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

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Brian C. Goodwin (1931–2009)

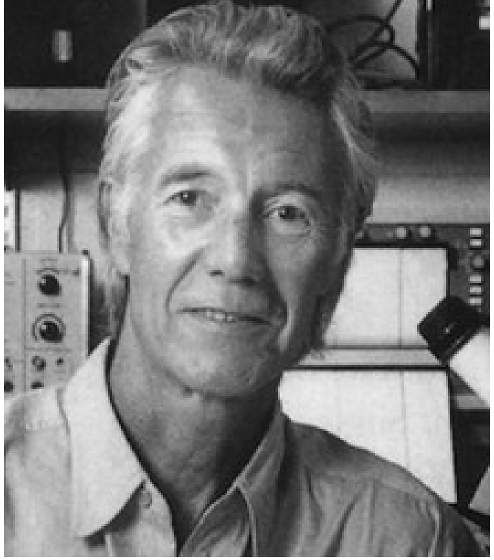
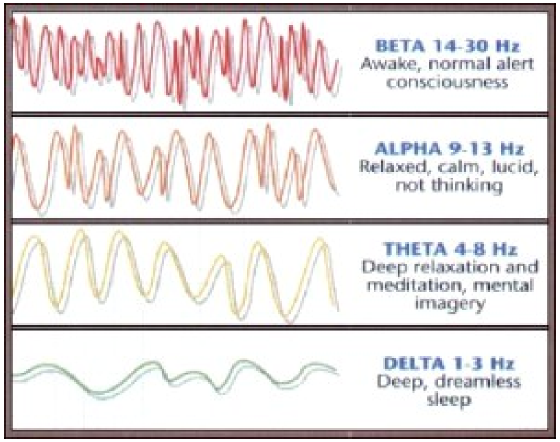


Image source: Wikipedia

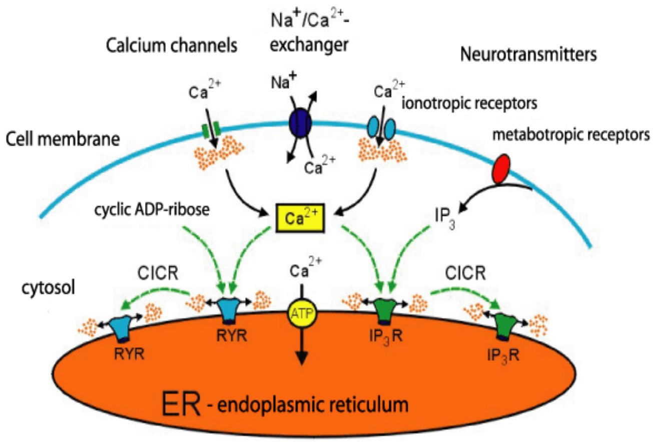
Oscillator Biology

Goodwin: Development of patterns arising from coupled biochemical oscillators

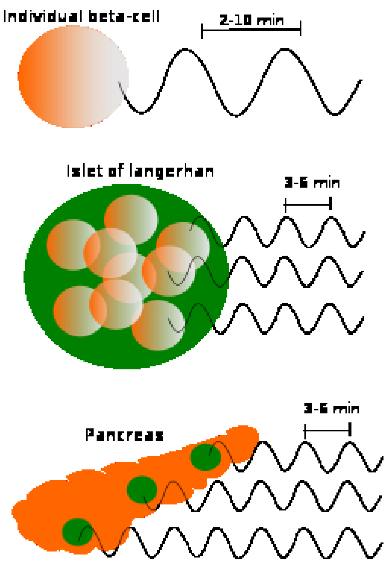
In many biological systems, the individual entities undergo periodic oscillations instead of remaining in a constant state



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

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

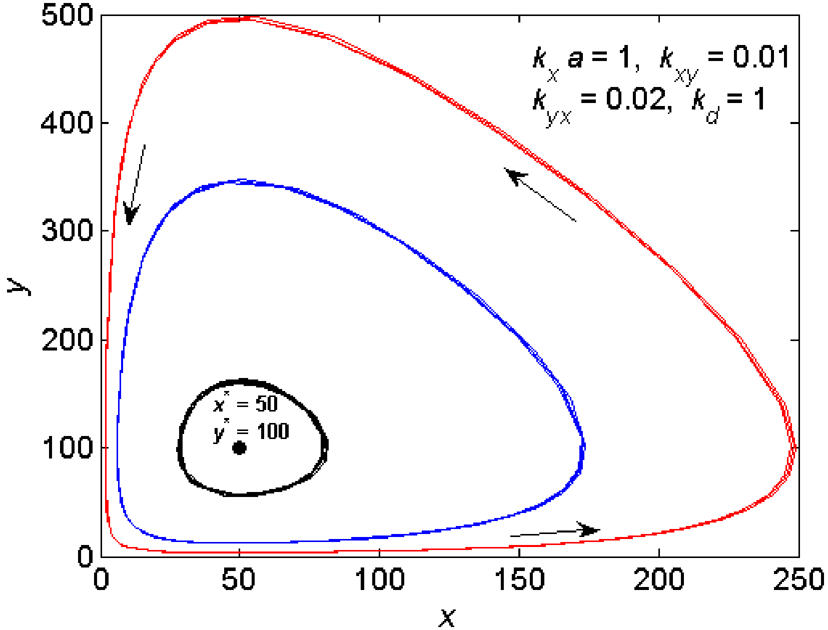
(Autocatalysis: +ve feedback)

