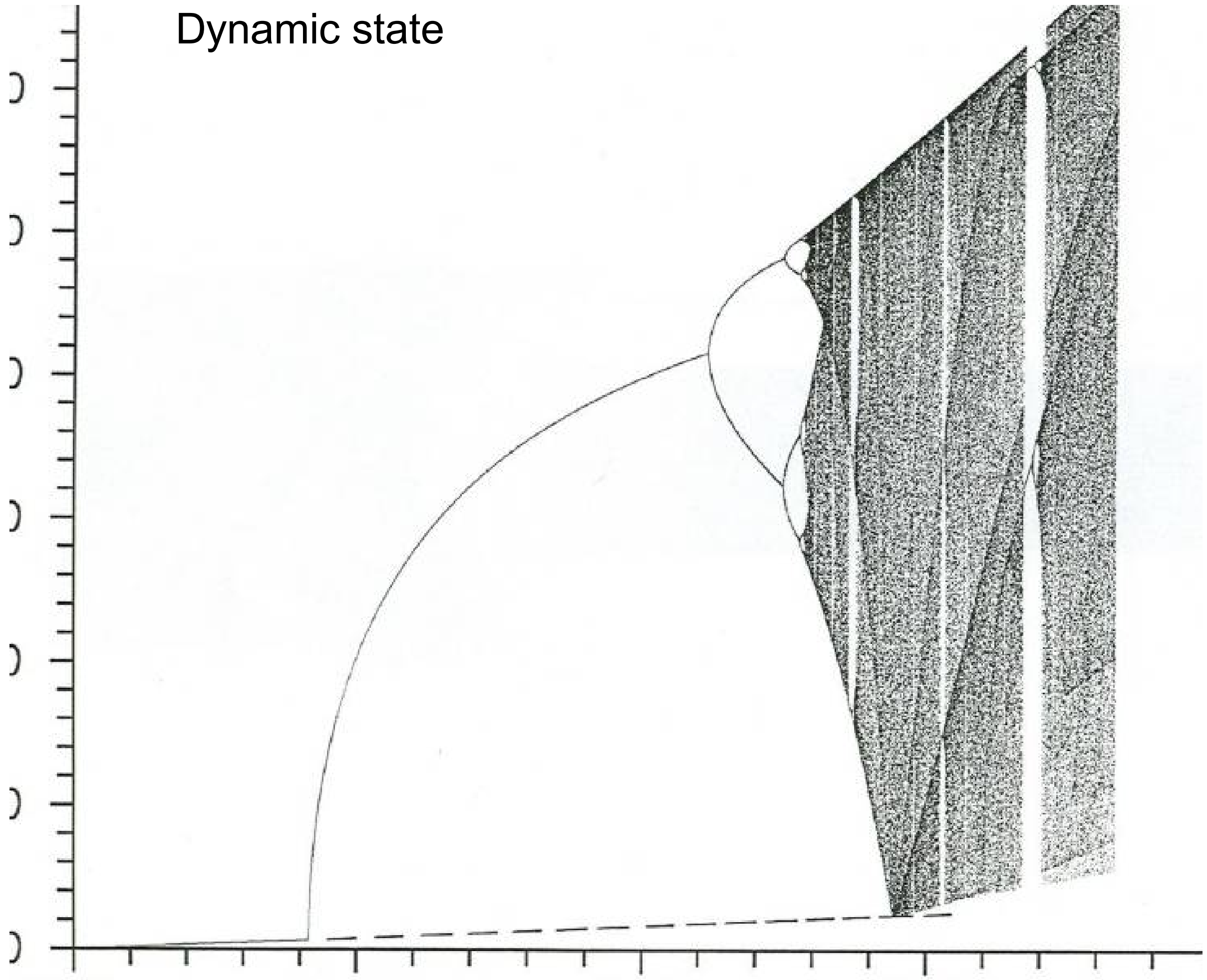
Operation under Far-From-Equilibrium Conditions

- As the supply of energy to a dissipative system increases, the equilibrium point will lose its stability, and complex spatial patterns and/or temporal behaviours will start to unfold.

- Nonlinear Dynamics aims at unravelling the sequence of instabilities that take place as the system is carried further and further into the unstable regime.

- Living systems generally operate under far-from-equilibrium conditions.



Hopf or saddle-node bifurcation

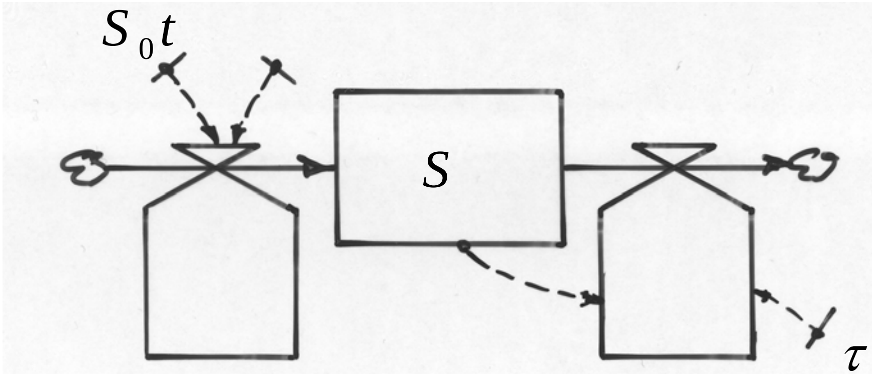
Onset of Self-Sustained Oscillations 1

1. Single reaction step

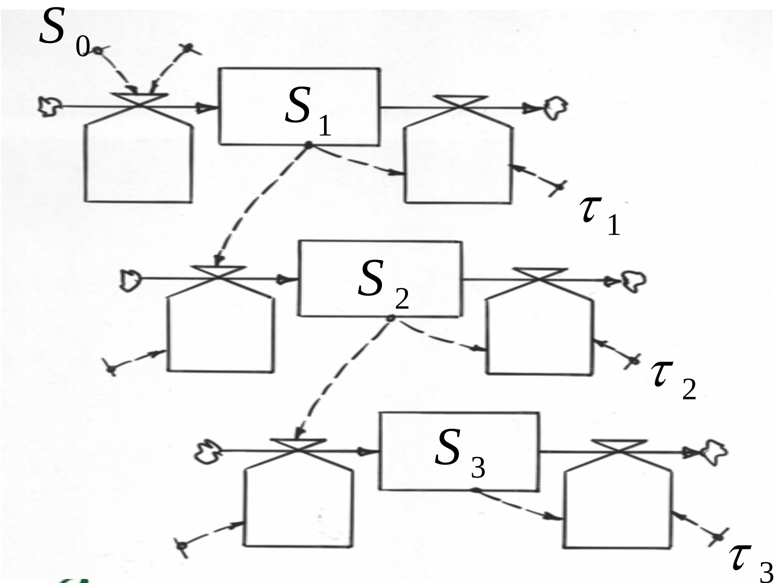
$$\frac{dS}{dt} = \frac{aS_o}{b + S_0} - \frac{S}{\tau}$$

