Introduction to Biomathematics
Lecture 5

Delay Models in Physiology: Periodic Dynamic Diseases

CO_2 arterial concentration $c(t)$

T

Volume per breath is given by Hill function

$$V(t) = V_{max} \frac{c^m(t-T)}{a^m + c^m(t-T)}$$

m, a – constants

p – constant production of CO_2 in the body –

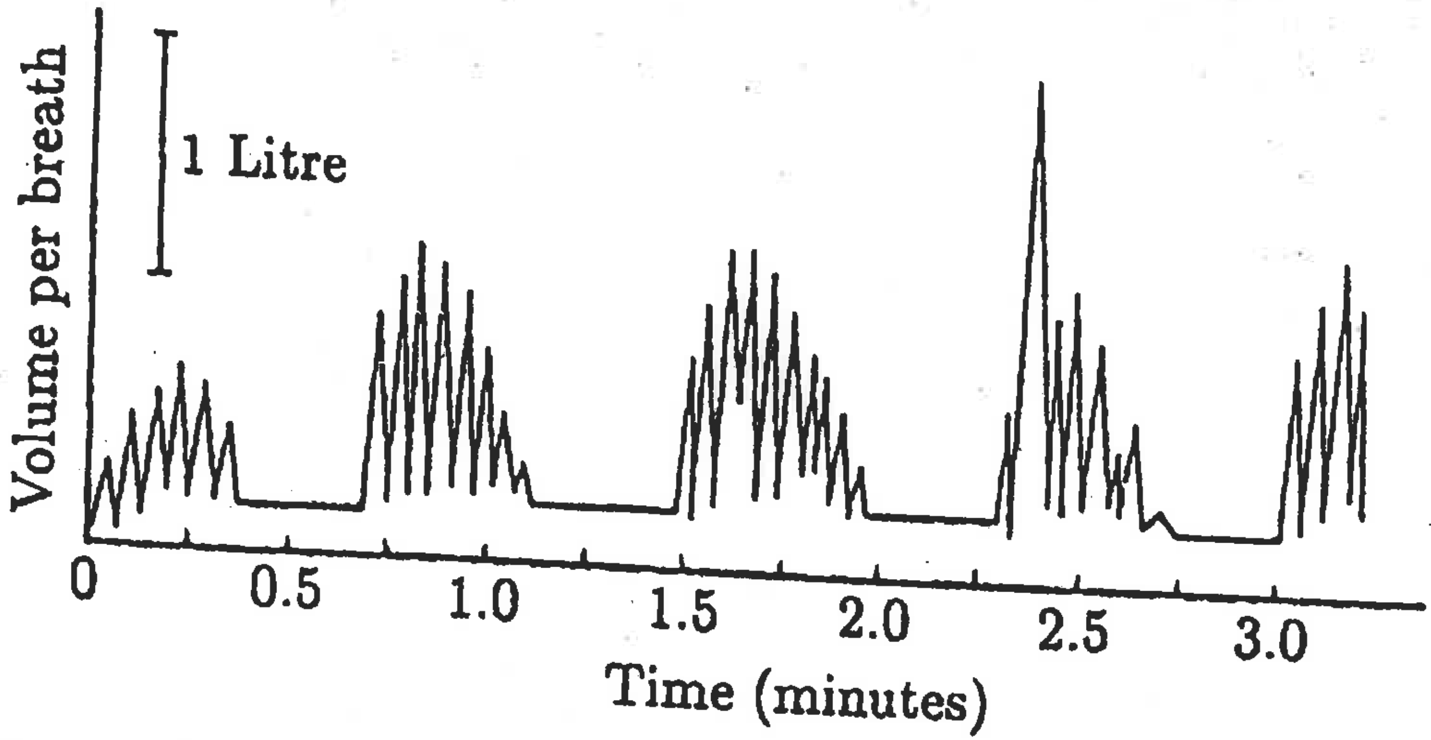
The dynamics of the CO_2 level is modeled by

$$\frac{dc(t)}{dt} = p - b\,c(t)\,V(t)$$

b – constant parameter

$$\frac{dc(t)}{dt} = p - b\,c(t)\,V_{max} \frac{c^m(t-T)}{a^m + c^m(t-T)}$$

- Nondimensional quantities $x(t) = \frac{c(t)}{a}$



ıre 1.13. A spirogram of the breathing pattern of a 29-year-old man with Cheyne–Stokes respiration. The ty
:al waxing and waning of the volume of breath is interspersed with periods of low ventilation levels; this is
neic breathing. (Redrawn with permission from Mackey and Glass 1977)

