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# BI 2223 - PHYSIOLOGY

Natural sciences - study of the natural world, as compared to social sciences

The same event can be analysed differently by physical, chemical and biological scientists

Teleological arguments - why it is the way its is?
Biologists make teleological arguments regularly - apple falling - dispersal - to propagate life - shaped by Natural Selection

By the nature of biology, and its age, there are no universal laws but there are generalisations which have exceptions.

Eg: Central Dogma: In a cellular system, information tends to [Information transfer] go from DNA → RNA → Protein

Cell theory - Cells are the basic unit and all cells come from pre-existing cells.

Reproduction - life begets life

Evolution

Structure and function relationship - they shape each other

Emergence - properties that arise from interaction & integration of individual components - more than the sum of its parts.

Physiology

The study of processes that allows living organisms to live

The term was coined by a French physician in 15th century. named Jean Fernel who wrote an influential treatise on human physiology, pathology and use of medicines

Physiology can be studied in different contexts - animal, plant, microbial, ecological and so on

Homeostasis - the tendency of a living organism to resist perturbations by maintaining constant internal conditions.

# Lecture 2

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## Homeostasis

The concept came about in 1800s.

In ancient medical systems, health was a result of balanced components (humours) and their imbalance caused diseases.

This is mainly associated with two people –

- Claude Bernard : insists on importance of experimentation to study physiology, rather than just observation

  He says that internal environment is different from external, and its maintained at some constancy. ↗ not consequence

  Says constancy of internal env. is a condition for free & independent life. If it breaks down it means death.

  "MILIEU INTÉREUR"

  Around this time – mid to late 1800s – Vital force theory is getting debunked by organic chemist ; and Pasteur has come up with Germ theory. ↳ could synthesize organic molecules so ultimately living beings are made of inorganic matter

  this idea doesn't get mileage but he was a major figure in French intelligentsia

- Walter Cannon
  - Coined the term. One of the first American scientist who was not trained in Europe physiologist at Harvard who studied gastric movements & consequently autonomic nervous system and hormones.
  - He then becomes interested in physiological responses to emotions (like Voodoo deaths).
  - During the course of his study he says that physiological responses are coordinated, & there responses of many organs ~~and~~ are called this 'Homeostasis'. "staying similar" not the same
  - It means a condition, which may vary but is relatively constant. this idea catches on

(2) Seat of implying that disease isn't caused by "imbalance of humours" but a general imbalance of internal conditions

Cannon moved the discussion from the 'fixed state' to the control factors

## Modern concept of Homeostasis

The next addition to the concept came from physics / engg.

They needed some mechanism to regulate the feedback system in machinery through dynamic processes

This was used in gunnery control during WW1 and WW II

Centrifugal feedback valve

Picture — Refer Pg.5 of Homeostasis Frontiers review

1943 : Rosenblueth, Wiener & Bigelow in their paper 'Behavior, Purpose and Teleology' drew an analogy between control theory in machines to living organisms — that we need a control system which maintains constancy of system through feedback mechanisms.

Definitions of Homeostasis

1. Self regulating system by which biological systems maintain stability while adjusting to changing external conditions
2. Tendency of an organism to maintain internal stability as a result of coordinated response of its parts in response to a stimulus that disturbs normal function or condition.
3. Disruption of homeostatic mechanisms is what leads to disease & effective therapy must be directed as re-establishing homeostatic conditions, working with rather than against nature

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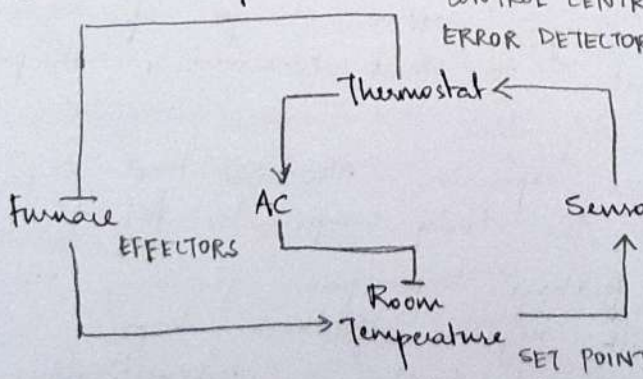
## Lecture 3

Homeostasis and control theory

Classic example : Thermostat - regulating room temperature




Regulation is a perpetually "on" system

Its regulated through positive and negative feedback loops

Using engineered systems is useful because we they have a purpose (to maintain ambient T) - there's a teleological component

Experiment – Measuring resting, post exercise & recovery heart rate

Resting heart rate is the set point – it varies from person to person but its within a range

We can say that its a set point because after recovery, the heart rate moves towards the set point.

Why have a set point? Probably because its the most efficient value i.e. the value at which the system's function has been optimised.

In reality, the pulse increases because the oxygen demand in muscle increases. So in a way, the pulse is the effector for that loop.

Set point – Resting heart rate
Sensor – Hypothalamus
Effector – Muscles of the heart
Feedback – Negative feedback loop.

Heart rate can be high even before the stimulus occurs – in anticipation. Homeostasis can't account for anticipatory changes (which is actually a positive feedback.)

→ Allostatic processes / Allostasis [Feedforward regulation] Requires info about the nature & extent of potential disturbance

Here, you produce anticipatory changes so that when you need to reestablish homeostasis, you can do it more efficiently

Science Direct # Allostasis is defined as the process of maintaining homeostasis through adaptive change of organism's internal environment to meet perceived & anticipated demands independent of changes in regulated variable

Anticipatory changes are expensive – Allostatic load says more about how the body compensates for it.

To prevent Positive feedback loop from spiralling, we need to have inbuilt negative feedback loops.

At a molecular level, habituation & desensitization are processes that facilitate the dampening

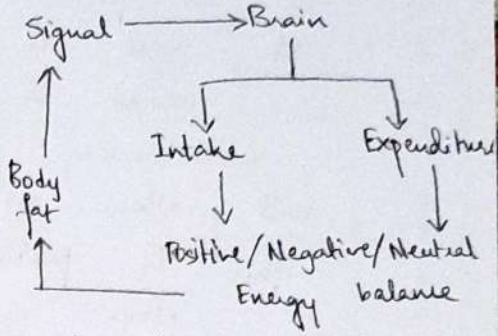
# Adaptation can be viewed as an emergent property of homeostasis

## Case Study

**Lipostatic model : Applying Set point theory to physiology**

This was developed in 1950s as a mechanism of regulating energy homeostasis in body through body fat regulation.

- The model says that there's a set point of body fat / adiposity.
- The adipocites, when above/below set point send signals to brain so it can increase the expenditure / intake accordingly.




# This response is multisystem - molecular to behavioral
- This results in maintainance of some constant value of adiposity.

EVIDENCE : * When you start dieting, initially you lose a lot of weight, then the rate decreases because the brain regulates expenditure so you lose wt less efficiently

Signal

Bolstered the model * Leptin : adipokine, its a hormone made by adipocytes has receptors in the hypothalamus.

Discovered in 1994 (40 yrs later) This was discovered in mice (through genetics) where an obese (∵ hyperphagic) mouse was analysed & if had a homozygous loss of ~~control~~ function mutation for this hormone

* Similar cases were reported in humans - non-functional leptin ⇒ obesity problems.

CONTRADICTIONS : • The fraction of obese people who have inactive or low levels of leptin is very small
Most obese people have very high levels of it

• Leptin-resistance is very very common in the current population. This also established there are other adipokines which act as signals.
So, the initial model was an oversimplification

* Time period of regulation - weeks to months
Signaling - hours to days
* Only focuses on fat mass (5-45% of body mass)

# Lecture 4

Control theory is a concept in engineering, which is used to label components of biological system to understand homeostasis.

## Set point

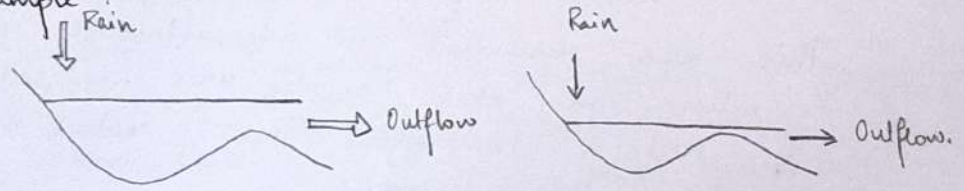
How do we define it and how is it constructed?
So set point emerges rather than being constructed.
Set point is a concept based on genetic determinism, which is a reductionist approach that says understanding all the genes and their function will allow us to understand the organism.
This is problematic because we know that the environment plays a major role.

## Settling point theory

This concept says that there's no set point but behaves that way. There is a constant value that emerges from the intake and expenditure of different processes. There is no active process that works towards maintaining ~~active~~ a set point.
This theory focuses on the role of environment.

Input → Body energy store → Expenditure

Example: Reservoir




Reservoir comes to a natural equilibrium if input is downregulated out output is upregulated in proportion to the reservoirs volume. There is no 'regulated' water parameter, yet it behaves

This is neither an actual set point nor a feedback signal from the reservoir. According to Settling pt, obesity → increased availability of food → downward shift is used to engage in physical activity

This explains the dieting thing by saying that, initially when you diet you lose body fat and lean mass. And you need lean mass to expend energy, so after a while after losing some lean mass, expenditure also decreases and you start losing weight more slowly.
Hybrid models have emerged that use a range of set points & features of settling point theory.

Settling point con: In Minnesotta Starvation expt, it was found that they increased body and fat mass rapidly as there is some active control over intake that is actively related to changes in body composition.

⟹ General model of Intake regulation

- Food intake is regulated by compensated (internal) and uncompensated (environmental) factors
  Compensated factors have negative feedback loops.
- Model doesn't assume a set point, suggests that level defended is malleable
- The effect of the factors (weightage) is determined genetically so the magnitude of respon varies based on inherited responsiveness
- Con: focuses only on regulation of intake; expenditure is subsumed as a compensated factor.

⟹ Dual intervention model

- Upper and lower boundaries that define the points beyond which physiological regulation becomes dominant & in between environmental factors hold sway
- Combination of set point (active regulation beyond points) & setting point theories (passive regulation)
- The two points are determined independently & varies from person to person. There's also an evolutionary rationale: lower pt - risk of starvation
  upper pt - risk of predation

- Humans have been relaxed from risk of predation, so alleles coding for upper intervention point have drifted over time.
- This also explains obesity pandemic as a consequence of increased availability of food while also explaining why only some people become overweight in an obesogenic environment

Against Setting Pt Theory

* Minnesotta Starvation expt - some active control over the intake that is related to body composition i.e. hyperphagy depended on the extent to which body fat & lean mass were depleted



Also doesn't explain how only a few people become obese in an obesogenic environment

Homeorhesis - Return to a trajectory rather than a state or set point (Homeostasis).

Allostasis - anticipatory changes that enhance the efficiency of maintaining homeostasis.

* During weight loss, energy expenditure is actively driven down

Nutritional homeostasis

The idea that the body modifies certain processes to make sure that some nutritional needs are met.

Macronutrients — needed in bulk to build body mass and gain energy

Micronutrients - needed in smaller quantities that are used as cofactors in enzymes and vitamins.

Essential nutrients — nutrients that can't be synthesized in the body, so they are entirely obtained from outside.

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## Lecture 05

Regulation of Blood glucose

A set of coordinated mechanisms that maintain the level of glucose in blood.

Why maintain?

- Osmoregulation: If it fluctuates it affects the level of water that goes in and out of cells
- Energy balance: glucose serves as the major fuel.
  * Cardiac muscle prefers fatty acid over glucose.
- Also acts as an important signal/cue for the brain to modulate behavior accordingly.

For these reasons, in a human, glucose is exquisitely regulated at 4-6 mmol.

Major players in the regulatory system —

Small Intestine + Food → Kidneys + Gluconeogenesis

Liver +/− (Glycogenolysis/gluconeogenesis) Pancreas 0 (background consumption)

Brain − (Glycogenesis/lipogenesis) Skeletal muscles +/− (Glycogenolysis / Glycogenesis)

60% of glucose is consumed by brain

All tissues remove glucose from the blood, but these organs affect the conc. of glucose significantly by adding / removing glucose

Glycogenolysis - breaking down glycogen
Gluconeogenesis - produces glucose from non-carbohydrate compounds
Glycogenesis - making glycogen from glucose
Lipogenesis - making fat from glucose that's stored in adipose cells

Kidney - they also actively pump the glucose back from 'urine'
Brain is also thought to have some gluconeogenesis activity.

Pancreas

It makes digestive enzyme to break down protein and fat. Its produced by 90% of cells called Acinar cells.

The other 10-20% of cells called Islets of Langerhans (majority of islets) which produce Insulin (β cells) & glucagon (α-cells)

They are released into blood stream.

The function of insulin and glucagon are exactly opposite — insulin removes glucose from blood
glucagon adds glucose from blood.

So the conc. of these hormones varies with the level of glucose i.e. there's an insulin spike when there's a glucose spike after consuming food.

The main receptors of insulin / glucagon i.e the effectors are liver, muscles and kidney.

Lecture 6 19/2

Insulin

→ Glucose sensing and insulin release

* The presence of glucose in blood stream is detected/ taken into the β cells through GLUT 2 membrane protein. (channel)

* The glucose is used to produce energy and ATP : ADP ratio increases. The increased ATP binds to an ATP binding channel which generally keeps pumping $K^+$. But now this channel is closed

* From resting potential of ~ -70 mV, the membrane potential depolarises because $K^+$ is not being pumped out. Membrane potential goes to ~ -40 mV

* This depolarisation results in opening of voltage gated $Ca^{2+}$ channel. So $Ca^{2+}$ ions enter the cell.

* $Ca^{2+}$ is detected by Ca-sensitive proteins eg. synaptotagmin and they facilitate the protein-containing vesicles to fuse with the membrane and release the proteins into interstitial fluid.

This is how secretion / release of insulin is regulated

The response time is dependent on the spike of blood glucose (i.e. coke vs. chapati)

The fast response takes about 5 mins.

Desensitisation through internalisation?

When the other cells develop resistance to insulin, glucose levels don't fall — so β cells keep producing insulin and get 'exhausted' and ultimately die. Leads to diabetes

Incretin observation: more insulin was released when glucose was ingested rather than when the same ~~protein~~ glucose was injected into blood stream

- Intergen regulation of insulin release & synthesis
- GIP (Incretins) released by gut
- Incretins are hormone proteins produced by the gut when food is ingested
- They bind to the GLP-1 receptors on the membranes of β-cells. Its a kind of G-protein-coupled-Receptor (GPCR) that is heterotrimeric made of β, γ and $G_{\alpha s}$ units
- When GIP binds to GLP-1, $G_{\alpha s}$ dissociates and stimulates/ activates an enzyme called adenylyl cyclase by binding to it
- Adenylyl cyclase converts ATP to cAMP, which in turn activates protein kinase A
- This enzyme phosphorylates proteins i.e the ion channels and helps them work more efficiently. So, $K^+$ ion closer and $Ca^{2+}$ is pumped in more — results in faster production of insulin by making the system more sensitive

In a way, this is an allostatic response i.e insulin is produced in anticipation.

β-cells are not sensitive to level of glucose itself, rather they're sensitive to energy levels (ATP). This is because insulin is also involved in satiatory response by binding to receptors in the brain

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## Lecture 7

- Norepinephrine, sympathetic nervous system
  - ↳ essentially adrenaline But norepinephrine is produced by sympathetic NS which kicks in during fight or flight response
- This hormone also binds to a GPCR and $G_{\alpha i}$ gets dissociated, binds to adenylyl cyclase and <u>inhibits</u> the activity of the enzyme
- This process reduces insulin secretion, allowing glucose to persist in the blood. This is thought to be because more energy i.e. glucose is needed for fight/flight response

Other stress hormones like cortisols also have some effect.

→ Glucose metabolism at target organs (self study)

→ Diabetes and insulin resistance.

Diabetes insipidus — disorder of salt & water metabolism — intense thirst & heavy urine

Diabetes mellitus — unregulated blood sugar concentrations.
i.e glucose levels can be very high or very low

Type I — • early onset, more lethal (expectancy < 20 yrs)
• auto-immune & strong genetic component
• destruction of β-cells of pancreas — no insulin is produced

Type II — • insulin insufficiency due to insulin resistance
• strongly associated with lifestyle, though genetics also play a role
• late onset

Due to insulin resistance, the β-cells produce more and more insulin, leading to exhaustion and death
Then its like Type I.

Type III — Gestational diabetes lasts for the duration of pregnancy and takes care of itself after parturition.
But sometimes it may persist.

Insulin resistance

- Its the inability of body to respond to insulin.
- The genetic factor is mutations in the receptor making it hard for insulin to bind or weakening the subsequent signal transduction.
- Lifestyle choices — Strong association of obesity with diabetes.
Obese individuals have lot of adipocytes and hence lot of free fatty acids. Many organs, including liver have receptors for free fatty acid.
When fatty acid triggers response in hepatocytes, the response of insulin is impinged upon
Other molecules like leptin also affect the insulin response negatively. This maybe the reason for insulin resistance.

High levels of corticosteroids [Cushing's syndrome] are also associated with diabetes

In gestational diabetes (generally occurs in older women), the hormones related to pregnancy (placental) cause glucose levels to build up in the blood.
Usually, pancreas can produce enough insulin to handle it, but when it can't, the insulin insufficiency causes diabetes

Symptoms of Diabetes

Increased glucose in blood makes the kidney decrease its reabsorption in DCT, increasing glucose levels in urine. This pulls out water from the body to dilute the urine. Increased and frequents urination (polyurea) and subsequently thirst (polydipsia) are one of the first symptoms.

- High glucose levels reduce the levels of NO (vasodilator), constricting the blood vessels, thus increasing BP.
- This high BP causes the kidneys to overwork, impair their function & cause renal failure
- Along with constricting, it also hardens the blood vessels, causing atherosclerosis - build up of fat, cholesterol in vessel, restricting blood flow.
- This constriction reduces the blood flow to the periphery - affect the nerves, causing tingling, losing sensation and causing wounds (neuropathy).

