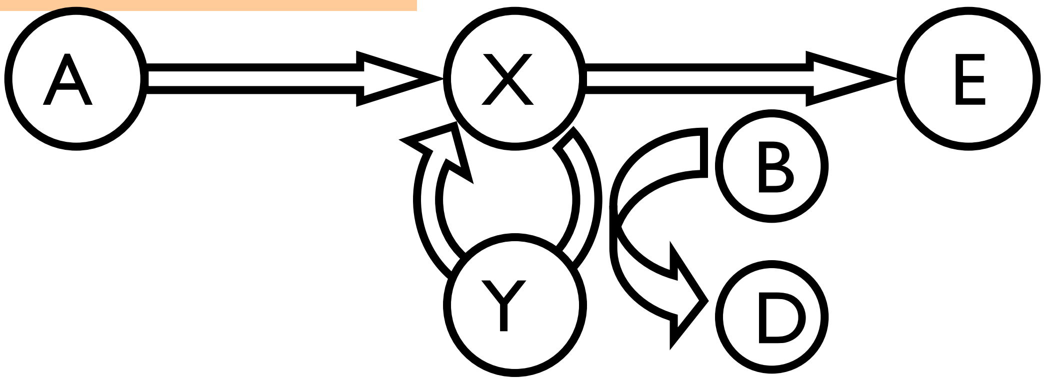
7 : $2\,Ce(IV) + BrCH(COOH)_2 + CH_2(CO_2H)_2 \rightarrow$
$2\,Ce(III) + f\,Br^- + \text{products}$

The Brusselator (1968)

Prigogine & Lefever

First chemically reasonable model for oscillations

$$A \xrightarrow{k_1} X$$
$$B + X \xrightarrow{k_2} Y + D \quad \text{(Cross-catalysis: -ve feedback)}$$
$$2X + Y \xrightarrow{k_3} 3X \quad \text{(Autocatalysis: +ve feedback)}$$
$$X \xrightarrow{k_4} E$$



Ilya Prigogine, 1977

1977

Self-organization in far from equilibrium systems

Assuming A and B concentrations held constant

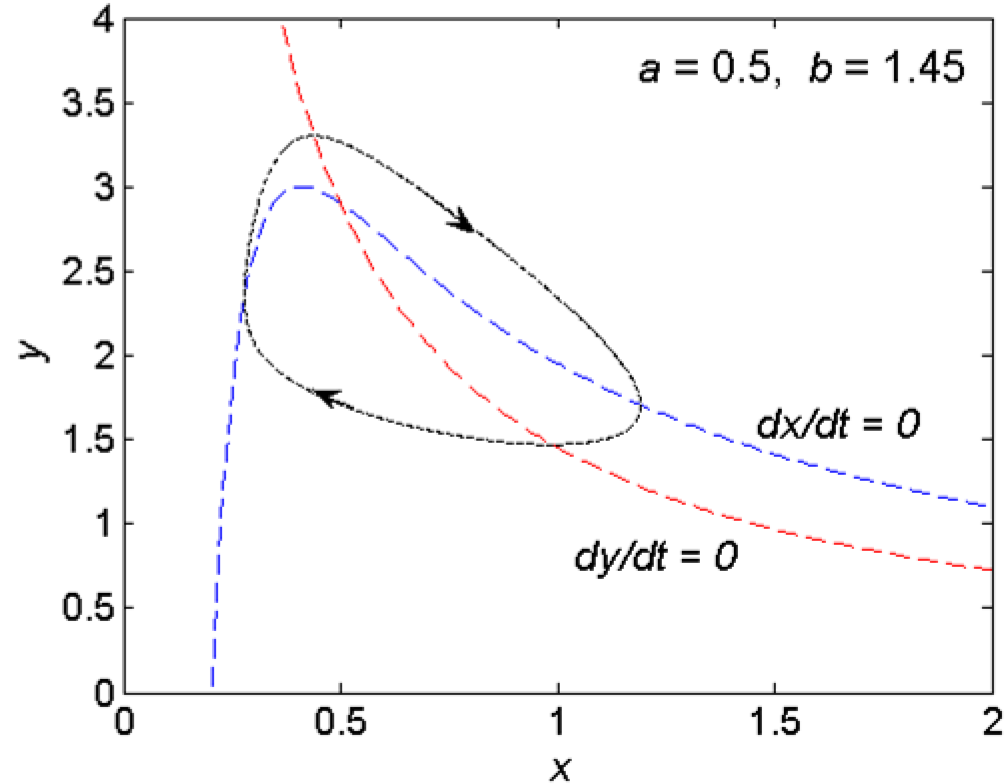
$$dX/dt = k_1 A - k_2 BX + k_3 X^2 Y - k_4 X$$
$$dY/dt = k_2 BX - k_3 X^2 Y$$

