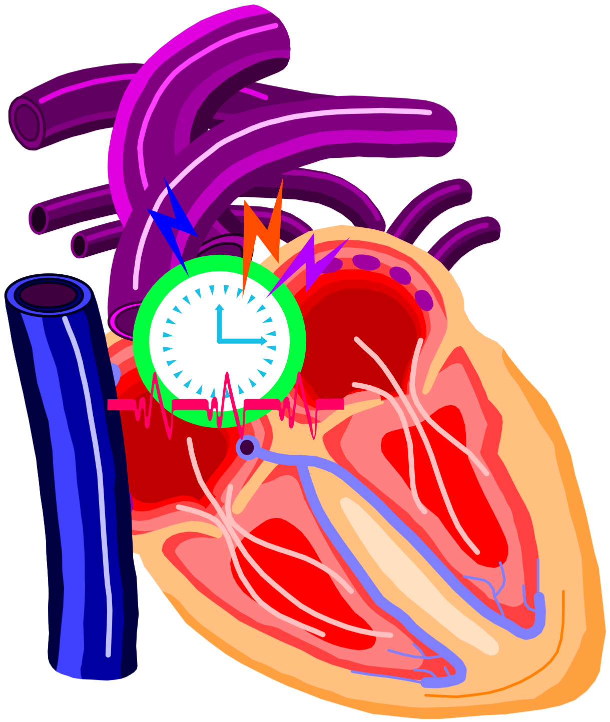
Feed Sideward

Applications to Biological & Biomedical Systems Session 2



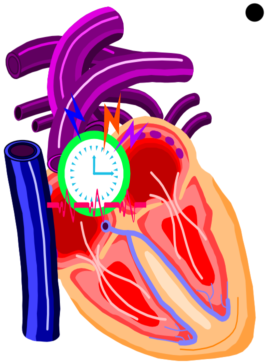
Jim Holte

2/7/2002

Sessions

- Session 1 - Feed Sideward – Concepts and Examples, *1/15*
- Session 2 – Feed Sideward – Applications to Biological & Biomedical Systems, *2/7*
- Session 3 – Chronobiology, *2/21* ***?***
  Franz Hallberg and Germaine Cornelissen

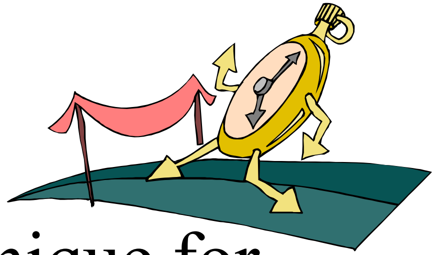
Biomedical Devices



- **Pacemakers** - Companies are introducing circadian rhythm based pacemakers. The *pacing strategy* (amplitude & timing of pacing stimulus) for effective cardiac capture depends on the ***time of day***. (eg. work & sleep).

- **Drug Delivery** - Medtronic/Minimed's insulin pump has a *drug delivery strategy*. It is preprogrammed for continuous insulin delivery which depends on exercise, food intake, patient endogenous performance, may now use adjustment of dose as a function of ***time of day***.

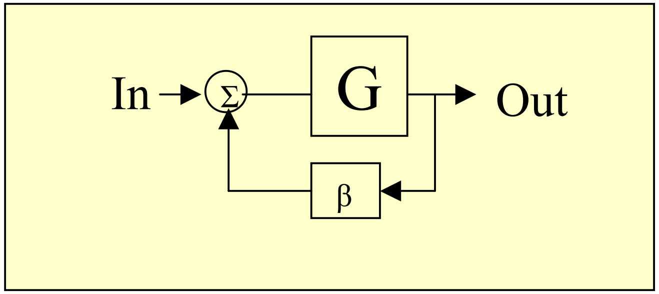
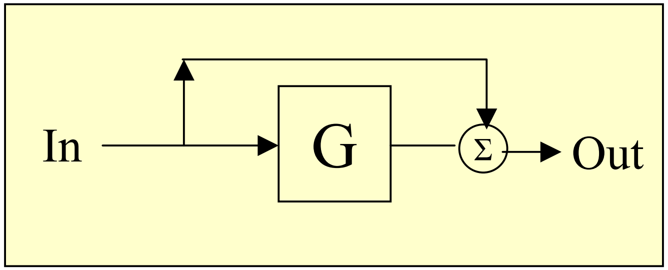
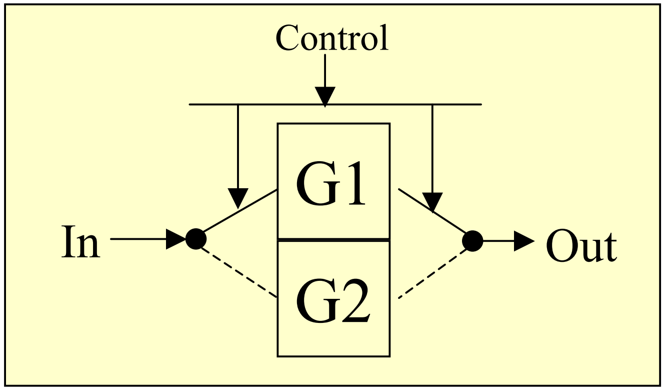
Summary



- ***Dynamical systems*** analysis provides a technique for designing ***rate-control*** biomedical devices for therapeutic diagnosis & intervention.
- Rate-control provides ***direct access to bio-rhythms***.
- Rate control techniques can apply the extensive ***knowledge of heart rate variability*** without requiring knowledge of the causes.
- The above builds on the extensive modeling of controllability and extensibility - ***opaque-box techniques***.

DS <-> Rate Control <-> bio-rhythm rate variability knowledge <-> opaque-box engineering techniques

Feed Sideward

Terms	Simple Example	
• Feed Back	Reinvesting dividends	
• Feed Foreward	Setting money aside	
• Feed Sideward	Moving money to another account	

Introduction

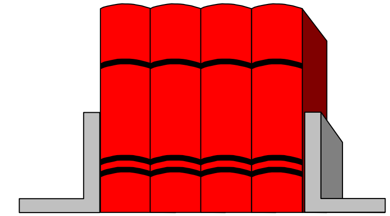
Feed Sideward is a coupling that shifts resources from one subsystem to another

- Feed Sideward #1 – feeds ***values of other variables*** into the specified variable
- Feed Sideward #2 – feeds ***changes of parameters*** into the specified variable. (time varying parameters)
- Feed Sideward #3 – feeds ***changes of topology*** by switch operations (switched systems)

Tool for global analysis

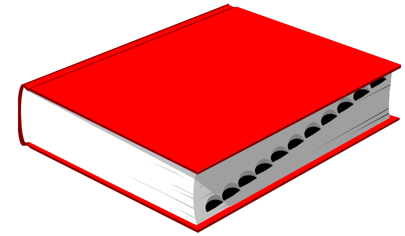
especially useful for biological systems

References



- Colin Pittendrigh & VC Bruce, ***An Oscillator Model for Biological Clocks***, in Rhythmic and Synthetic Processes in Growth, Princeton, 1957.
- Theodosios Pavlidis, Biological Oscillators: Their mathematical analysis, Princeton, 1973, Chapter 5, ***Dynamics of Circadian Oscillators***
- J.D. Murray, *Mathematical Biology*, Springer-Verlag, 1993, Chapter 8 ***"Perturbed and Coupled Oscillators …"***
- Arthur Winfree, ***The Timing of Biological Clocks***, Scientific American Books, 1987

Inherent Biological Rhythms

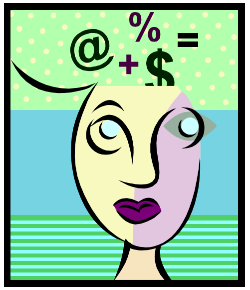


- Biosystems Rhythms
  - second cycles (sec) - cardiac
  - circadian (day) - sleep cycle) - melatonin (pineal)
  - circaseptan (week) - mitotic activity of human bone marrow, balneology, bilirubin cycle neonatology
  - circalunar cycles (month) - menstrual cycle
  - annual (year) cycles - animal's coats – weight loss & gain by the season.

Synchronizers

- **Exogenous** (external)
  - stimulated by ***light***, ***temperature*** & sleep/wake, ***barometric pressure*** & headaches/joint aches,
- **Endogenous** (internal):
  - ***heart rates***
    - escape beats
    - preventricular contractions - ectopic beats
    - Sino-atreal node (associations of myocardial fibers on basis of enervation by vagus nerve)
    - SA node beats spontaneously, governed by nerve & chemical, *SA node stimulates the AV node providing a time delay.*
    - AV node sends excitation through conduction system to the purkinje fibers which stimulate the heart walls to contract.
  - ***EEG rhythms*** (4-30 Hz, alpha, beta, theta & delta)

Mathematics



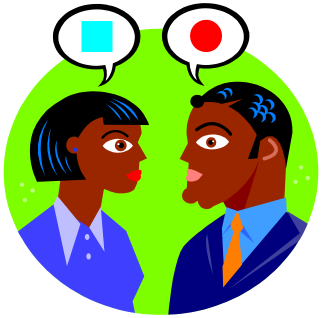
- Mathematical linkage to synchronizers
  - Endogenous rhythms refer to the ***eigenvectors.***
  - Exogenous rhythms refer to the ***particular integrals*** (forcing function).

dX/dt = AX +B,

B provides a forcing function.

AX provides the eigenvectors.

Viewpoint Challenge



- Traditional view – biological rhythms are ***exogenous***
  - Focus on particular integrals (heterogenous eqn, x'=ax+b)
    - Blood pressure variation is interpreted as an <u>activity variation</u>, thus external.

- Now, many claim that biological rhythms are ***endogenous***
  - Focus on eigenvectors (homogeneous eqn, x'=ax).
  - ***Chronobiology viewpoint***
    - Blood pressure variation is interpreted as a <u>hormonal variation</u>, thus internal.