ıth is exceedi...

$$x(t) = \frac{c}{a}$$

$$\frac{d(c/a)}{dt} = \frac{p}{a} - bV_{max}\frac{c(t)}{a} \cdot \frac{\frac{c^m(t-T)}{a^m}}{1 + \frac{c^m(t-T)}{a^m}}$$

$$\frac{dx(t)}{dt} = \frac{p}{a} - bV_{max}\, x(t)\, \frac{x^m(t-T)}{1+x^m(t-T)} \quad \Big| \otimes \frac{a}{p}$$

$$\frac{dx(t)}{d\left(t\frac{p}{a}\right)} = 1 - \underbrace{\boxed{\frac{abV_{max}}{p}}}_{\alpha}\, x(t)\, \frac{x^m(t-T)}{1+x^m(t-T)}$$

$$t^* = t\frac{p}{a} \qquad T^* = T\frac{p}{a} \qquad V^*(x) = \frac{x^m}{1+x^m}$$

$$\frac{dx(t^*)}{dt^*} = 1 - \alpha\, x(t^*)\, V^*(x(t^* - T^*))$$

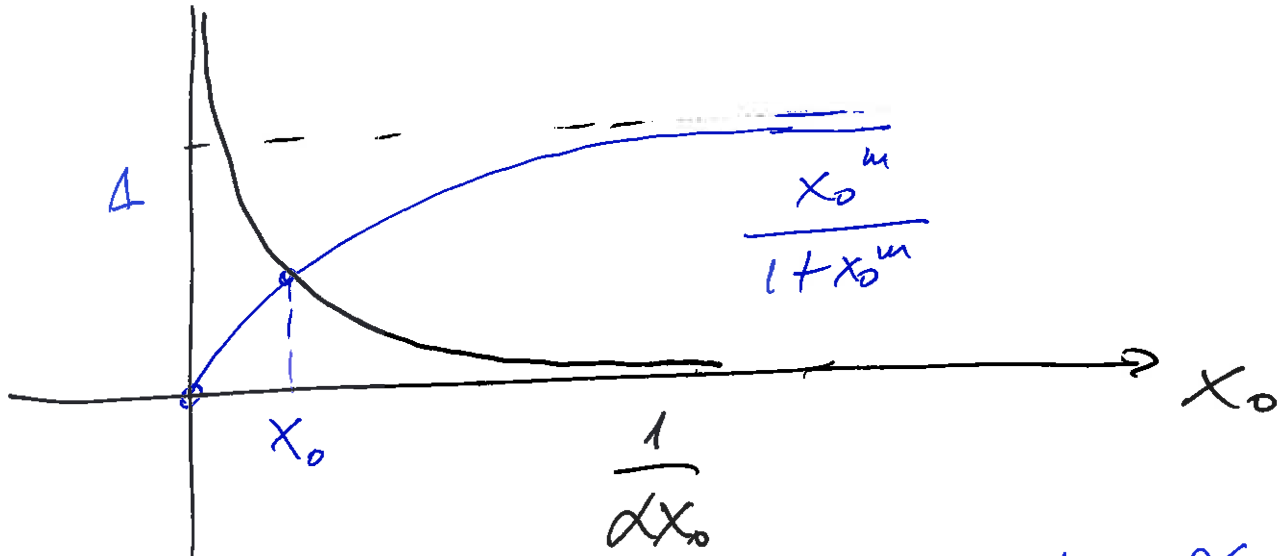
Let us 'dprop' the star notations

$$\frac{dx(t)}{dt} = 1 - \alpha\, x(t)\, \frac{x^m(t-T)}{1+x^m(t-T)} = 1 - \alpha x(t) V(t-T)$$

where $V(t) = \dfrac{x^m(t)}{1+x^m(t)}$

Steady state ? x_0

$$1 - \alpha x_0 \frac{x_0^m}{1+x_0^m} = 0, \quad \frac{1}{\alpha x_0} = \frac{x_0^m}{1+x_0^m}$$



unique positive steady state x_0.