- Increased blood sugar also affects the responses of immune system - taking longer to heal wounds & contracting diseases easily.
- Retinopathy - tiny blood vessels in eye can get damaged & may lead to blindness.
- Ketoacidosis - insulin resistance means cells can't take up glucose & can't activate metabolising enzymes. So they break down fat which increases ketone bodies in blood, leading to an acidic condition (more serious in Type I)
- Measuring ketone levels is used as a test for diabetes along with oral glucose tolerance test & other tests
- There is no cure but the syndrome can be managed through lifestyle changes

Lecture 09

Cellular homeostasis of energy and nutrition

- Homeostasis is the ability of an organism to regulate its internal environment.
- For a cell, anything inside the cell boundary is considered as the internal environment.
- Ion levels, osmotic pressure, nutrients etc are the factors that are maintained by the cell.
- But consider temperature — an internal regulation of T is absent, so they don't have homeostatic response rather than have adaptive responses

A eukaryotic cell has better regulation because it has specialised responses and its environment is less likely to fluctuate because its part of an organism

Energetic balance of a cell

We measure ATP, GTP, reductases and polyphosphates (in bacteria mostly) to measure the energy in a cell.

It is maintained by catabolism (adding to energy level) and anabolism (taking from energy level).

To maintain the energy level, the cell should be able to sense it (ATP levels), compare it to a 'set point' and a control system to regulate metabolism

A pan-eukaryotic energy sensor — AMPK

AMP-activated protein kinase phosphorylates many proteins in cell. Its a hetero-trimer — $\alpha$, $\beta$ and $\gamma$ sub-units and $\alpha$ is the enzymatic part of the protein.

- The protein is activated by AMP i.e. when the cell is low on energy.

# There are several isoforms of AMPK in different cells and organisms

CATABOLISM →

$$AMP \underset{\text{Kinase}}{\overset{\text{Adenylate}}{\rightleftharpoons}} ADP \underset{\text{Energy consuming reactions}}{\overset{\text{ATP synthase}}{\rightleftharpoons}} ATP$$

← ANABOLISM

- In an energy rich cell, conc. of ATP is high When energy levels are low, 2 ADP ~~levels~~ molecules are used to make 1 AMP and 1 ATP to maintain usable levels of ATP. But this means AMP conc increases because less of it's used to make ATP
- So AMPK has evolved to detect high levels of AMP because ADP is used to make ATP and AMP, so while ADP levels go down, AMP levels go up.
- AMPK acts on many processes, increasing catabolic (breaking down) activities and decreasing anabolic ones.

⊕ Glut4 translocation — Glut4 is an insulin independent glucose transporter that is stored in the membrane of vesicles. AMPK causes the fusion of these vesicles with plasma membrane

⊕ phosphorylates catabolic enzymes of glycolysis and beta-oxidation so they are more efficient, and also phosphorylates the corresponding Tx factors

⊖ Glycogen synthase

⊖ Gluconeogenic enzymes — takes more energy than how much it yields.

⊖ Acetyl-CoA Carboxylase (ACC) — this is the first enzyme required for biosynthesis of fats

⊖ mTor (mammalian Target of rapamycin) which regulates protein synthesis. ↳ also cell proliferation, autophagy and cell motility

| Synthase | Synthetase |
| --- | --- |
| Does not require ATP | Requires ATP |
| Classified as lyase / transferase | Classified as ligase |



This AMPK pathway of Glut4 translocation is exploited for a medicine for type II diabetes to force the cells to take up glucose from bloodstream. make it possible / simulate Its a successful medicine called Metformin.

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## Lecture 9

### Homeostasis of elemental composition

Elemental composition in bacteria is regulated

Cyanobacteria - C:N = 5:1

Proteobacteria - C:N = 5.5 : 1

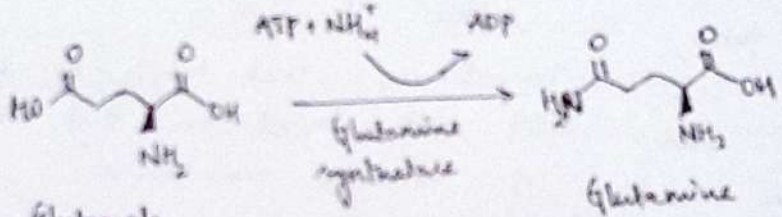
Is it under homeostatic control?

Carbon and Nitrogen assimilation are linked in bacteria

* Carbon metabolism

  Glucose → Pyruvate → Acetyl CoA → Citric acid Cycle

* Nitrogen assimilation (through inorganic source)



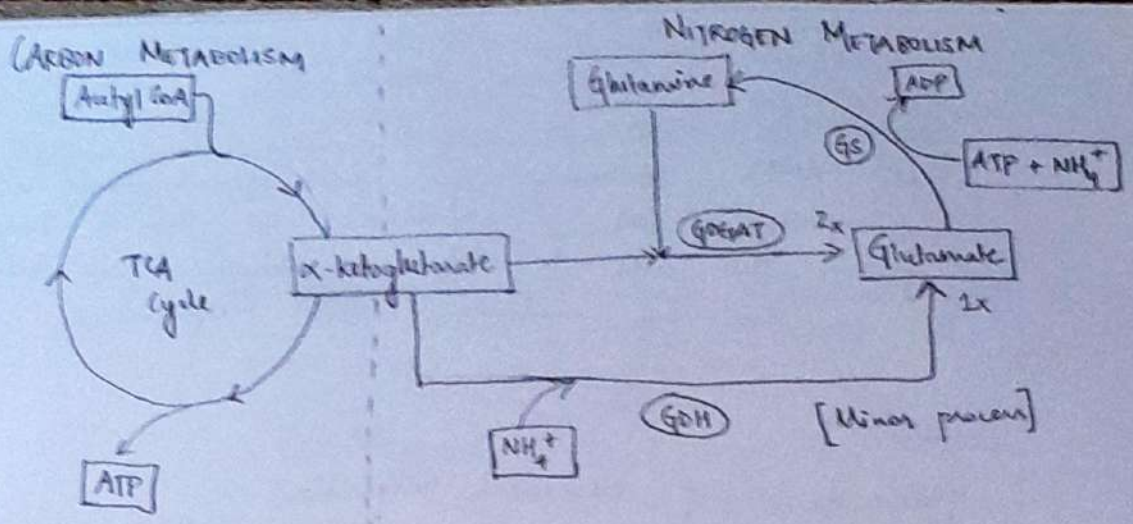

Glutamate

Glutamine

This process consumes energy / ATP and limited by glutamate, because unlike TCA cycle, this is not a cyclic process. So the backbone for the reaction is not self-fulfilled

But the bacteria regenerates glutamate by using one molecule each of Glutamine and α-Ketoglutarate through the enzyme Glutamate synthase also known as Glutamine oxoglutarate aminotransferase (GOGAT).

So the two metabolic processes are linked through this process.




When nitrogen is limiting and carbon is in excess, the level of 2-OG increases; and when $N_2$ is in excess, 2-OG is used up and its levels are low.

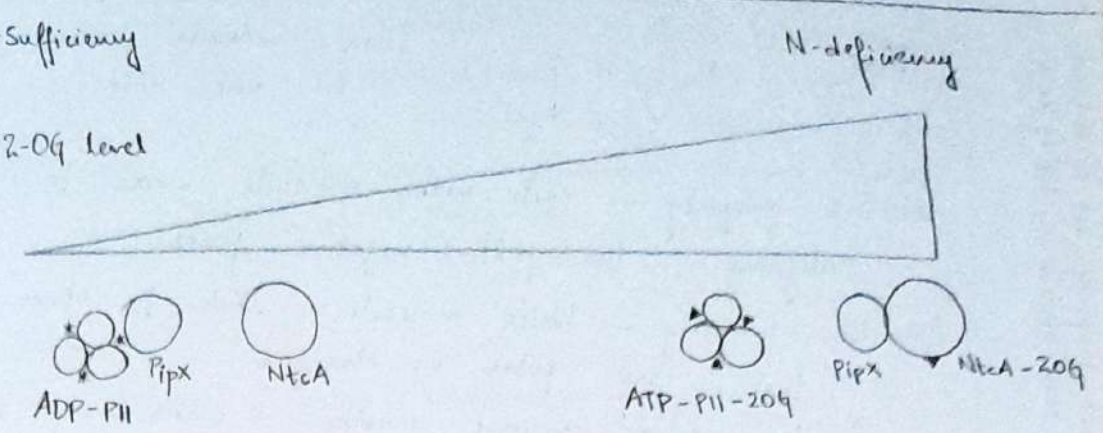
So, 2-OG levels serve as a signal of C vs N metabolism

Sensors of 2-OG – PII family of proteins

- It was first identified in E.coli & protein there is called GlnB.
- GlnB is a homotrimer that binds to both ATP and 2-OG, and based on that, it regulates the level of nitrogen metabolism
- GlnB only binds to ATP & 2-OG when all the ATP-binding sites are filled. And each successive 2-OG molecule is bound less efficiently i.e. negative cooperativity (positive cooperativity – haemoglobin).
- So this protein is activated to do its work when energy levels are high (3 ATP needs to bind) and 2-OG levels are very high, so they also bind to all 3 sites.

Cyanobacteria — thought to be precursors of plastids
have chlorophyll molecule






- At low levels of 2-OG (N-sufficiency), ADP-PII complex binds strongly with PipX (transcriptional co-activator of NtcA).
- But when there is N-deficiency i.e PII has been bounds by 3ATP and 3-2OG, PipX is free to bind with 2OG-NtcA complex and increase its activity in regulating Nitrogen assimilation genes.
- NtcA activates genes coding for → transporters of nitrogen scavenging (nitrates, nitrites, ammonia, urea)
  - N-assimilating enzymes like GS and GOGAT

Whereas, GS inhibitor protein-encoding genes are suppressed

This was discovered in cyanobacteria.

Redfeild ratio : Community level elemental ratios in marine plankton

In 1934, Alfred Redfeild discovered that elemental ratios in biomass, throughout the world's oceans is found to be more or less constant —

C : N : P = 106 : 16 : 1

* Not always true — could vary a little with depth & place

This tells us that communities tend to maintain certain ratio and studying how they're changing is important for conservation.

* nutrient cycling in ecosystems due to climate change
— could act as indicators.

Lecture 10

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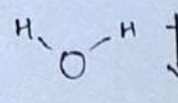
Introduction to Water and Ionic balance

$H_2O$




Polar molecule because of charge on one side

- Cohesive property – each water molecule binds to another by aligning the positive-negative parts
- Adhesive property – Water molecules stick to other surface that are polar or charged
- Capillary action against gravity – water moves up the xylem
- Water can also dissolve polar compounds by solvating them – water molecules surround the dissolved ion (positive/negative). This is called the sphere of hydration.
- Water can also dissolves glucose by solvating it. – the -OH groups get surrounded by $H_2O$.
- Water also helps is the formation and maintainence of membranes surrounding cells. This is because phospholipids are amphipatric cylindrical molecules and when put in water, they form a bilayer so that polar heads are exposed to the hydrophilic environment.
- Amino acids can be polar or non-polar. In a nascent polypeptide chain, these are both polar and non polar side chains of amino-acids. Due to the hydrophobic effect, the protein folds in such a way that non-polar groups are inside and polar ones are exposed to the water environment.

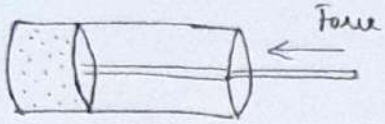
This determines the tertiary structure of protein, which in turn decides the function of the protein.

Also: - Thermal property: lot of H-bonds ⇒ it can absorb a lot of heat

- Water at interface of protein-DNA interface — bovine papilloma-1 E2 protein (dimer) interacting with DNA is because of water molecules. Both hydrophobic and hydrophilic effects are dominant driving forces for biochemical processes.

## Osmosis

* Water moves across membrane in response to concentration of dissolved solutes.
* Measuring osmotic pressure.




Osmotic pressure is the opposite of hydrostatic force required to maintain the solution at that conc.

Measuring osmolarity : 180 g of glucose in 1L — 1 osmole

* Osmolarity is entirely dependent on the number of solute molecules and not on the nature of solute

This is known as colligative property.

Remember van't Hoff factor i.e. NaCl → $Na^+$, $Cl^-$ i = 2

* If we look at the conc of different solutes —

| | Extracellular | Intracellular |
|---|---|---|
| $Na^+$ | 142 mEq/L | 10 |
| $K^+$ | 4 | 140 |
| $Ca^+$ | 5 | 0.0001 |
| $Cl^-$ | 103 | 4 |
| $pO_2$ | 35 mmHg | 40 mmHg |
| Osmolality | 281 mOsm/L | 281 mOsm/L |

Water is in thermodynamic equilibrium — the total conc of solutes and water across the plasma membrane is maintained / balanced. Changes in solute conc results in an osmotic gradient that might swell / shrink the cell

(20) → Cellular dehydration

Water creates pressure inside the cell that helps it maintain shape. In a hydrated cell, water pushes outward and maintains a round shape. The shape is important for biochemical processes

Hydrated : $P_{in} > P_{out}$

Shrunken : $P_{in} < P_{out}$.

* Tonicity – measure of effective osmotic pressure gradient – determines the direction and extent of diffusion

Solutions can by hypo-, hyper- or isotonic. i.e water either enters or leaves the cell at greater rates

Osmolarity – conc. of osmotically active particles in the solution

→ Cell volume regulation

- Important homeostatic function that regulates cell growth, cell migration, death etc.
- Most cells are able to counteract volume perturbations following a shift in intracellular or extracellular osmolarity
- It does so by increasing / decreasing the no. of dissolved solute molecules inside the cell.
- This accumulation / loss of electrolytes are mediated by activity of membrane carriers and channels. These pathways are activated seconds after volume change ⇒ they're already in cell membrane or rapidly inserted from cytosol.

→ Water compartments in the body –

Intracellular and Extracellular (interstitial fluid + blood) fluids

~ 30 kg ~ 10 kg ~ 2 kg

- Water makes up 60% of body mass
- 3 compartments are seperated by selectively permeable membranes. All have same osmolarity i.e they are isoosmolal.

→ Transport of water

Water can diffuse through the lipid bilayer, but its very slow and temperature sensitive

Water is more effectively & passively transported by membrane channels called aquaporins – rapid movement and T insensitive

Peter Agre received a Nobel (2003) for his discovery of structure and function of these prokin channels

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Lecture 11

Water and ionic homeostasis in Freshwater animals.

Although ionic concentrations are different in different fluids, the osmolality is closely maintained

Freshwater teleost fish

Osmolarity of body fluid ~ 300 mOsm/L

surrounding water ~ 0.5 - 5 mOsm/L

To maintain this, it has to regulate water uptake by exosmosis and ion uptake from water

They take in a lot of water inside through gills, to absorb oxygen. But this is so much water, that it doesn't need to drink water; it excretes almost the same amount of very dilute urine

Freshwater mussel – dilutest blood – 44 mOsm

Gills : problem and solution

↳ have very ~~small~~ thin, semipermeable gill epithelia for efficient transport of gases

are lined with many capillaries

Gills

As fish opens its mouth, water runs over gills and $O_2$ diffuses from water to blood

Recap : Osmolarity of — Water: 300 5 Blood 300

Freshwater animals expend energy to maintain ionic concentrations.

So they produce copious amount of dilute wine (hyposmotic to the blood)

To replace ions lost (gills & wine), they take up $Na^+$ and $Cl^-$ by active transport

# Goldfish — wt = 100g Water flux = 30g

The kidney and nephron is bit primitive in fish but it works in the same way.

Its not perfect so some ions are lost through wine

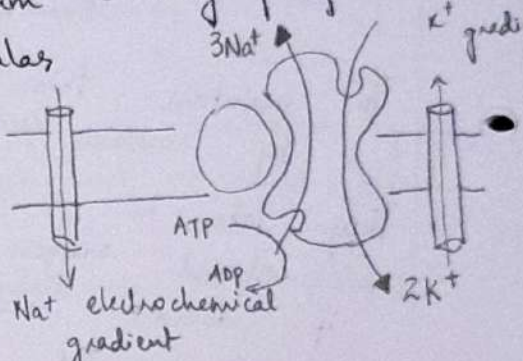
The success of freshwater animal can be measured by ratio of Osmotic pressure of Urine / Plasma.

Goes as low as 0.1 for crayfish

∴ They need to pick up ions from water through speciall cells in gills known as ionocyte.

→ $Na^+$ $K^+$ ATPase — Sodium-Potassium exchang pump

* This ensures that extracellular $Na^+$ conc. is greater than intracellular conc. by actively pumping 3 $Na^+$ out for every 2 $K^+$ in using 1 ATP




* Why doesn't the extracellular conc. keep increasing?

Because there are leaky channels that allow $Na^+$ to diffuse passively at the same rate at which these pumps send it out.

So conc. of $Na^+$ is maintained at constant 14:1

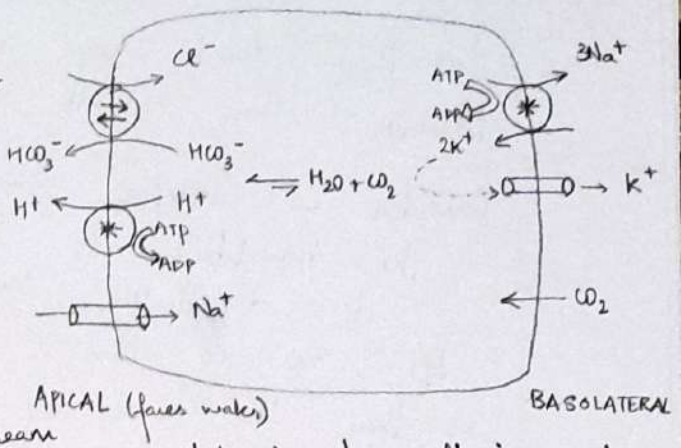
Resting polarised state of cell : ≈ -70 mV

≠ No. of $K^+$ leakage channels are much greater than $Na^+$ channels & 50 times more facilitatory.

Box extension 5.2 bookmark

# Cellular mechanism of active $Na^+$ uptake across epithelial cells of freshwater fish gills

- Mechanisms of ion uptake
- This process is carried out by Mitochondria Rich cell (MRC) in the gill epithelium.

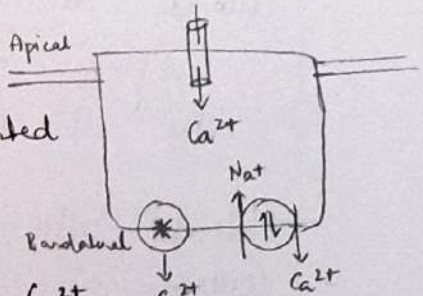



- $Na^+$ intake
- The excess $H^+$ in the cell is actively (i) pumped out.
- The $Na^+$ in the cell is pumped into the blood stream by Na-K pump. So the conc. of $Na^+$ in the cell is very less
- $Na^+$ in the water, thus comes in through Na channel because of the electrochemical gradient and to balance the charge for $H^+$ being thrown out.