Nollte Model

- *Variation of Pavlidis, Eqns 5.4.1 & 5.4.2*
- Dynamical System

$$r' = r - cs + b, \quad r >= 0$$

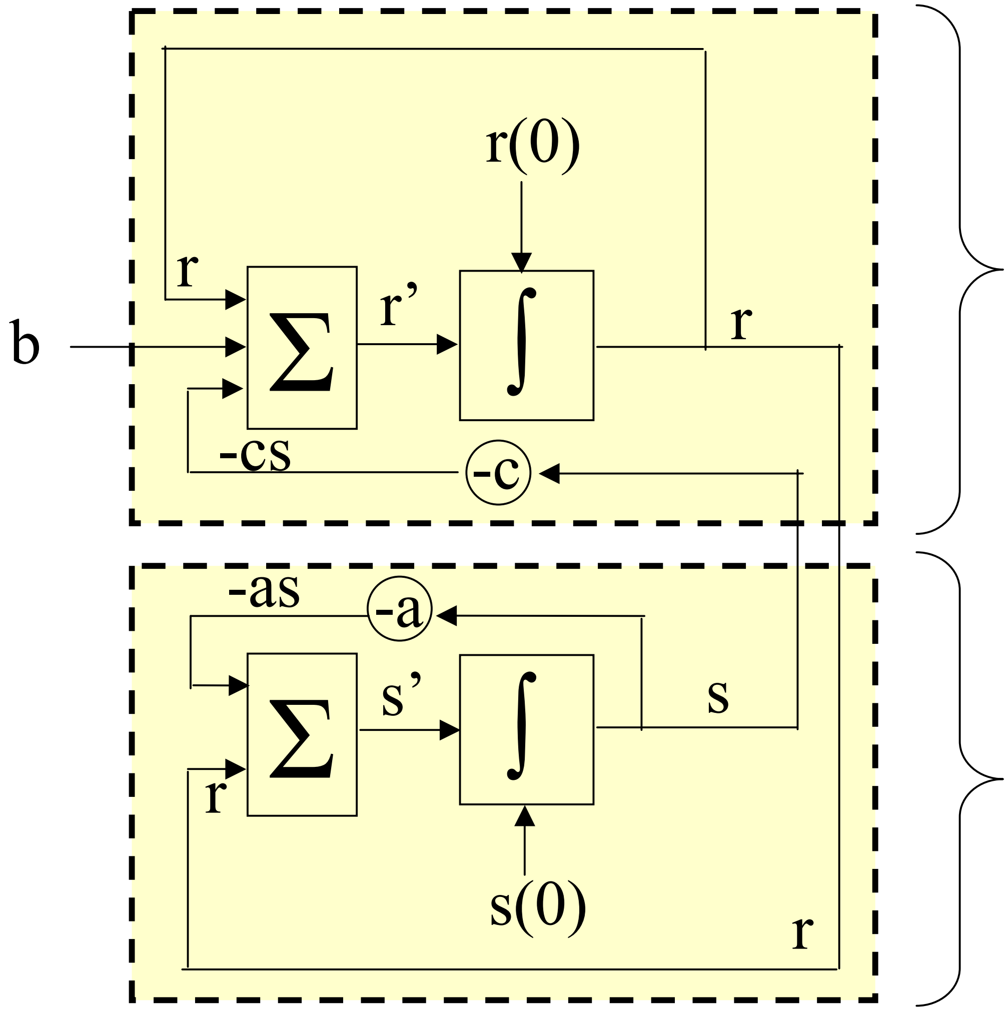
$$s' = r - as \qquad s >= 0$$

r is heart rate, r' is dr/dt

s is blood pressure, s' is ds/dt

b is ambient temperature

Dynamical System – Circuit Map



A half-oscillator

r'=r-cs+b

s'=r-as

B half-oscillator

Jim Holte
University of Minnesota

Limit Cycle

$r' = r - cs + b, \quad r >= 0$

$s' = r - as \quad s >= 0$

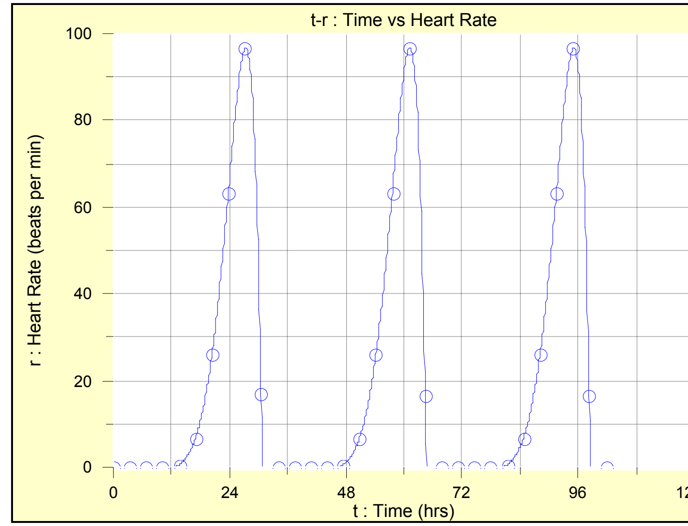
r is ***heart rate***, r' is dr/dt

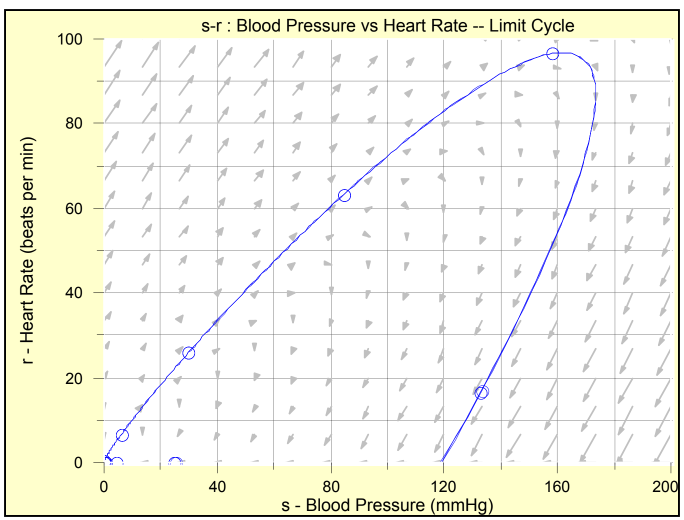
s is ***blood pressure***, s' is ds/dt

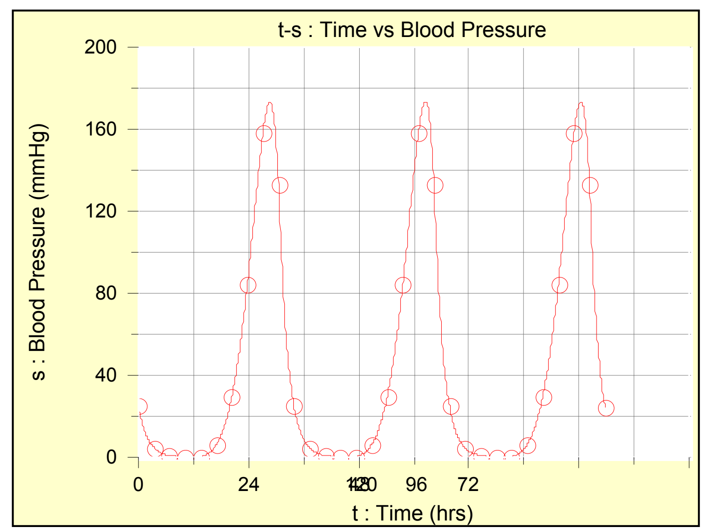
b is ***ambient temperature***

a = 0.5, c = 0.6, e = 0.5, ep = 0.1, b = 0.3

Initial r = 0, s = 25, file = CIRC-CL10.ODX







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Effect of Increased Heart Rate