Equilibrium: $S_{eq} = \frac{a\tau S_o}{b + S_0}$

Eigenvalue: $-\frac{1}{\tau}$



2. Reaction cascade



$$\frac{dS_1}{dt} = \frac{a_0 S_o}{b_0 + S_0} - \frac{S_1}{\tau_1}$$

$$\frac{dS_2}{dt} = \frac{a_1 S_1}{b_1 + S_1} - \frac{S_2}{\tau_2}$$

$$\frac{dS_3}{dt} = \frac{a_2 S_2}{b_2 + S_2} - \frac{S_3}{\tau_3}$$

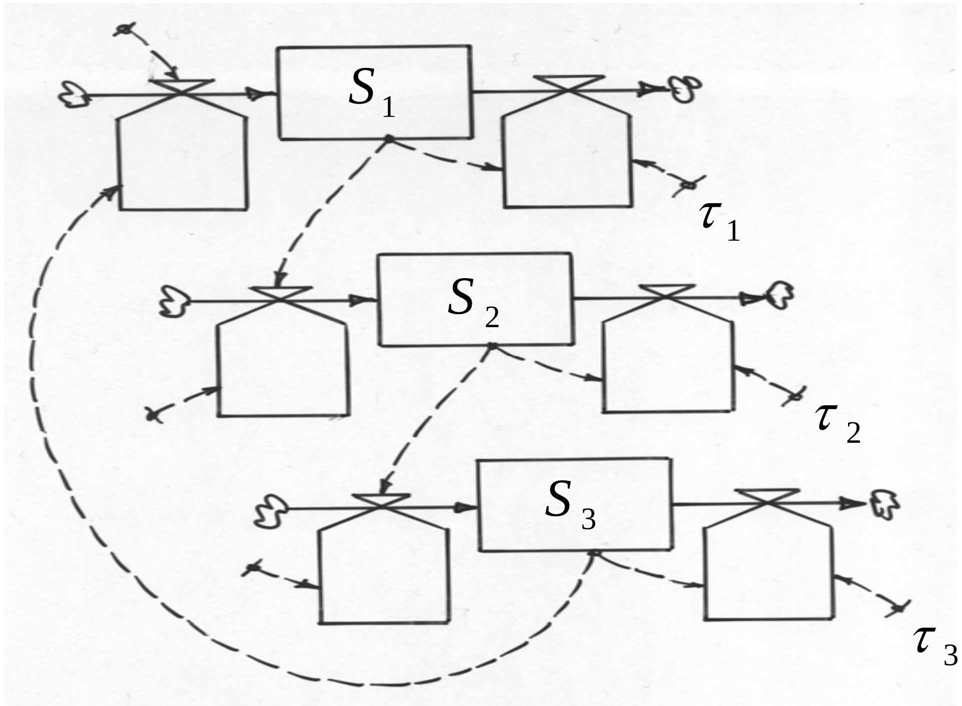
Eigenvalues: real and negative

No oscillatory dynamics

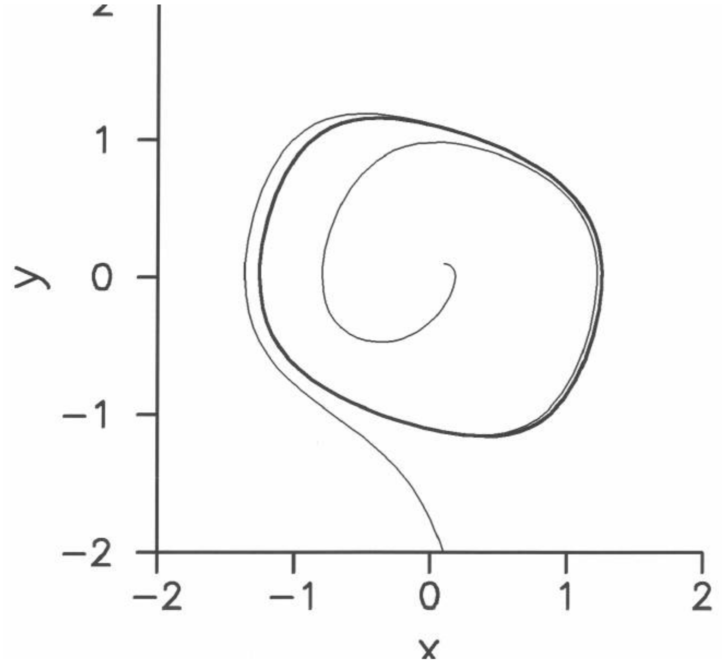
Onset of Self-Sustained Oscillations 2

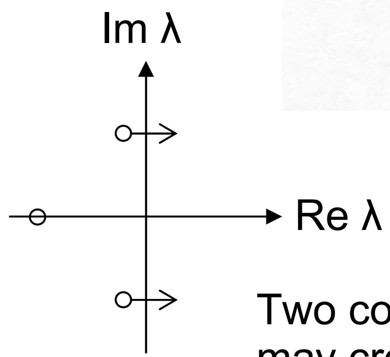
3. Negative feedback

   Eigenvalues can become complex conjugated: Oscillatory response



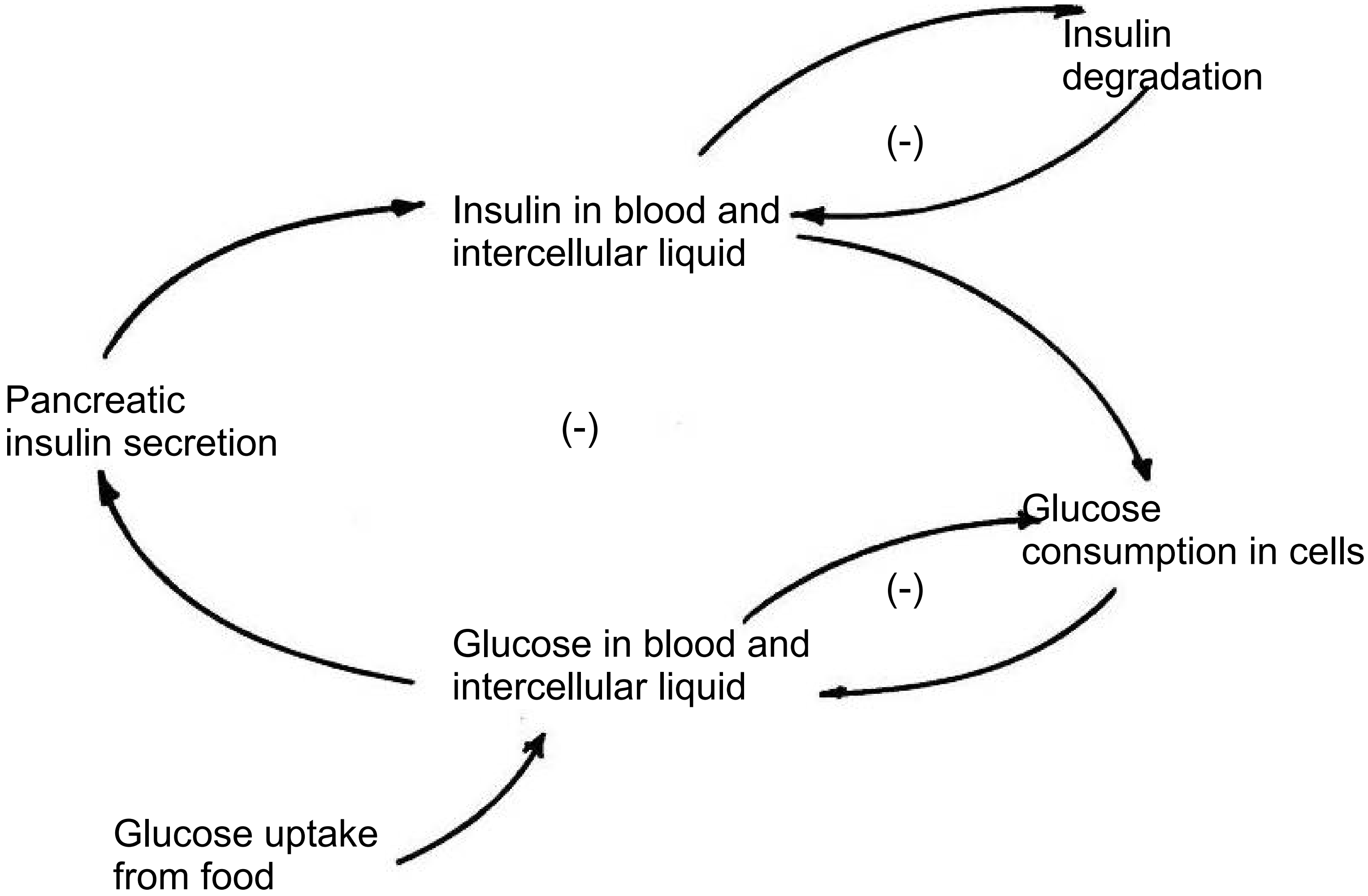
4. Larger loop gain





Two complex conjugated eigenvalues may cross the imaginary axis. The equilibrium point turns unstable (Hopf bifurcation) and the system starts to perform self-sustained oscillations.

Causal loop diagram for glucose metabolism



The system is controlled by the large negative feedback loop, and its stability ensured through the dissipative degradation and consumption loops.

Basic Flow Diagram

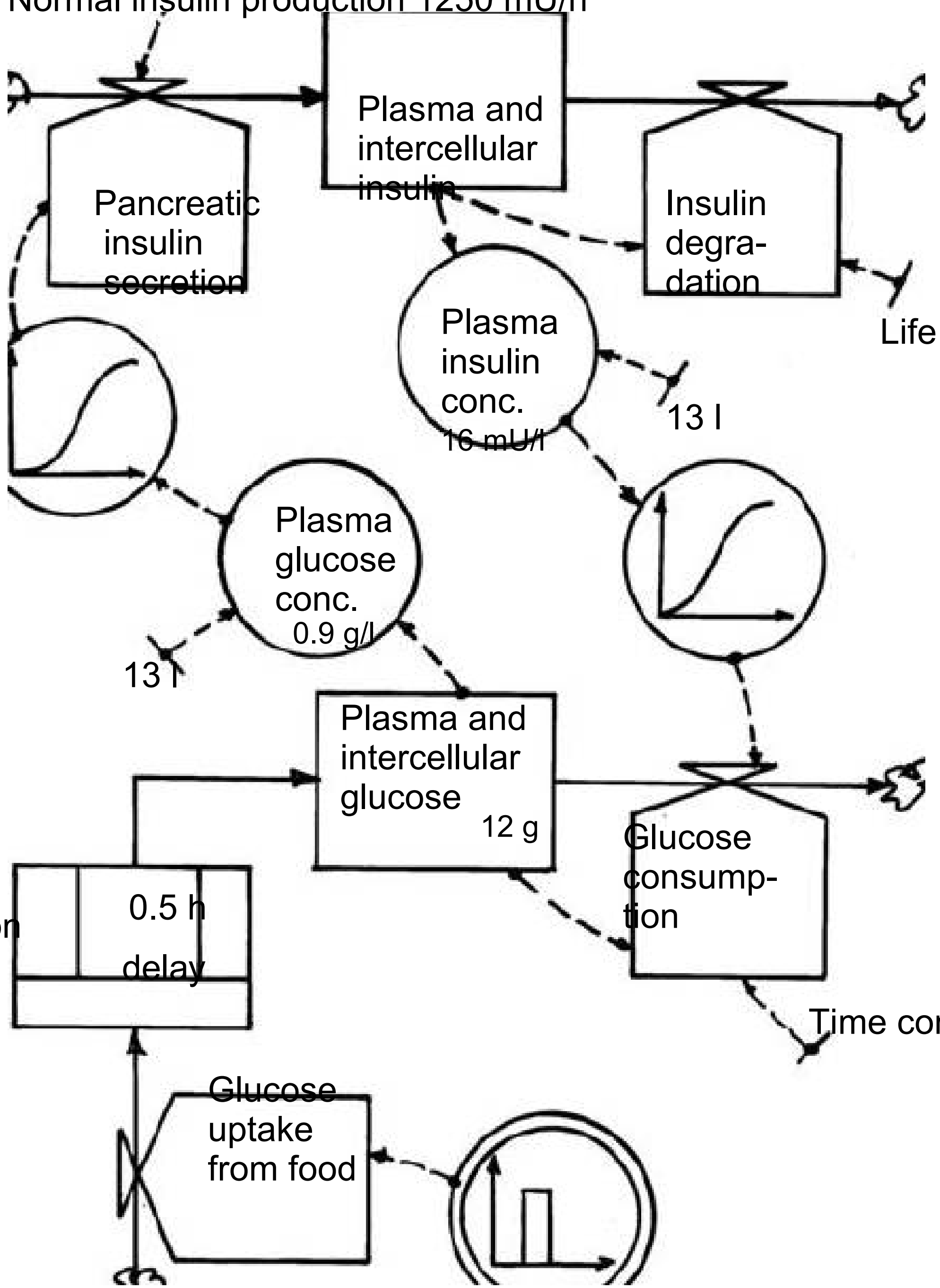
Each "box" represents the amount of some chemical species in a specific compartment.

Full lines denote material flows and conservation conditions. Dotted curves denote causal relations.