Linear stability analysis

$$x(t) = x_0 + u(t) \qquad |u| \ll 1$$

$$\frac{dx(t)}{dt} = \frac{du(t)}{dt}, \qquad V(x) = V(x_0) + V'(x_0)\underbrace{(x - x_0)}_{u}$$

$$V(x(t)) = V(x_0) + V_0' \cdot u(t) = V_0 + V_0' u(t)$$

$$x'(t) = 1 - \alpha x(t) V(x(t-T))$$

$$u'(t) = 1 - \alpha [x_0 + u(t)] \cdot [V_0 + V_0' u(\cancel{t-T})]$$

$t-T$

$$u'(t) = \underbrace{1 - \alpha x_0 V_0}_{0} - \alpha u(t) V_0 - \alpha x_0 V_0' u(t-T) + \underbrace{\dots}_{uu}$$

neglect

Since $1 - \alpha x_0 \frac{x_0^m}{1+x_0^m} = 0$

$$\boxed{u'(t) = -\alpha V_0 u(t) - \alpha x_0 V_0' u(t-T)}$$

$$A = \alpha V_0 = \alpha \frac{x_0^m}{1+x_0^m} > 0$$

$$B = \alpha x_0 V_0' > 0$$

$$V_0' = \frac{d}{dx_0}\left(\frac{x_0^m}{1+x_0^m}\right) = \frac{m x_0^{m-1}(1+\cancel{x_0^m}) - \cancel{x_0^m m x_0^{m-1}}}{(1+x_0^m)^2}$$

$$= \frac{m x_0^{m-1}}{(1+x_0^m)^2} > 0 \quad , \quad \underline{m>0}$$

$$\boxed{u'(t) = -Au - Bu(t-T)} , \quad \underline{A, B > 0}$$

Looking for solutions $u = ke^{\lambda t}$

$$k\lambda e^{\lambda t} = -Ake^{\lambda t} - Bk e^{\lambda(t-T)}$$

$$\boxed{\lambda = -A - Be^{-\lambda T}}$$ Transcendental eqn. for λ

$$\lambda = \mu + i\omega$$

$$\mu + i\omega = -A - Be^{-T\mu - iT\omega}$$

$$\mu + i\omega = -A - Be^{-\mu T}\underbrace{(\cos\omega T - i\sin\omega T)}$$

Euler's formula: $e^{-i\omega T} = \cos(-\omega T) + i\sin(-\omega T)$

$$= \cos\omega T - i\sin\omega T$$

$$\mu + i\omega = -A - Be^{-\mu T}\cos\omega T + iBe^{-\mu T}\sin\omega T$$

$$\left|\begin{array}{l}\mu = -A - Be^{-\mu T}\cos\omega T\\ \omega = Be^{-\mu T}\sin\omega T\end{array}\right.$$

$\mu = \mu(T)$, $\omega = \omega(T)$

Start from $T = 0$, $\mu = -A - B < 0$

the system is stable.

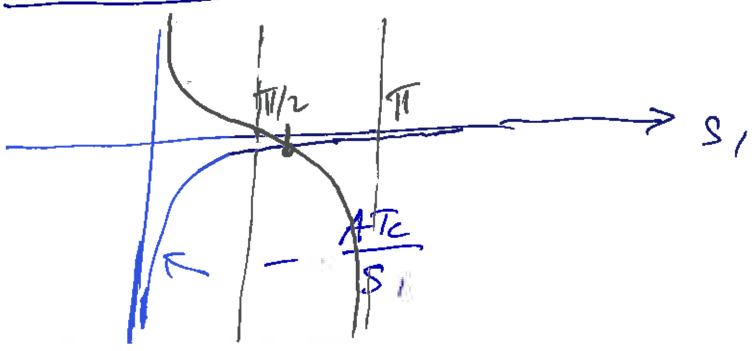
'Bifurcation' occurs when $\mu(T_c) = 0$