$r' = r - cs + b$, $r >= 0$

$s' = r - as$, $s >= 0$

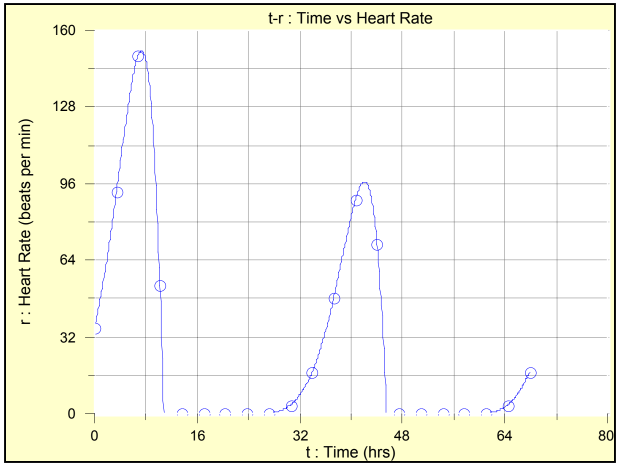
r is ***heart rate***, r' is dr/dt

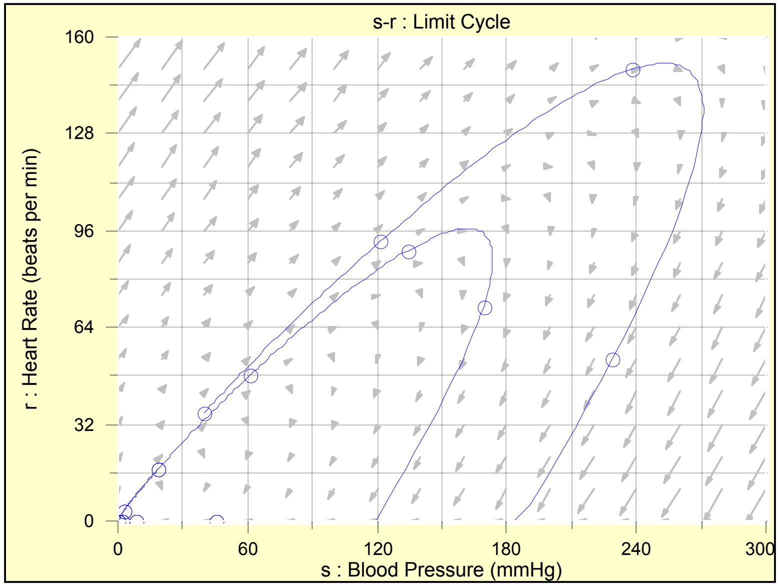
s is ***blood pressure***, s' is ds/dt

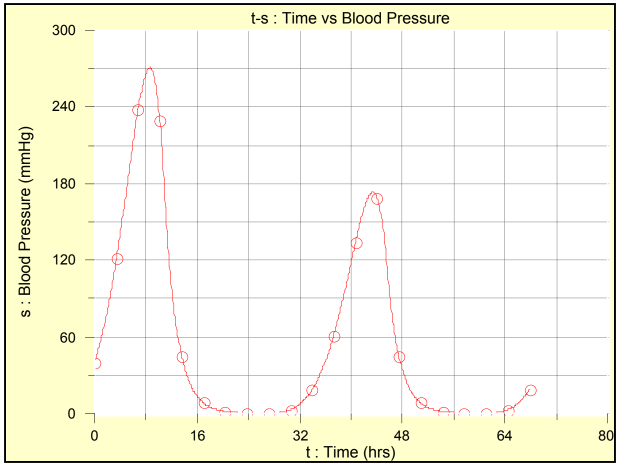
b is ***ambient temperature***

a = 0.5, c = 0.6, e = 0.5, ep = 0.1, b = 0.3

Initial r = 36, s = 40, file = CIRC-CL11.ODX







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Effect of Decreased Heart Rate

$r' = r - cs + b, \quad r >= 0$

$s' = r - as \quad s >= 0$

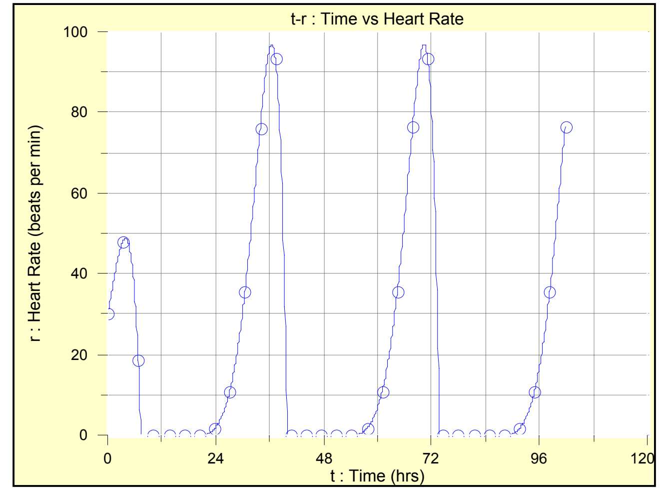
r is ***heart rate***, r' is dr/dt

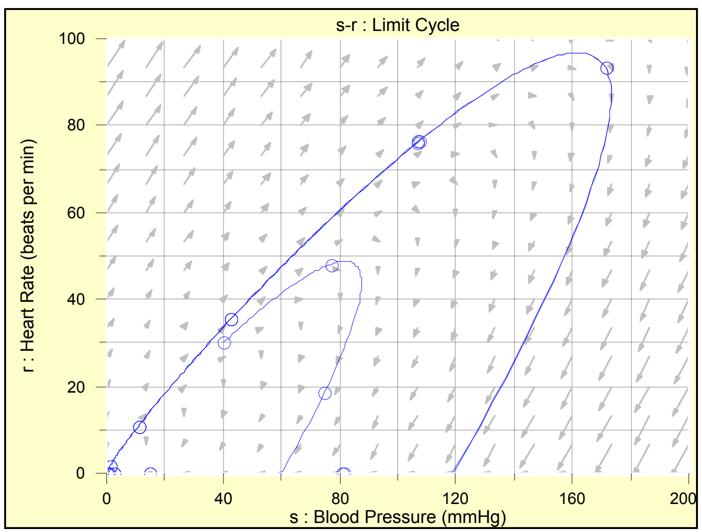
s is ***blood pressure***, s' is ds/dt

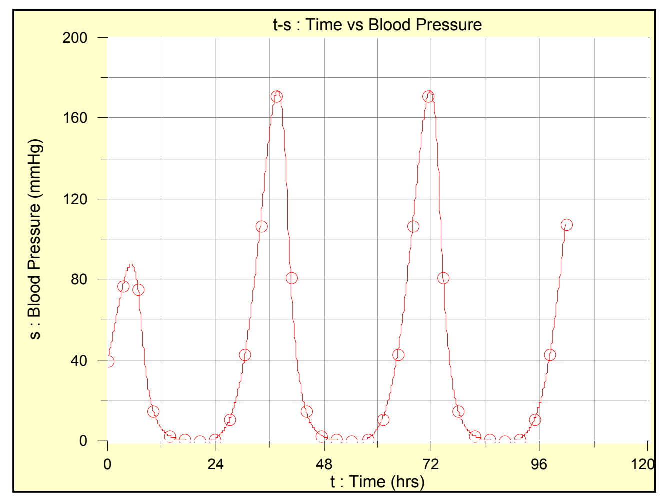
b is ***ambient temperature***

a = 0.5, c = 0.6, e = 0.5, ep = 0.1, b = 0.3

Initial r = 30, s = 40, file = CIRC-CL12.ODX







Effect of Critical Heart Rate & Pressure

$r' = r - cs + b$, $r >= 0$

$s' = r - as$ $s >= 0$

r is ***heart rate***, r' is dr/dt

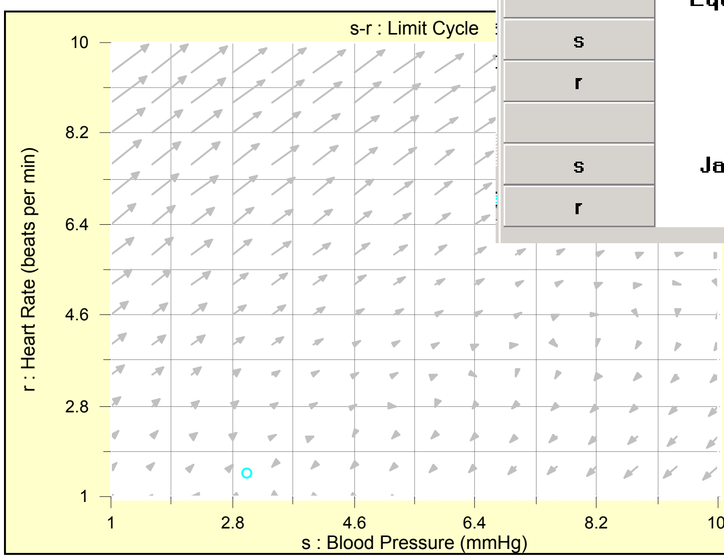
s is ***blood pressure***, s' is ds/dt

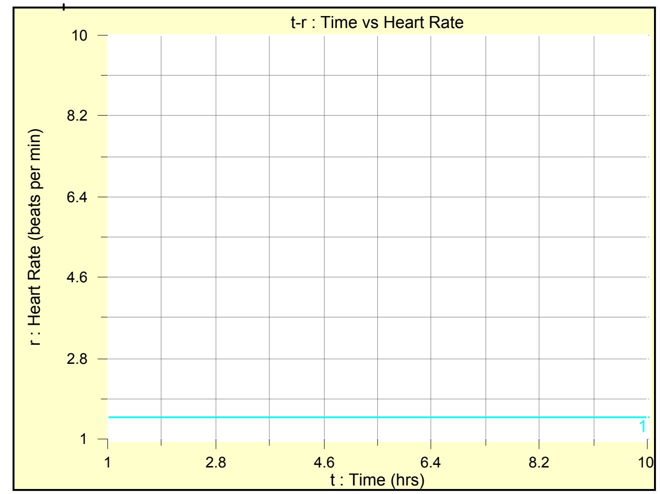
b is ***ambient temperature***

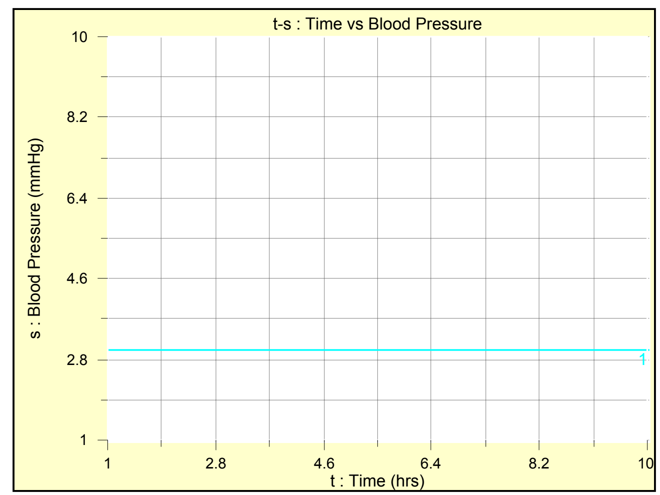
a = 0.5, c = 0.6, e = 0.5, ep = 0.1, b = 0.3

Initial r = 1.5, s = 3, file = CIRC-CL13.ODX

		1	2
EigenValues	Repelling spiral	0.25 + 0.1936i	0.25 - 0.1936i
	Equilibrium	EigenVector	EigenVector
s	3	0.7655 + 0.1976i	0.7655 - 0.1976i
r	1.5	0.6124	0.6124
s	Jacobian	-0.5	1
r		-0.6	1