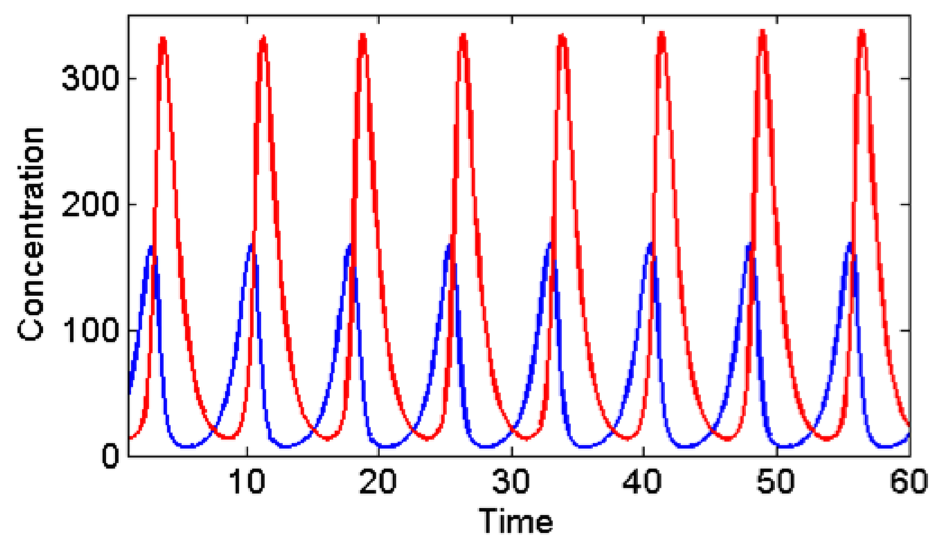
Prey (x) – Predator (y) eqns

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

Volterra (1926)

More reasonable in the context of ecology

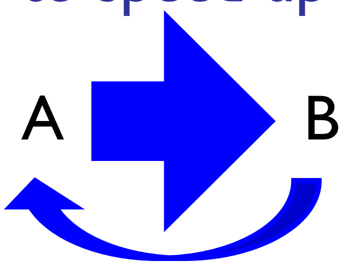




What is Auto-catalysis ?

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



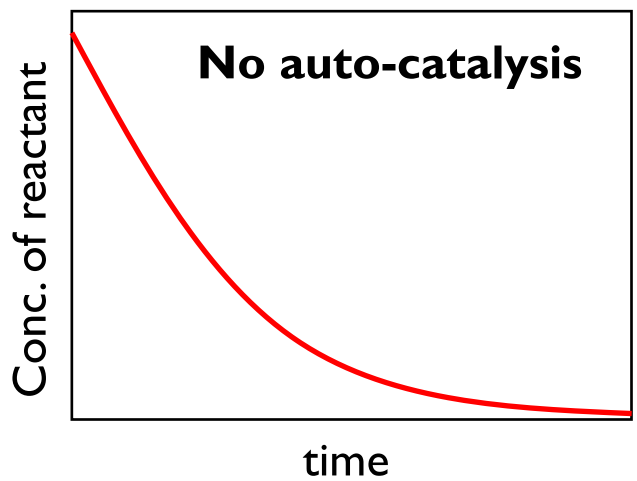
$$A + B \rightarrow 2B$$

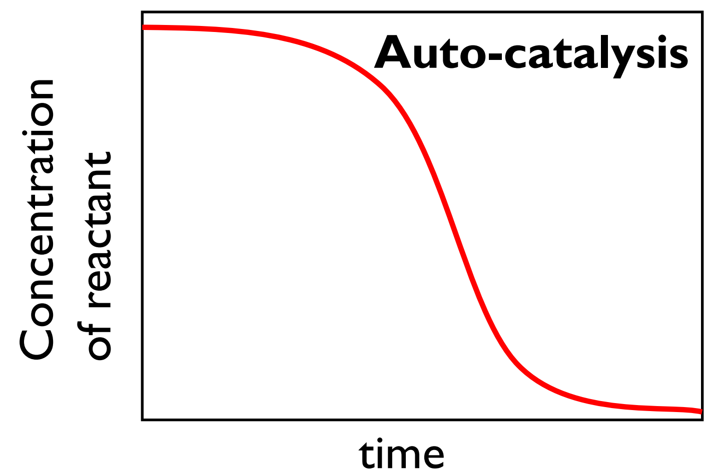
$$v = k[A][B]$$

As product concentration increases, the reaction proceeds faster

Examples:

