Math 437 Notes

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Contents

1 Periodic/Cheyne-Stokes Breathing

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1.1 Introduction

Cheyne-Stokes breathing is a pattern of breathing characterized by a rise and fall in breathing depth. Breaths have regular frequency, but the depth varies sinusoidally with a brief period of apnea occuring at the lowest point.

This pattern is common in the obese and in individuals with damaged brainstems (e.g. stroke victims). It is associated with imminent death. However, it has also been observed in healthy individuals following a transition to high altitude, and Haldane observed that it could be triggered by prolonged hyperventilation.

Periodic breathing is similar, but without the apnea in each cycle.

1.2 Analysis

The stimulus for breathing comes from increased levels of CO_2 in the bloodstream. Diffusion rate of CO_2 out of the pulmonary capillaries is proportional to the partial pressure PCO_2 in the capillaries. However, the stimulus which is directly responsible for increased ventilation rate is pH in the CSF surrounding the brainstem. There is a delay (normally about 15s) between a change in the capillary PCO_2 and the corresponding change in CSF pH. A simple model of CO_2 is then

$$\begin{aligned} \dot{x} &= \text{production} - \text{clearance} \\ &= \lambda - \alpha x V(x_\tau) \qquad (1) \end{aligned}$$

where

$$\begin{aligned} x &= \text{arterial PCO}_2 (mmHg) \\ \lambda &= \text{rate of CO}_2 \text{ production in body} \\ V(x_\tau) &= \text{ventilation rate } (L/min) \\ x_\tau &= x(t-\tau) \\ [\alpha] &\sim 1/L \text{ (constant)} \end{aligned}$$

Because this equation depends not only on $x(t)$ but also on $x_\tau(t) = x(t-\tau)$, it is a *delay differential equation* (DDE). We seek a steady state solution, *i.e.* a solution of the form $x = x^*$ such that $\dot{x}|_* \equiv 0$. Such a solution must satisfy $\lambda = \alpha x^* V(x^*)$. Note that since $\dot{x} \equiv 0$, $x_\tau^* = x^*$. Solving this equation for ventilation rate gives

$$V^* := V(x^*) = \frac{\lambda}{\alpha x^*}. \qquad (2)$$

An additional condition that we impose on the solution is that it is *unstable*. Steady states can have different types of stability:

Locally Stable If the system undergoes a small perturbation ϵ away from the solution, it will eventually return to the steady state.

Globally Stable If the system undergoes *any* perturbation, it will eventually return to the steady state.

In this case, we will test for local stability in the case of a small perturbation ϵ. We begin by taking a Taylor expansion of (1), considering x and x_τ as independent variables:

$$\begin{aligned} \dot{x} = \mathscr{F}(x, x_\tau) &= \mathscr{F}(x^*, x^*) + (x - x^*)\frac{\partial \mathscr{F}}{\partial x}\bigg|_* + (x_\tau - x^*)\frac{\partial \mathscr{F}}{\partial x_\tau}\bigg|_* + O\left(\epsilon^2\right) \\ &\approx (x - x^*)\frac{\partial \mathscr{F}}{\partial x}\bigg|_* + (x_\tau - x^*)\frac{\partial \mathscr{F}}{\partial x_\tau}\bigg|_* \\ &= (x - x^*)\left(-\alpha V^*\right) + (x_\tau - x^*)(-\alpha x^* S^*) \end{aligned}$$

Where $S^* = V'(x)|_*$. Note that $\mathscr{F}(x^*, x^*) = 0$ by the definition of a steady state solution.

A quick substitution $z(t) := x(t) - x^* \Rightarrow z_\tau = x_\tau - x^*$ leads to the simplification

$$\dot{z} = -z\alpha V^* - z_\tau \alpha x^* S^*.$$

Substituting in (2), we have

$$\begin{aligned} \dot{z} &= -\frac{\lambda}{x^*}z - \frac{\lambda S^*}{V^*}z_\tau \\ &= -Az - Bz_\tau \end{aligned}$$

where $A = \frac{\lambda}{x^*}$ and $B = \frac{\lambda S^*}{V^*}$ are parameters of the system.