$\Rightarrow$

Non-dimensionalizing,

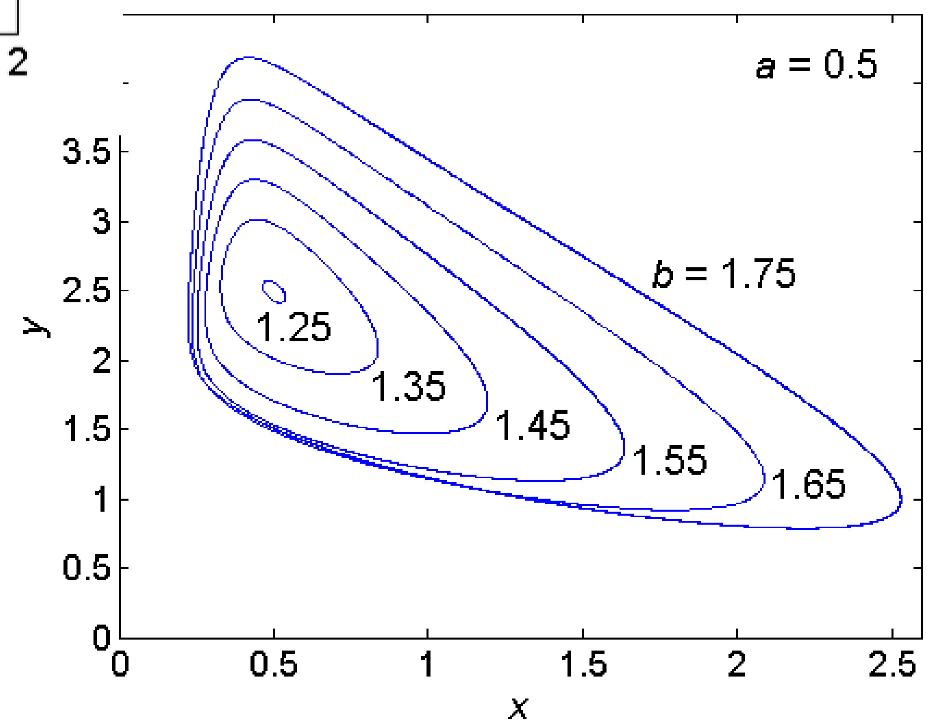
$$dx/dt = a - bx + x^2 y - x$$
$$dy/dt = bx - x^2 y$$

Nonlinearity



'he onset of oscillations as a
ifurcation in (x,y) phase space

'he equilibrium point
x*, y*} = { a, b/a}
ɔses stability when
› > a^2 + 1
hrough a Hopf bifurcation