The model is equivalent to two coupled differential equations

$$\frac{dI}{dt} = \text{insulin secretion} - \text{insulin degradation}$$

$$\frac{dG}{dt} = \text{glucose uptake} - \text{glucose consumption}$$

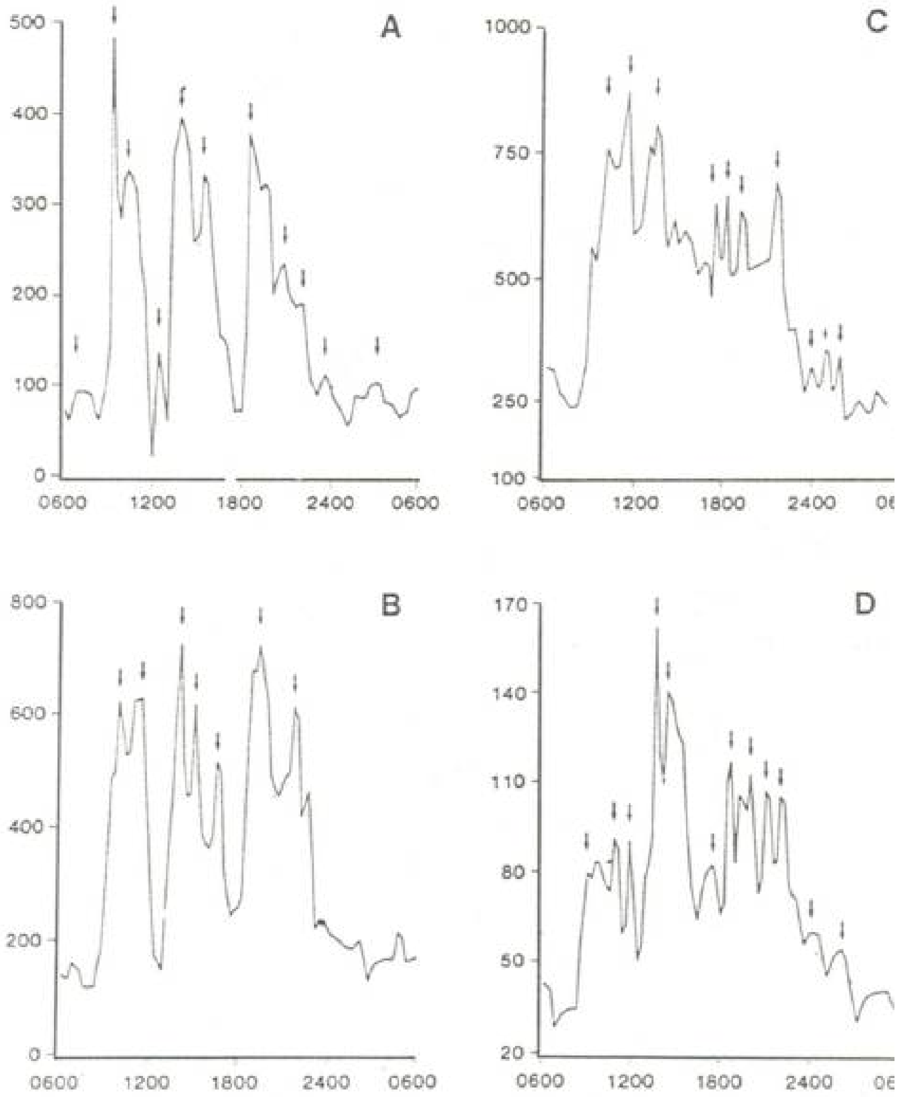


The mechanism-based modeling approach

In mechanism-based modeling

- The relevant biological processes are represented as realistically as possible, and the parameters and nonlinear relations are determined from independent experiments.
- The functional form of nonlinear relations are based on microscopic considerations (often from physics and chemistry).
- The model respects conservation laws, dimensions and time scales.
- The model is initially validated by its ability to reproduce observed wave forms, frequencies, amplitudes, phase relationships, parameter dependences, and stability properties.
- Further validation of the model is based on its ability to predict the outcome of new experiments, performed under conditions not previously investigated.

Ultradian Pulses of Insulin Secretion



Polonsky et al. New Eng. J. Med. (1988).

24 h insulin secretion profiles for two type-II diabetics and two age-matched controls. 10 min. temporal resolution. Meals were eaten at 09.00, 13.00 and 18.00.

Arrows indicate statistically significant pulses of insulin secretion.

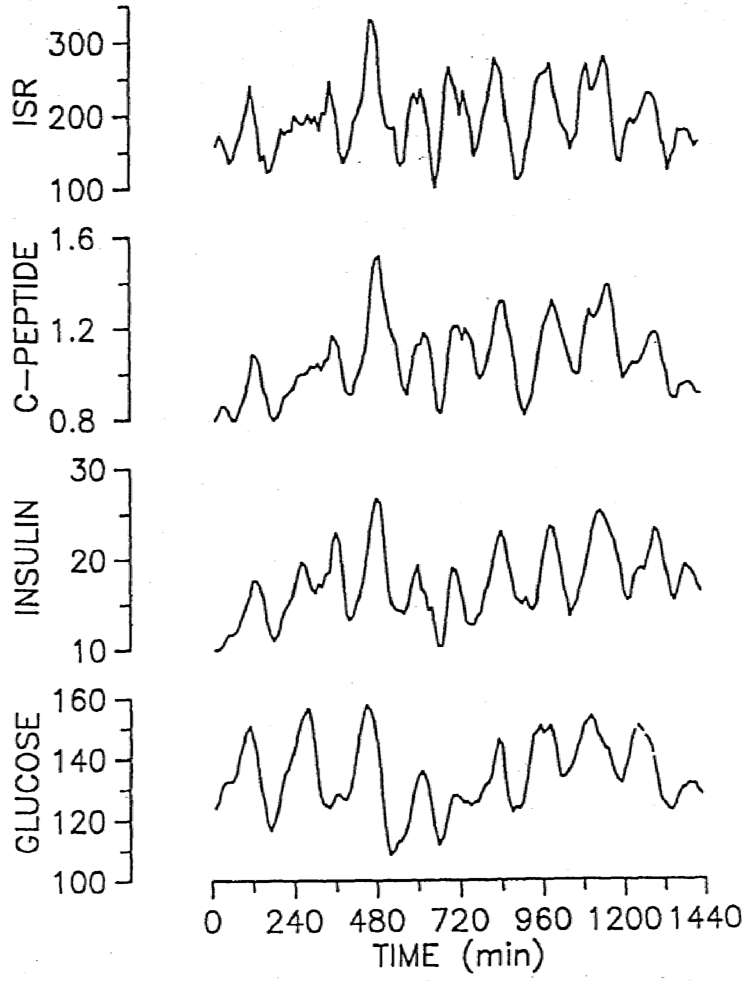
There is an obvious “ringing” in response to a meal. This is even more pronounced for type-II diabetics.

Can the “ringing” be used as a preclinical diagnostics of type-II diabetes?

Pulsatile Insulin Secretion in Fasting Subjects

- Young male subject fasting during (and for 12 hours before) the experiments
- Continuous intravenous glucose infusion at the rate of 6 mg/(kg min)
- Blood samples were taken every 10 min and examined for glucose, insulin and C-peptide
- Glucose-clamp experiments demonstrated that the oscillations were not associated with a pancreatic pacemaker
- Experiments with patients having undergone pancreas transplantation showed that they were not caused by signals from the central nervous system.

Sturis et al., Am. J. Physiol. (1991)



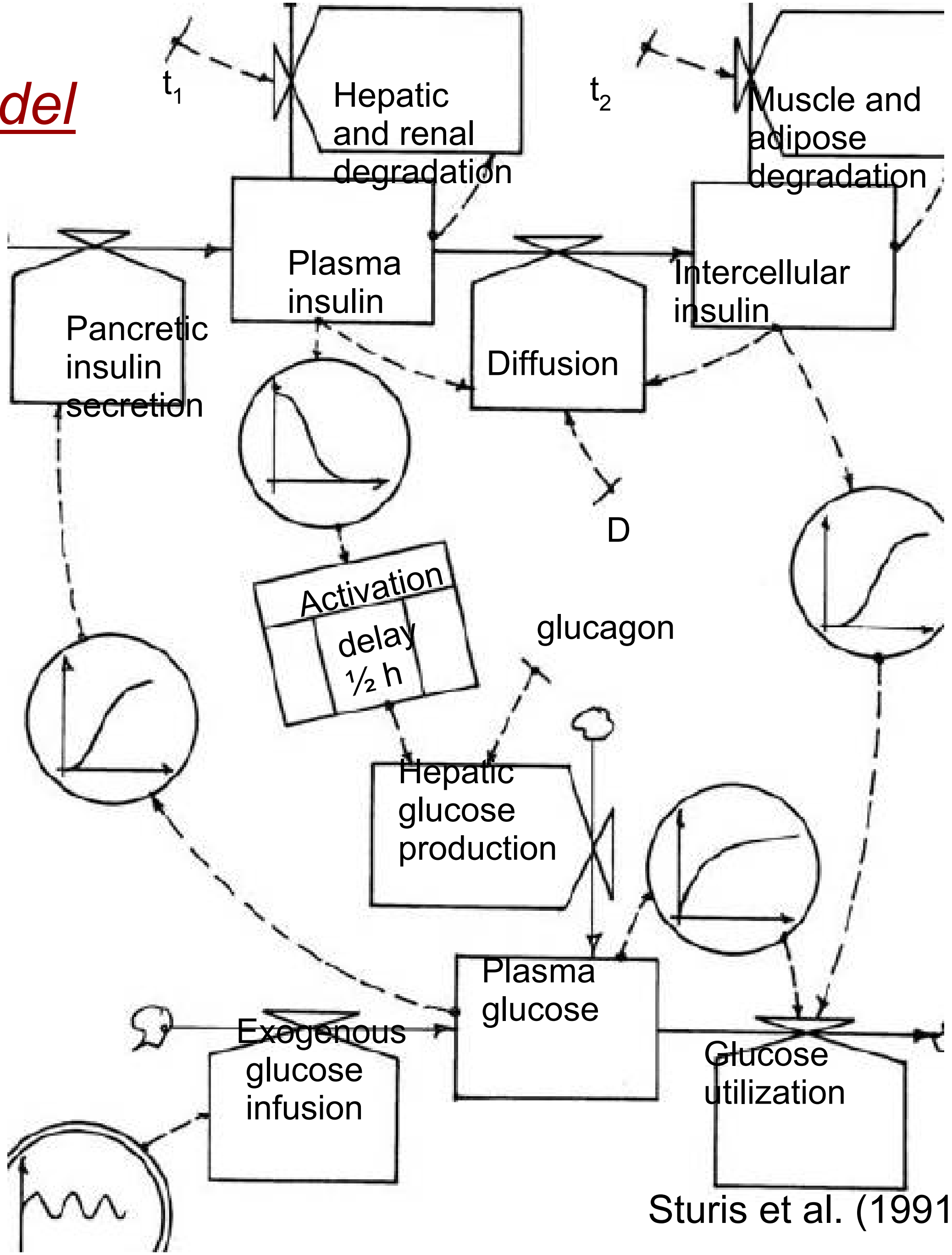
Alternative Hypotheses for Pulsatile Insulin Secretion

- The ringing phenomenon is characteristic for an early stage of type-II diabetes and may be used for preclinical diagnosis?
- The ”ringing” represents a pulsatile release of insulin similar to the ultradian rhythms known for many other hormones?
- The pulsatile release of insulin is triggered by signals from the brain, or caused by a pancreatic pacemaker?
- The oscillations are produced by a delay in the insulin-glucose feedback regulation. This delay is associated with the response of muscle and adipose tissue cells, or pancreatic β-cells?
- The oscillations are caused by processes in the liver (hepatic glucose release, glucagon)?
- The oscillations promote glucose uptake in the cells through interaction with the insulin receptor dynamics?