- Combustion
- Nuclear chain-reaction
- Population growth





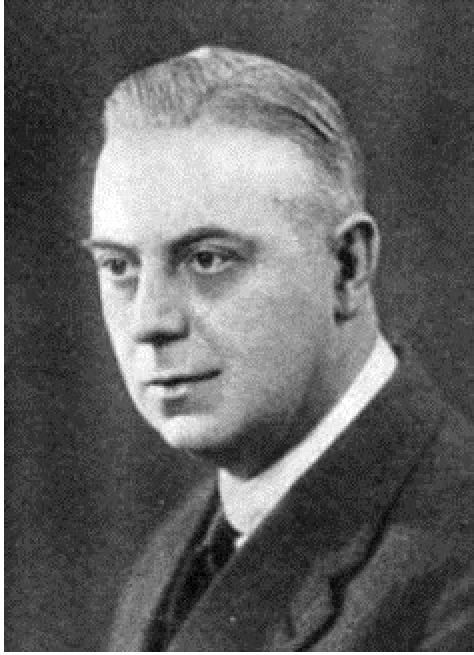
Cross-catalysis: A promotes formation of B, and B of A

⇒ may result in inhibition (-ve feedback) preventing run-away auto-catalysis

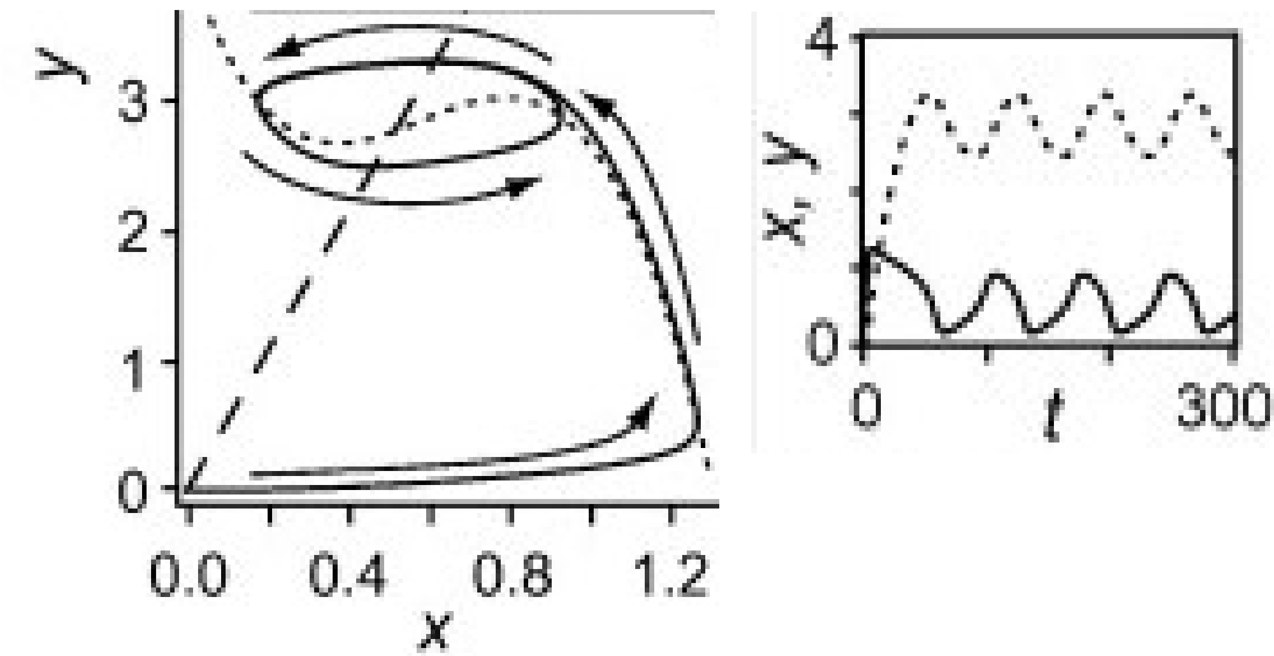
Van der Pol oscillator (1927)

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 homogeneous chemical reactions

Boris P Belousov (1951)

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

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

Transition metal ions (e.g., Ce or Fe) catalyze oxidation of (usually) organic reductants by bromic acid in acidic (supplying H^+ ions) soln.

