Physiology of Integrated Organ Function

Statistics

Parametric

- Nominal variable – comes in groups like male/female, and the number of groups defines the number of levels
- **Univariant** – variability in one direction i.e. only one measured variable which has random variation
    - Single Factor ANOVA = 1 measured and 1 controlled with many levels
    - T-test works on date with 1 measured and 1 controlled with 2 levels only
    - Summary statistics: Mean ± SD
    - Two-way ANOVA = used for 2 controlled and 1 measured
        - Number of controlled variables = factors
        - Repeated measures if paired data
- Main effects – 2 controlled variables
- Interaction – was the effect of factor 2 the same on all levels on factor 1??
    - Are the graphs parallel?
- **Bivariant** – variability in two directions i.e. two measured variables
    - Uncontrolled variables
    - Pearson correlation co-efficient (r) – test for association between
        - Hypothesis testing statistic
    - Summary statistic: line of best fit
        - Intercept and slope are the bivariant equivalent to the mean
        - Coefficient of Determination (R^2) – how well line fits data
- Paired t-test = highest power, assumes normal distribution and correlation
- Student's t-test = high power, assumed normal distribution and same SD
    - F-test = tests to see if difference between SD is significant or not
- Welch's t-test = moderate power, assumes normal distribution

Non-Parametric

- DO NOT assume a normal distribution! Assumes measurements are ORDINAL
    - Ignore how much bigger or smaller the value is, look at the rank order only
- Mann-Whitney U-test – equivalent to an unpaired t-test
    - Tells you 1 group mostly has higher ranked members
    - If distributions are the same it tests if the medians are the same
- Wilcoxon signed-rank test (W-test) – equivalent to paired t-test
    - Repeated measures that assumes correlation

Non-Normal Data

- For normal distribution – mean and median are the same
    - if very different, data is not normal

- Easiest test for normality = plot frequency histogram
    - Skew – shows different mean and median
    - Kurtosis – too flat or too pointy

Control Systems

- **Homeostasis** – maintenance of a similar internal environment, limit change
    - E.g. MAP is not constant – random fluctuations even when all systems are working normally
        - Note: removal of baroreceptors increases variability

Types of Homeostasis Regulation

- **Acceptor** – animals that accept and cope with external environmental change, proteins are expressed to help cope with slow change
- **Avoider** – variable is regulated behaviourally, avoids environmental change
- **Regulator** – physiological regulation
- Mammals regulate most physiologically important variables
- All animals regulate SOME variables

Integration – Cell-to-cell signalling

- Gap-junctions, local control
- Paracrine (autacoid) – hormone/steroid released into ECF and received at target cell
    - Action limited to region around releasing cell, local control
    - E.g. Histamine released from mast cells to dilate local arterioles
- Autocrine – hormone/steroid released by cell for the cell itself
    - E.g. Smooth muscle response to stretch
- Endocrine – hormone/steroid released into blood stream and then reaches target
    - Acts on the whole body
    - E.g. Insulin and Adr
- Neural – signals transmitted as action potentials
    - neurotransmitter released at synapse to target cell
    - rapid communication to specific target cells
    - acts across long distances
- Neuroendocrine – hormone released from a nerve into the blood stream
    - E.g. ADH/Vasopressin

Control Circuits

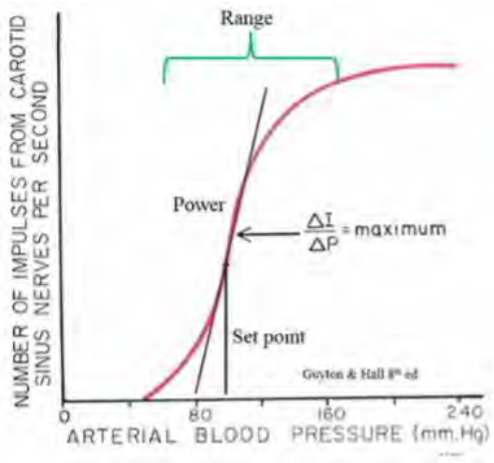
- Command circuits – open loops
- Negative feedback – self-limiting loops, limits change, referenced and unreferenced
    - Unreferenced – no reference point or controller
    - Referenced – output of sensor compared to a reference point

        - Error signal – difference between set point and measured
        - Controller – produces output that limits error signal
- Positive feedback – amplifying loops, rare
    - E.g. platelet activation - ADP, Thromboxane A_2, Thrombin, von Willebrand
        - Damaged endothelium reveals collagen
        - Collagen binds + activates von Willebrand factor
        - Activated platelets bind and activate more platelets
            - By releasing other activators!
        - Inhibition – NO, prostacyclin released from endothelial cell
- NOTE: feedforward implies anticipation, feedback CAN include anticipation
    - Feedback has latency
- Afferent pathway – Controlled variable → sensor → input to central processor → controller
- Efferent pathway – controller → output to effector → effector → response
    - E.g. Muscle Tendon Reflex
- Gain of negative feedback control = $\frac{\Delta E}{\Delta R}$ = effect/residual
    - The amplification on the feedback system – if -ve feedback, -ve gain
    - How well the feedback can counter change
    - ΔR – difference from set point after feedback
    - ΔC – difference from set point without feedback
    - ΔE = ΔR - ΔC
- Set-point – the value the control system regulates to

Simple Switching

- Simplest feedback control system – on/off
- E.g. tropical fish heater – if temp is below set point, heater turns on and vice versa
    - Latency is response + thermal inertia = overshoot in both directions and oscillation around set point

Input/Output Function



- Complex control – not a step curve like simple switching, more sigmoidal
- Slope is power - More power is less stable
- Circuit cannot cope outside of range
- Smaller error to set point = smaller change in drive and vice versa
    - Larger error signal = stronger drive to effector
- E.g. ventilatory response to CO_2 – input is P_{aCO2}, output is ventilation drive, set point ~40mmHg

Gain vs Power

- Gain – change stopped by/left after feedback
- Power – slope of input/output function
- Related but not the same
- E.g. muscle spindle reflex – opposes length change
    - Low power produces small gain – slower response, does not reach set point
    - Higher power – more gain, faster correction
    - Too much power – length overshoots, over corrects, oscillation around set point grows
- To improve stability – as error signal falls, reduce power
    - Control systems might cause overshoot below the set point

PD Control

- Uses power and derivative term – derivative of error signal used to predict error
    - Effector drive now depends on error signal and its rate of change
- Leaves an error – lower gain is more stable but larger final error, add all errors on

Antagonist Pairs

- Uses a pair of muscles with opposite actions – provides more range + stability
- E.g. Posture, HR, blood glucose concentration, blood [Ca^{2+}]
- > 8 control loops for MAP regulation – different gain latencies and durations
- Desensitisation of receptor can cause feedback control system to fail over time
    - After a few days – baroreceptor will change set point to current MAP

Feedforward Control

- E.g. Vestibular ocular reflex – eye movement in opposite direction to head
- Sends information to control a different variable to that which is measured
- Note: anticipation uses delayed negative feedback and memory