- $Cl^-$ intake
- $CO_2$ is dissolved to form $HCO_3^-$ and $H^+$.
- $HCO_3^-$ is exchanged for $Cl^-$ in countertransport (antiport) that doesn't require energy.
- $H^+$ is exchanged for $Na^+$ (model ii – countertransport)
- This way, the fish uses excretory ions to increase the intake of useful $Na^+$ & $Cl^-$ ions

Role of Prolactin (Pituitary hormone, very conserved) → controls number, morphology & distribution of MRC

This hormone stimulates the MRC so that they actively intake $Na^+$, $Cl^-$ and $Ca^{2+}$.




$Ca^{2+}$ uptake : The conc. of $Ca^{2+}$ is very less in the cell – its transported in by active and counter-transport through basolateral membrane. Because of electrochemical gradient established, $Ca^{2+}$ from water enters the MRC

Lecture 12 5/3/21

Marine animals

The ocean water has higher conc of ions i.e. hypertonic

Many marine invertebrates are isosmotic with their environment ~ 1000 mOsm/L

⇒ They don't have to expend energy to maintain osmolarity

However, they exhibit ionic regulation.

Consider — Cuttlefish and Teleost fish

The invertebrate is isosmotic, but the fish blood is drastically hyposmotic to seawater.

Ie 300 - 500 mOsm

⇒ They lose water by osmosis and gain ions by diffusion

Ions like $Cl^-$ tend to concentrate in the blood

i.e if ends up dehydrating continuously.

There is also salt and water in the food and seawater ingested (source of net water gain).

They maintain osmolarity by —

- Active extrusion of $Cl^-$, active or passive outflux of $Na^+$
- Small amounts of urine, nearly isosmotic to plasma (they can't concentrate if more than that)
- Salt and water in faeces. → Divalent ions

Role of gills in NaCl excretion

- Gills primarily excrete excess major ions - $Na^+$ & $Cl^-$
- Chloride cells (ionocytes) actively excrete $Cl^-$ and outflux of $Na^+$ is active or passive (attracted by extra $Cl^-$ just outside the membrane).

Chloride cells / ionocytes / MRC

- Contain a lot of mitochondria & extensive tubular system ER has maximised area to have max no. of Na-k pumps.

# Marine teleost are likely descended from freshwater ancestor.

Hagfish - cyclostoma - evolved in sea - isosmotic to sea water

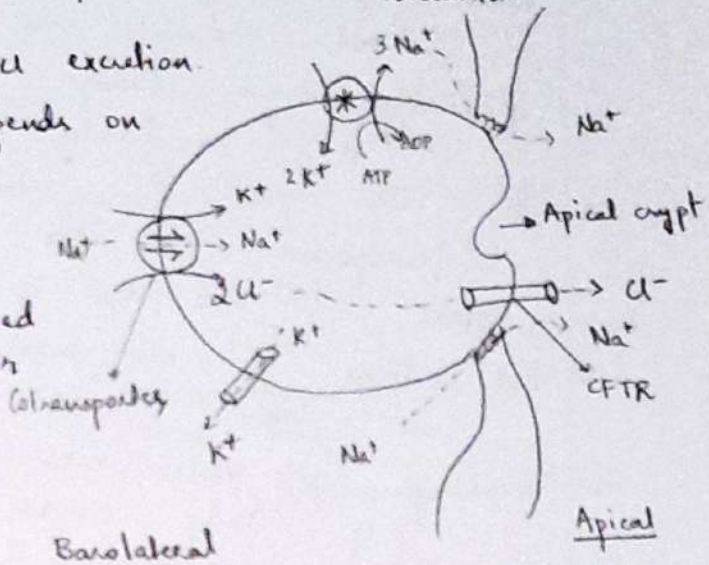
Seawater — apical crypt ; freshwater - broad apex with numerous microvilli.

→ Probable mechanism of NaCl excretion

Rate of ion diffusion depends on
- electrical gradient
- gill permeability
- ion conc gradient

Excretion of NaCl is carried out by increasing their conc. in the ionocytes

This is done by —




Apical

Basolateral

1. $Na^+$ & $Cl^-$ are imported by the NaKCC cotransporter. This is powered by $Na^+$ electrochemical gradient that $Cl^-$ and $K^+$ side.

⇒ This increases $Cl^-$ conc so much in the cell that it goes out passively by Cystic Fibrosis Transmembrane Conductance Regulator (CFTR).

2. $Na^+$ are driven out by paracellular pathway — it will just go out because they're attracted by the $Cl^-$ just outside the membrane

Japanese eel/s — acclimated to freshwater

Its a catadromous fish (goes to ocean) to spawn

The number of ATPase containing cells is greatly increased as it enters seawater.

Killifish — chloride cells are adapted to both freshwater and seawater i.e. its the structure of chloride cell (apical crypt vs microvilli) changes based on its habitat.

(28)

Replacement of water loses

- To replace the water lost through gills, they drink seawater
- When this hyperosmotic is ingested, water flows out of blood plasma and into the gut fluid.
- Gradually, gut fluid expands and becomes isosmotic to the body fluid
- In later part of intestine, $Na^+$ and $Cl^-$ are actively transported into the blood. This favours osmotic uptake ($50-80\%$ $H_2O$ in seawater)
- But there is an influx of $Na^+$ and $Cl^-$, which is later thrown out by the gills.
- Drinking rate varies with salinity — regularly 10-20% of body weight with ability to drink upto 35-40% if salinity is high (∴ losing more water)
- Aquaporins in intestinal epithelia are instrumental in facilitating water uptake

Tentative model of water absorption

- The NKCC channels on the cells absorb lots of ions into the cell — $Cl^-$ and $Na^+$ are diffused into the plasma membrane (∵ of the gradient ($Cl^-$) and through Na-K -atpase).
- The water from lumen directly enters the plasma through Tight Junction in between cells.
- There are also many no. & types of aquaporins on the membrane that are put there by vesicles

* Humans: 2-7 mM

- Marine elasmobranchs are hyperosmotic but hypoionic to seawater.
- Shark / chondrychthes — their plasma is hyperosmotic because of high conc of urea in their plasma (300-400 mM)*
- Salt gain by gills ⇒ water gain by osmosis (no drinking)
- Modest amt of urine, rich in $Mg^{2+}$, $SO_4^{2-}$
- Rectal glands secrete $Na^+$ & $Cl^-$, salts in feces.
- Role of gills in salt excretion — uncertain.

# Kidneys of fish and amphibians can't produce wine hyperosmotic to blood.

9/3 (27)

Lecture 13

Terrestrial animals

For these, $O_2$ is abundant but water is the scarce resource. Water is lost from the body through perspiration, urination, defecation and exhalation.

Main adaptations —

1. Waterproof integument - keratinous scales of reptiles and cornified epithelium of mammals provide physical protection and insulation from water loss.
2. Reabsorbing water from kidneys - by hormonal regulation (ADH), making conc. urine
3. Behavioural adaptation - Kangaroo rat stays burrowed all day by and cutting down evaporation from lungs (by 25%) Many animals seek out damp/moist environments.
4. Metabolic water - breaking down of glucose gives $H_2O$. Breaking down carbs (0.56 g) and fats (1.07) differs.
   # Fats are less oxidised than carbs
   Kangaroo rat prefers to breakdown fats.

Osmolality: Plasma ~ 300 mOsm $L^{-1}$
Urine ~ 400 - 500 mOsm $L^{-1}$ / 900 - 1200 mOsm $L^{-1}$ (cone)

Two extreme examples —

- Australian hopping mouse - food and metabolism are only sources of water because osmolality of its urine is 10,000 mOsm
- Beaver - aquatic environment - minimal urine conc. ability ~ 500 mOsm $L^{-1}$

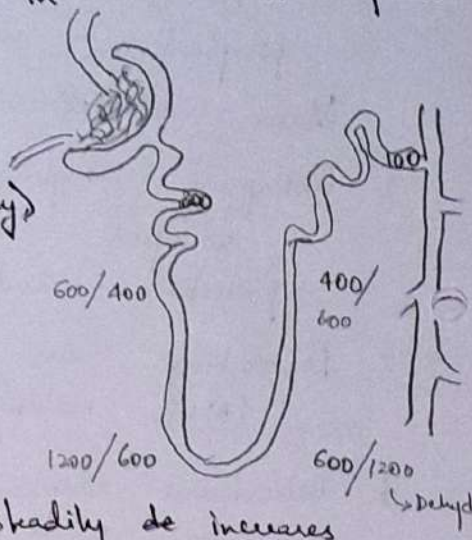
Their kidney functions are optimised to their environments

Kidneys play an important role in excreting dilute urine if there's excess water, kidneys absorb most ions and not any of water.

Dilute urine ~ 50 mOsm.

Persons plasma osmolality reflects the state of hydration.

Kidney has capability to vary the relative proportions of solutes and water in urine in response to various changes.




- Bowman's capsule – ultrafiltration
- Down the loop of Henle (vertically) the osmolality increases

Renal medullary interstitium is hyperosmotic

From cortex to medulla, it steadily increases from 300 to 900–1200 mOsm i.e if it has accumulated solutes in great excess of water.

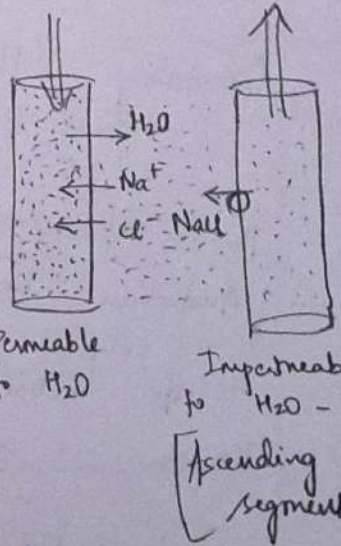
Bowman's capsule – cortex Tubule & Henle's loop – medulla

This ability of kidney to concentrate the urine comes from the gradient set up in nephron

→ Single effect in loop of Henle

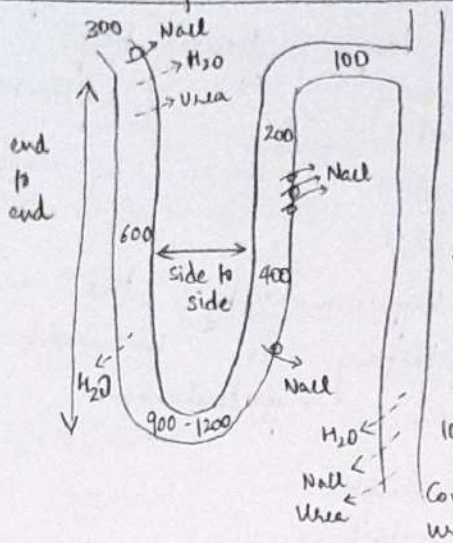
Its the difference in osmotic pressure between descending loop and interstitial / ascending loop.

NaCl is actively transported into interstitial fluid. So, the water from descending limb is passively drawn out, increasing the conc of the filtrate



PCT — NaCl, glucose reabsorbed & water follows so that filtrate remains isosmolar — Upto 60-80%

DCT — differentially reabsorb water & solutes, thus regulating ratio




## Countercurrent Mechanism

→ Immediate concentrating process for non-urea solutes

Walls of collecting duct are poorly permeable to solutes

When $H_2O$ is pulled out bcuz of high conc of medullary interstitial fluid, the non-urea solutes inside the collecting duct are concentrated.

→ Countercurrent multiplier

This process multiplies the effect of single effect, which creates a gradient side to side

But this processor creates an end to end gradient

This results in setting up a gradient in medulla, thus making it possible to increase the conc of urine

The longer the loop of Henle (running into renal pelvis), and the parallel running collecting tubule, the more concentrated the urine gets.

→ The conc of urea & urine

Collecting tubule — impermeable to solutes, permeable to urea (Aquaporins) Variable permeability to water.

In anti-diuretic state, the aquaporins are increased in the membrane of collecting duct cells are increased so that water can go from collecting duct to the medullary interstitium.

In diuretic state, aquaporins are decreased so that the urine is dilute

In antidiuretic state, urea is allowed to diffuse from CT to interstitial fluid (when conc. of urea is high). So this concentrates urine further.

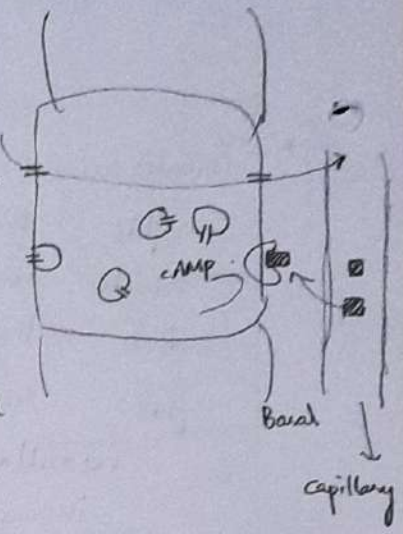
# Vasa recta (capillaries around loop of Henle) help reabsorb water so only <5% of filtrate reaches the collecting duct.

ADH is secreted by hypothalamic neurons. It

Osmoreceptor - ADH feedback

When osmoreceptors detect hyperosmolarity, the ~~secretion~~ stored ADH in posterior pituitary is increased released through signals from hypothalamus.

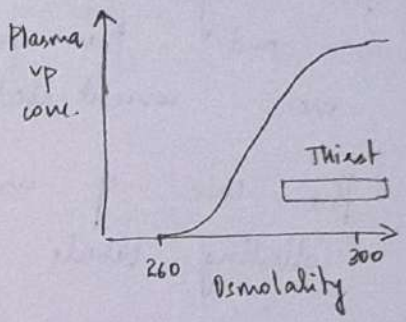
1. Vasopressin binds to membrane receptor in the cells of collecting duct
2. This activates cAMP which in turn results in insertion of aquaporins on the apical side
3. So water is absorbed from the filtrate and returned to plasma. This concentrates the filtrate




ADH / Vasopressin — 9 amino acid sequences

Its half-life : 16 - 24 mins

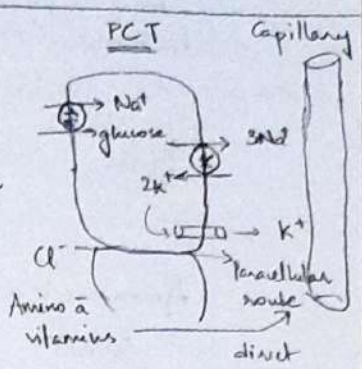
Increase in ADH increases thirst — behavioural response to decrease blood osmolality.




→ Regulation of Sodium ion conc in biological fluid

- Most Na in our body is outside the cells in extracellular fluid, at a conc. of 135 mEq/L
- It is essential for maintaining water balance, nerve impulse conduction and muscle contraction.
- Important determinant of volume and osmolality of ECF
- Kidneys are important for sodium homeostasis.

The tubule cell of PCT absorbs $Na^+$ and glucose by symport.
$Na^+$ is transported to plasma by Na-k-ATPase. 67% of Na is absorbed and water follows by isosmotic reabsorption




## Aldosterone

* Steroidal hormone secreted by adrenal cortex.
It helps maintain ion conc in the plasma by —
- Simulating renal tubule to absorb $Na^+$
- Secrete $K^+$ into urine

→ Some reptiles and birds living by the sea excrete sodium by way of salt glands.
- Avian salt glands located above the eyes. They secrete salts into nasal passage and secretions drip from nostrils.
- Its dramatically hyperosmotic to plasma — so that they could drink seawater and void major monovalent ions through salt glands

18/3
22

## Lecture 18 14

## Physiology of Excretion

Breakdown of amino ā releases amine groups which are toxic and need to be excreted.
Animals can't store excess amino ā, so excess is degraded in the liver & mammals have developed an elaborate way to get rid of it.
Fish / aquatic animals diffuse ammonia out through their respiratory surface

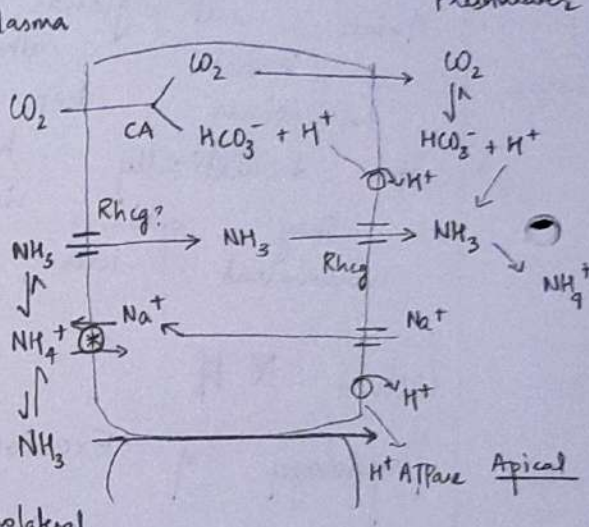
Purines / pyramidines, ATP also contain nitrogen

Aquatic animals – ammonia (v. toxic) – no energy
Mammals, most amphibians, sharks, some bony fish – urea (less toxic) – requires energy (2N is excreted using ATP)
Birds, reptiles, insects, snails – uric acid (not soluble) – excretes 4 N (uses ATP).

Ammonotelism is the primitive state
About 0.5 L of water is required to excrete 1 gm of nitrogen as ammonia. Also cheapest excretion.
However 0.05 L of water is required to excrete 1 g of nitrogen in form of urea

- Urea is tolerable, ammonia – v. toxic : disrupt neuron fn. blood brain barrier and gill permeability so its kept at ~0.3 mM in vertebrates
- Ammonia excretion in freshwater teleost is by diffusion of ammonia gas down $P_{NH_3}$ gradient from blood to water.

CA Carbonic anhydrase




- Phospholipids of $NH_4^+$ isn't permeable to cell membrane
Ammonia passes out as $NH_3$
- Rhesus glycoprotein (Rhcg, Rhbg) along with Na-K-ATPase and $H^+$-ATPase play a role in ammonia excretion
(↘ Apical membrane – removes $H^+$ which combines with $NH_3$ and forms ammonia in water.
- Rhcg, Rhbg were discovered in early 1990s. They're present on both basal and apical membrane
It helps remove $NH_3$ from plasma to freshwater.