Bromate + Malonic Acid → Bromomalonic Acid +CO_2 Intermediate compounds: Bromide and Bromous Acid

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

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

Replaced citric acid with malonic acid and used the redox indicator ferroin to heighten the color change (red=reduced, blue=oxidised)

Boris P. Belousov

A. M. Zhabotinskii

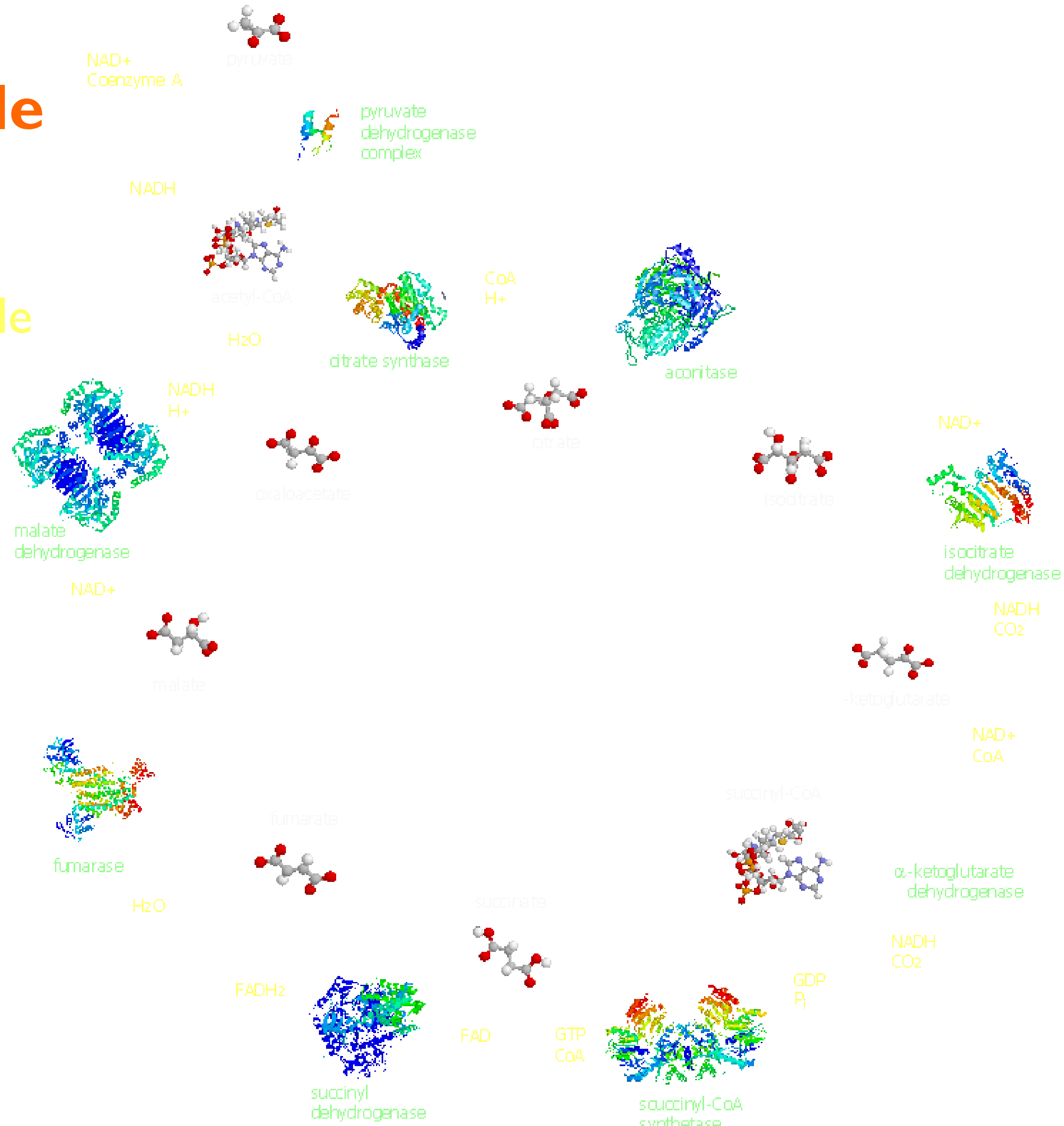
The original reaction was developed by Belousov as an inorganic analog of the Citric acid cycle

Citric acid cycle

Also known as Tricarboxylic Acid (TCA) or Krebs cycle

is a series of enzyme-catalysed chemical reactions lying at the heart of aerobic metabolism.