Extended metabolism model

The model accounts for:

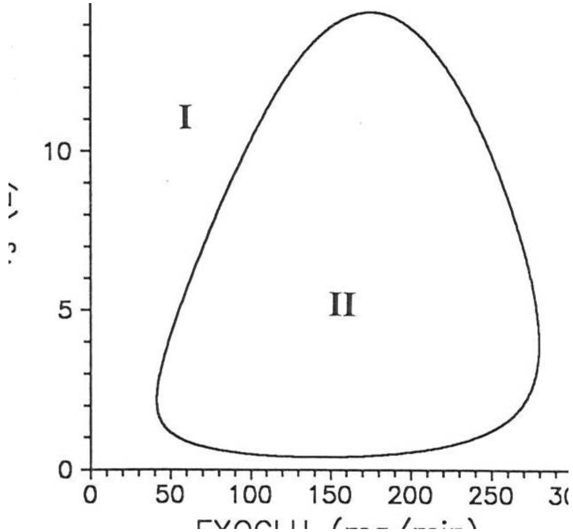
- the finite equilibration rate of insulin between the plasma and interstitial volumes.
- the separate degradation of insulin in the two compartments
- the release of glucose from the liver at low insulin concentrations.
- parameters and nonlinear relations are determined through separate experiments.

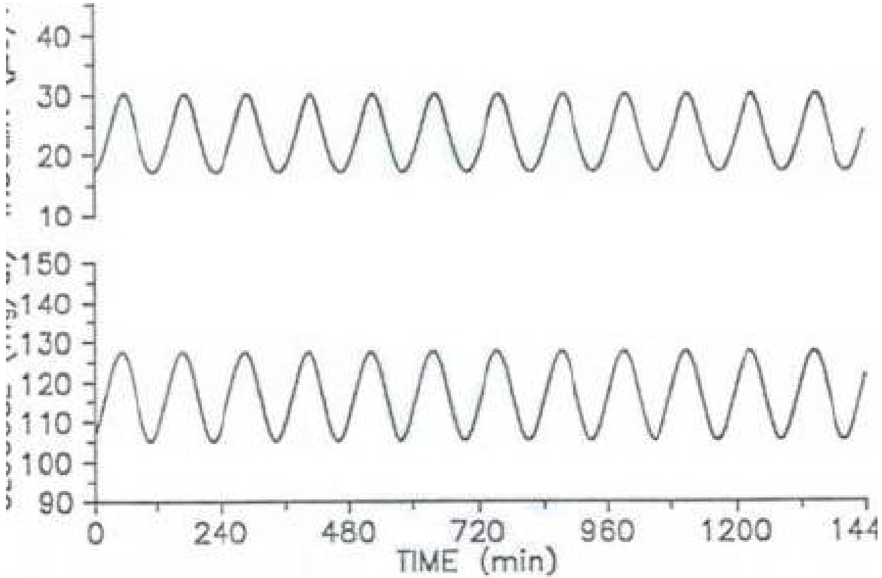


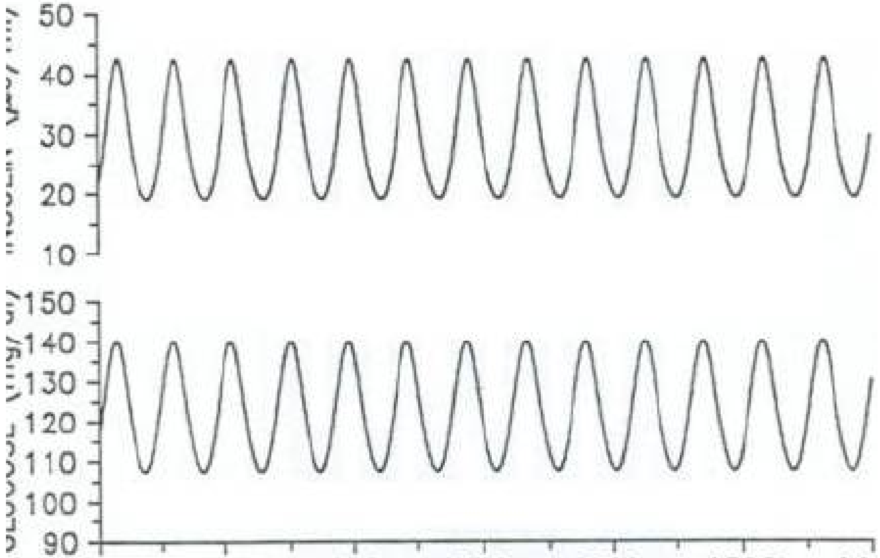
Sturis et al. (1991)

Forced Insulin Secretion Model

Oscillations only occur in a limited region of parameter space.

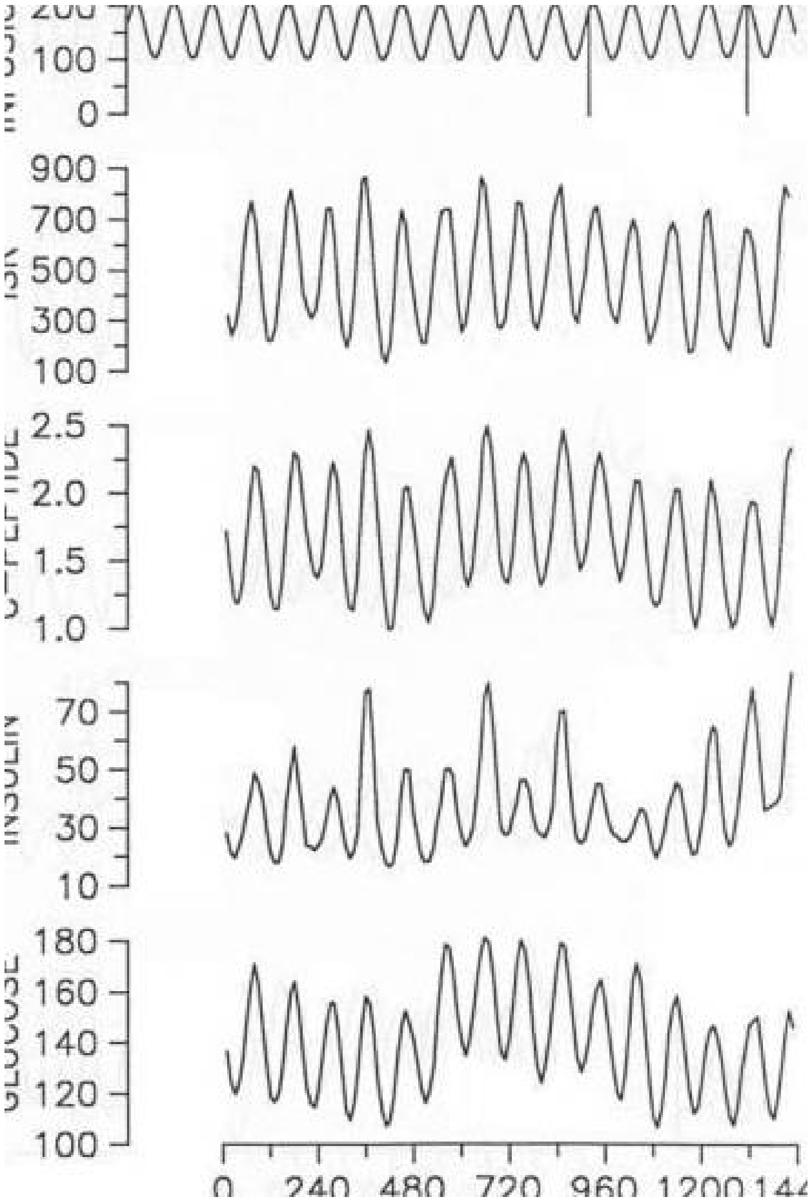






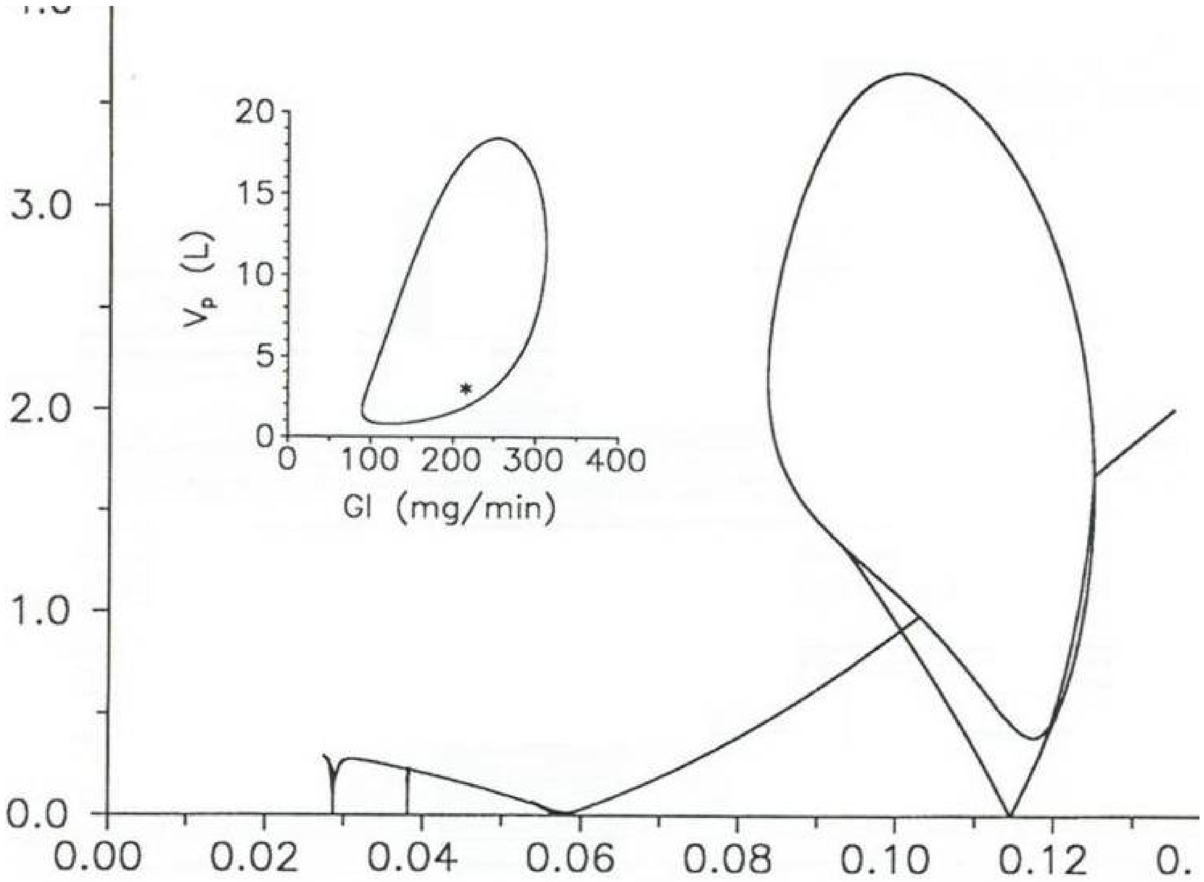
When forcing the model by a sinusoidal variation in the glucose infusion, the internal oscillation is found to synchronize to the forcing period. With a relative forcing amplitude of 30%, this synchronization can be observed over a frequency range of +-20%.