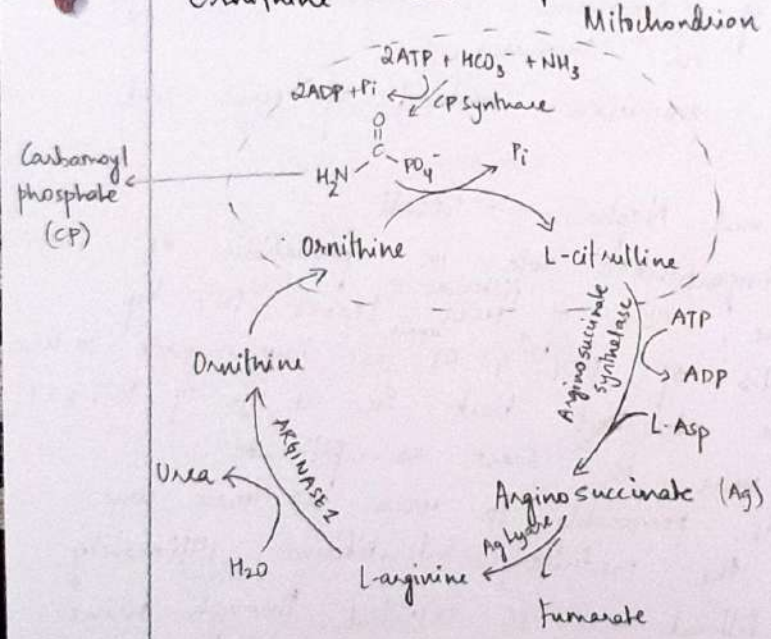
# Gut bacteria also produce $NH_3$
Some ammonia also goes out through paracellular transport

There is also a $Na^+ - NH_4^+$ ATPase which exchanges $Na^+$ to plasma for $NH_4^+$ (which is exported as $NH_3 + H^+$).
In the freshwater fish, this is an additional advantage — $Na^+$ is taken up and transported ~~outrid~~ to the plasma and in return ammonia is excreted.
The process is not regulated, but if $NH_3$ is accumulated, the fish respires aggressively to get rid of it.

## ⇒ Ureotelism

Synthesis of urea takes 5 ATP per molecule, but requires much less water
Vertebrate (including some fish) synthesize urea primarily in liver, (and 5-10% in kidney) through the urea - ornithine cycle
All ammonia goes to liver. Its combined with $CO_2$ to form urea, which is excreted out using kidneys

### Ornithine - Urea cycle




Enzymes
Carbamoyl phosphate synthetase
Ornithine transcarbamoylase
Arginine synthetase
Argininosuccinate lyase
Arginase 1

Insufficiency of urea cycle occurs in some genetic disorders & in liver failure, which leads to accumulation of nitrogenous waste, leading to hepatic encephelopathy.

This urea-ornithine cycle is characteristic of all vertebrates. Even fish have the genes for these enzymes, but they don't express them (one or more of them) △

In frogs, the tadpoles are ammonotellic, but as it undergoes metamorphosis, the expression of these enzymes starts & increases and it switches to becoming a ureotellic adult. (stage xxiv)

# Roman numerals are used to indicate the stages in development of frog, instead of days. Because depending on conditions, the time taken for development can vary differently.

↘ This benefits the frog bcuz its now terrestrial and there isn't enough water available.

△ Toadfish, coelacanth and lungfish have urea excretion mechanisms

But some amount of ammonia is excreted through the kidneys in humans.

Crocodiles – excrete ammonia instead of uric acid.

Structure of Kidney and Nephron – recall

Urea plays an important role in formation of concentrated urine. 50% of filtered urea leaves PCT by diffusion. The walls of DCT & upper CT are impermeable to urea But other ions are absorbed back so, at jn of DCT & CT, the conc of urea is same as filtrate.

Then, lower CT is permeable to urea ⇒ urea conc. increases in the medullary interstitium. Ultimately, 40% of Urea is being used to reabsorb water from filtrate

# Lecture 15

Biological functions occur at various levels/scales of interaction
- Biomolecular interactions function in containment zones where their conc & all can be regulated i.e there's a 3D organisation & compartmentalisation in cells and tissues
- This compartmental organisation ie how cells are stacked. More like cell biology.
- The next level is intercellularity — signaling and communication b/w cells in an organism. This is considered physiology.
- The next level is interaction between organisms. This is the ecological level

Biological functions are integrated across all these levels.

Physiology of Gases

Anatomy and function are two sides of same coin — structures that make the functions possible

Living organisms — cells — can only deal with gases if they're dissolved in water. The solubility of gases & the mechanisms involved in modulating it are important constraints on the design logic of structures & processes of physiological systems that involve gases — both use and excrete them.

Tissues can't directly face air because they'll dessicate

Other systems involving air — respiration, nitrogen fixing and methanogenesis.

There is a film of fluid on the cells of alveoli. So, technically those cells breathe through the fluid and not directly.

In root nodules of leguminous plants, bacteria – endosymbiotic cyanobacteria is in the cells that have nitrogenase that convert $N_2$ to soluble nitrogen compounds that can be used.

The nodes have many zones – the bacteria is in vacuole. Is the access control of $N_2$ unit the root nodule?

$O_2$ and $N_2$ are pretty inert – they can't modify biomolecules like other chemically active gases like NO or $H_2S$. So how do these gases get recruited into biochemical processes?

These gases can bind to metals! There's an evolutionary convergence in humans and bacteria –
haemoglobin – Fe Nitrogenase – Fe, Mo, V

In cellular respiration, glucose is oxidised. In balance, something needs to be reduced.
Fe (?) acts as final $e^-$ acceptor.

This need not involve gases – so respiration i.e. breaking down bonds to make ATP is free of gases.
But if its $O_2$ dependent, its called aerobic and anaerobic is independent of $O_2$.

16/3

Lecture 16

$N_2$ fixation – only observed in cyanobacteria
In plant roots, an organ system is formed by integrating cyanobacteria as endosymbionts.
But unlike mitochondria, they're still autonomous – not completely part of plant root cell.
This is despite the advantages (massive!) that it confers – it's remained specialised to plants

Breathing pure $O_2$ causes lung failure because of reactive oxygen species (ROS) simulating inflammatory reactions and degradation, disrupting biological proceses by reacting with cells.

Too much $N_2$ — not like excess oxygen; this increases in conc. and causes air embolisms in human body. It doesn't react like $O_2$ because $N_2$ is very inert.

This takes us to how organisms handle oxygen.
The cells take in $O_2$ from fluid layer outside the cell by diffusion which in turn diffuses into fluid from air. Thus a gradient is set up.

We're going to consider multicellular animals (metazoans)
Multicellularity — features of this are :-
- Specialization : one cell can't do the work of another
- Spatial heterogeneity — cells proliferate and form local lineages which perform same function. same specialisation.

But for the organism to function well, the tissues communicate with each other.
The metazoan body design evolutionary progress goes from colony-esque to highly mutually dependent organ system. The communication (by chemical signals) is possible because all cells are bathed in a body fluid that needs to move to provide directionality and efficiency to signalling.

Also, acquisition of extensalities and excretion are specialised functional requirement hooked onto some connected pathway on this fluid cycling system

Lecture 17



Functional anatomy of respiratory system involves processes to pick up, utilize and remove $O_2$/$CO_2$.

Metazoan body plan - directional circulation of body fluid transports oxygen.

But $O_2$ needs to diffuse and solvate into the fluid. So this rate of diffusion gradient sets up major limits

In aquatic system, water is continuously flowing, so $O_2$ is available to organisms. But if the flow of water is too fast against gas-exchanger surface, then that is also counterproductive

This applies even to the rate of flow of body fluid. How much flow is enough flow? - core of functional anatomy in metazoans.

→ Simplest model of gas exchanger - the whole body surface exchanges gas and $O_2$ diffuses around the body and is sufficient.

Conditions - stable and a pretty low oxygen demand.

→ The move from this to a specialised organ is a result of larger body size and specialized functions that require more energy at some times.

→ One of the ways of increasing efficiency of system is to increase surface area of gas-exchanger. This is done by increasing folds - evagination and invagination.

Having evaginations is useful when the medium surrounding it is water. But if the surrounding medium is air, then the folds dry up very fast (unless amphibuous).

But in terrestrial metazoans (who are compelled to create invaginations), the bottleneck that is created is the passage of air.

→ Circulation

This is the next problem.
The simplest model is moving some muscles and moving the fluid around irregularly.
The next stage is having a pump that pushes fluid. In open circulation, this is directionless and not very efficient.
Closed circulation helps with that — creating directionality and increasing diffusion gradient.
But the design problem with this are —
- increase in respiratory phy — the no. of layers that $O_2$ needs to cross to get to the plasma/blood.
- Ventilation/perfusion ratio — Its used to assess the efficiency of air that reaches alveoli and blood that reaches the alveoli via capillaries.
Ideal value would be closer to 1 : 1L of air has 210 ml of $O_2$ and 1L of blood has 200 ml of $O_2$
Usually its about 0.8 taken as a whole.

19/8

## Lecture 18

Gas exchanges organ
Most efficient circulation system (directional flow driven by regular pumping of myogenic heart) can deal with a localised gas exchanger ~~or~~ organ
If the circulation is open, the gas needs to directly brought in contact with extracellular fluid directly. Here a localised gas exchanger won't work.

- On the other hand, the gas exchanger organ design model should consider the direction and velocity of flow of vascular fluid and surrounding medium.
- Mammal lung: expands and contracts to take air in to a blind space and let exchanges gases and lets it out. This has some problems - stretching alveli and surrounding lining.
- Bird lung: here, the perfusive and exchange function of lungs is seperated - the gas is exchanged at bronchial network and the air sacs control the ventilation and act (robustly) like bellows. The flow is unidirectional.

This very cool lung design is thought to be an evolutionary adaptation as a consequence of increased oxygen demand.

Cellular Respiration

Conceptual oddity: Glucose is converted to pyruvate in cytoplasm (only 2 ATP).

Then pyruvate goes into an elaborate, multi-step process that involves an electron transport chain which helps in establishing a proton gradient to generate ATP.

In aerobic respiration, $O_2$ is the final electron acceptor. In anaerobic, it can be anything else

Bacteria respire by creating a gradient in the PM - mesosome by creating a gradient in periplasmic space - between membrane folds and cell wall

The what about mycoplasma? (No cell wall)

Transporters

To make the ~~selection~~ circulation more efficient, some storage proteins (containing metal prosthetic group) got converted to transporter proteins.

Haemocyanin is a soluble globular protein in the plasma. Haemoglobin is a transporter packed inside cells.

A group of fish – Channichthyidae – crocodile icefish that live in Antarctica have lost haemoglobin. How? Adaptive? Consequences?

Lecture 19



What is physiology?

- How form and function come together, to respond to environment conditions and help sustain life

Study of biological processes — their function, how they operate under various environmental conditions and how they're regulated & integrated.

How does physiology connect different levels of organisation in biology?

Physiology: Tissue → Organism

Lower levels are studied to understand cellular physiology

Higher levels for comparative physiology, & how physiology affects population dynamics & interactions.

- How does evolution figure into this?

To understand the purpose of the processes, how they evolved & how it differs from other species.

Selection acts on organisms (phenotypes)

Physiology of Temperature

One of the most important abiotic factors that limits life on earth

Effects of T are universal and pervasive → influences processes occuring at all levels of organisation

Biochemical constraints on structure and function of proteins & membranes limit the absolute temperature range in which organisms can survive —

−15°C to 113°C

Temperature dependence of physiological processes is consistent with thermodynamic expectations ie. * Boltzmann - Arrhenius * formulations.

Look up: Metabolic Theory of Ecology

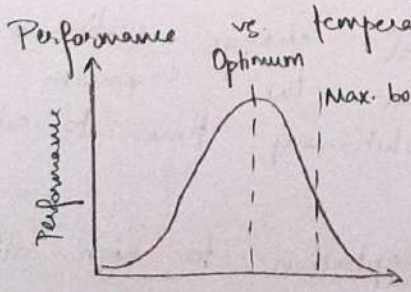
The thermal sensitivity of these processes are 'near' universal, with some variation.

Temperature effects
Molecular configuration
Enzyme reaction rates
Cellular function
Organismal ~~fun~~ performance (ant walking speed)
Growth, survival, reproduction
Body size
Population distribution pattern
Population growth, density
Speciation, extinction, species diversity

Temperature variation
There is periodic / regular variation and also a stochastic variation — all organisms have to learn to adapt to it.

- Diurnal, seasonal
- Latitude, Altitude (0.5-1°C with 100m increase)
- Proximity to ocean; ocean currents
- Aspect: Northern vs. Southern slope
- Microclimate: canopy position, topography

Eg: Desert with trees landscape: Variation
Seasonal: 70°C
Diurnal: 50°C
Between patches: 40°C




Organisms function best across relatively narrower ranges of T that they experience in their natural environments.

Lecture 20

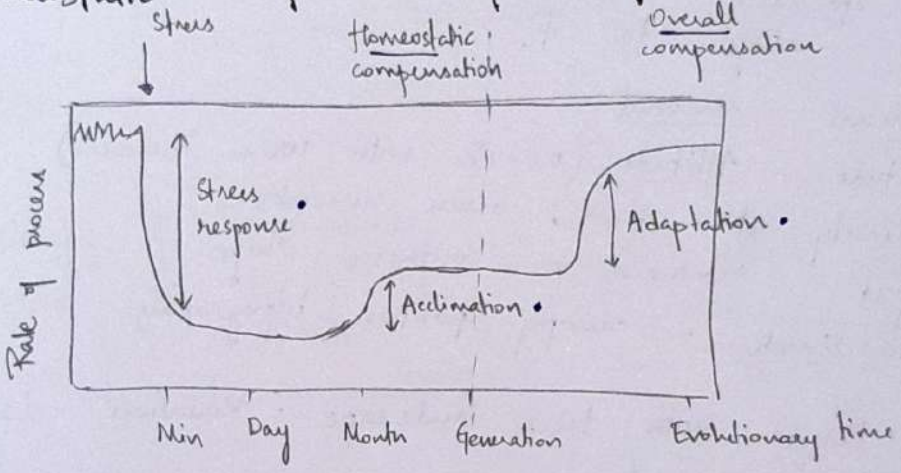


Maintaining internal T is important for organisms
They do it through homeostatic mechanisms which usually involve negative feedback loops.
i.e. perturbation away from set point results in corrective action that tries to bring it back to the set point through effectors.

Too hot : increases blood flow & sweating
Too cold : constricts blood vessels and causes muscles to start shivering

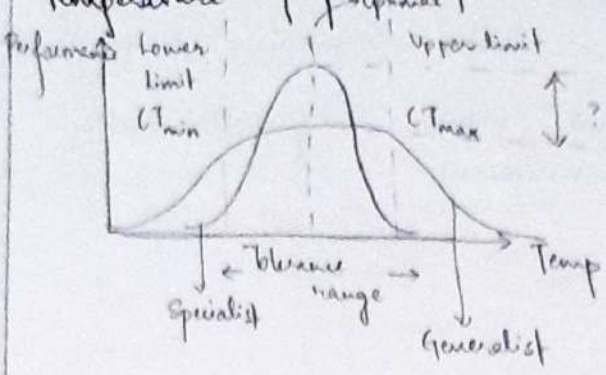
Thermoregulation is linked to form, function and behavior (integrated).
Body mass / form - affect heat transfer
Behavior - regulates choice of ext. environment (Lizards basking in the sun)
Above and over this, physiology can regulate heat generation and loss.

Homeostatic compensation of biological process




Homeostatic compensation - in the context of lifetime of an organism
But when the environmental change continues over a very long time, then the organism can change over evolutionary time to adapt to the surroundings
Eg: Response, acclimation & adaptation to high altitudes.

## Temperature performance curve




Typically: Bell-shaped unimodal curve

$CT_{min}$ critical thermal minima. Below this, the process cannot occur

$CT_{max}$ critical thermal maxima

A generalist species, that can withstand a greater range of T has a wider niche breadth.

So, there are thermal niches.

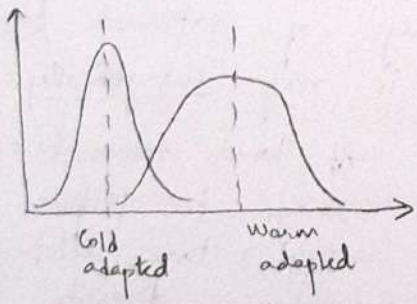
(?) The performance trade-off b/w generalist & specialist species?

Most reaction rates increase with T, then put together, why does the organism show a bell-shaped performance curve?

We see that most enzymatic processes have a similar curve i.e. they have an optimal range.

The LHS of curve is thermodynamics. The decrease in performance in RHS is because enzymes get denatured at higher T.

Its not because of reversability.




Studied in ants in different habitats.

Trade-off thing:

T costs to maintaining wider thermal breadth can come in form of reduction in overall performance. Maybe generalization leads to higher energetic cost; or enzymatic fn over a range of T might lead to poorer substrate affinity

# Thermoregulation

Terms:

Body T
- Homeotherm : regulators
- Poikilotherm : conformers
- Heterotherms : they can switch regulation temporally / spatially

Source of heat
- Endotherm : generate heat within body metabolically
- Ectotherm : rely on environment

Range of T & Strategy
- Eurytherm - Generalist
- Stenotherm - Specialist

Heterotherm
They choose to regulate internal temperature either spatially or temporally.

Eg: Tuna fish : they have certain darker muscles (with increased mitochondria & haemoglobin) that generate heat. These muscles are used to increase speed of swimming

Bees and moths show similar spatial heterothermy in their thorax muscles

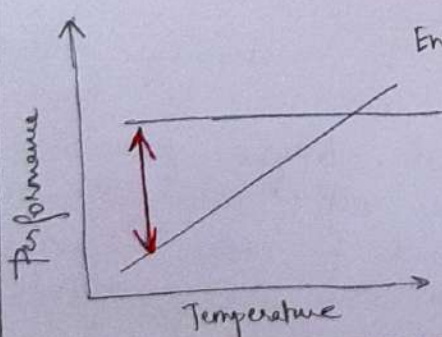
Temporal heterothermy - hibernating animals significantly decrease their T.