Involved in the breakdown of all 3 major food groups: carbohydrates, lipids and proteins.



Reception of Belousov's results

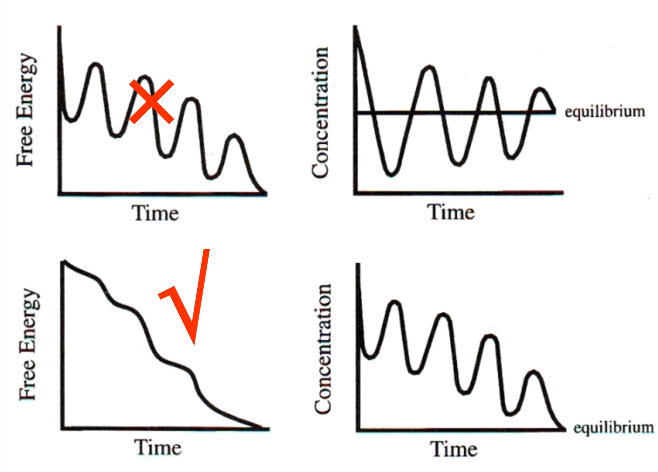
Utter Disbelief ! Paper rejected !
Typical responses:"It violates the 2nd law !" "It must be heterogeneous"
"He has made mistakes in doing the experiment"

Controversy: Are oscillations allowed by the 2nd law ?

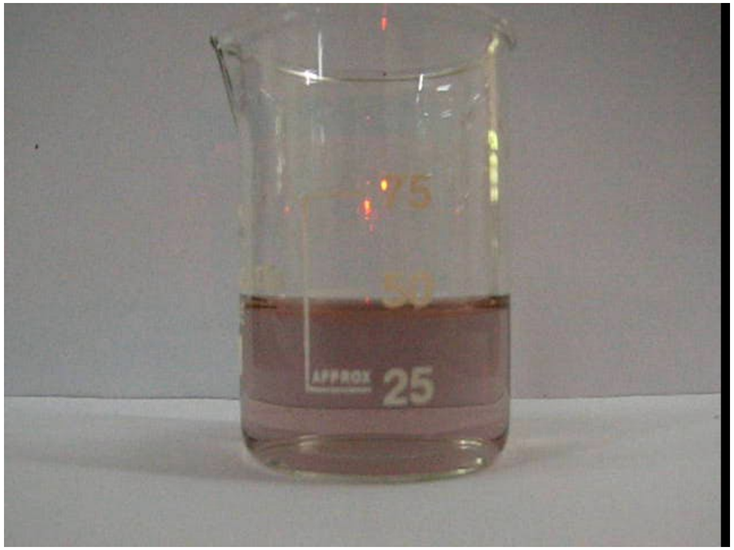
According to the traditional interpretation of 2nd law, oscillations in a homogeneous chemical reactions are impossible!
Close to thermodynamic equilibrium, the direction of any process is governed by the Gibbs free energy G:
Only those processes are allowed for which $\Delta G < 0$
So oscillations not possible!

But the principle of detailed balance forbidding oscillations applies only close to equilibrium.

Far from equilibrium, the intermediates can oscillate on th way to equilibrium
Indeed, if you wait long enough, a closed BZ system stops changing color



Movies



Color contrast increases but frequency decreases as ferroin concentration is increased

Color change in well-mixed soln

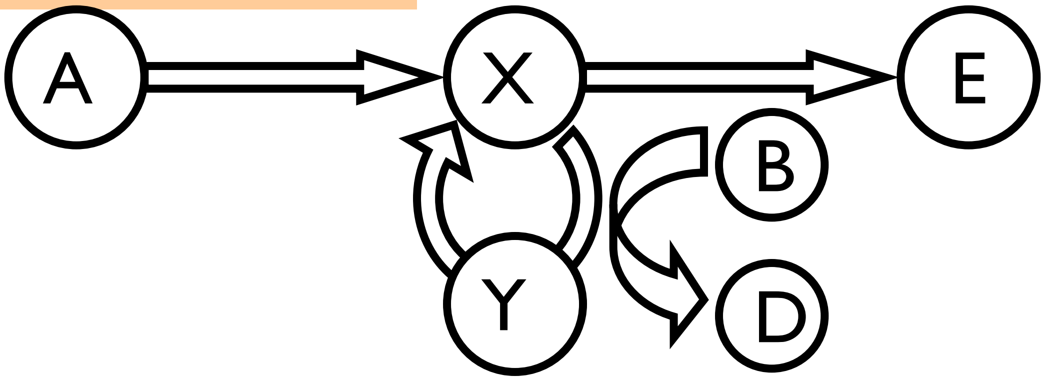
Wave-like spread of activity in unstirred solution