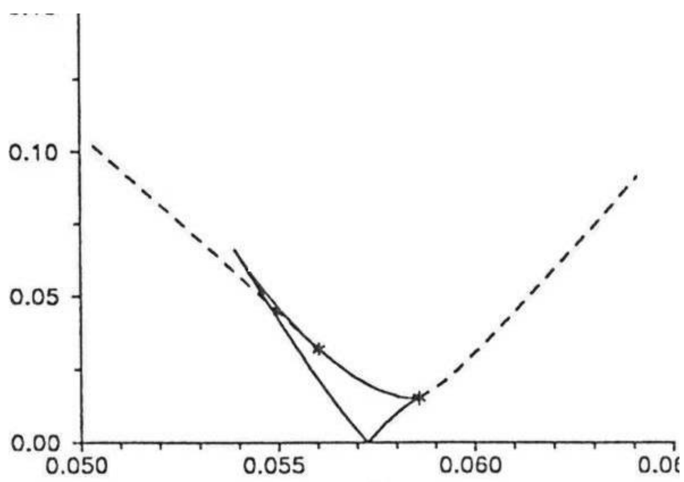
Forced insulin secretion



- The secretion of insulin can synchronize with the periodically varying glucose infusion.
- By studying the ability to synchronize as a function of the amplitude and frequency of the oscillatory glucose infusion, one can determine the strength of the nonlinear interactions in the system.
- If the same period is observed in other variables, one can conclude that they are coupled to the insulin secretion.

Forcing across a Hopf bifurcation (oscillator death)





1:1 resonance tongue

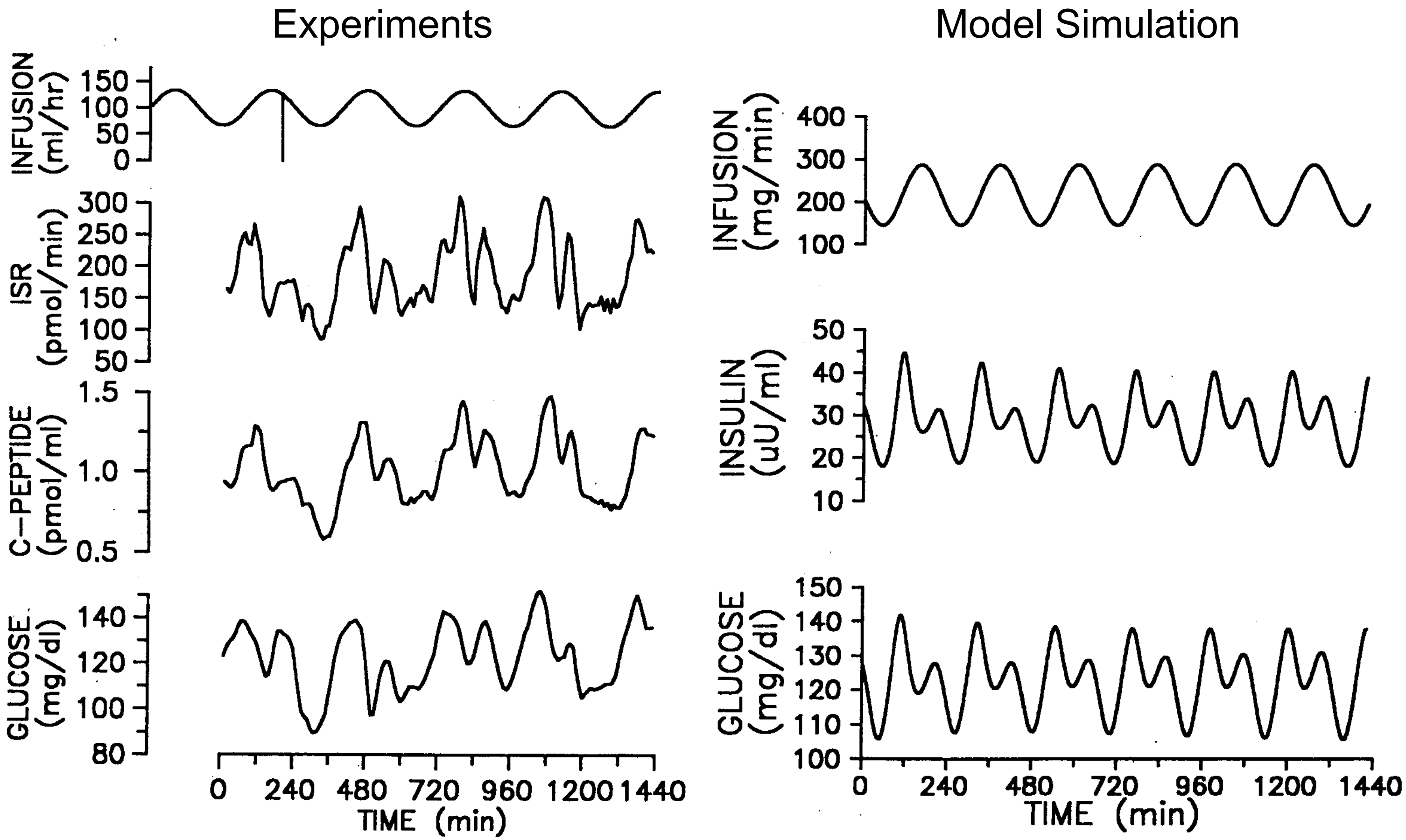
The 1:1 tongue is triangular, quite small and delineated by saddle-node bifurcation curves.

The 1:2 tongue displays a period-doubling. Other tongues are very narrow.

For higher forcing amplitudes the internal oscillations are quenched.

2:1 Synchronization of the Pulsatile Insulin Secretion

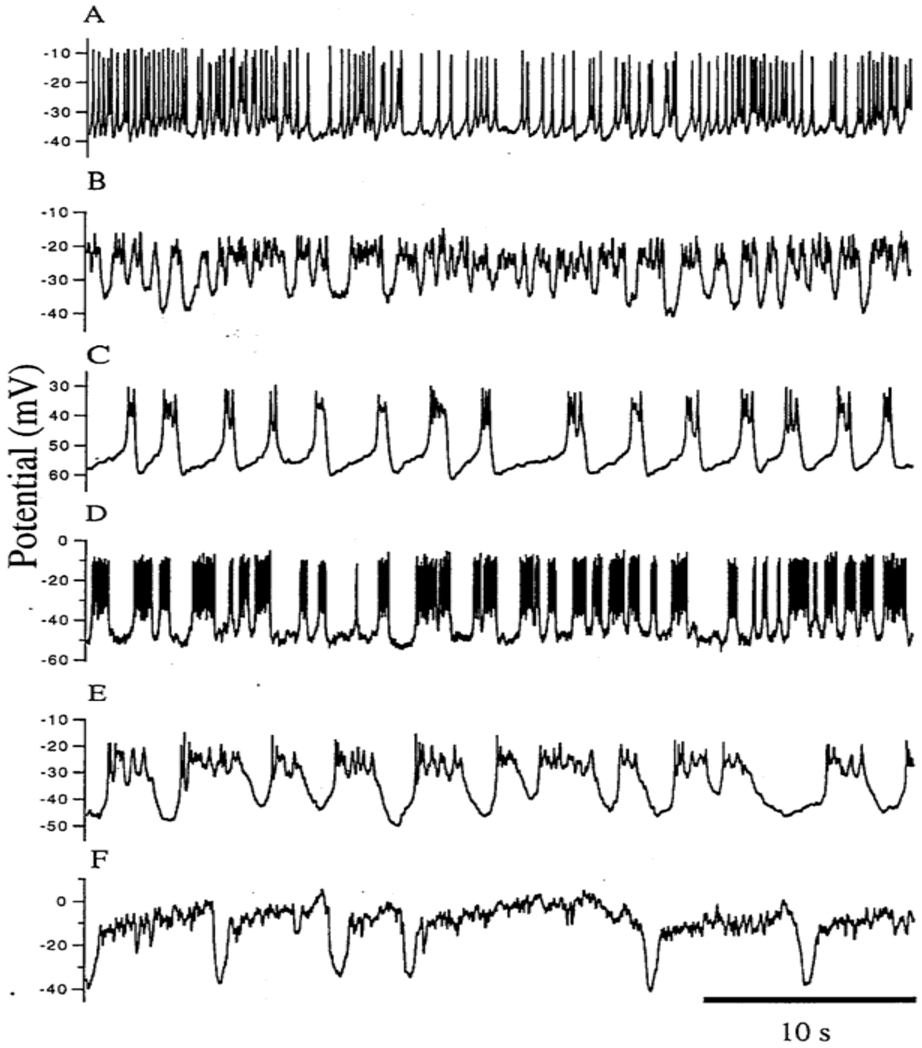
Sturis et al., Chaos (1995)



In this mode, the pancreas delivers two pulses of insulin for every peak in the blood glucose concentration.

Membrane Potentials for Bursting and Spiking Pancreatic Beta-cells

- Isolated beta-cells tend to produce randomly looking spike sequences
- Intact cells in pancreatic islets produce bursts of spikes with a bursting fraction that varies with the glucose concentration
- Insulin is released during the bursting period. Isolated cells typically release insulin at significantly lower rates than islet cells.
- Several diseases (such as Parkinsonian tremor, epilepsy, depression, etc.) are likely to involve a malfunctioning interaction among the cells.