Ectotherms - can perform well in a wide range of internal temperature

Endotherms - they can maintain T and hence do well in a wide range of external temperatures

But this strategy is very energetically expensive ★

At lower temperatures, endotherm manage to perform much better than ectotherms. So, endotherm diversity is greater at the poles, while ectotherm distribution is more near the equator / sub tropical regions.




★ Heterotherms fall in between.

Lecture 21 8/4

Heat budgets

Heat generation and loss determines body temperature

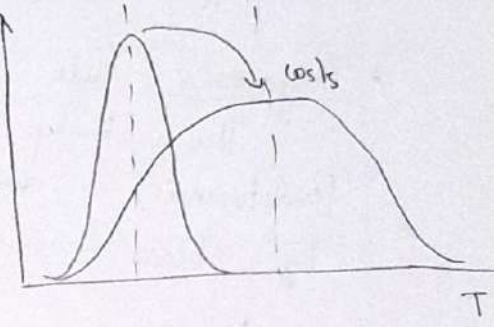
→ Performance gap b/w specialist and generalist species:

If the temperature of surroundings increases, the organism adapts by changing its thermal performance curve

When $CT_{max}$ is pulled to the right, the $CT_{min}$ is also pulled because enzymes are constrained to work in a particular T range.

If the organism wants to maintain a wide range of temperatures, then it incurs costs which reduces its performance

But why?




Heat budget

Body T is a balance between internal heat generation and heat loss.

Methods of heat transfer - conduction, convection, radiation & evaporation b/w organism & surroundings

Leaf energy budget -

$R_{abs}$ = E + C + Remit

Absorbed shortwave — Latent heat flux (Transpiration) — Sensible heat flux (Conduction convection) — Net longwave (Radiation out)

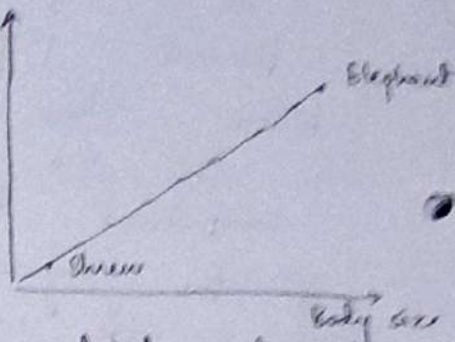
So we can treat it as a biophysical process and calculate leaf T & plot it against T

We see that leafs can regulate their temperatu

Heat exchange mechanisms

1. Behavioral avoidance - first line of defense
   Both endotherms and ectotherms use
   Some terrestrial invertebrates change postures to max/min absorbance

2. Body size and form
   Body size, energy and metabolism, & body temperatures are intricately linked
   The slope of linear relation is < 1.
   ⇒ Shrew has higher relative BMR as compared to elephant




★ Bergman's rule
The body size of closely related [endothermic] animals increases with latitude
Eg: Bears

Equator → Pole

Sun bear | Black bear | Brown bear | Grizzly bear | Polar bear

Body size →
Heat loss ←
Surface Area / volume →

★ Allen's Rule
Extinities (ear, paws) and latitude — the size of extinities decreases with increasing latitude
Eg. Rabbits, foxes
They're optimized for heat loss (large ear) or heat conservation

★ Insulation

Major thermoregulatory adaptation in endotherms — fur, blubber, feathers insulates the organism.

Its specially important for marine mammals and animals that live in cooler environments.

Even insects have a dense, fur-like coat (bristles)

In plants — hair & puberence, thick cuticular layer

3. Circulatory mechanisms

→ Countercurrent exchange — arrangement of blood vessels in mammals & birds, especially at extremities

It transfers heat between fluids flowing in opposite direction and reduces overall heat loss

→ Cooling by evaporative heat loss

Animals lose heat through evaporation of water through skin.

Why not behavioral?

Panting increases cooling effect in birds & mammals

Some bathe their skin in water to help cool.

Gular flutering : vibration of throat tissue which rapidly pumps air back and forth — efficient way of evaporative cooling.

Transpiration — major thermoregulatory mechanism for leaves

4. Adjusting metabolic heat production

Thermogenesis : adjustment of metabolic heat production to maintain body temperature

It's increased by muscle activity — moving or shivering

Non-shivering thermogenesis : hormones stimulate mitochondria to increase their metabolic activity

Eg. Brown adipose tissue in mammals.

- Ectotherms can also shivers to increase body T —
  - Snake contracts its muscles to produce heat and incubate the eggs
  - Moth - rapidly flutters its wings as pre-flight warm-up This increases the T of thorax to be ~10°C greater than abdomen T
- In plants — Skunk cabbage
  It generates heat (in mitochondria) so that its T is 15 - 35°C above air T In spring, it melts the ice around itself and grows shoot earlier.
  Has thermoregulatory ability.

## Energy budgets and allocation

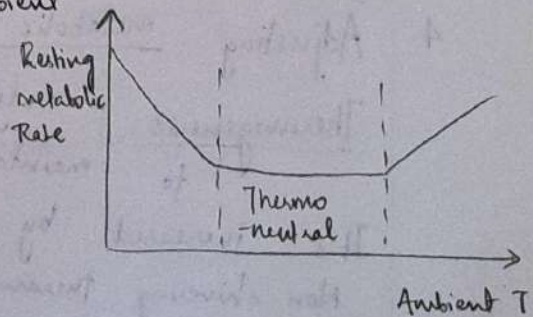
Energy requirements of an animal are closely linked to body size, activity and environment

Energy is partitioned to growth, maintainence, reproduction
↳ BMR + thermoregulation

Endotherms have to spend more energy per body wt because thermoregulation is expensive — especially for smaller mammals.

* Thermoneutral zone *: Range of ambient temperature within which, metabolic rates are minimal.

Outside, energy is spent either to prevent heat loss or promote evaporative cooling.



Lecture 22

Torpor and energy conservation

- Physiological state in which activity is low and metabolism decreases, enabling organisms to save energy while avoiding extreme conditions.
- Hibernation: long term torpor in winter – avoid extreme cold and food scarcity
- Aestivation: summer torpor – avoid high T & scarce water
- Daily torpor is exhibited by small mammals and birds, seems adapted to feeding patterns.

Acclima(tiza)tion & Thermoregulation

Birds & mammals can vary their insulation to acclimatize to seasonal temp. changes

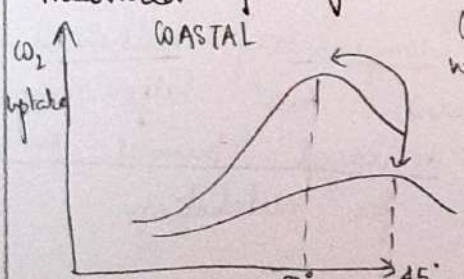
When T is <0, some ectotherms produce antifreeze compounds to prevent formation of ~~heat~~ ice.

Body T is controlled by hypothalamus – triggers heat loss / generating mechanisms.

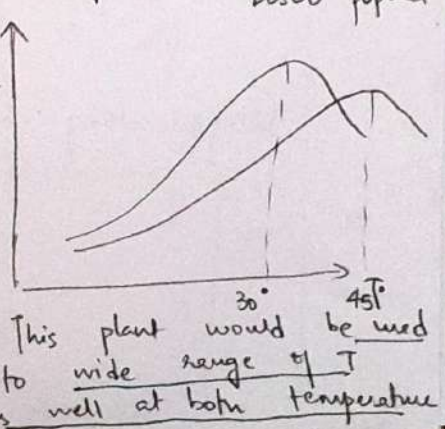
Fever: result of change of set-point for a biological thermostat, to increase metabolic activities.

→ Eg: Atriplex (salt bush) – found in western coast of America

They grew the plants in low T & high T and acclimated them. Then they measured photosynthesis uptake.




Coastal population would be used to cooler climate
⇒ wasn't able to acclimate to hot T.



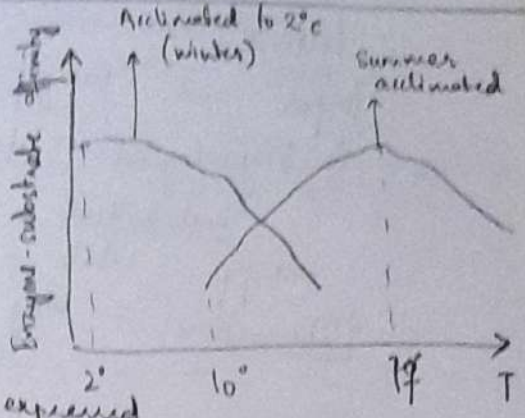

This plant would be used to wide range of T
⇒ Does well at both temperature

→ Enzyme activity in trout

Rainbow trout – cool streams

winter T : 0-4°C

Summer T ~ 20°C




Two forms of acetyl cholinesterase

We can see near-perfect compensation in the graph.

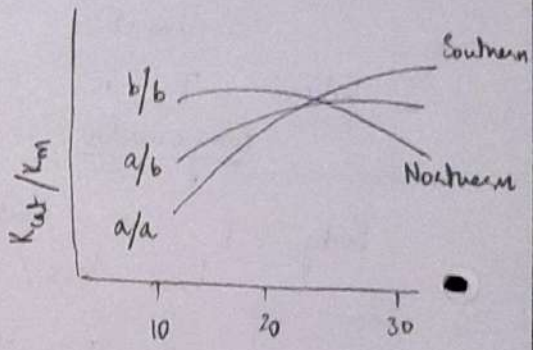
→ Differentially the 2 forms are expressed based on surrounding T

→ T adaptation of enzymes – lactate dehydrogenase alleles

In fish Fundulus heteroclitus, the populations are distributed along East coast (~ 10°C difference in water T) such that allelic distribution of LDH are related to water temperatures

$K_{cat}/K_m$ – measure of efficiency of the enzyme

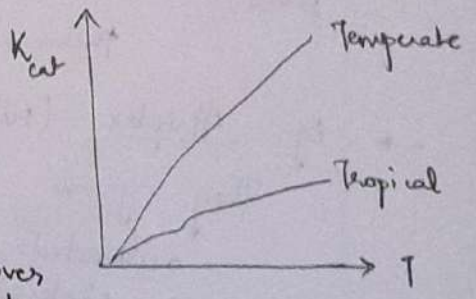
Northern enzyme did better at lower T & vice versa



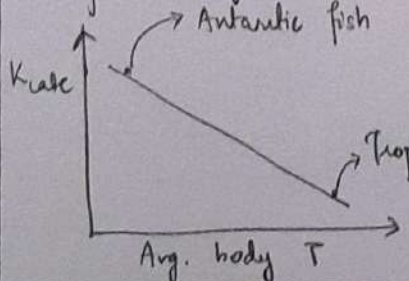

→ Somero example

$K_{cat}$ : catalytic turnover of enzyme increases with temperature

But steeper increase in temperate fish & lower in tropical ones




Compensatory adaptation of enzyme turnover rate thought to be a compensatory mechanism – ↑ increased $K_{cat}$ helps compensate for decreased thermal energy available for metabolism



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Lecture 23

Climate change and Temp. adaptation

Global warming

Its unequivocal happening due to the greenhouse gases. ⇒ Sea level is rising and snow covers shrinking.

Multi-model averages and observed rates - best case worst case.

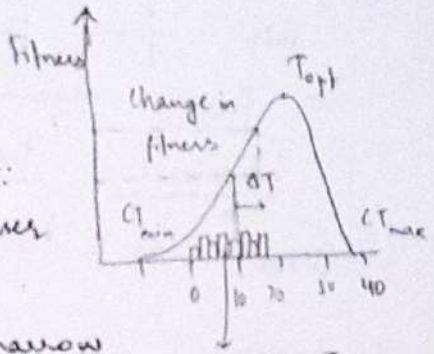
There are impacts on various fields (food, water, extreme events) but we're focused on its effects on ecosystems

Coral reefs will be affected with just 1°c rise

Not just increase in mean T, but the time spent by animals in relatively hot weather will also increase.

Paper: Impact on terrestrial ectotherms across latitude (36 insects)

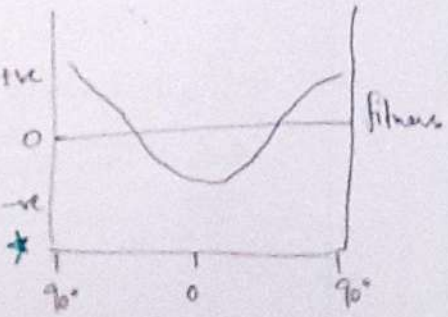
From the graph, we can see that temperate insects increase their fitness with global warming ∵ their habitat temp is much lesser than $T_{opt}$




But tropical insects have a very narrow range of T and their habitat T is closer to $T_{opt}$. So increase in T will negatively impact their fitness

Similar trend is observed in other ectotherms

* Absolute change in temperatures is predicted to be higher in higher latitudes.



The study doesn't account for other factors that may affect their fitness like competition.

Also, another assumption : air T = body T for ectotherms but this always needn't be true.

The organism may regulate (to some extent) by behavioral and physiological methods.

Follow up study – 2014

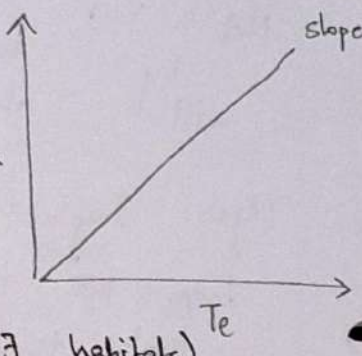
Thermal safety margin : $CT_{max} - T_e$

$CT_{max}$ : critical thermal maxima

$T_e$ : effective body temperature

If $CT_{max} < T_e$ ⇒ thermal danger zone (effective T is greater than the $T_{max}$ it can handle)

$CT_{max} > T_e$ ⇒ thermal safety zone




Usually, $T_e > CT_{max}$ for insects, amphibians & reptiles.

This gave them lower safety margins

⇒ These organisms must rely on behavioral thermoregulation (assuming ∃ habitats)

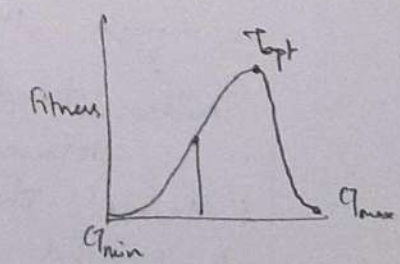
Same as before, more negative effects in tropics

Questions: Asymmetric → True for most biological phenomena. nature of performance curve

Advantage to maintaining $T_{opt}$ at temperature higher than average habitat T?

Why choose habitats with T less than $T_{opt}$?

Maybe bcuz in case of perturbation, they won't face a steep drop on either side.



Challenges faced by mammals in drylands due to climate change (2021)

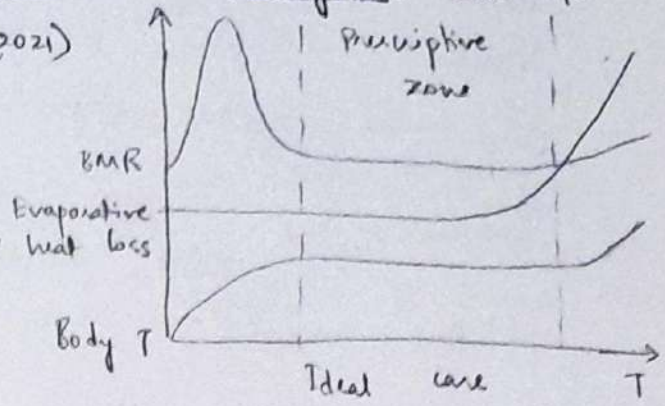
→ No water

Evaporative cooling decreases

⇒ Body T increases faster

So the prescriptive zone shifts leftward

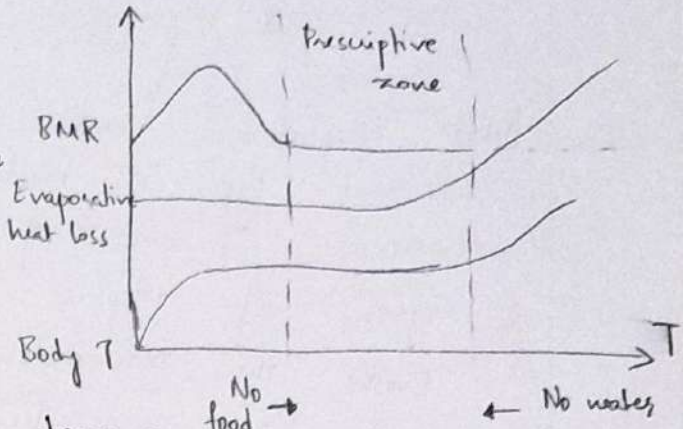
Performance decreases at higher T




→ No food

It decreases BMR at lower T. So body T can't be maintained

⇒ Performance decreases at lower T




→ Combined effect of both decreases the prescriptive zone significantly

Thermal safety margins of leaf function of deciduous and evergreen trees.

There are varying differential effects

But more productive tree species have lower thermal tolerance and less productive ones have higher limit.

⇒ Global warming affects more productive trees more.

Biological mechanisms – Species interaction, evolution, environment, physiology, demography, dispersal

$\eta = \frac{K_{cat}}{K_m}$ indicates how velocity varies acc. to how often E & S combine

10/4

Lecture 24 - George Somero

Molecular Adaptation to Environmental Stress

Deep Sea - Two physical challenges : Temperature (4 - 130°C)
Pressure (1, 100 atm)

Intertidal Zone - T : -5°C to 35°C
Snails, limpets & mussels

Hottest animal : Snail in China - 55°C.

Biounity - Same metabolic pathways
all organisms use mostly the same macromolecules

Q: What adaptations enable organisms to carry out the same types of biochemical functions across enormous range of physical stressors?

2 types of adaptive solutions -
Evolve the macromolecule
Change the micromolecular milieu (in which macromolecules are working)

Macro - filamentous & Globular protein

Micro - Inorganic ions, water (background) & Organic osmolytes
low mol. wt. organic molecule that contri-butes to osmotic pressure & plays other imp. roles eg. stabilization of proteins
Eg: urea, carbohydrates, free aa, methylammonium (TMAO)
* All except urea stabilise proteins *

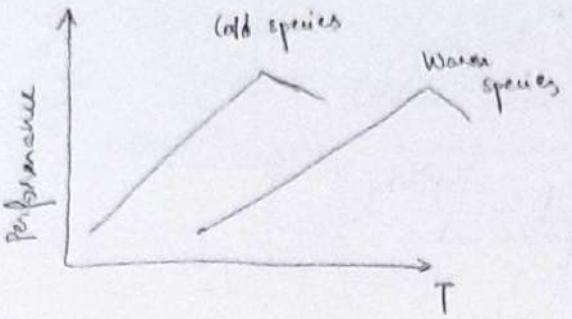
Micromolecules make up the bulk of the cell, but without studying them, we'll never understand the full story of adaptation, & acclimation.