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

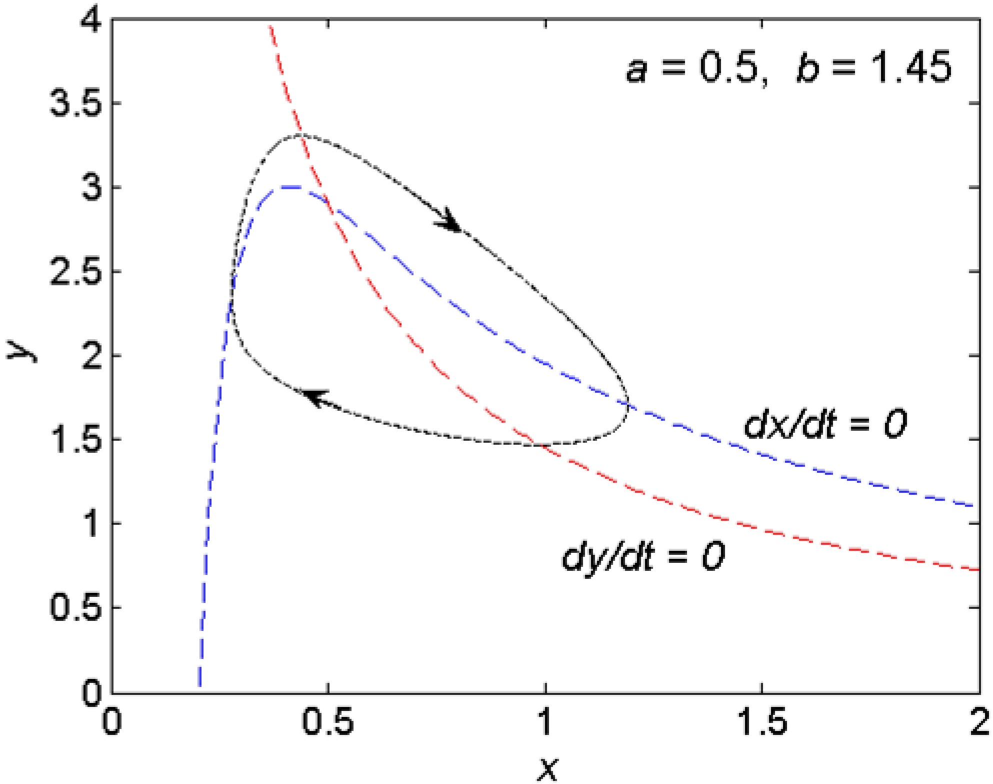
$$dX/dt = k_1A - k_2BX + k_3X^2Y - k_4X$$
$$dY/dt = k_2BX - k_3X^2Y$$

$\Rightarrow$

Non-dimensionalizing,

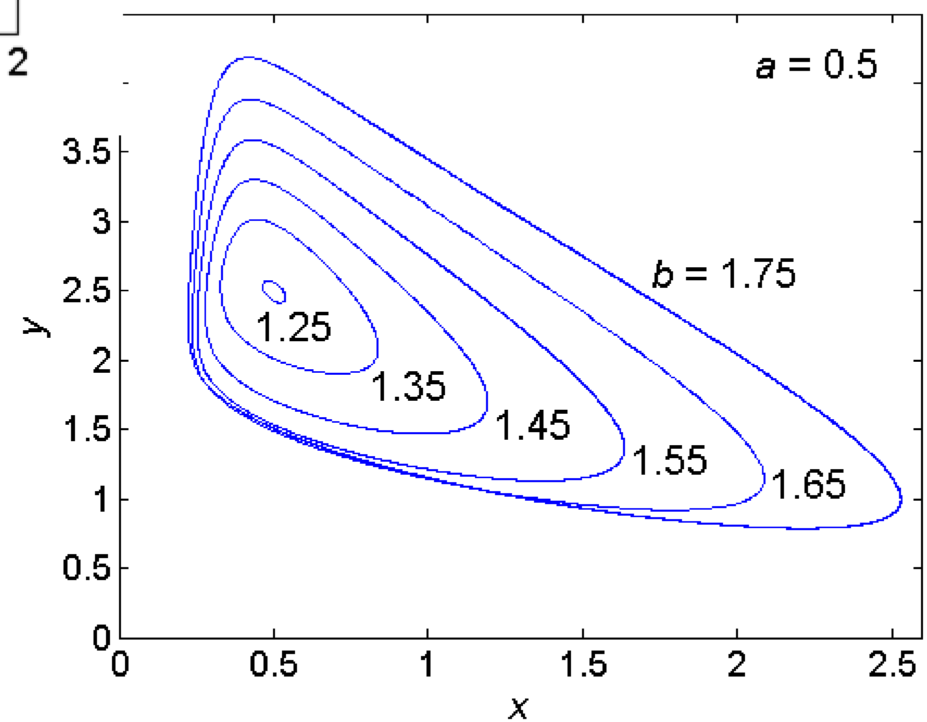
$$dx/dt = a - bx + x^2y - x$$
$$dy/dt = bx - x^2y$$