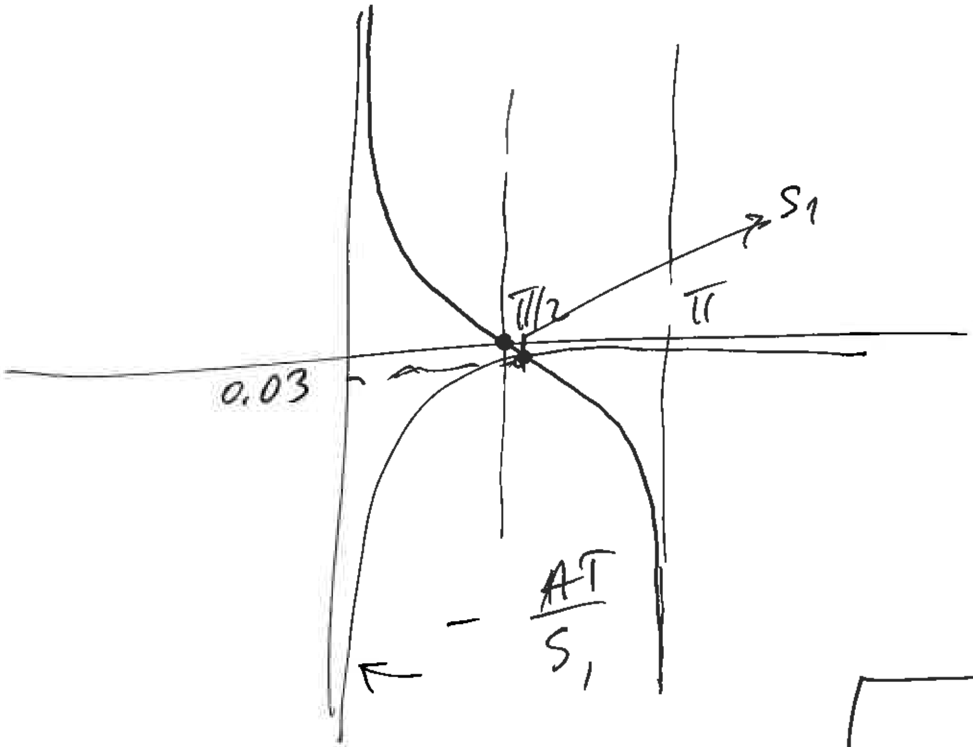
$$\left|\begin{array}{l}0 = -A - B\cos\omega T_c\\ \omega = B\sin\omega T_c\end{array}\right.$$

$$\left|\begin{array}{l}A = -B\cos\omega T_c\\ \omega = B\sin\omega T_c\end{array}\right. \qquad s_1 = \omega T_c$$

$$\frac{AT_c}{\omega T_c} = -\frac{\cancel{B}\cos\omega T_c}{\cancel{B}\sin\omega T_c} = -\cot(\omega T_c)$$

$$\boxed{\frac{AT_c}{s_1} = -\cot(s_1)} \qquad -\frac{AT_c}{s_1} = \cot s_1$$





$\frac{\pi}{2} < s_1 < \pi$

Can we justify that $\boxed{s_1 \approx \frac{\pi}{2}}$

$AT \ll 1$

Experimental data: $C_0 = 40$ mm Hg
$p = 6$ mm Hg / min
$T = 0.25$ min

$AT = \alpha V_0 T$ But $\alpha x_0 V_0 = 1$ $\quad V_0 = \frac{1}{\alpha x_0}$

$$AT = \frac{1}{x_0} T = \frac{T}{x_0} = \frac{\frac{p}{a} T_{dimensional}}{x_0} =$$

$$= \frac{p\, T_{dimensional}}{a x_0} = \frac{p\, T_{dim}}{C_0} = 0.0375 \ll 1$$

$$-\frac{AT}{s_1} \approx -\frac{0.0375}{\pi/2} \ll 1 \Rightarrow \boxed{s_1 \approx \frac{\pi}{2}}$$