$K_{cat} = \frac{V_{max}}{[E]}$ $K_m = [S]$ at $\frac{1}{2} V_{max}$ $V = \frac{V_{max}[S]}{[K_m] + [S]}$ $V = \frac{[E]\, K_{cat} \cdot [S]}{K_m + [S]}$



Temp Range of life: -70°C to 130°C

Pattern → "Gestalt" of T adaptation



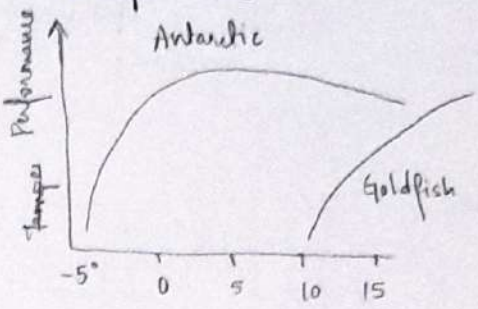

Thermal optimal and tolerance limits differ adaptively

Eg: Cardiac thermal tolerance in tropical & temperate snails

Rates show adaptive compensation to temperature

The rate of metabolism or performance of organisms is more or less the same in their habitat T, regardless of its absolute value

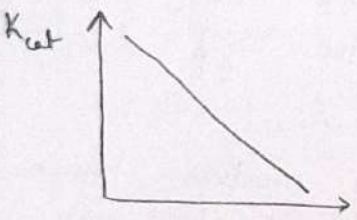
Why?




What is the underlying biochemistry?

To increase rate, we can either increase [enzyme] or $K_{cat}$. $V_{max}$ = Rate = $K_{cat} \cdot [E]$

*Enzymes of cold-adapted species work faster*

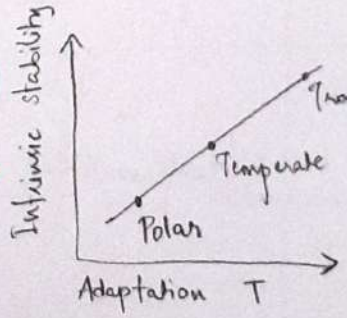



LDH molecules of Antarctic fish is 4-5 times faster than the LDH of birds/mammals.

Why should mammals have lost their $K_{cat}$?

1. Corresponding States

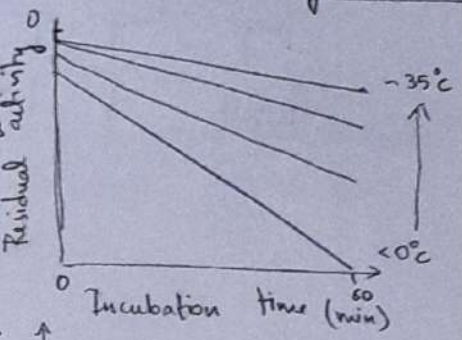
Natural selection favors modification of protein structural stability so that intrinsic stability is positively correlated with adaptation temp.



Loss of activity during in-vitro heating

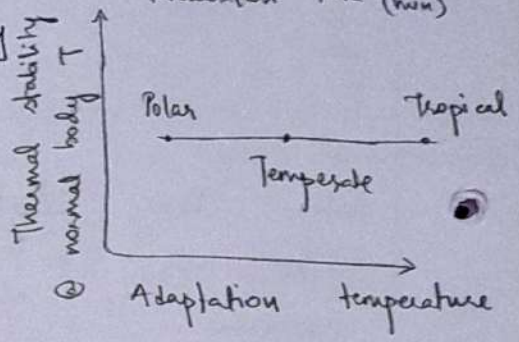
Intrinsic stability (sort of inverse of how quickly protein degrades) is a measure of 'toughness' of proteins

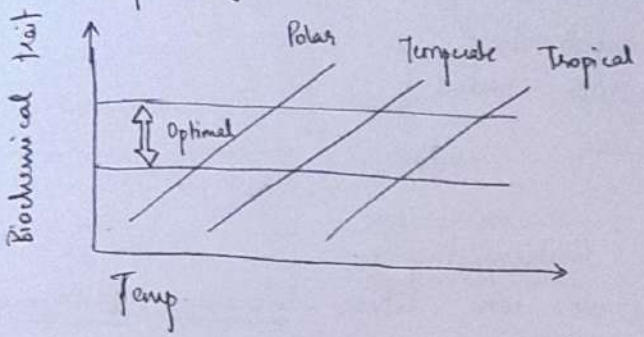
The hotter you live, the tougher are your proteins (remain stable)




⇒ A 'corresponding state' of stability is found across species at their normal body T

Similar stability at normal operating temperatures.




Adaptation must conserve traits in optimal range

Why should it matter to proteins?

∵ Structural properties of macromolecules ~~the~~ must be retained within a mid range [Golden mean paradigm]
i.e not too flexible, not too rigid

Marginal stability - Golden mean paradigm

* Biochemical function normally involves changes in conformation — true for all big molecules
i.e: rigid enough to maintain basic 3D structure
yet flexible enough to allow needed changes in conformation to occur during function
* Conformational changes — Rate limiting steps in catalysis
⇒ Rate of function ∝ Flexibility

$k_{cat}$ Rate at which substrate is converted to product per active site

By the $k_{cat}$ data, we can say that cold adapted organisms have more flexible structures

This also somewhat explains the thermal adaptation curve — but adapted animals have rigid proteins ⇒ can withstand larger range of T (heating)

Are functionally important regions more flexible than others?

Molecular Dynamics Simulations (MDS)

In silico predictions of T effects on protein structural movements — backbone & sidechain

- Side chain movement is highest in binding and catalytic sites

How does flexibility of these regions vary with adaptation temperature?

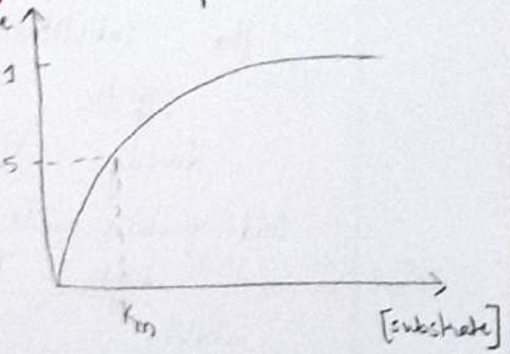
Cold species has greater flexibility in regions ("hinges") that govern movements of binding & catalytic * regions ("doors").

Flexibility is inversely related to adaptation temp.

Ligand binding by Enzymes

$K_m$ - conc of substrate

Michaelis-Menten constant at which reaction rate is half-maximal




Low $K_m$ ⇔ high binding ability

Binding ability decreases ($K_m$ ↑) with rise in T.

Thermal distortion of binding site leads to decrease in the ability to recognise & bind substrates

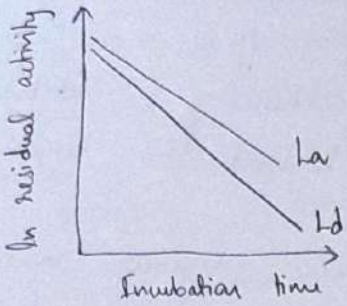
Corresponding states — Binding ability ($K_m$) is conserved at the habitat T range of the organism

[Similar to fig. 3 in Pg. 56]

How are corresponding states conserved?

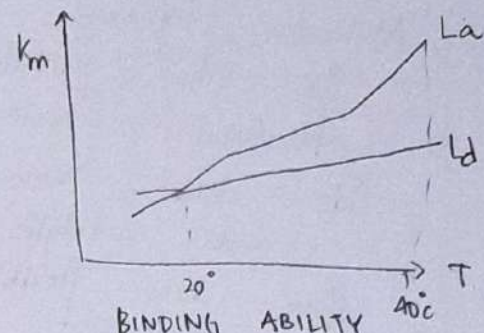
Example: Malate dehydrogenase (cMDH) in cryptic congeners of limpets

Lottia digitalis - cold adapted
Lottia austrodigitalis - warm adapted
} Found in west coast of N. America




THERMAL STABILITY

of "hot" cMDH is greater than "cold" cMDH




BINDING ABILITY

Binding ability lost rapidly at high T in cold-adapted species

1. How many aā substitutions?

333 aā in sequence

3 more H-bonds in La ⇒ "hot" cMDH is tougher

Glycine → Serine

2. Where do the substitutions occur?

The substitutions occure in 'hinge' region i.e. affects flexibility of mobile region that moves during binding

Cold-protein is more flexible ⇒ $K_m$ is high at high T values thus reducing binding ability. Denaturation is also more likely

3. How (mechanistically) do these changes lead to adaptation in stability and function?

## Protein Adaptation

- Corresponding states of marginal stability at normal body T * result from protein evolution *
- functional properties ($K_{cat}$ & $K_m$) are conserved at body T
- Minor changes in aa sequence are enough to achieve these adaptations.

## Change in micromolecular milieu

Focus on organic osmolytes – affect protein stability

But do they provide a 'global' solution for coping with physical stress?

Hypothesis: Titrating stability with osmolytes could sustain corresponding states – correct marginal stability of structure in face of stressors

global ⇒ a given perturbing osmolyte has similar effects on all types of proteins

Organic osmolytes have different effects – (super-stabilisers) are accumulated by extremophiles.

DGP, DIP – super-thermoprotectants – strongest protein stabilisers yet known ↘ very very high T

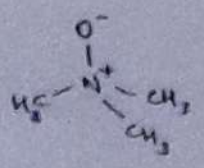
↳ Archea – A. fulgidus

## Hydrostatic Pressure

Biological effects:
- Compresses volume of cell
- Perturbs protein function (increases $K_m$)
- Perturbs membranes
- Alters gene expression.

- Paul Yancey

A 'global' solution to high pressure —
TMAO : strong protein stabilizer
≠ Used by sharks to offset urea's denaturing effects



TMAO conc. rises regularly with depth
It's true for both fishes and invertebrates
If increases in same fish as they mature and migrate to lower depths.

High P also increases $K_m$ → of 250 atm
Addition of 250 nM TMAO restores $K_m$ to 1 atm value

Conclusion : Conservative nature of molecular adaptation
Organisms are very similar despite very different working conditions.

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Lecture 24

Integrative ~~System~~ Control

Homeostasis — coordinated response that requires integrative control in the organism.

Long distance cell to cell communication (eg endocrine) is essential for multicellular & unicellular organisms & this is how responses are coordinated
≠ Nervous system is another way.

Cells communicate via chemical signals
Eg: Quorum sensing in bacteria
Mating cells in yeast (a, α) produce pheromones

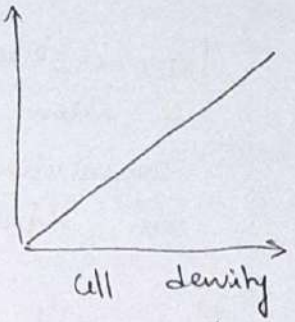
Hawaiian bobtail squid
Hunts at night — shadowless : the top surface figures out the ambient light and bottom surface produces the same amount of light to become shadow-less

# Fick's law of diffusion – 1 Things diffuse from high → low conc
2 Diffusion ∝ surface area / distance to travel

AIP : Autoinducer peptide

The squid harbors bacteria called Vibrio fischeri
When grown in a culture, and when they sense a certain concentration they start to fluoresce

Basic principle
The bacteria produce a compound called autoinducer
In low density, autoinducer conc is low, so it doesn't do anything
In high density, the autoinducer high level is detected (high levels of autoinducer both within and outside the cell) and transcription of luciferase (& possibly other genes) is increased when autoinducer binds to its receptor inside the cell.




Gram -ve bacteria – very thin peptidoglycan cell wall
⇒ doesn't retain the stain
~~V fischeri~~ is Gram -ve ⇒ autoinducers can simply diffuse out
Gram +ve bacteria will have to opt for active transport across a channel and if has to have the receptor on the outside which triggers downstream processes when activated

Evolution of multicellularity results in a rich diversity of life forms

Advantage
- ✓ Division of labours which allows you to expand into new niches
- ✓ Extended life span
- ✓ Increase in size of organism

Rate of diffusion is limited by Unicellularity

Central requirements of multicellularity —
- Cell - cell adherance
- Cell - to - cell communication

Adherion in organisms -
- Plants : middle lamella enriched with modified pectin that keeps cells bound
- Animals : homophilic and heterophilic interactions of membrane proteins.

There intercellular matrix / basement membrane in animals allow cells to communicate through a concentration gradient because the matrix can trap the signaling molecule.

Local and long distance signaling

Local
- Direct cell - cell contact
- Chemical signals secreted that activate the same cell or neighboring cells (autocrine / paracrine)
- Cells may have direct access to cytoplasm of neighboring cells - plasmodesmata / septal pores / gap junction.

Long distance
- Modifications like membrane nanotubes (run for ~100s μm and allow exchange of signalling molecules & organelle) and exosysts (signaling molecule / even RNA, DNA are packed into membranes and transported)
- Chemical signal maybe transferred at specialized, local sites (synaptic) via specialised cells that form a network / relay (nervous)
- Signals can be sent via circulatory systems (which is essential for big ~~multi~~ metazoans)

Endocrine system in animals

Lecture 25

Signalling

Target cell has receptors for chemical signals and its further transduced inside the cell.

Recall local and long distance signalling

Once animals get bigger, than a few mm, they have to evolve an active circulation to transport signals

Plasmodesmata - not a passive tunnel, it has a selective filter that can deal with bacteria

But a defense to stop viral infection is when the plant kills the cells around the infected cell.

Gap junction: Protein 'tunnels' / connections between cells
Very small opening - only allows water, ions and small molecules

Mammals - closed circulatory system
Body / tissue is bathed in tissue fluid

Xylem and Phloem
↳ solid column of water. Experience high radial pressure, so the cells are thick - lignified

Signalling in plants

Plants are sedentary

It receives spatiotemporally diverse stimuli

Stimuli can be local but adaptive response maybe necessary in a distant part

Wounding due to herbivory

Plant senses tissue damage and responds with a plant-wide adaptive response

Common response is upregulation of Jasmonate which in turn upregulates defense genes

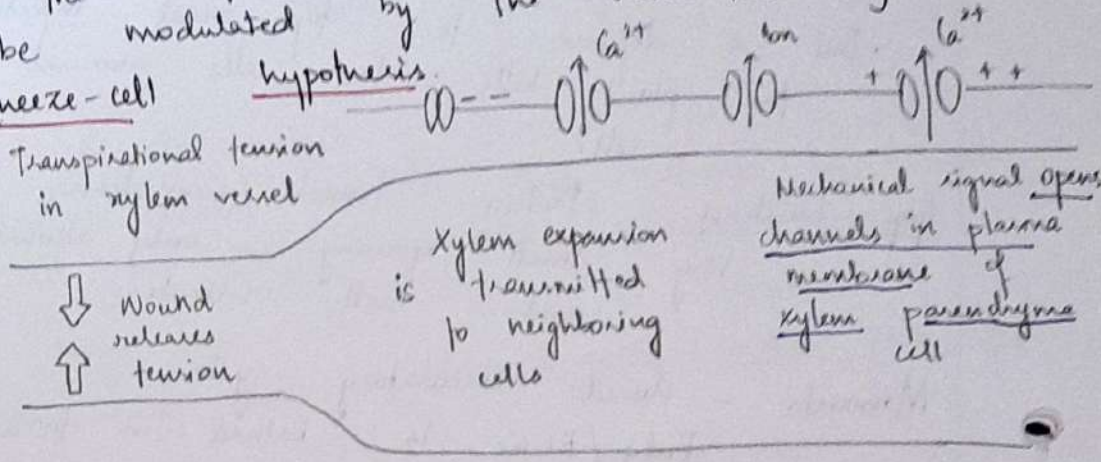
# Wound → JA in entire plant

It can induce defense molecules that block digestive processes in insects or release volatiles that prime defense in neighboring plants

How to mount a rapid response? (~ $10^8$ nm/s)

Transport of molecules in xylem / phloem ~ 300 nm $s^{-1}$

But the response needs to be faster. It could be modulated by the vasculature by squeeze-cell hypothesis




When the channels open, $Ca^{2+}$ and $Na^+$ rush in and make the inside of cell positive.

Electrical signal like an 'action potential' can propogate across cells through plasmodesmata (cm/s to m/s)

Wounding in the cells also releases the $Ca^{2+}$ stored in the vacuole. This also triggers a wave of electrical signal ~ 500 nm/s

This is hypothetical / potential speed

Plant - Fungi - Plant communication

Mycorrhizae : symbiotic relationship

Below the soil, the network / mycelium of fungi is connected with roots of plants and trees. This network facilitates easy absorption of water, and ions from soil by roots (w/ help of mycelium) and the fungi gets nutrients in return.

But this network can transfer N, C, water, P, defense molecules, allelochemicals, kin recognition information, genetic material between plants & fungi and b/w plants & other plants through the fungi !!!

Eg: Fungal carbohydrates, amino a, lipids, N ions, phosphates and phytohormones (auxin, jasmonates)

Wood wide web — Analysis of these networks throughout the forest has revealed motifs, mother trees and how their connection with their 'daughter trees' i.e kin strongest.

These networks have different features in tropical and temperate climate, which is being affected ∵ climate change

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Lecture 26

Nervous System - CNS & PNS

- Mainly made of neurons
- System helps maintain and regulate homeostasis

In very small organisms, diffusion is fast enough to transfer & regulate information

Due to their size, eukaryotes, even paramecium has electrical signalling i.e. very fast response.
Even plants have relatively decent coordination and response

Nervous system allows organisms to respond with rapid and highly coordinated movement.