The Sherman β-Cell Model

$$\tau \frac{dV}{dt} = -I_{Ca}(V) - I_K(V,n) - g_s S(V - V_K)$$

$$\tau \frac{dn}{dt} = \sigma(n_\infty(V) - n)$$

$$\tau_S \frac{dS}{dt} = S_\infty - S$$ (slow subsystem)

with

$$I_{Ca}(V) = g_{Ca} m_\infty(V)(V - V_{Ca})$$

$$I_K(V,n) = g_K n(V - V_K)$$

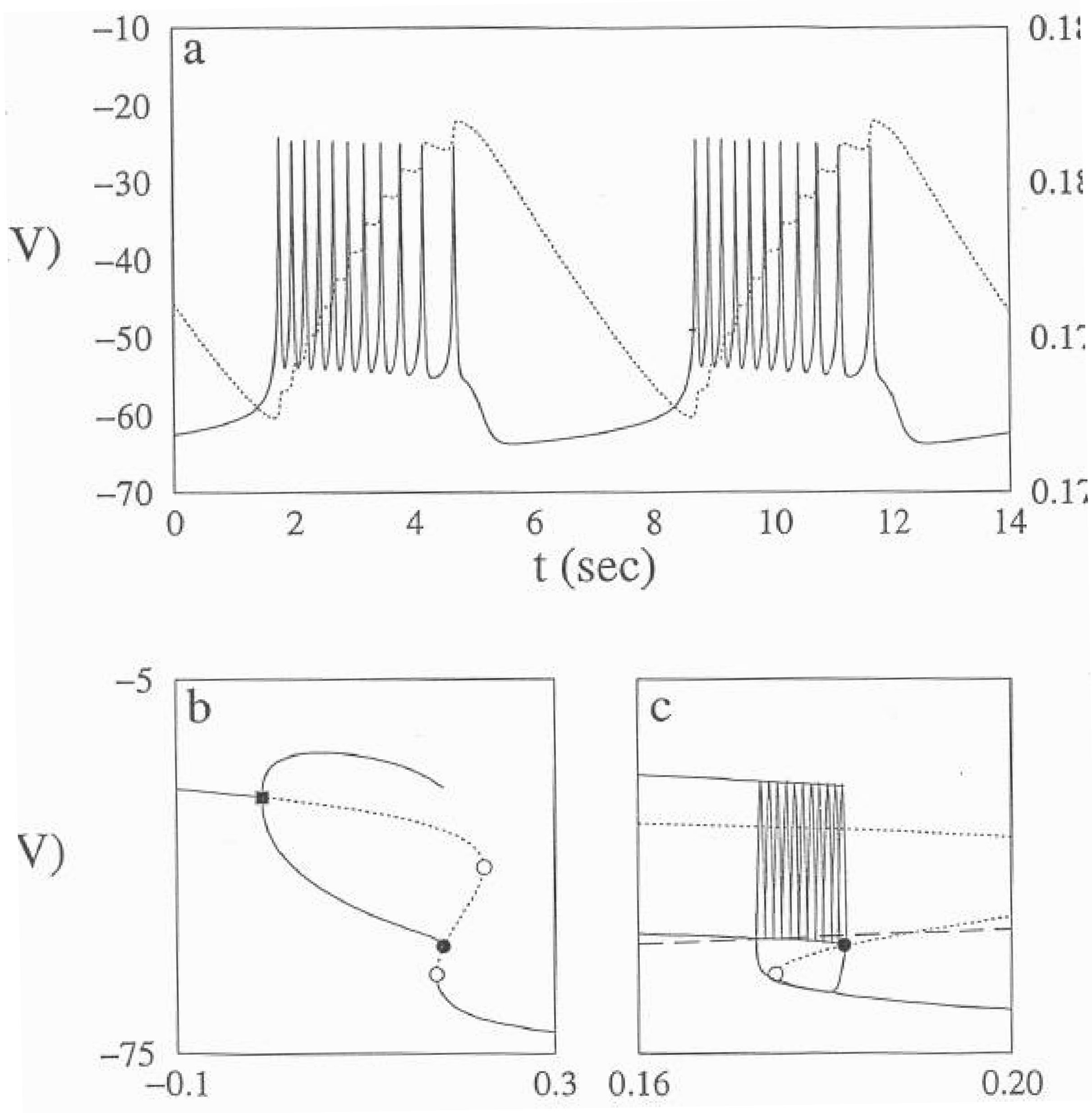
$$z_\infty = [1 + \exp((V_z - V)/\theta_z)]$$ for *z*=*m*,*n* and *s*

Equilibrium point for fast $\frac{dV}{dt} = \frac{dn}{dt} = 0$ and slow subsystem $\frac{dS}{dt} = 0$

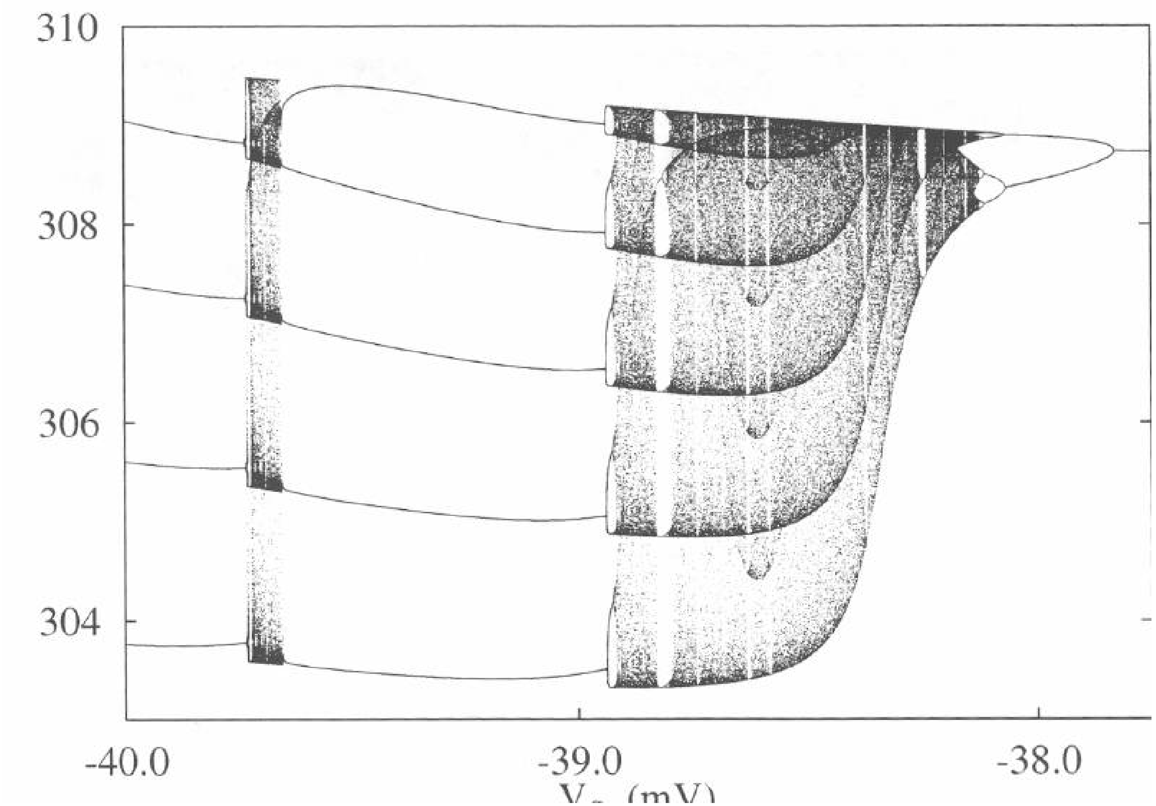
The Bursting β-Cell

- Temporal variation shows the gradual rise of the slow variable during the bursting phase.

- At a certain point the bursting stops, the slow variable starts to decline, and the membrane potential attains its resting value.



Bifurcation Diagram for Bursting β-Cell



- To the right in the diagram (V_s=-37.8 mV) the model displays tonic firing.

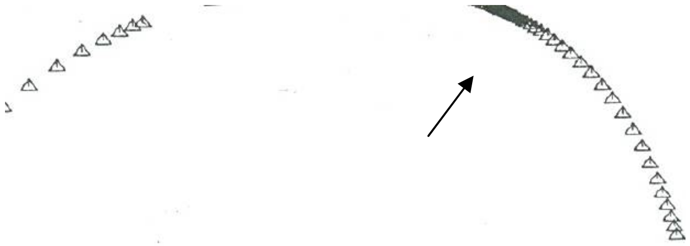
- As V_s is reduced the model develops through a period-doubling cascade to deterministic chaos.

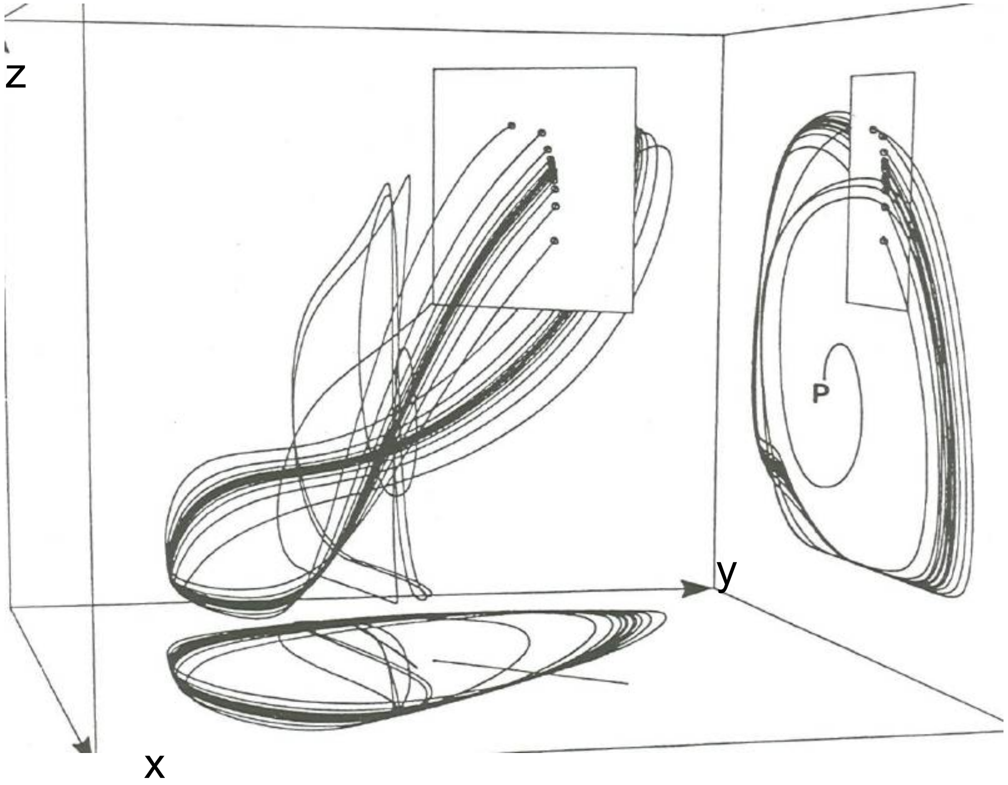
- To the left in the figure the model displays regular bursting which four spikes per burst. Transition from four to five spikes per burst takes the model through another region with deterministic chaos.