Effect of Perturbed Equilibrium

$r' = r - cs + b, \quad r >= 0$

$s' = r - as \quad s >= 0$

r is ***heart rate***, r' is dr/dt

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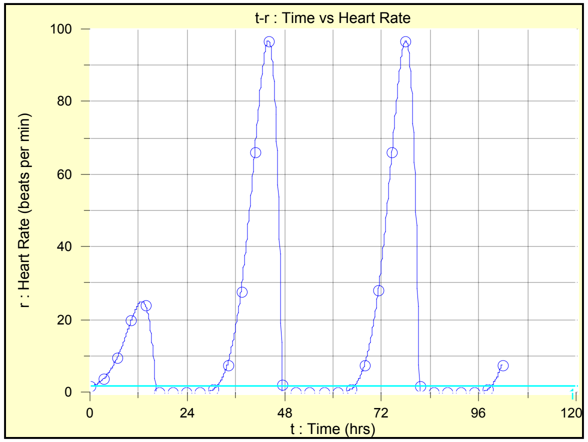
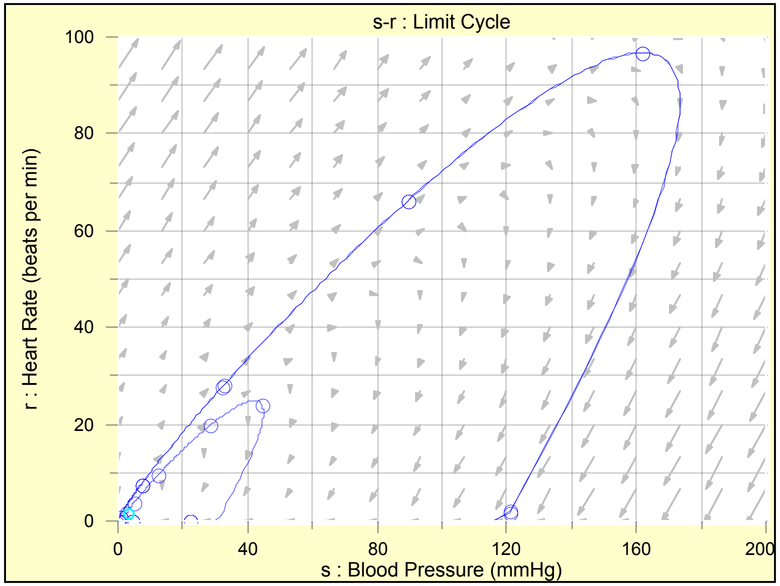
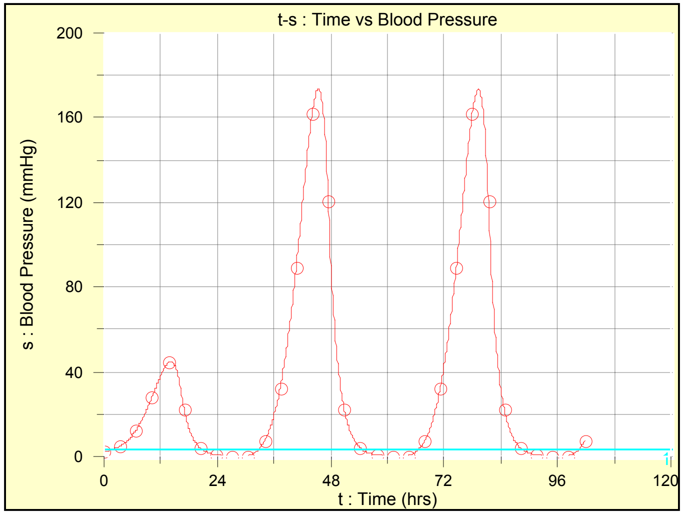
a = 0.5, c = 0.6, e = 0.5, ep = 0.1, b = 0.3

Initial r = 1.5, s = 2.5, file = CIRC-CL14.ODX







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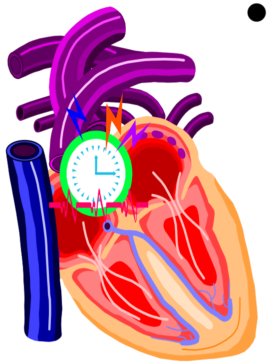
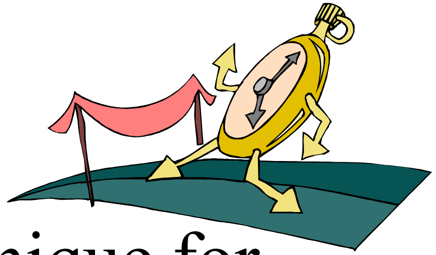
Biomedical Devices



- **Pacemakers** - Companies are introducing circadian rhythm based pacemakers. The *pacing strategy* (amplitude & timing of pacing stimulus) for effective cardiac capture depends on the ***time of day***. (eg. work & sleep).

- **Drug Delivery** - Medtronic/Minimed's insulin pump has a *drug delivery strategy*. It is preprogrammed for continuous insulin delivery which depends on exercise, food intake, patient endogenous performance, may now use adjustment of dose as a function of ***time of day***.

Summary



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- Rate-control provides ***direct access to bio-rhythms***.
- Rate control techniques can apply the extensive ***knowledge of heart rate variability*** without requiring knowledge of the causes.
- The above builds on the extensive modeling of controllability and extensibility - ***opaque-box techniques***.

DS <-> Rate Control <-> bio-rhythm rate variability knowledge <-> opaque-box engineering techniques

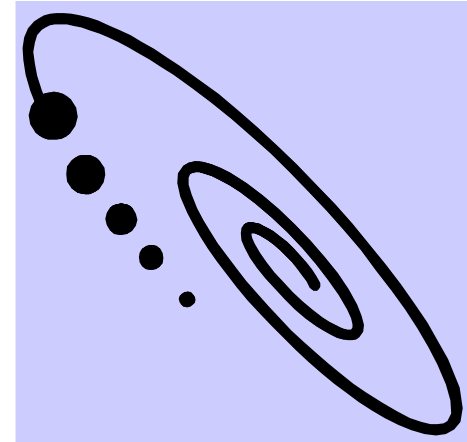
Next Session

- Session 1 - Feed Sideward – Concepts and Examples, *1/15*
- Session 2 – Feed Sideward – Applications to Biological & Biomedical Systems, 2/7
- Session 3 – Chronobiology, *2/21 ?*
  Franz Hallberg and Germaine Cornelissen

Thank you!

Backup

Solution



$$\dot{r} = r - cs + b$$

$$\dot{s} = r - as$$

$$r(t) = \frac{ab}{c-a}[1 - \frac{\sin(wt+\psi)}{\sin(\psi)} e^{-\mu t}]$$

$$s(t) = \frac{b}{c} + \frac{b}{c-a}\{1 - \frac{e^{-\mu t}}{\sin(\psi)}[\omega\cos(\omega t+\psi) + (1-\mu)\sin(\omega t+\psi)]\}$$

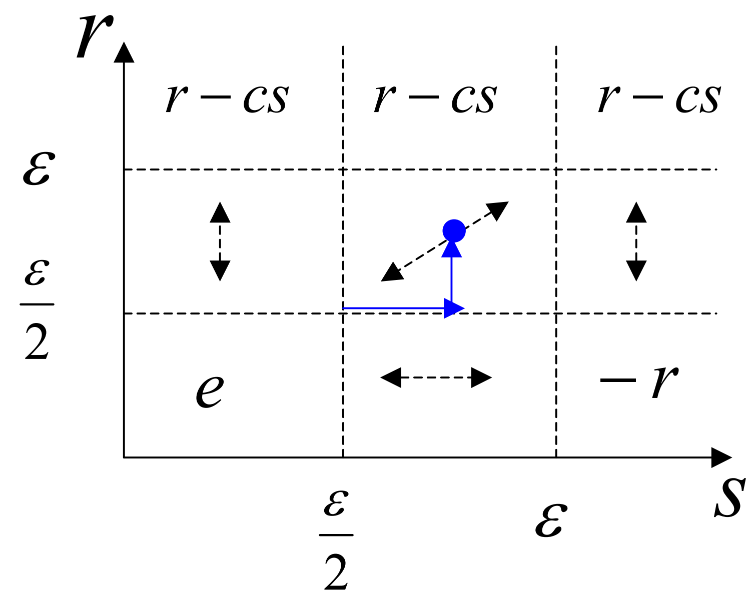
$$where \quad \mu = (1-a)/2$$

$$\omega = [c - (\frac{a+1}{2})^2]^{1/2}$$

$$\tan\psi = \mu/\omega$$

Source: Pavlidis, p. 109

Nollte Model: *Continuous Extension*



$$if\ s > \varepsilon$$

$$r = \begin{cases} r - cs,\ if\ r > \varepsilon \\ -r + [(r - cs) - (-r)]\dfrac{(r - \varepsilon/2)}{(\varepsilon - \varepsilon/2)},\ if\ r \in [\varepsilon/2, \varepsilon] \\ -r,\ if\ r < \varepsilon/2 \end{cases}$$

$$if\ s < \varepsilon/2$$

$$r = \begin{cases} r - cs,\ if\ r > \varepsilon \\ e + [(r - cs) - (e)](\dfrac{r - \varepsilon/2}{\varepsilon - \varepsilon/2}),\ if\ r \in [\varepsilon/2, \varepsilon] \\ e,\ if\ r < \varepsilon/2 \end{cases}$$

y = a + (b-a)*[(x-a1)/(b1-a1)]

$$if\ s \in [\varepsilon/2, \varepsilon]$$

$$r = \begin{cases} r - cs,\ if\ r > \varepsilon \\ \{e + [e - (-r)](\dfrac{s - \varepsilon/2}{\varepsilon - \varepsilon/2})\} + [(r - cs) - \{e + [e - (-r)](\dfrac{s - \varepsilon/2}{\varepsilon - \varepsilon/2})\}](\dfrac{r - \varepsilon/2}{\varepsilon - \varepsilon/2}),\ if\ r \in [\varepsilon/2, \varepsilon] \\ e + [e - (-r)](\dfrac{s - \varepsilon/2}{\varepsilon - \varepsilon/2}),\ if\ r < \varepsilon/2 \end{cases}$$