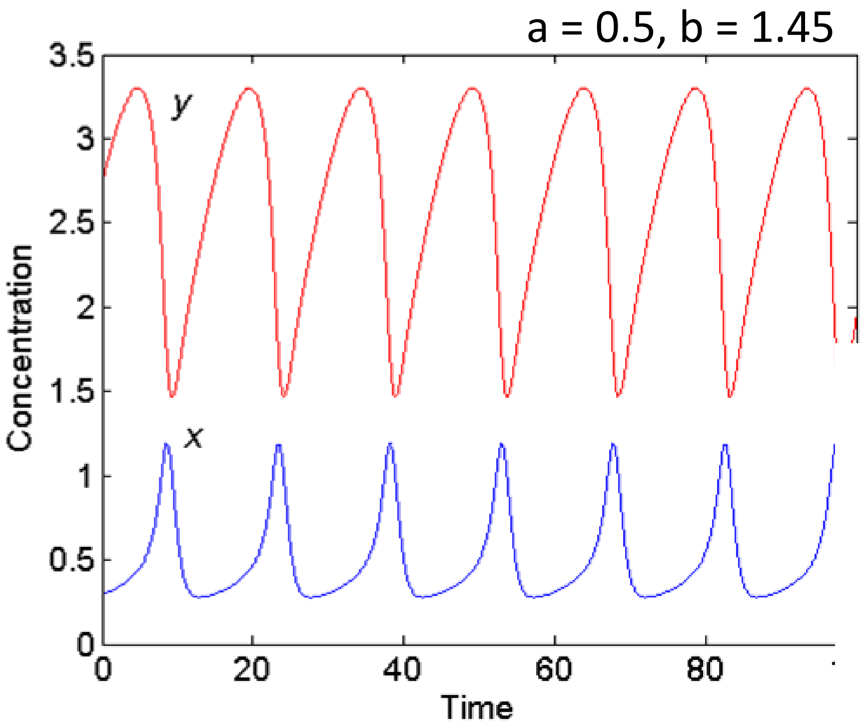


$$J = \begin{pmatrix} -b-1+2x^*y^* & x^2 \\ b - 2x^*y^* & -x^2 \end{pmatrix} = \begin{pmatrix} b-1 & a^2 \\ -b & -a^2 \end{pmatrix}$$

tr (J) = $-a^2+b-1$, det (J) = $a^2 > 0$

For an equilibrium to be unstable: trace(J), det (J) > 0

The Brusselator reproduces the BZ oscillations remarkably well despite being a simple phenomenological model !



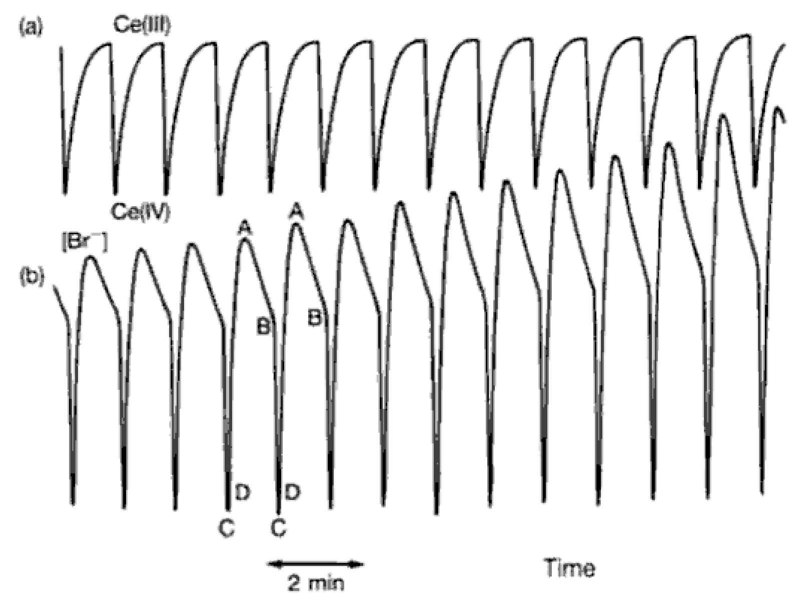


FIG. 8.1. Typical experimental records from (a) platinum electrode and (b) bromide ion sensitive electrode for the Belousov–Zhabotinskii reaction in a closed system. In each case the reference electrode is calomel.