Poincaré section

- Trajectories from neighboring points in phase space will approach the stable limit cycle from all sides.

- The Poincaré section allows us to follow this approach in the form of a discrete mapping.





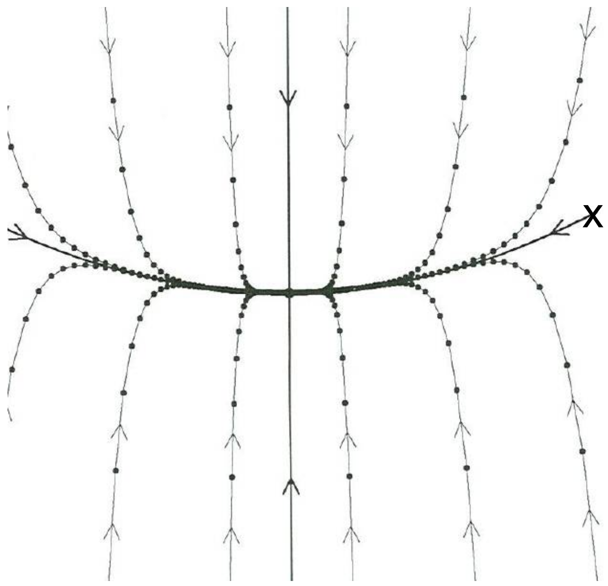
For highly dissipative systems, one often observes that the approach towards the stable limit cycle takes place along a one-dimensional curve in the Poincaré section.

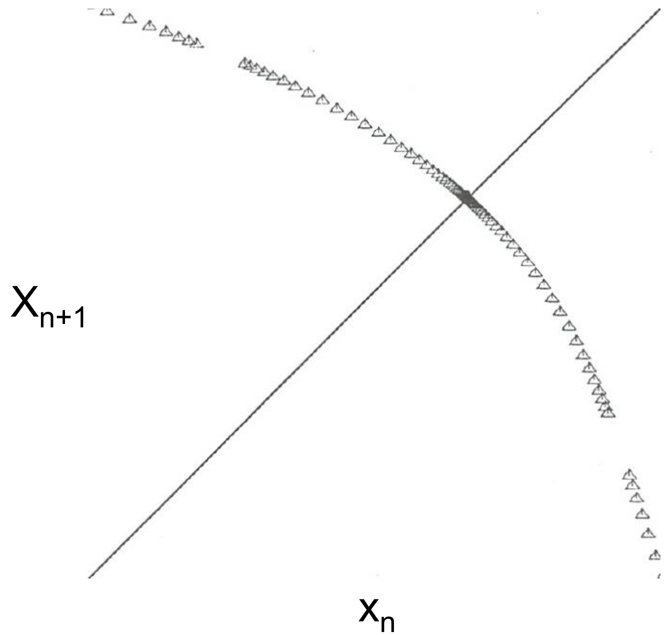
Return Map

- In general the approach to the stable limit cycle will be fast in certain directions and slower in others, and there will be one direction in which the approach is particularly slow.

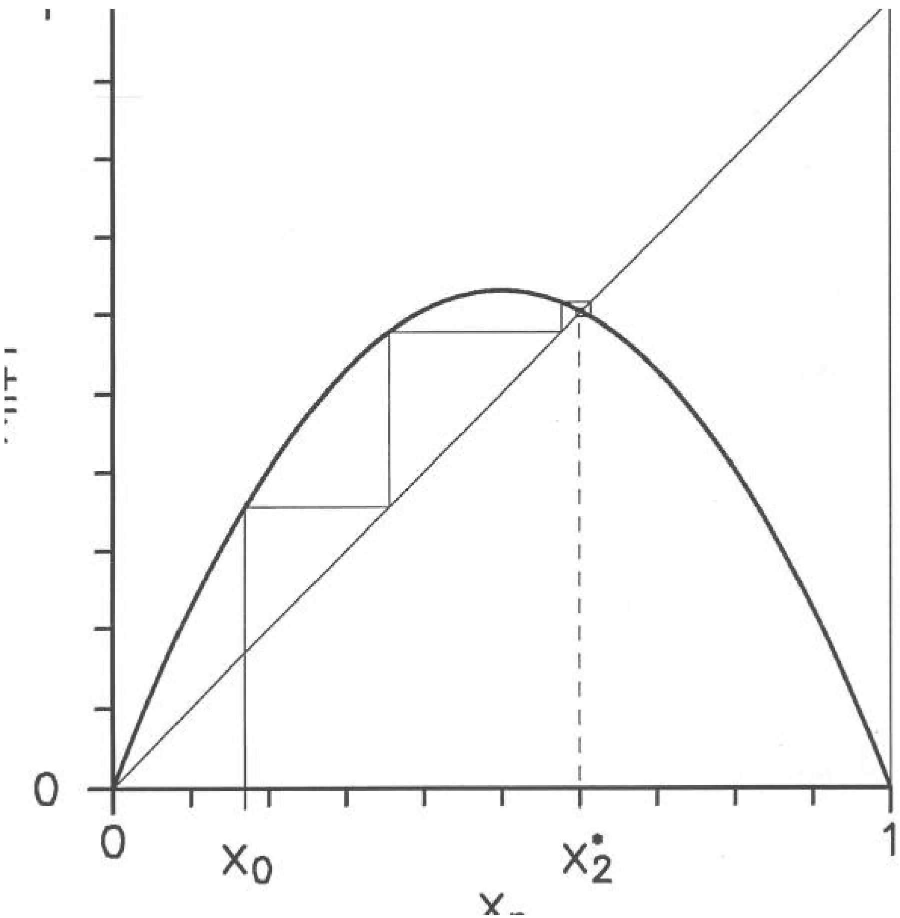
- This is the direction in which we follow the transient by measuring the distance of the intersection point to some particular point.

- In this way the original multidimensional time-continuous problem is turned into the simple problem of a iterating one-dimensional map.





The Logistic Map



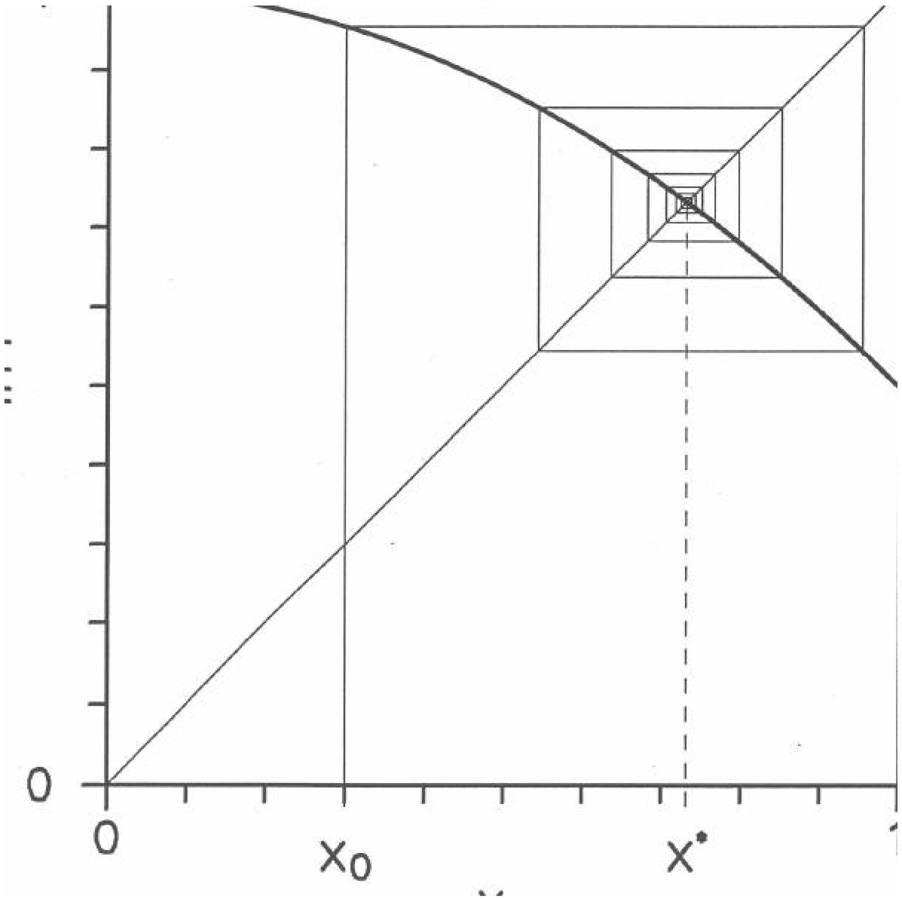
The logistic map is archetypic for studies of the period-doubling transition to chaos:

$x_{n+1}=f(x_n) = 4ax_n(1-x_n)$

The fixed points at $x_n = 0$ can be considered to represent the unstable equilibrium point of the original time-continuous system, and the fixed point at $x^* = 1 – 1/4a$ the surrounding limit cycle.

The rapid rise of the map for low values of x_n describes the expanding dynamics near the equilibrium point, and the negative slope for higher values of x_n describes the nonlinear restriction (folding) of the system.