ODE Architect Models

File	Description
CIR-CL01	
CIR-CL02	
CIR-CL03	r'=r-cs
CIR-CL04	r'=r-cs+b, b=0, initial r=0.6, s=0.5, interval=10
CIR-CL05	r'=r+cs+b, b=0.3, initial r=0.6, s=0.5, interval=10
CIR-CL06	r'=r+cs+b, b=0.3, interval=33.90, initial r=1, show the stable limit cycle
CIR-CL07	r'=r+cs+b,b=0.3, interval =33.90, initial r=100, s=0, show stable limit cycle
CIR-CL08	r'=r+cs+b,b=0.5, interval =35.00, show stable limit cycle
CIR-CL09	
CIR-CL10	Limit Cycle, r=0, s=25, titles, colors
CIR-CL11	External approach to Limit Cycle
CIR-CL12	Internal approach to Limit Cycle
CIR-CL13	Critical Point
CIR-CL14	Perturbation from Critical Point

References

- Colin Pittendrigh & VC Bruce, An Oscillator Model for Biological Clocks, in Rhythmic and Synthetic Processes in Growth, Princeton, 1957.
- Theodosios Pavlidis, ***Biological Oscillators: Their mathematical analysis***, Princeton, 1973, Chapter 5, ***Dynamics of Circadian Oscillators***
- J.D. Murray, Mathematical Biology, Springer-Verlag, 1993, Chapter 8 ***"Perturbed and Coupled Oscillators …"***
- Arthur Winfree, "The Temporal Morphology of a Biological Clock", Amer Math Soc, Lectures on Mathematics in the Life Sciences, Gerstenhaber, 1970, p 111-150
- Arthur Winfree, "Integrated View of Resetting a Circadian Clock, Journ Theoretical Biology, Vol 28, pp 327-374, 1970
- Arthur Winfree, The Timing of Biological Clocks, Scientific American Books, 1987

Feed Sideward - Topics (60 min)

Session 1 (14 slides)

- Background Concepts & Examples
  - Phase Space (1 slide)
  - Singularities (2 slides) *
  - Coupled Oscillators (2 slides)
  - Phase Resetting (2 slides) *
  - Oscillator Entrainment (1 slide)
- Feed Sideward as modulation (3 slides) **
- Summary (1 slide)

Session 2 (12 slides)

- Applications to Biological Systems
  - Circadian & other Rhythms (2 slides)
    - Model & Simulation Result (2 slides)
- Applications to Biomedical Systems
  - Blood Pressure Application (2 slides)
    - Model & Simulation Result (2 slides)
- Summary (1 slide)
- Segue to Chronobiology (1 slide)

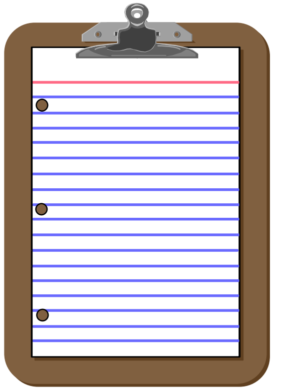
Feed Sideward

Understanding Biological Rhythms Session 1

Jim Holte

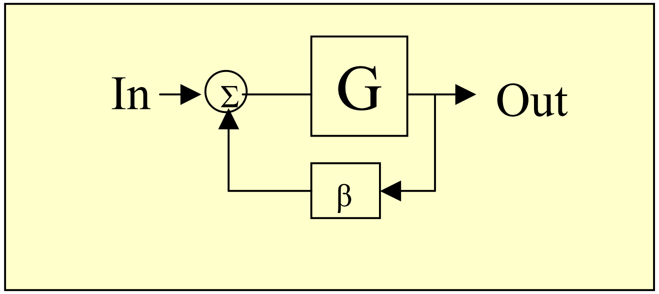
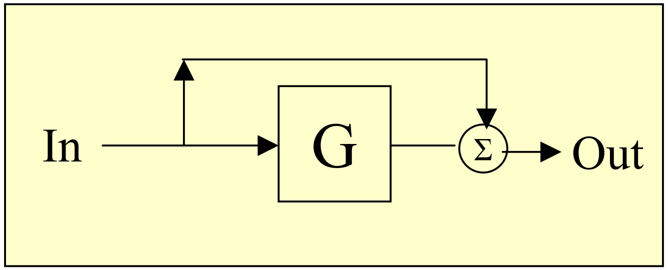
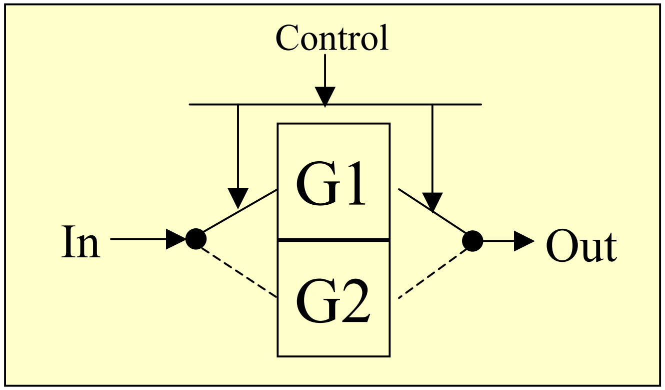
1/15/2002

Sessions



→ • Session 1 - Feed Sideward – Concepts and Examples, *1/15*
- Session 2 – Feed Sideward – Applications to Biological & Biomedical Systems, *1/31*
- Session 3 – Chronobiology, *2/12*
Franz Hallberg and Germaine Cornalissen

Feed Sideward

Terms	Simple Example	
• Feed Back	Reinvesting dividends	
• Feed Foreward	Setting money aside	
• Feed Sideward	Moving money to another account	

Introduction

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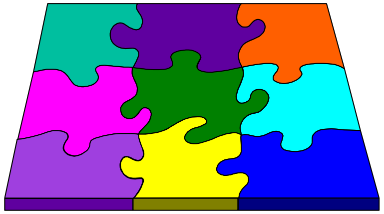
- Feed Sideward #2 – feeds ***changes of parameters*** into the specified variable. (time varying parameters)
- Feed Sideward #3 – feeds ***changes of topology*** by switch operations (switched systems)

Tool for global analysis

especially useful for biological systems

Phase Space



- Laws of the physical world
- Ordinary differential equations
- Visualization of Solutions
- Understanding

Phase Space

The Lotka-Volterra Equations for
Predator-Prey Systems

H' = b*H - a*H*P
P' = -d*P + c*H*P

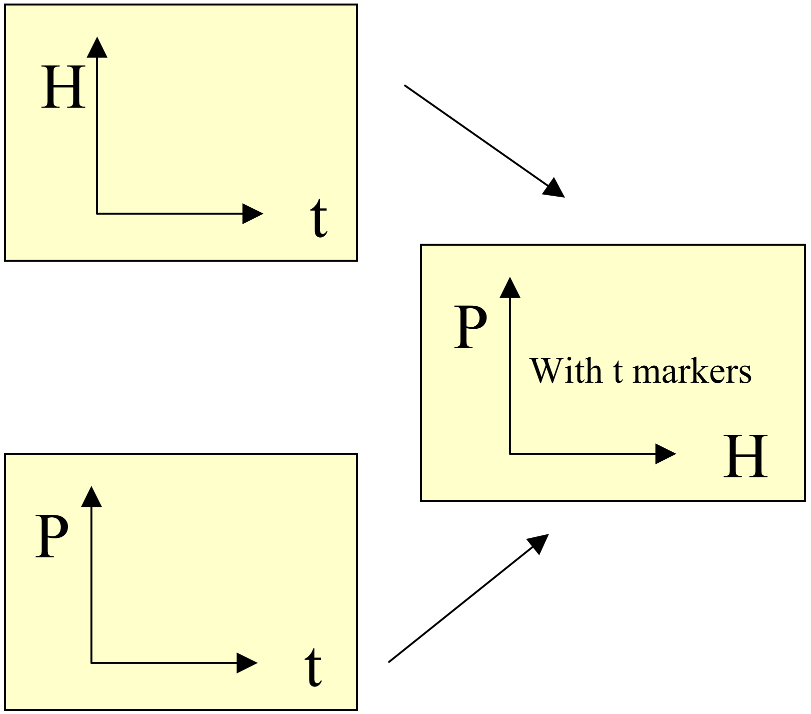
H = prey abundance, P = predator

<u>Set the parameters</u>
b = 2 growth coefficient of prey

d = 1 growth coefficient of predators

a = 1 rate of capture of prey per predator per unit time

c = 1 rate of "conversion" of prey to predators per unit time per predator.