However, there are chemically more accurate models of the BZ reaction…

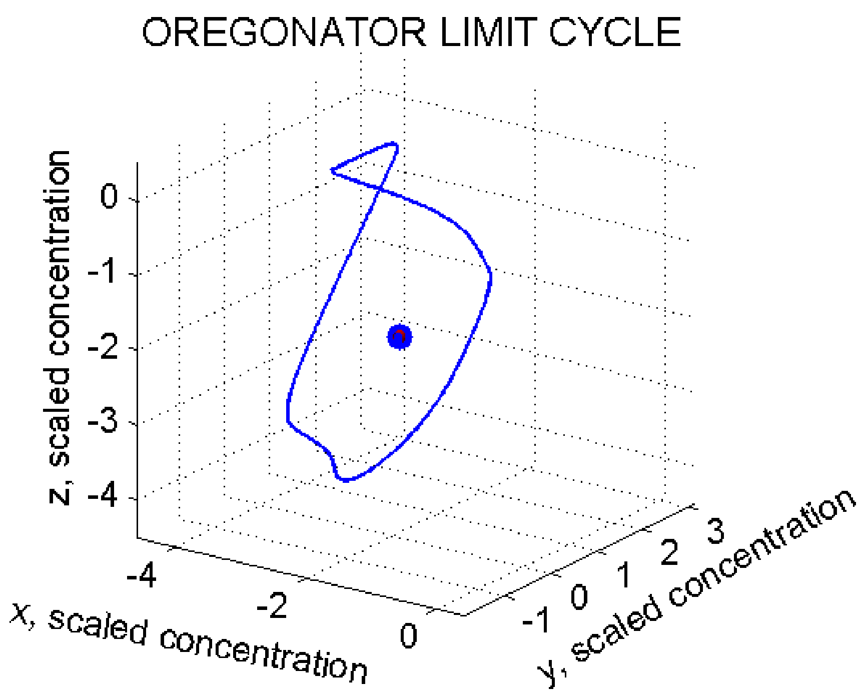
The Oregonator (1974)

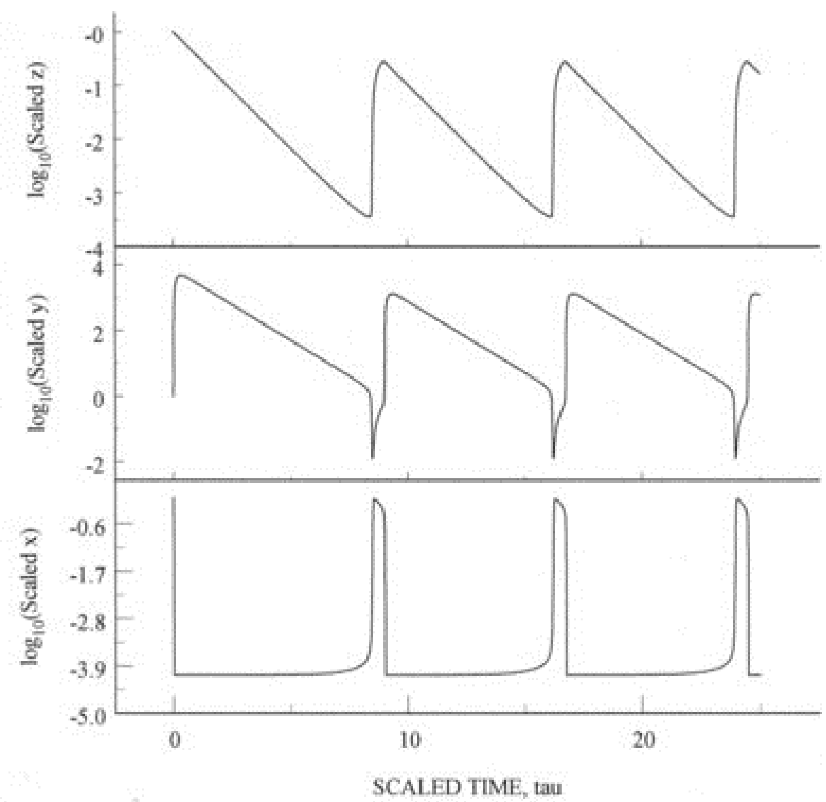
A 3-variable model for the intermediate species X, Y, Z of BZ reaction

[Reduction of the accurate Field-Koros-Noyes mechanism (1972)]

$$\varepsilon_1\, dx/dt = q\,y - x\,y + x\,(1 - x)$$
$$\varepsilon_2\, dy/dt = -\,q\,y - x\,y + f\,z$$
$$dz/dt = x - z$$

$\varepsilon_1 \sim 0.04,\ \varepsilon_2 \sim 4 \times 10^{-4}$





The "Tyson"-ator (1980)

As ε_2 is extremely small, we can take y to be a constant
(it is extremely fast relative to the other two variables)
Hence, we arrive at a 2-variable version of the Oregonator

$$\varepsilon_1 \, dx/dt = x\,(1 - x) + f\,(q - x)\,z/(q + x)$$

$$dz/dt = x - z$$

fast variable: $HBrO_2$ (x), slow variable: Ce^{4+} (z)