Iteration of the Map

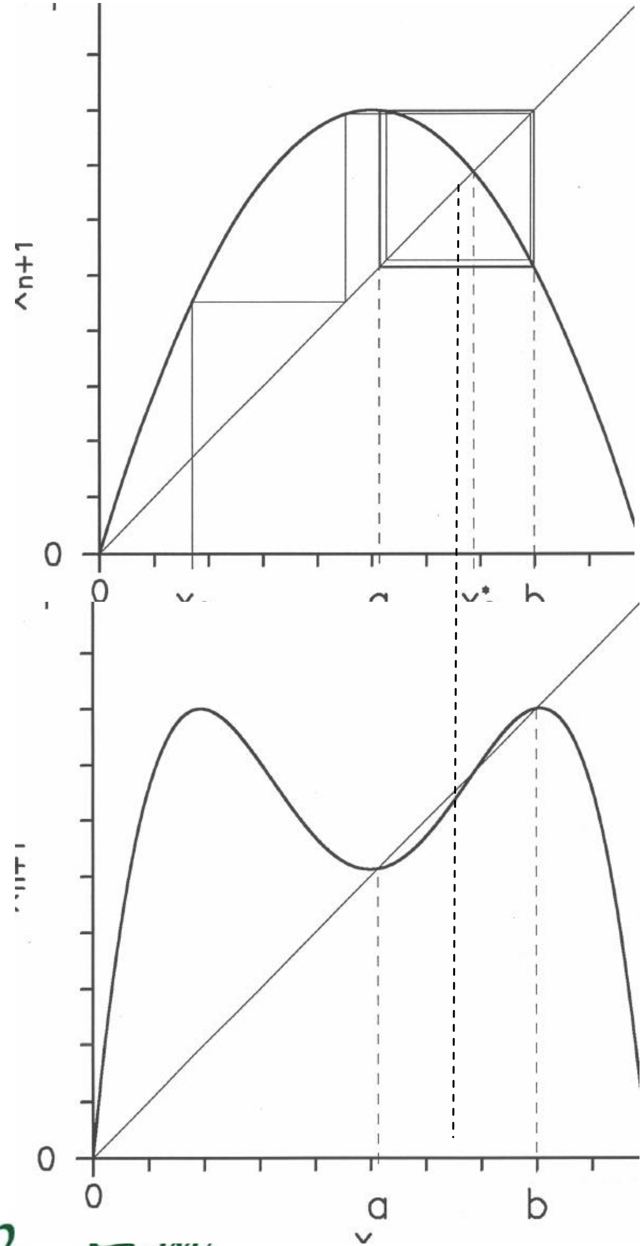


- Intersections with the diagonal determine fixed points of the map where $x^* = f(x^*)$. These points represent stable or unstable periodic orbits of the original time-continuous system (or equilibrium points).

- By iteration of the map $x_{n+1} = f(x_n)$, n = 1,2,3… we can follow the trajectory. E.g. the transient approach to stable fixed point.

A fixed point is table if the slope $|f'(x^*)| < 1$. The "eigenvalue" (Floquet multiplier) of the map is related to the slowest eigenvalue λ of the time-continuous system by $f'(x^*) = \exp\{\lambda_{re} T\}$

First Period-Doubling



The fixed point of the map is stable until a = ¾ at which point it undergoes a period-doubling bifurcations.

Iteration of the map now leads to a steady state in which the trajectory alternatives between two different values

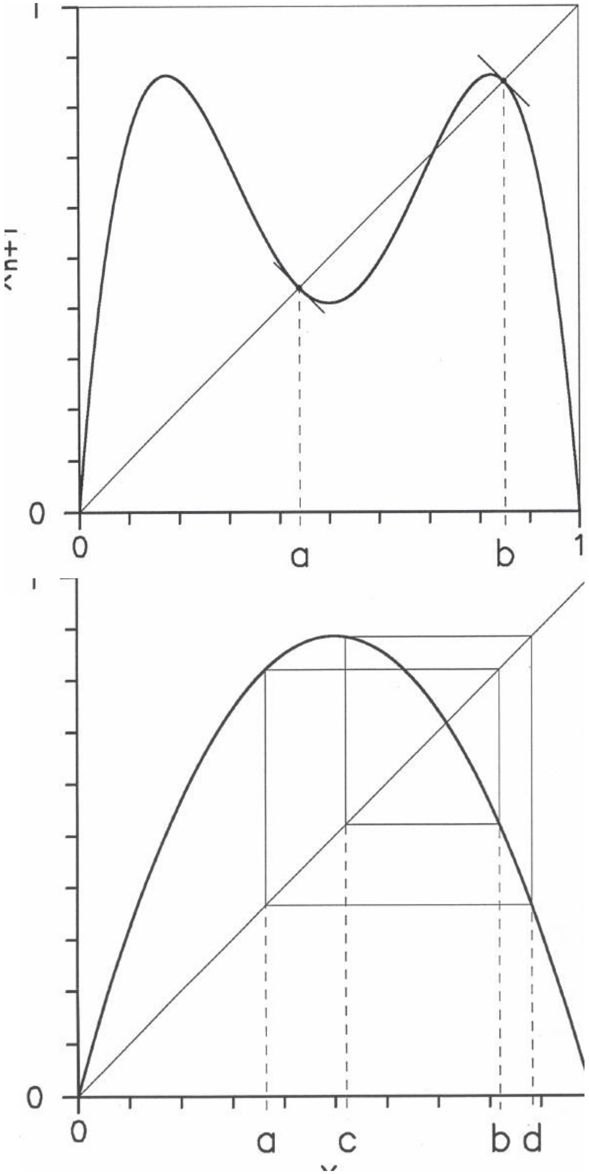
b = f(a) and a = f(b)

The second iterate of the map now has two stable fixed points

a = f(f(a)) and b = f(f(b)).

Note that these two fixed points have identical slopes.

Second Period-Doubling Bifurcation

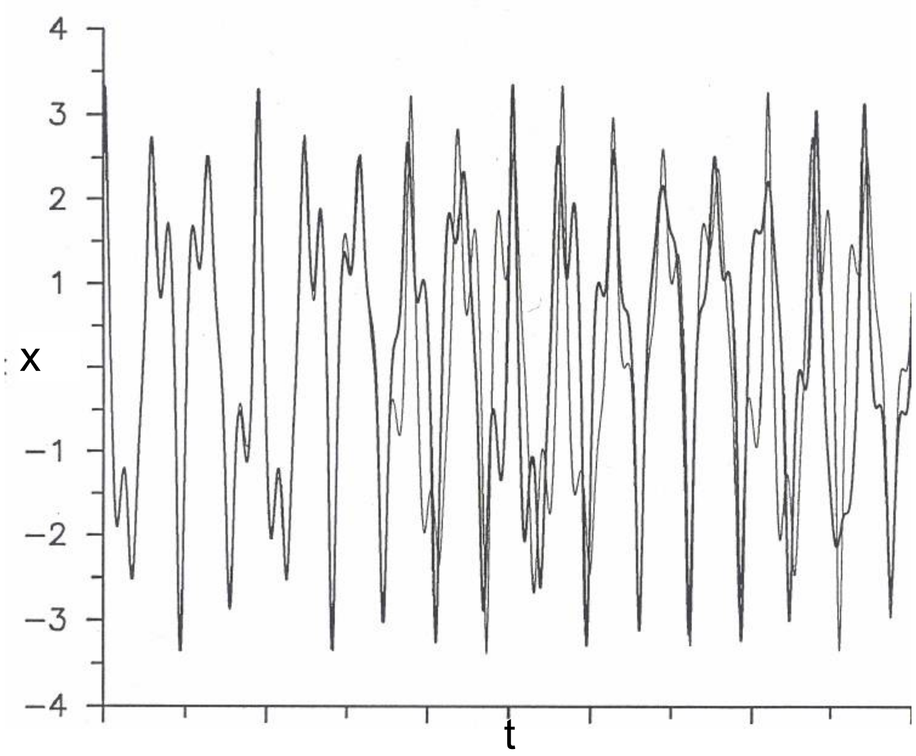


With increasing nonlinearly parameter, the two fixed points a and b of the iterated map f(f(x)) simultaneously undergo a new period-doubling when f'(a)f'(b) = -1.

The four times iterated map f(f(f(f(x))) ≡ $f^4(x)$ now has four stable fixed points, and the original map displays a stable period-4 orbit.

As a is further increased, the period-doublings continue and the system reaches a regime of deterministic chaos.

Deterministic Chaos



The chaotic state is characterized by the fact that although the system is deterministic

- the trajectory looks irregular and random

- long term prediction is impossible

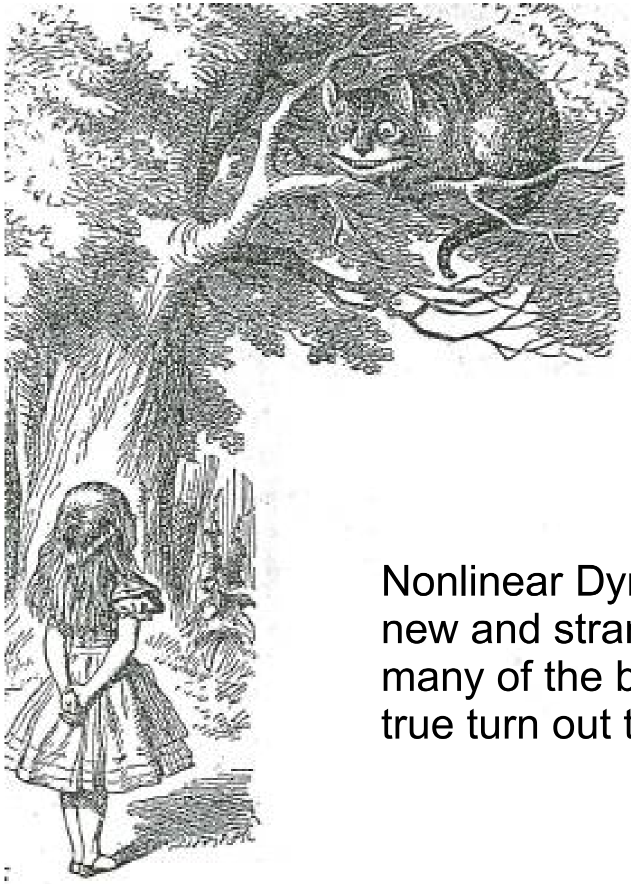
- the trajectory moves among a dense set of unstable periodic orbits.

- there are trajectories that come everywhere (ergodicity)

We distinguish between three main routes to chaos (through period-doubling, intermittency or torus breakdown).

The transitions to chaos are quantitatively and qualitatively universal, i.e., the same for large classes of systems, physical, biological, economical or technical.

Conclusions



Nonlinear Dynamics represents a new and strange world in which many of the beliefs we have held true turn out to be wrong.

Nonlinear Dynamics provides the tools and concepts we need for a detailed understanding of the functional complexity of living systems.