Source: ODE Architect, Wiley, 1999

Phase Space

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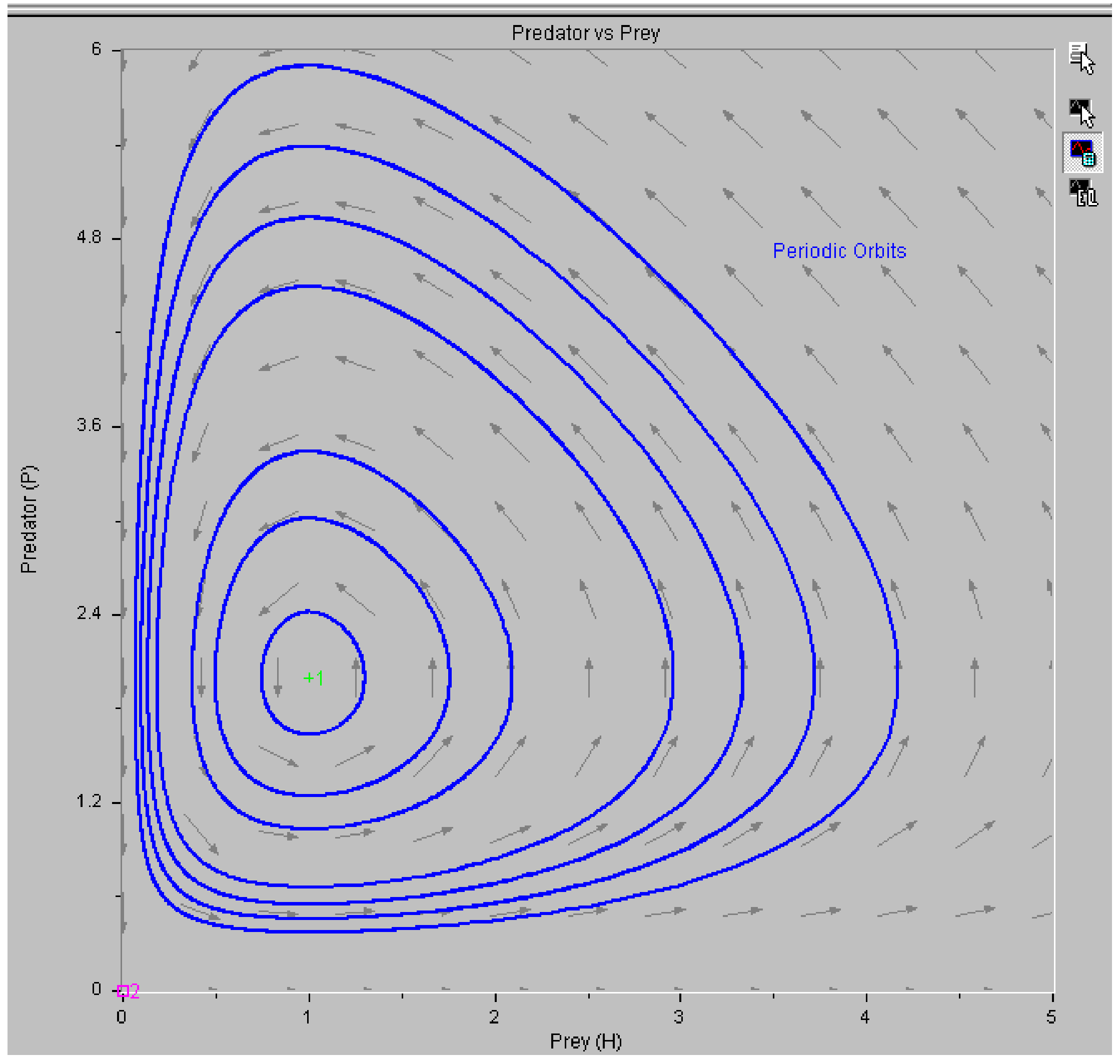
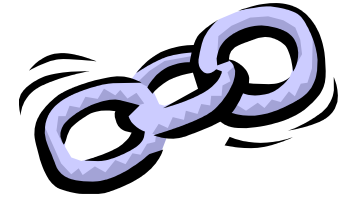


Source: ODE Architect, Wiley, 1999

Coupled Oscillators Model



- x and y represent the "phases“ of two oscillators.

  Think of x and y:
  - angular positions of two "particles"
  - moving around the unit circle
- a1 = 0
  - x has constant angular rate
- a2 = 0
  - y has constant angular rate.
- Coupling when a1 or a2 non-zero

Source: ODE Architect, Wiley, 1999

Example
Uncoupled Oscillators

The Tortoise and the Hare

x' = w1 + a1*sin(y - x)

y' = w2 + a2*sin(x - y)

u = (x mod(2*pi)) //Wrap around the

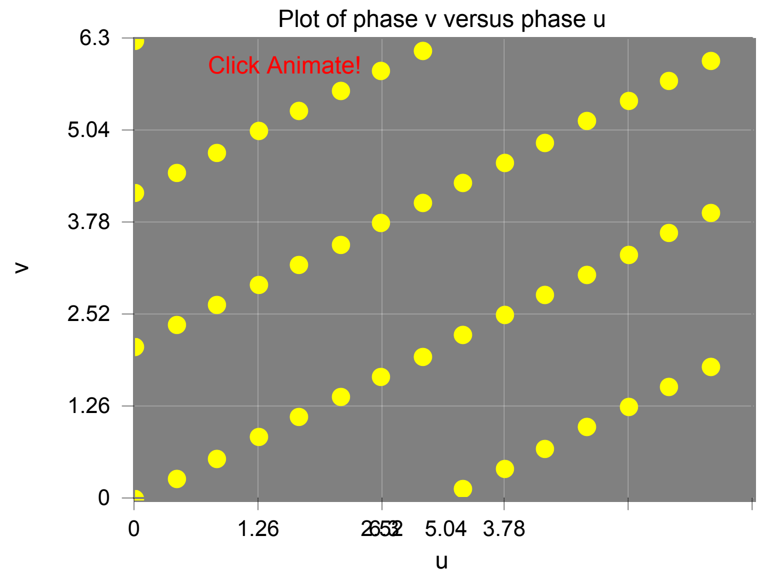
v = (y mod(2*pi)) //unit circle

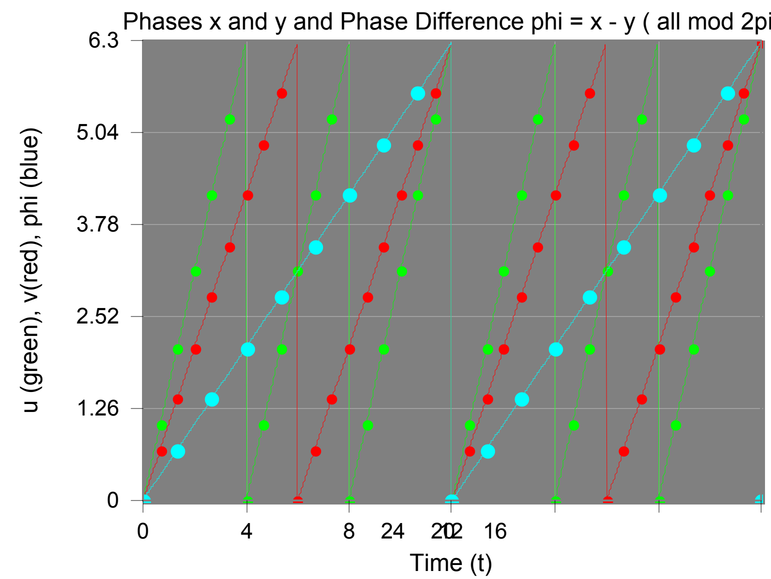
phi = (x - y)mod(2*pi)

<u>Set the parameters</u>

a1 = 0.0; a2 = 0.0

w1 = pi/2; w2 = pi/3





Source: ODE Architect, Wiley, 1999

Jim Holte
University of Minnesota

Example Coupled Oscillators

Coupled Oscillators:

The Tortoise and the Hare

x' = w1 + a1*sin(y - x)

y' = w2 + a2*sin(x - y)

u = (x mod(2*pi)) //Wrap around the

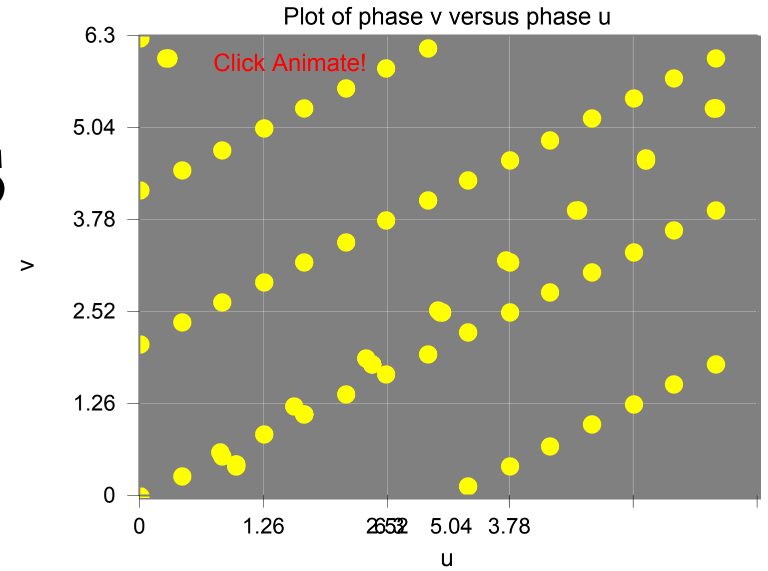
v = (y mod(2*pi)) //unit circle

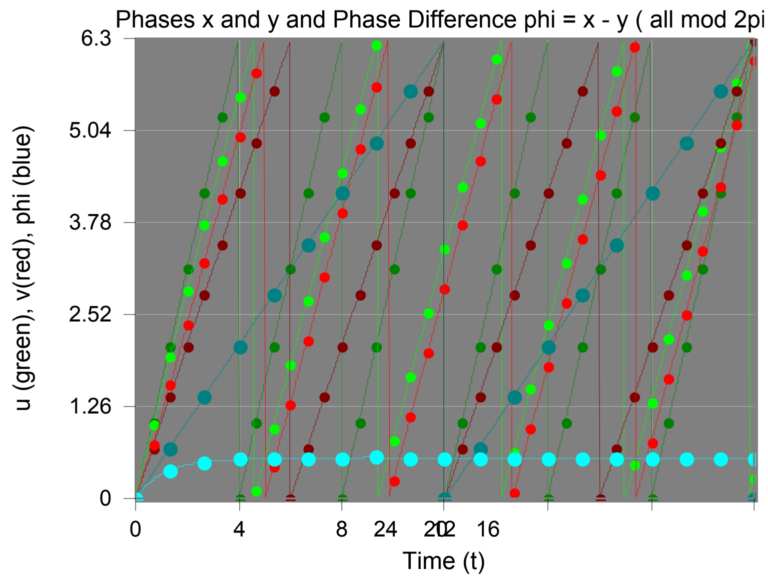
phi = (x - y)mod(2*pi)