Nonlinearity



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

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

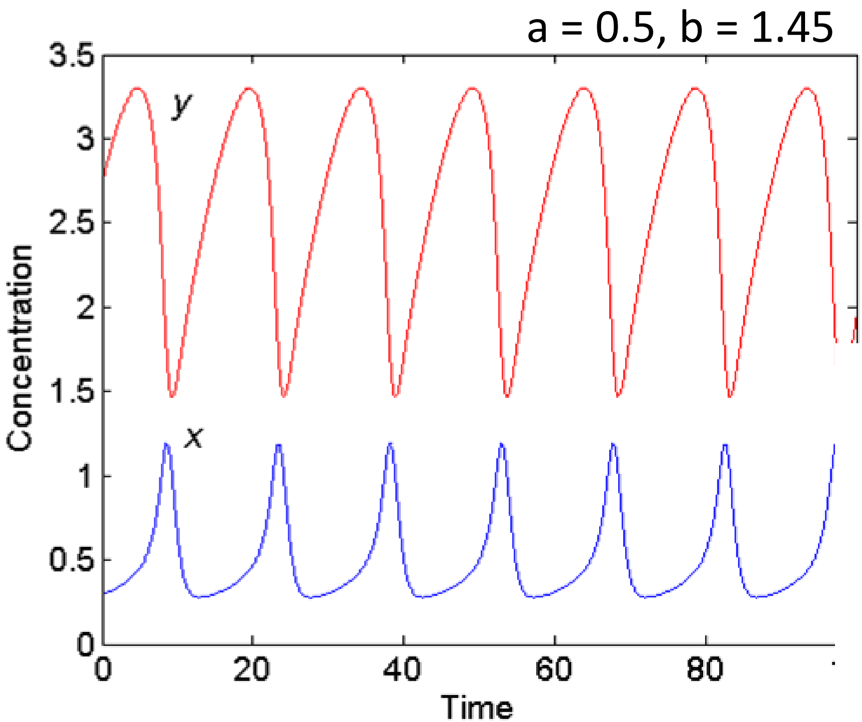


$$J = \begin{pmatrix} -b-1+2x^*y^* & x^2 \\ b - 2x^*y^* & -x^2 \end{pmatrix} = \begin{pmatrix} b-1 & a^2 \\ -b & -a^2 \end{pmatrix}$$

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

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 !



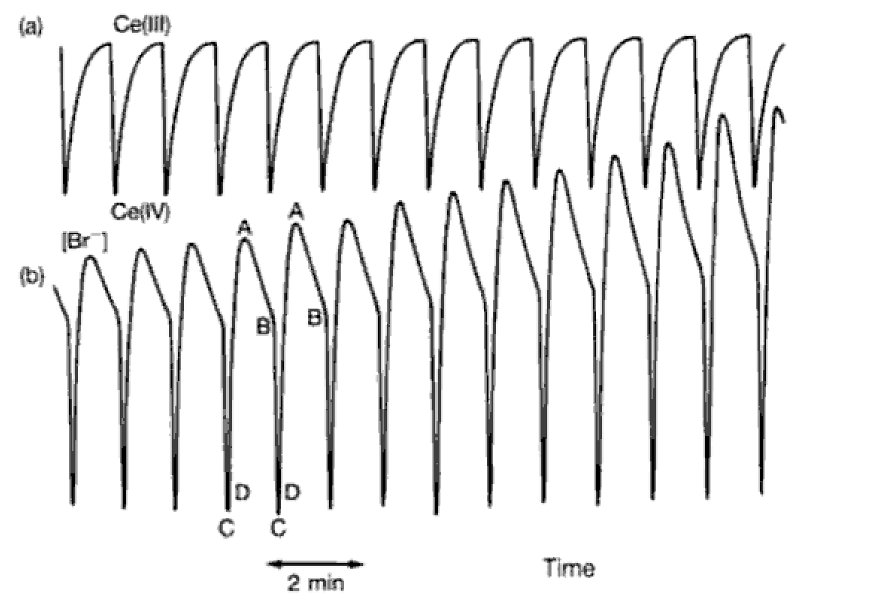


FIG. 8.1. Typical experimental records from (a) platinum electrode and (b) bromide ion sensitive electrode for the Belousov–Zhabotinskii reaction in a closed system. In each case the reference electrode is calomel.