Sea squirt - Tadpole → Sedentary animal
As adults, they digest their own nervous system

In Cnidaria, specialised cells are evolved -

* • highly polarised - signal on one side, transmission on another
  • high speed information propagation
  • Allows fine control

This is true of neurons which are specialised for electrical signalling over long distances

Glial cells - regulatory, support cells

Neurons form extensive circuits ⇒ they can affect effectors long distances away fairly quickly

Eg: Knee-jerk reflex circuit
From Patella to Spinal cord (sensory nerve), and from spinal cord to quadriceps and hamstring muscles (motor nerve)
This circuit has a wired component (action potential) and a wireless component (synaptic transmission).

Action potential

Neurons have a resting potential : ~ -70 mV i.e. inside of cell is more negative than outside

When negative current is injected, cell becomes hyperpolarised, but comes back to resting potential in some time

When positive potential (> −50 mV) is induced through positive current, the membrane becomes depolarised, and above the threshold, the potential spikes to +40 mV and then comes back down.

This is called Action Potential and its an all or none phenomenon. This ensures that the signal doesn't fade out.

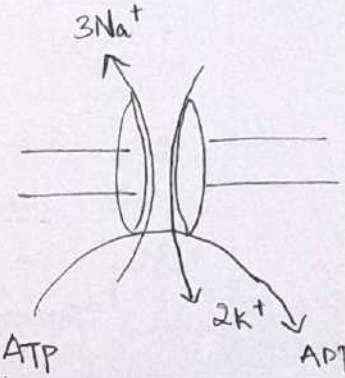
Unequal distribution of ions across membrane

| | Extracellular | Intracellular | Ratio |
|---|---|---|---|
| $Na^+$ | 145 | 12 | 12 |
| $K^+$ | 4 | 155 | 0.026 |
| $Cl^-$ | 120 | 4 | 30 |
| Anions (organic) | 0 | 100 | - |

This ionic imbalance is like a capacitor and its discharge is action potential

Resting membrane potential

This is mainly achieved by the Na-K pump and $K^+$ leak channels




The Na-K pump sets an electric gradient across membrane.

There are $K^+$ leak channels which allow $K^+$ to go outside i.e. along its chemical gradient but against the electrical gradient (its already positive outside).

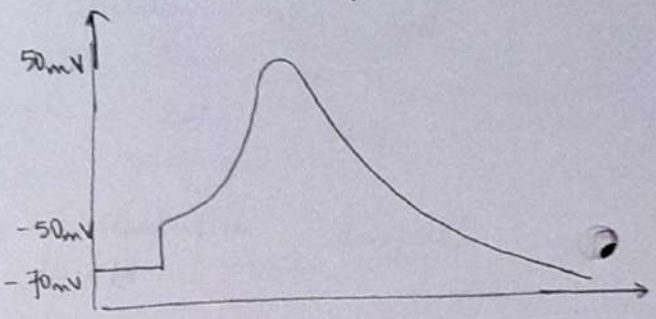
This equilibrates at ~ −70 mV.

(68) ⇒ Voltage gated $Na^+$ channels

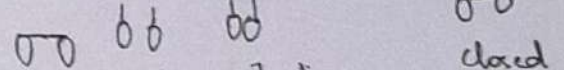
These gated channels are usually closed, but they open when membrane is depolarised to ~ -50 mV

A change of 20 mV over a membrane of 3 nm is an electric field of ~ 60,000 — HUGE.

When this amt of electric field is changed, the proteins in the channel (acting as dipole) change conformation and open.



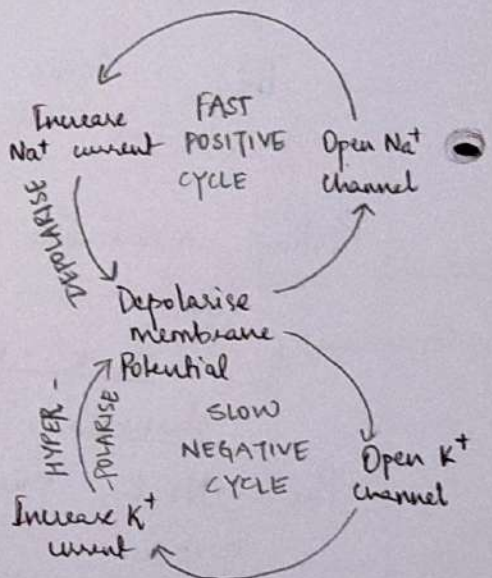

Because of chemical and electrical gradient, $Na^+$ ions rush in and creates a +ve environment locally across the membrane, taking the potential to 50 mV.




At one point, even though potential is 50 mV, the channels become inactivated and remain so.

⇒ Voltage gated $K^+$ channel

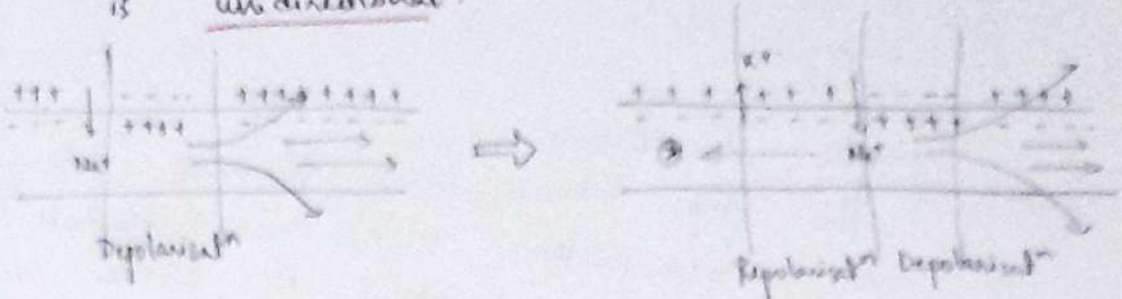
There channels open at +30 mV and allow $K^+$ channels to move $K^+$ from inside the cell to outside — due to chemical gradient; and locally as $Na^+$ ions rush in, there's a dip in +ve charge outside, which facilitates the movement of $K^+$ ions outside




This channel along with $Na^+$ - $K^+$ pump helps in repolarisation of the membrane

# Propagation of Action Potential

APs are regenerative and AP propagation is unidirectional.




- Since there is +ve charge in one segment, ∴ a current moves on the inside of the axon, depolarising the consequent segments so the action potential is regenerative.
- This current travels both forward & backward, but it can't trigger an AP in previous segment bcuz $Na^+$ channels there are in a refractory period i.e they're inactive for some time even if potential is > -50 mV
- Hence, propogation of AP is unidirectional
- If you artificially stimulate a signal in the middle of the axon, then the AP will go in both directions *
- Some neurons have insulation - Schwann cells filled with fat that covers the axon. So the signal moves rapidly from one node of Ranvier to the next at a speed of about ~100 m/s. This is called Saltatory Conduction
- This protects the membrane against leakage. so the current can travel longer distances

Lecture 27

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Another way of increasing length constant is by decreasing axial resistance - so invertebrates have very thick axons while vertebrates have insulation to increase the speed of propogation

Synaptic Transmission

The gap between axon terminal (rich in mitochondria and neurotransmitter vesicle) and dendrite / post-synaptic neuron (with receptors) is known as the synaptic cleft.

The axon terminals have voltage gated $Ca^{2+}$ channel which open when AP comes there. ($Ca^{2+}$ rushes in) This triggers the neurotransmitter vesicles to release their content into the synapse.

When they bind to the receptors, the ion channels (ligand-gated) open depolarising or hyperpolarising the cell.

Neurotransmitters

Small signalling molecules that help transfer information across a synapse

- Excitatory - Glutamate, acetylcholine
  They open cation channels, promoting depolarisation and generation of AP
- Inhibitory - Gamma aminobutyric aid (GABA), glycine
  Opens anion channels (mainly $Cl^-$ channels), so the cell becomes hyperpolarised, making it harder for AP to be generated

There are thousands of inputs (axon terminals) onto 1 neuron - both excitatory and inhibitory. If the sum of these inputs makes the potential go above -50 mV, then the axon fires.

Generation of AP also depends on -

★
- Geometry of network
- Timing of their signals
- Strength of signal

Graded Post Synaptic Potential (GPSP)

Summation of excitatory and inhibitory PSP - potential of post-synaptic membrane brought about by neurotransmitters

If GPSP is enough to depolarise the axon hillock to -50 mV, action potential is initiated.

Synaptic transmission i.e chemical signalling is the rate determining step. *

Another important aspect is the regulation of neurotransmitters. Some are degraded in the cleft while others are taken back up by the pre-synaptic neuron (reabsorbed) and reused or metabolised so that the transmitters don't linger there.

Many poisons / venoms act on neurotransmitter receptors. eg. acetylcholine receptor on muscle

Puffer fish, snake venom, Saline, selective serotonin reuptake inhibitors.

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There are different kinds of stresses.

Consider predator stress - physiological response - elevated heartbeat, rapid breathing, adrenaline release, increased alertness, digestive system shuts down → dry mouth

These responses are triggered by a wide range of stresses.

Stress response: an adaptation that allows animals to respond immediately, in a generalised manner, to a threatening / challenging situation

strong memory of intense emotional experience

Stress is perceived by the brain

Autonomic nervous System

Sympathetic NS

Sympathetic Adrenal medulla System

HPA Hypothalamus - pituitary - Adrenal axis

↓

Noradrenaline [Neurotransmitter]

Spinal cord → Adrenal medulla

↓

(stored) Adrenaline [Hormone]

+ 20% of noradrenaline

ACTH → Adrenal cortex

↓

Cortisol [Hormone]

Instantaneous

seconds - minutes

tens of minutes

- Cortisol helps in managing long-term stress

Amygdala - emotion processing center of fear, anger, anxiety

Stress information arrives at amygdala, it relays it to hypothalamus which activates the Sympathetic NS.

Autonomous NS does the following -

- Dilates pupils
- Makes the organism more alert.

SUMMARY

- It inhibits digestive processes
- Constricts blood vessels at skin — feels cold, and prevents bleeding
- Increases breathing rate and expand bronchioles
- Increases heartbeat and sweating
- Importantly, stimulates the release of epinephrine and norepinephrine — SAM (neuroendocrine system)

Epinephrine functions

1. Glycogen → glucose (inhibits insulin release & stimulates glucagon)
2. Increased BP, breathing rate, metabolic rate
3. Change in blood flow patterns — blood redirected to skeletal muscles, away from digestive system and skin.

HPA axis

Hypothalamus secretes corticotropin releasing hormone (CRH) which enters the blood and stimulates pituitary to secrete Adrenocorticotropic hormone (ACTH). ACTH acts on adrenal cortex and makes it release a no. of hormones — mineralocorticoids and glucocorticoids (Cortisol).

This helps in sustaining the response (not short lived) and amplification is possible

Long-term response

Cortisol : Proteins, fats → glucose (Gluconeogenesis)
Opposes insulin function
Facilitates vasoconstriction by epinephrine

Mineralocorticoids : Retention of $Na^+$ & water by kidneys.
Increased blood volume & BP.

CRH & ACTH act on amygdala & hippocampus and assists formation of memories of emotionally charged events.

ACTH promotes analgesia by increasing β-endorphins
In early phases, lower conc of cortisol and epinepheine stimulate the immune system
At late stage, during recovery, high conc of cortisol inhibits inflammation to protect tissues from an immune over-reaction.

Once stressor is removed, sympathetic drive diminishes. Short half-life (seconds) of epinephine reduces the response quickly

Cortisol → negative fredback on ACTH, CRH

Chronic stress can be maladaptive – heart conditions, diminishes reproductive function, anxiety, panic attacks

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Lecture 29

Biomechanics

Respones and adaptations of life forms to forces and displacements, and the generation of movement

Endurance running in humans

Evolution ? Adaptations ?

Humans are pretty good endurance runners.

Biomechanical adaptations for ER ?

Elite human sprinters : ~ 10.2 $ms^{-1}$ for 15 seconds
Mammalian ~~Marathon~~ runners : 15 - 20 $ms^{-1}$ for several mins

Endurance running is unique to humans among primates
Not common in mammals except in social carnivores (hyenas, dogs) & migratory ungulates (horses, wildebeests).

After running a while, these quadruples gallop (all 4 feet are not on ground) which allows them achieve high speed

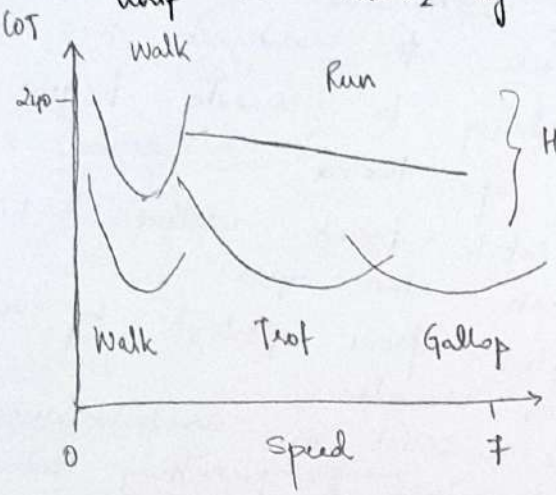
Running generates a lot of heat — the animals pant to release the heat. But they can't pant while galloping, so they overheat dramatically and collapse if pushed

If we compare normalized (to body mass) speed ranges, the quadrupeds gallop speed is within one 'jogging' speed.

Efficiency of running

COT: Cost of transport - energy efficiency of transporting an animal over a distance

Unit - ml $O_2$ $kg^{-1}$ $km^{-1}$




Walking efficiency U-shaped curve

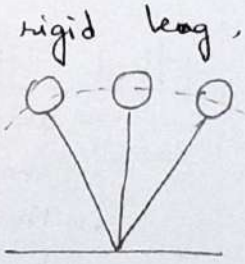
Human ER has a relatively high metabolic cost.

But - humans can access a larger speed range with little change in efficiency.

Walking

The centre of mass vaults over a rigid leg, like an inverted pendulum.

The PE and KE vary at different positions



Running - very different mechanism: more like a mass-spring style of running - bounce onto and off the background, using spring-like nature of tendons & muscles to act as

Spring-like nature of tendons & muscles act as shock absorber, followed by recoil from energy stored to drive us upwards and forward

Compared to chimpanzee, humans have 1. longer achilles tendon and 2. stabilized plantar arch which assist in shock absorption, storage and recoil.

Skeletal modifications

-3. Long legs increases stride length (not increasing freq)

-4. Expanded joints to reduce ground reaction force induced joint stress

- Compact foot with 5. short toes to reduce distal mass

-6. Adducted hallux (big toe) gives greater stability. but we've lost prehensility.

- For bipedal runner, there's a tendency to pitch forward of -7. massive development (hypertrophy) gluteal muscle to counteract this

- There's also a tendency to generate torque, so ∃ 8 counterrotation of thorax and arms

- a) humans can rotate trunk relative to hips more than other apes

- b) Head is decoupled from pectoral by reduction of shoulder muscles

- c) Wider shoulders assist in counterbalancing by arm swinging & permitting reduction of fore-arm mass.

-9. Head stabilisation in case of pitching forward

- a) Central attachment of neck to head
- b) Short snout
- c) Nuchal ligament connecting skull to vertebra
- d) larger semi-circular canals (for balance)

Having a stable head => less tripping & falling also maintaining a constant visual field

* While galloping, the viscera keeps slapping against the diaphragm, so they can't produce the sharp breaths required for panting

- Enhanced thermoregulation
  - a) elaboration and multiplication of sweat glands
  - b) loss of body hair
  - c) cooling by countercurrent of carotid artery by venous blood so that relatively cooler blood goes to the brain
  - d) Mouth breathing during running to meet high ventilatory demand & more efficient heat loss

Importance of ER for human evolution

* Persistence hunting – meat heating ~ 2.6 mya
  spears ~ 50 kya
  Hypothesis: The humans chased large animal till it collapses because they can't pant while galloping * & have no thermoregulation

Extinction of megafauna

* Scavenging
  compete with other scavengers for scattered, short-lived resources.

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## Lecture 30

Biomechanics of plants

Growth – adding new cells in a particular direction (phototropic, chemotropic)

Movement – elongation growth (?) – days
Germination – breaking Hypocotyl out of soil surface is done largely without adding new cells

Examples

Touch-me-not plant, Venus fly trap, sunflower (tracks)

There movements occur in different time scales

Plant cells have a stiff cell wall covering the cell membrane
↳ Most cells do

Plant cell wall — primary & secondary cell walls

This is the primary source of structural support

The cell wall is more or less continuous across cells, with some middle lamella, so all cells are tightly packed together.

Composition

Differing conc. of polysaccharides, mainly cellulose which are highly organised microfibrils. They're embedded in a pectin (another polysaccharide) gel.

Cellulose is crosslinked by hemicellulose which makes it more rigid.

Lignin (phenolic crosslinkers) links it even closer, major component of wood.

The cell wall also helps maintaining shape when cell is placed in different osmolarities.

Hypotonic - keeps cell from bursting (resists turgor pressure)

Hypertonic - cell membrane detaches from cell wall and cell shrinks

Car tire : 0.2 MPa

Typical plant cell : 1 MPa

Guard cell : 4 MPa

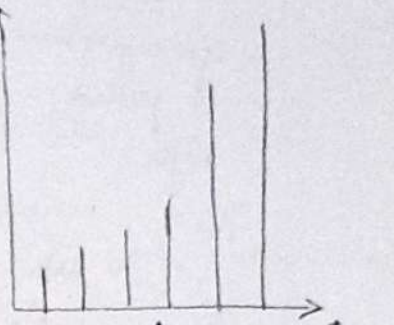
Plants cannot have contractile proteins to generate movement (like actomyosin in muscles) because the pressure they generate is not enough to deform cell wall & generate movement.

So, movement in plants is through clever usage of hydrostatic (turgor) pressure by modification of cell wall properties allows anisotropic cell change.

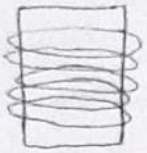
Hypocotyl elongation

This occurs over (2-3 days) without adding any new cells. The plant can be tricked by keeping them in dark (cue) & providing water

This movement is achieved by elongating the cells vertically without changing width




If the microfibrils were arranged like a cylinder around the cell then



it would resist expansion in width.

So, the cell is biased towards anisotropic longitudinal elongation.

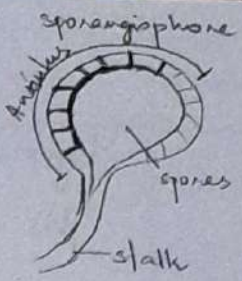
Also, the neighboring cell (even if it has isotropic arrangement of cell walls) can undergo assisted elongation due to strong cell wall connection

Turns out, axial cell wall is more elastic that transverse walls due to increased pectin crosslinking (discovered using atomic force microscope [cantilever]).