$$S_1 \approx \frac{\pi}{2} = \omega T_c$$

Second equ. $T_c \omega = B T_c \sin \omega T_c$

$$\frac{\pi}{2} = B T_c \underbrace{\sin \frac{\pi}{2}}_{= 1.}$$

$$T_c = \frac{\pi}{2B} = \frac{\pi}{2 \alpha X_0 V_0'}$$

$$0 < T < T_c = \frac{\pi}{2 \alpha X_0 V_0'}$$ <u>stability</u> condition

$$\boxed{V_0' < \frac{\pi}{2 \alpha X_0 T}}$$ - stability condition

Gradient of the ventilation at the steady state

$$V_0' \sim 7.44 \ \text{litre}/\text{min mm Hg}$$

$$V_0' = \frac{m X_0^{m-1}}{(1+X_0^m)^2}$$

$$\frac{m X_0^{m-1}}{(1+X_0^m)^2} < \frac{\pi}{2 \alpha X_0 T}$$

$$m T < \frac{\pi}{2\alpha} \cdot \frac{(1+X_0^m)^2}{X_0^m}$$

Regulation of Haematopoiesis

$c(t)$ - concentration of blood cells

$$[c] = \frac{\text{cells}}{mm^3}$$

$T = 6$ days.

$$\frac{dc}{dt} = F(c(t-T)) - g\,c(t)$$

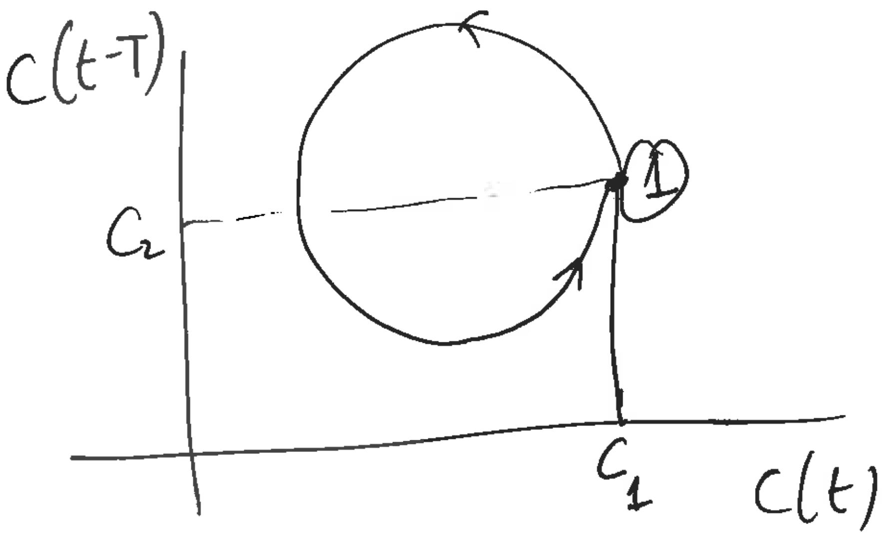
$$[g] = \text{day}^{-1}$$

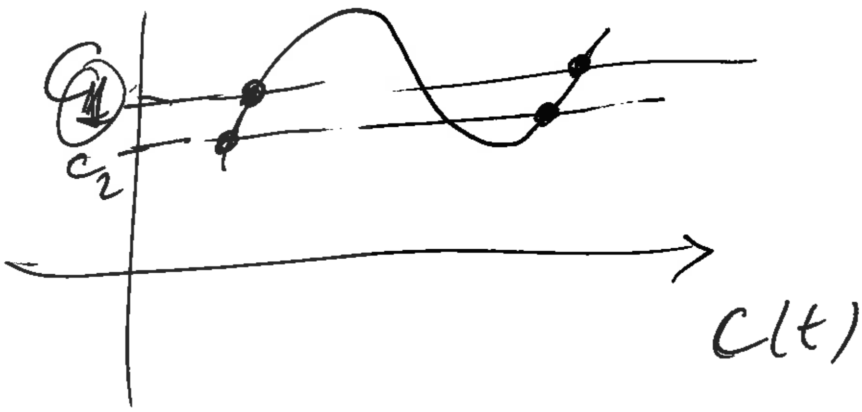
$$\frac{dc}{dt} = \frac{\lambda a^m c(t-T)}{a^m + c^m(t-T)} - g\,c(t)$$

Mackey & Glass (1977)

λ, a, g, T, m positive constant.

Chaos aperiodic behavior in a deterministic system which depends intimately on the initial conditions


c(t-T)
c_2
1
c_1
c(t)


1
c_2
c(t)