<u>Set the parameters</u>

a1 = 0.5; a2 = 0.5

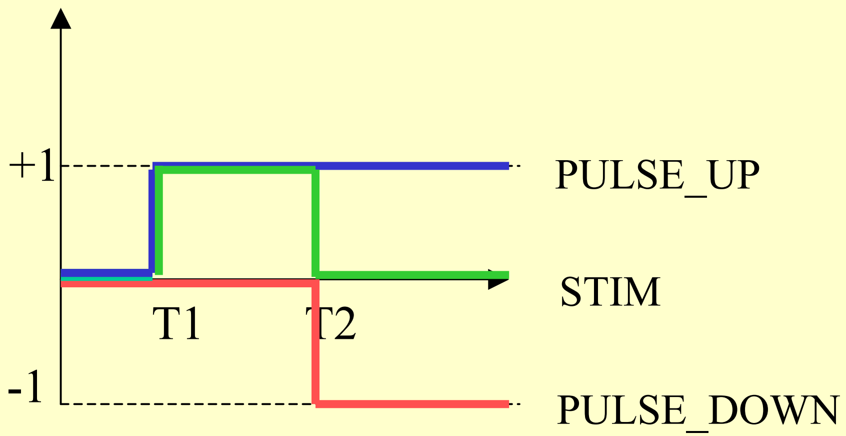
w1 = pi/2; w2 = pi/3





Source: ODE Architect, Wiley, 1999

Phase Resetting




```
FUNCTION PULSE_UP(t, T1, STIM_H)
IF (t >= T1) THEN
  PULSE_UP = STIM_H
ELSE
  PULSE_UP = 0
ENDIF
RETURN PULSE_UP
END
```

```
FUNCTION STIM(t,T1,T2,STIM_L,STIM_H)
STIM = PULSE_UP(t, T1, STIM_H) +
PULSE_DOWN(t, T2, STIM_L)
RETURN STIM
END
```

```
FUNCTION PULSE_DOWN(t,T2,STIM_L)
IF (t <= T2) THEN
  PULSE_DOWN = 0
ELSE
  PULSE_DOWN = STIM_L
ENDIF
RETURN PULSE_DOWN
END
```

Example
Phase Resetting

Theta' = 1 + STIM(t,T1,T2,STIM_L,STIM_H)*cos(2*Theta)

T1 = 4

T2 = 4

STIM_L = -1

STIM_H = +1

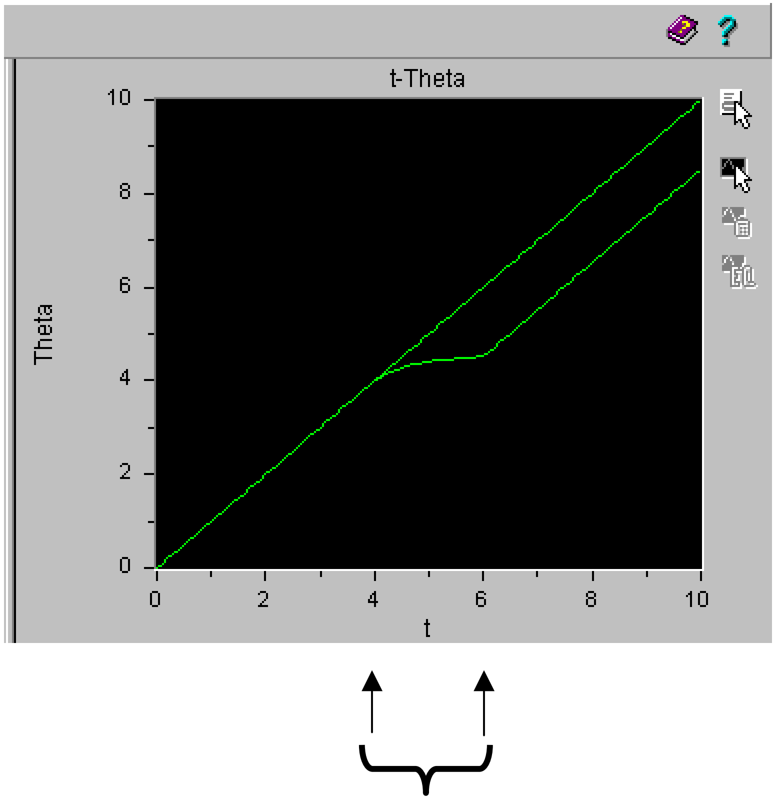
Theta' = 1 + STIM(t,T1,T2,STIM_L,STIM_H)*cos(2*Theta)

T1 = 4

T2 = 6

STIM_L = -1

STIM_H = +1



Source: ODE Architect, Wiley, 1999

Jim Holte
University of Minnesota

Oscillator Entrainment

- x and y represent the "phases“ of two oscillators.

  Think of x and y:
  - angular positions of two "particles"
  - moving around the unit circle
- a1 = 0
  - x has constant angular rate
- a2 = 0
  - y has constant angular rate.
- Coupling when a1 & a2 non-zero

- Entrainment occurs when the **coupling causes**
  - angular rate of **x** to
  - approach angular rate of **y**
- x and y generally differ
  - Typical for Chronobiology
- Dominant oscillator **‘entrains’** the other

Source: ODE Architect, Wiley, 1999

Oscillator Entrainment Example

x' = w1 + a1*sin(y - x)

y' = w2 + a2*sin(x - y)

u = (x mod(2*pi)) //Wrap around the

v = (y mod(2*pi)) //unit circle

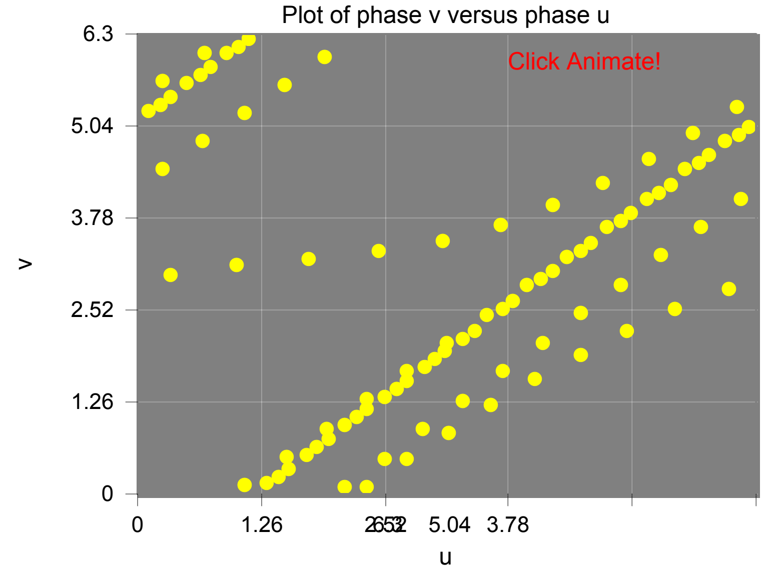
phi = (x - y)mod(2*pi)

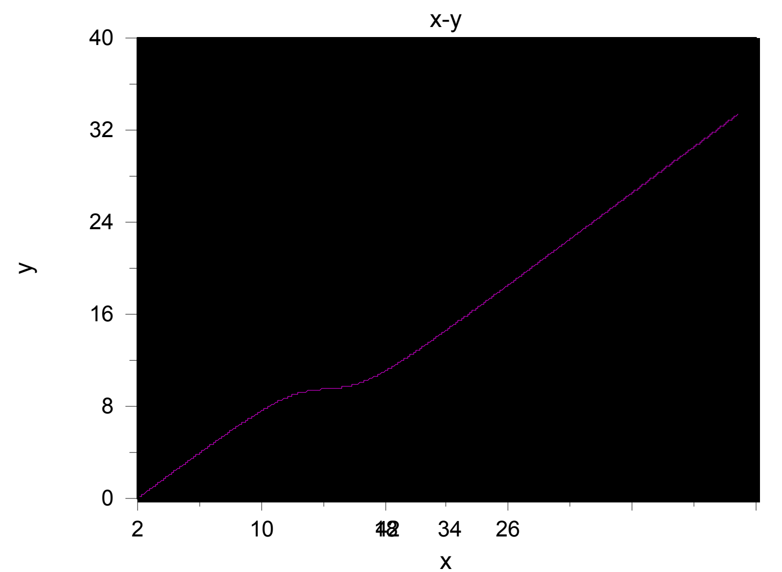
Set the parameters

a1 =.0775*pi; a2 =.075*pi

w1 = pi/4; w2 = pi/4 - .14*pi

Source: ODE Architect, Wiley, 1999





Singularities

```
r' = -(r-0)*(r-1/2)*(r-1) - a*STIM(t,T1,T2,STIM_L,STIM_H)
theta' = 1
x = r*cos(theta)
y = r*sin(theta)


T1 = 4
T2 = 6
a=0.0
STIM_L = -1
STIM_H = +1
```