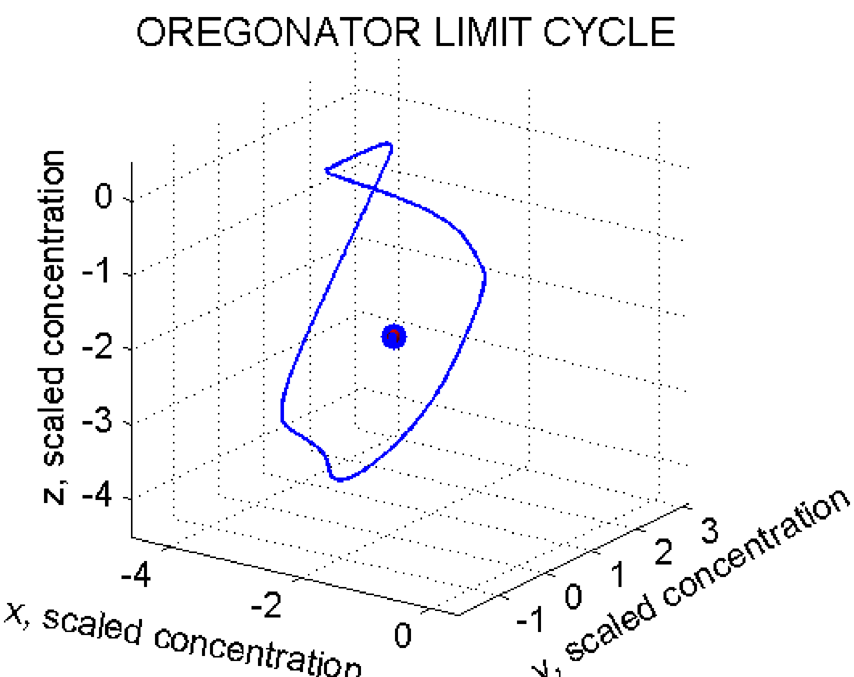
However, there are chemically more accurate models of the BZ reaction…

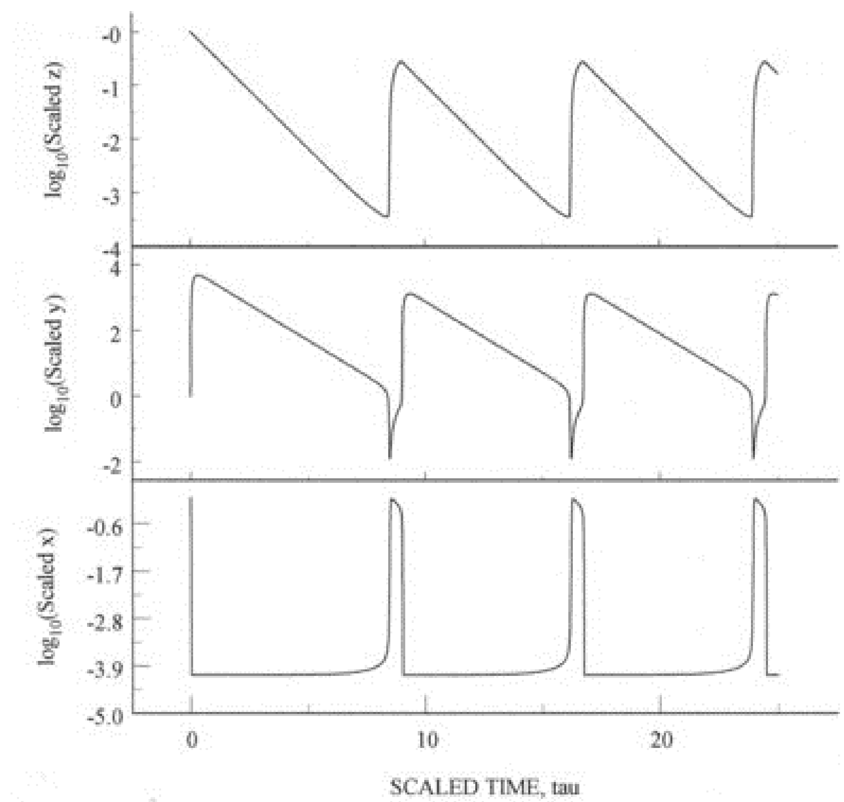
The Oregonator (1974)

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)