If we now assume a solution of the form $z(t) = e^{\nu t}$, the equation becomes

$$\begin{aligned} \nu e^{\nu t} &= -Ae^{\nu t} - Be^{\nu(t-\tau)} \\ &= -Ae^{\nu t} - Be^{\nu t}e^{-\nu\tau} \\ \Rightarrow \nu &= -A - Be^{-\nu\tau} \end{aligned}$$

Our condition that the solution be periodic implies a purely imaginary coefficient $\nu = i\omega$. Note that if ν had a positive (or negative) real component, $||z||$ would grow (or decay) exponentially. Recall that $z(t)$ measures the difference between PCO_2 at time t and the equilibrium value. Exponential growth of this quantity would be nonphysiological for large enough values of t, and exponential decay would indicate that the steady state is in fact stable, which is contrary to hypothesis.

$$\begin{aligned} i\omega &= -A - Be^{-i\omega\tau} = -A - B\left(\cos(\omega\tau) - i\sin(\omega\tau)\right) \\ \Rightarrow 0 &= A + B\cos(\omega\tau) \\ \Rightarrow \omega &= \sin(\omega\tau) \end{aligned}$$

We can use these equations to find a relationship between A, B, and τ which must be satisfied for periodic breathing to occur.

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Recall last lecture we analysed $\dot{x} = \lambda - \alpha x V x_\tau$ by

1. finding a steady state solution $x = x^*2$
2. linearalizing in the neighbourhood of the solution
3. changing variables to $z = x - x^*$
4. using the eigenvalue equation to find
$$\tau = \frac{\cos^{-1}(-A/B)}{\sqrt{B^2 - A^2}}$$

Note that we must have $\frac{A}{B} \leq 1$. Additionally, since $\omega = \sqrt{B^2 - A^2}$, we can show that

$$T \geq 2\tau, \arccos(-A/B) \in [0, \pi]$$

and

$$2\tau \leq T \leq 4\tau, \arccos(-A/B) \in [\pi/2, \pi]$$

$$\tau = \frac{cos(-A/B)}{B\sqrt{(1 - (A/B)^2)}}$$

Note that since $x \sim mmHg, v \sim L/min, S \sim L/(min \cdot mmHg)$, A/B is dimensionless.
Normal values for the parameters are

$$\begin{aligned}
\tau &\sim 0.25min \\
x^* &\sim 40mmHg \\
V^* &\sim 7L/min \\
\lambda &\sim 6mmHg/min \\
S^* &\sim 4L/(min \cdot mmHg)
\end{aligned}$$

$A/B = 7/(40 \cdot 4) = 7/160 \approx 0.04$
Since A/B is small, $\arccos -A/B \approx \pi/2 \Rightarrow \omega\tau = \arccos(-A/B) \approx \pi/2$.
$\tau \approx \pi/(2 \cdot 3.4) \approx 0.46 minutes$
$\tau = \frac{cos(-A/B)}{B\sqrt{(1-(A/B)^2)}}$
Assertion: If $\tau < \tau_c$, then x^* is locally stable. Physiological $\tau = 0.25min$, calculated $\tau_c = 0.46min$.
Approximately: $\omega\tau_c = \pi/2 = B\tau_c = \lambda S^*/V^*\tau_c$
Should have local stability if $\tau \leq \pi/2 \cdot V^*/(\lambda S^*)$.

recall $\nu = -A - Be^{-\nu\tau_c}$. Suppose we make perturbations in the form

$$\begin{aligned}
A &\to A + a \\
B &\to B + b \\
\tau_c &\to \tau_c + \epsilon
\end{aligned}$$

This expands (since $\epsilon\Delta\nu \in O(\epsilon^2)$) to:

$$\nu + \Delta\nu \approx -(A + A) - (B + b)e^{-\nu\tau_c} + (B + b)(\tau_c\Delta\nu + \nu\epsilon)e^{-\nu\tau_c}$$

So $\Delta\nu \approx -a - be^{-\nu\tau_c} + Be{-}\nu\tau_c(\tau_c\Delta\nu + \epsilon\nu)$
Assuming only changes in $\tau \Rightarrow a = b = 0$.
$\Delta\nu \approx Be^{-\nu\tau_c}(\tau_c\Delta\nu + \epsilon\nu)$
Recall $\nu = i\omega$. Then

$$\begin{aligned}
Re[\Delta\nu] &= -\epsilon/D[-\omega^2(A\tau_c) + A\omega^2\tau_c] \\
&= \epsilon\omega^2/D
\end{aligned}$$

Assumed small change in 3 parameters. Then solved for change in nu given small changes, simplified by assuming change in one variable. Attempt to answer question: if $\tau \to \tau + \epsilon, \quad \epsilon > 0$, what happens to the real part of nu? We started with a solution where nu was purely imaginary, and had the requirement that it develop a real solution when tau becomes less than the critical value. We showed this... apparently.