Example - Singularities

Run	r	a	Commment
#1	1.25	0	approaches r=1
#2	1.0	0	stable periodic orbit
#3	0.75	0	approaches r=1
#4	0.5	0	unstable periodic orbit
#5	0.25	0	approaches r=0
#6	0	0	stable periodic orbit
#7	0.75	0.4	starts in r=1 domain, STIM moves it to r=0 domain

r' = -(r-0)*(r-1/2)*(r-1) - a*STIM(t,T1,T2,STIM_L,STIM_H)

theta' = 1

x = r*cos(theta)

y = r*sin(theta)

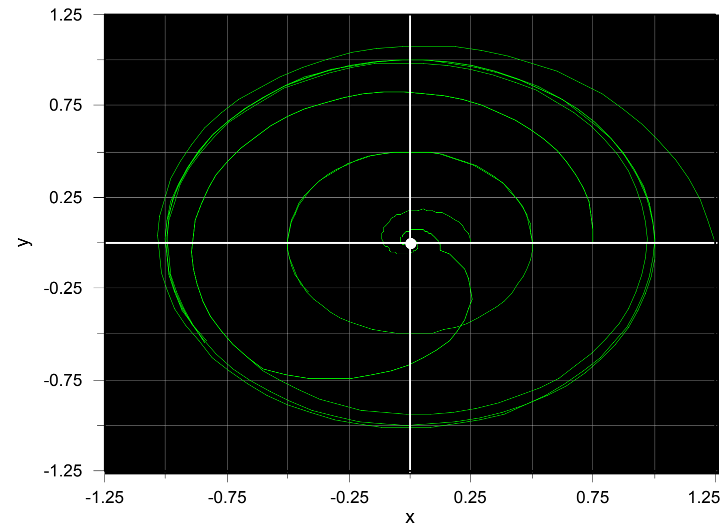
T1 = 4

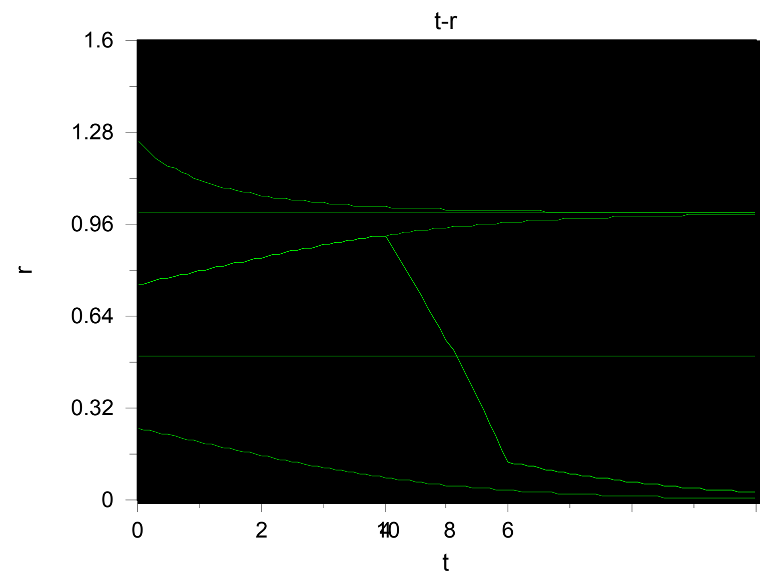
T2 = 6

a=0.0

STIM_L = -1

STIM_H = +1

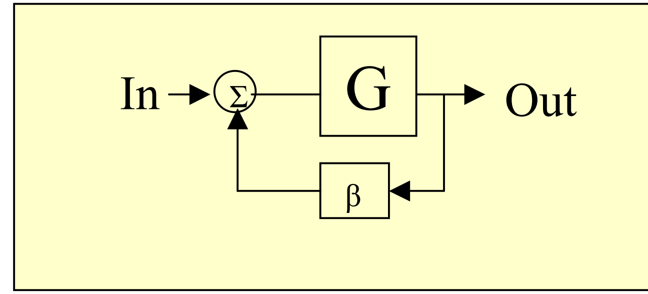


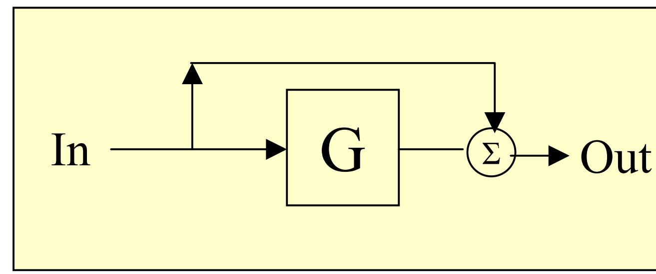


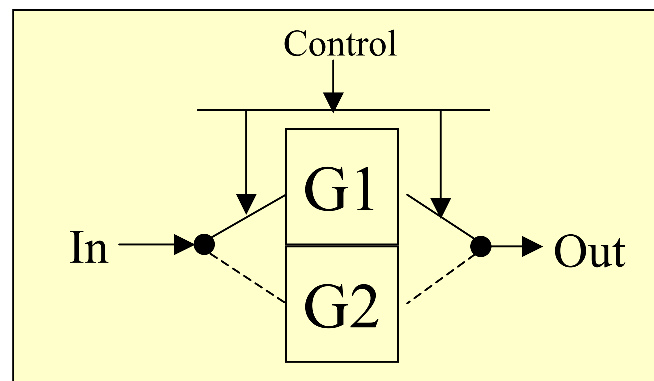
Source: Holte & Nolley, 2002

Feed Sideward

Terms	**Simple Example**
• Feed Back	Reinvesting dividends
• Feed Foreward	Setting money aside
• Feed Sideward	Moving money to another account







Feed Sideward Example

The Oregonator Model for Chemical Oscillations

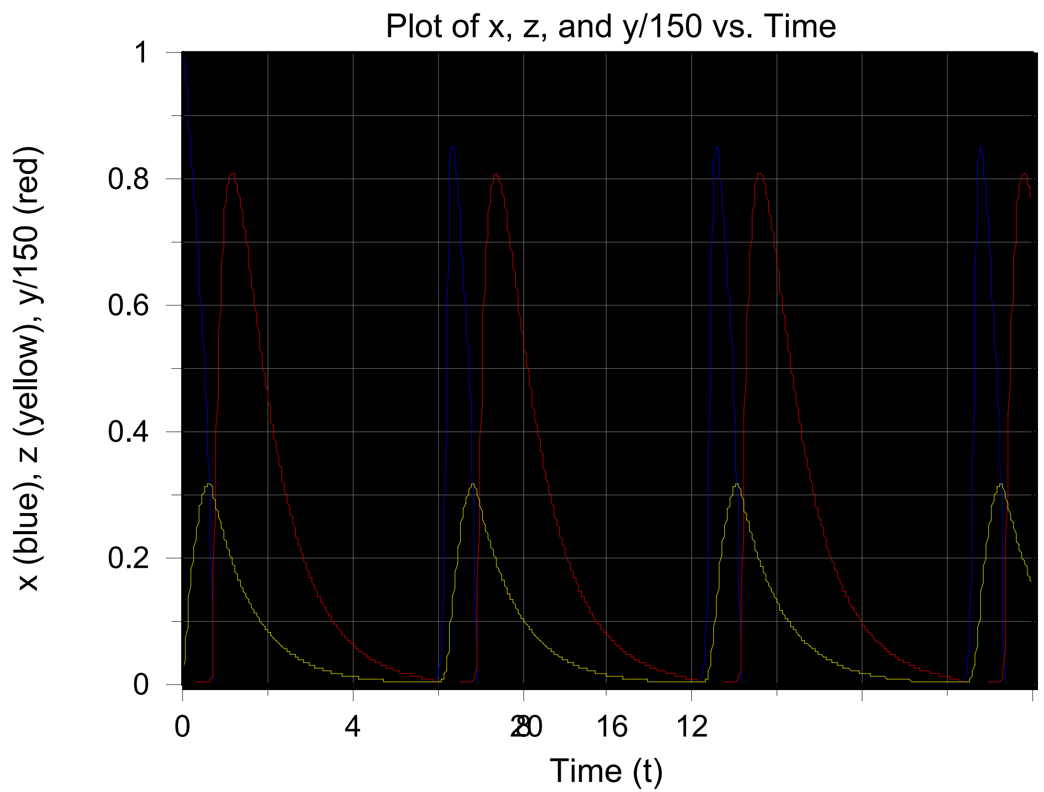
$x' = a1*(a3*\mathbf{y} - x*\mathbf{y} + x*(1-x))$

$y' = a2*(-a3*y - \mathbf{x}*y + f*\mathbf{z})$

$z' = x - z$

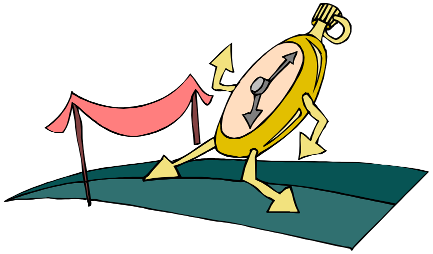
smally = y/150

$a1 = 25;\ a3 = 0.0008;\ a2 = 2500;\ f = 1$



Source: ODE Architect, Wiley, 1999

Summary



Feed Sideward is a coupling that shifts resources from one subsystem to another

- Feed Sideward #1 – feeds ***values of other variables*** into the specified variable
- Feed Sideward #2 – feeds ***changes of parameters*** into the specified variable. (time varying parameters)
- Feed Sideward #3 – feeds ***changes of topology*** by switch operations (switched systems)

Tool for global analysis

especially useful for biological systems

Next Session

- Session 1 - Feed Sideward – Concepts and Examples, *1/15*
- Session 2 – Feed Sideward – Applications to Biological & Biomedical Systems, *1/31*
- Session 3 – Chronobiology, *2/12*
  Franz Hallberg and Germaine Cornelissen