Regulation of stomatal opening

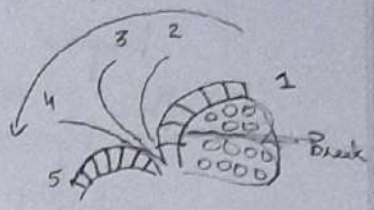
- light triggers a $H^+$ pump resulting in hyperpolarisation which opens voltage gated $K^+$ channel, so there's a $K^+$ influx
- $K^+$ reduces water potential resulting in endosmosis and increase in turgor
- Asymmetry in cell wall (inside is 2-5 times thicker) results in stomatal opening

"Catapult" spore release in Leptosporangium




There is unequal deposition of cell wall in the sporangiophore. The annulus cells have thick deposition of cell wall.

There is differential evaporation of water because of this. The sporangiophore breaks and the back is pulled backwards, creating a high strung 'catapult'.




The increasing -ve pressure (water tension can reach ~ 30 MPa) creates cavitation bubbles in cells.

The implosion of cavitation bubbles causes release of stored energy, catapulting the spores at initial velocity of ~ 10 ms$^{-1}$ (cells)

As the annulus is released, it expands. For this, the water needs to travel through cell wall and diffuse to each cell. This is limited by water viscosity. So the recoil slows down

The winding of sporangiophore takes ~ seconds whereas catapulting takes ~ milliseconds.

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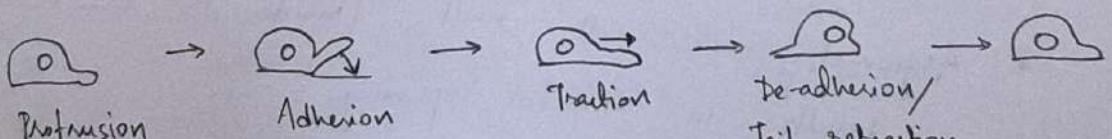
Lecture 31

Biomechanics - Single cell movement

Movement of cell can happen through cilia or flagella; or through internally generated force. Eg: Neutrophil chasing bacteria

Lot of cell movement occurs during ▸ development, ▸ wound healing, ▸ unicellular organisms

Amoeboid movement.



This kind of movement is carried out by self-assembling polymers for generation of deforming forces. There are cytoskeletal elements which is actin. the major primary one of

Actin

Individual actin : G-actin Size : 4nm

Filamentous actin : F-actin

G-actin bound to ATP is likely to get incorporated into the filament at the plus end

The ~~monomer~~ actin then hydrolyses ATP at a certain rate, so the molecules at minus end are bound to ADP

These processes are happening at a constant, equilibrating rate so the turnover rate is uniform, creating a 'treadmill'.

RDS of actin building is nucleation - 3 G-actin have to be arranged in a conformer

Other enzymes influence the rate of growth, they depolymerise, activate G-actin, capping proteins etc

Actin polymerisation creates force - different theories, but it creates force using/ rectifying Brownian motion to act in 1 direction

This is known as Brownian / Feynman ratchet, which allows direction of force.

The addition of a monomer is consequent fore application of membrane is possible through thermal expansion.

Force generated by 1 filament ~ 2pN

Intracellular bacterial motility - Listeria monocytogenes

The bacteria replicates in a cell, and wiggles out of plasma membrane to infect other cells.

To move in the cell, the bacteria uses actin polymerisation. At one end of bacteria, it has protein called ActA which nucleates an actin filament whose rapid polymerisation creates a recoil force that bacteria uses to propel itself.

Length of bacteria : 2 μm  Actin monomer : 4nm

Speed : 0.2 μm s⁻¹

This movement is similar to movent of a submarine - 170 m long, 9 ms⁻¹

Scaled length of bacterial movement -

Length : 150 m  Speed : 50 ms⁻¹

Listeria infact is moving through cytoplasm - a much more viscous medium.

→ Actin filaments form a very dense network in the leading edge of membrane. This is used to generate protrusion, which collectively is called lamellipodia.

→ Substrate adhesion

There are transmembrane proteins (focal adhesions) that couple the ~~ex~~ ECM / surrounding surface to the internal cytoskeleton.

The actin network is attached to these focal adhesions & they're (actin) in turn contracted by myosin (motor protein) which creates traction force so the cell can pull itself forward

Contraction and cortical tension aids detachment of lagging edge

→ Unidirectional stepper motor

Acto-myosin force generation

Myosin is attached to a bare with high inertial mass Myosin can bind to actin & to ATP and hydrolyse it.

The head is bound to actin, but when it binds to ATP, it detaches from actin. It hydrolyses ATP, so now its bound to ADP and its conformation changes so it moves forward.

* If detaches from ADP, attaches to actin in a forward position and changes its conformation so that actin is pulled back.

* This is unidirectional. contractile so actin filaments slide past each other and contract.

Aside from contractile movement, cytoskeletal elements are important in determining the shape of the cell.

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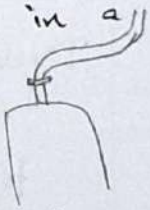
Lecture 32

Single cell movements using flagella & cilia

Many unicellular organisms have flagell & cilia. Bacteria, sea urchin sperm, paramecium.

The bacterial flagella

The flagella is attached to the cell in a bent manner to a hook.



Components:
- filament
- Hook
- Basal body (motor) — ✓ Stator (static)
  ✓ Rotor (rotating part)

The assembly happens from inside to outside of cell.

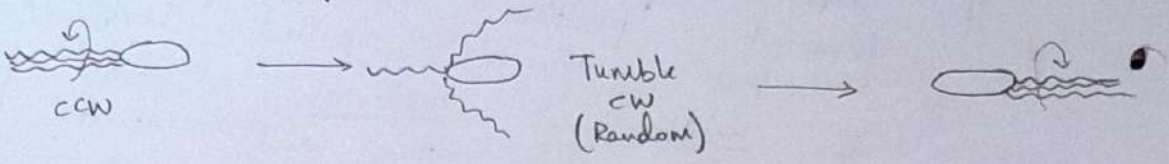
A proton motive force drives the rotation.

Proton motive force

There's a high conc. of $H^+$ outside the cell and low conc inside the membrane. So protons move from outside to inside which drives the motor at several thousand rpm

There are 2 important proteins — MotA & MotB. When $H^+$ binds to aspartic acid in MotB, the motor moves by half rotation (power stroke 1) and when it dissociates, the rotation is complete

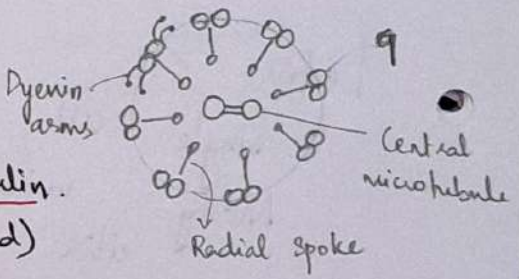
Bacteria have many flagella & their orientation ~~can~~ influences movement — speed & direction




This results in random walk movement.

Cilia and flagella have same basic schematic — flagella is longer.

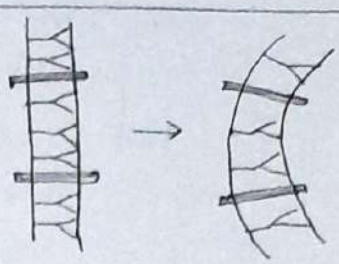
They're made by microtubules and powered by dynein motors



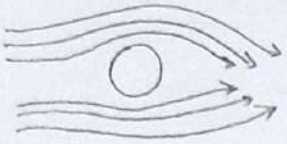

The structure and formation of microtubule — α & β tubulin.
+ end and - end (GDP bound)

Dynein - molecular motor
Uses directionality of microtubule (+ end to - end) to "walk" along it and transport vesicles.
It can also bind to another microtubule. When it walks on one & bound to other, so microtubules can slide past each other. But when they're crosslinked, instead of sliding, it bends the filament.

This requires energy (ATP) to move dyenins. This bending causes undulating movement which propels the cell forward.



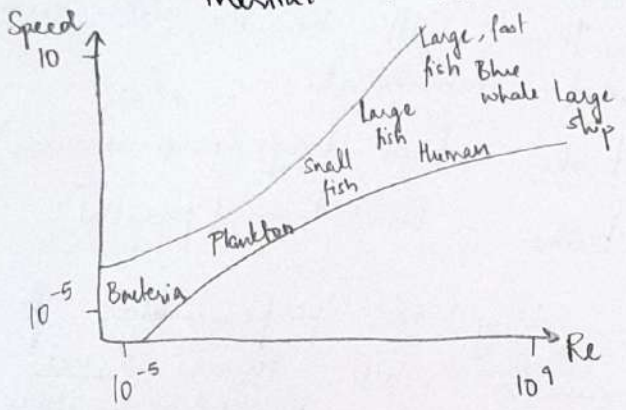
Fast ⇒ low P [Bernoulli]



The fluid experiences 2 forces.
- Inertial due to collision with object
- Viscous drag.

$$\frac{F_{inertial}}{F_{viscous}} = \frac{\text{density} \times \text{velocity} \times \text{length}}{\text{viscosity}} = Re = \frac{\rho v L}{\eta}$$

If
- inertial > viscous ↑ Re Turbulent
- inertial < viscous ↓ Re Laminar




Microbes & single cells operate in low Re i.e viscous forces dominate, inertial forces are negligible.

Bacteria swimming in water ~ Humans swimming in tar

So they're pretty fast when accounted for this.

Since inertial forces are low/negligible, the bacteria need to constantly beat flagella to move. Cessation of motion leads to dead stop.

Big animals - whales - can use inertial force to propel themselves forward - coasting in water after just 1 stroke

!! Strategy for feeding !!

* wheel apparatus

Rotifers have a circular disk* with cilia which move in a certain pattern so it creates a vortex of water — drawing in debris from far away (∵ no ~~inerti~~ laminar flow). The second that cilia stops moving, the debris also stops. So these organisms can't afford intermittent movement.

Since the organism is linked to fluid far away (∵ laminar), when it moves, water also follows. This is called 'added mass'.

Cylinder with high viscous fluid + colours - video !!
No inertia, laminar flow, so colours come back

Movement of scallops (bivalves)

< ⇌ <

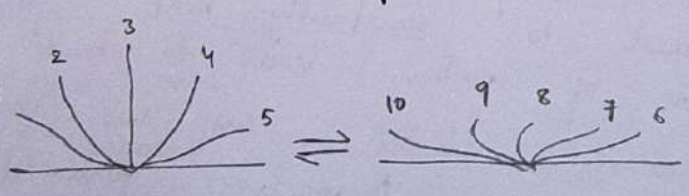
At low $R_e$, a if power stroke and ~~and~~ recovery stroke are symmetric, then there will be no net movement ∴ no inertial movement.

Cilia : effective stroke - high drag (perpendicular)
recovery stroke - low drag (parallel) → to body surface

Flagella : Helical - drag in perpendicular direction cancels while there's a net additive force in parallel direction.

Asymmetry in effective and recovery strokes is an important feature of movement of unicellular organisms.

Cilia



Lecture 31

Immune system

Immunity in the context of homeostasis.

Life in ecosystems involves biotic interactions between dissimilar organisms. What kind of 'biotic' interactions would act as 'stressors', generating responses to the stress to maintain homeostasis?

Direct stress - predation

One individual consumes another (biomass of another) leading to morbidity and mortality

Parasitism can also be considered as a form of predation

Ecological modelling of predator-prey interactions commonly assume that predation inevitably leads to death of prey. This only allows for certain kinds of scenario.

Would a predator eating detached tail of lizard be any more of predation than mosquito drinking blood?

If parasitism is considered predation (with a wide range of interactions) then there would be a diverse set of responses emerging from co-evolution of predators and prey? Collectively called immune responses.

'Immune' - latin - tax-free i.e. protected from having to give away some of your biomass.

Virulence - mechanisms that make parasites/predators more efficient, making them successful.

Successful ⇒ optimising attack strategies so that no. of parasites are increased

Mechanisms of invasion / infection strategies shouldn't be confused with virulence i.e. causing greater morbidity or mortality.

Parasite-host interactions are complex with many differing potential trajectories & outcomes.

The roles of 'predator' (parasite) & 'prey' (host) are circumstantial and situational. So any organism should develop immune / defense strategies and attack strategies

Immune system
A physiological system that responds to parasitic stresses. 'Quiescent' until activated – it doesn't do anything on its own.
Different though overlapping response pathways and directions.

Activation by recognition / detection
Does the immune system recognise the parasite or the stresses (like tissue disfunt"),
Evolutionarily.

The dynamic responsiveness (Quiescent ⇌ Responsive) is a key feature of immune systems
Essential property of response : effective contribution [effectors responses]
Energy cost of a quiescent system — the frequency of infections attack and the cost of a catastrophic event determine if the energy spent in maintaining the system is worth it.
If freq / severity goes down, the pressure to maintain a robust immune system.

Another peculiar feature :

Difference in Defence mechanism. immune system of different organisms against virus is / must be an ancient from bacteria to metazoans.

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Lecture 34

Immune system - set of immune responses which respond to parasitic stresses.

It is quiescent until activated.

Issues about recognising targets :
- Differentiating b/w dead bacteria and live ones
- Localised response — to act only where the bacteria is recognised.

The effector pathways are responses that restore homeostasis when disturbed by parasitic stresses. To do so, the effector pathways can reduce parasitic response, or a combination of both. the stress itself

These stress responses are negative feedback pathways. This is shaped by optimising the time in which system can be brought under control, became immune to responses are costly.

Immune responses of prokaryotes
They struggle to consider plasmids & phages as parasitic or not

Innate immunity in bacteria - differentiating between self and non-self?
Horizontal gene transfer

Lamarckian ?

Design of the receptor repertoire - what to identify and how to when its outside the cell?

Bacterial cells are not individuals in the sense we're used to - not differential survival but differential replication i.e what they pass on to daughter cells

Third component of immunity : producing toxins / compounds that block infection.

Some bacterial cells kill themselves before the virus can lyse i-e saving the colony at the expense of self.

Bacteria don't have "true" compartments, but they do have cytoplasmic vs. periplasmic spaces (especially Gram -ve). So can there be compartment-tropic pathogen?

Periplasmic space has lots of complex biomolecules but no access to genetic material unless to virus ∴

Eg: Bdellovibrio (wolf pack bacteria) - has long flagella. It makes a hole in cell wall & invades the periplasmic space, they detach flagella & close the cell wall. Then they change the shape of host bailli to sphere so other Bdellovibrio can't get in. When prey genome is still present, its called Bdelloplast.

Then Bdellovibrio grows & replicates using host machinery and genome. Then they lyse out. This is a parasite-host interaction - Bdellovibrio bacteriovorus. This calls for immune responses

# Bdellovibrio exovorus - predator : eats bacteria from outside

Mimivirus - giant viruses which infect free-living protozoa. Free-living protozoa eat bacteria. * Bacteria can evolve mechanism to stay alive in the phagosome itself or become cytosolic parasites. * Predator-prey interaction becomes parasite host, through escape strategies for the prey. Phagocytic immunity in multicellular immunity is similar to these interactions.
ie phagosome becomes a niche in the host.

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## Lecture 35

Plant immunity

Parasites / pathogens have to peirce the cell wall to access the biomass inside. WKT, in some situations, detecting parasitic molecules and in others detecting stress targets. Plants have both. Pathogen triggered immunity (PTI) and Effector TI (ETI) are two kinds of responses in plants - they have separate signalling & biochemistry & so on.

Plants have no motile / migratory cell population. So there's no immunocyte lineage. => plants have to depend of soluble compound mediated immunity. Multicellularity - there's lineage differentiation and there are fluid-filled intercellular spaces.

For plants to detect parasitic ingress and respond to it, plants have two strategies –

- releasing molecules that diffuse and alert the rest of the plant – molecules must be small (so large amounts can be produced) and must be a strong inducer with a long-range effector pathway.
- Modularity in plant body design – it can replace its body part with relatively less cost. An infected leaf can be made to fall off. Cell death – even organ death – is a good immune response

Metazoan host bodies.

There's an organismal integument, and specialised, differentiated cell lineages inside the body. Flowing of macromolecule rich fluid is an essential feature. This circulatory system bathes the cells in fluid. Two types – closed & open.

Injury (by thorn or mosquito bite) is an entry point for parasites. Then there parasites have to find their niche – intravascular fluid, extravascular (interstitial) fluid, intracellular spaces and ——— : 4 niches

# Capillary lumen – incredibly restricted – it collapses in between heart beats. So some mosquitoes pulse and break the capillary. But even if not, if pierces capillary and skin, which draws a bruise ie a pool of blood. and it drinks from there

So parasites that enter through a thorn / similar injury enters into extravascular, intercellular fluid.
Staphylococcus bacteria - can sit there or drift.
Plasmodium - has to enter blood & reach liver cells.

These parasites are evolutionary novelty - extracellular, but using the organisms' resources to propagate.
To this, the response is effector (enzymatic) molecules that are secreted locally or something that migrates quickly (fast response has been selected for).

Bacteria might repair enzymatic breakdown, so they're not long-term effective But its a good defense where bacteria enters frequently. Such enzymatic molecules are effective defense against viruses because no repair.

Differentiated cell lineage that's inducible - immunocytes.
We need immunocytes to be present everywhere
Since its not possible, we need them to be mobile so they can reach the required place - could be any part of body

Problem: Quantitative, mechanistic - how - evolutionarily - the immune cells can go through any place in the body

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Lecture 36

Quantitative problem: immunocytes should be able to patrol through any given volume
Its drifting as a quiescent cell when it recognizes the molecular target. The first thing it should do is stop!! - retain the cell in that

spare through adhesion to the ECM. Then it engulfs the pathogen ⇒ phagocytosis should be induced. One macrophage eats one bakteria. To improve response, we assume that there was more than one — number unknown. But the macrophage now passes on information that there is a breach.

Funtional paradox of emergent immune response — seal off the tissue vs. recruiting more immunocytes. There is slow down of blood flow, fluid accumulation so pressure builds and outflow is restricted. Meanwhile gradients are established (through chemokines and cytokines) to draw more immunocytes to the local area and activate them to retain the cells, amplify inflammatory response and increase the strength of oxidative enzymes in their lysozome to digest durable pathogen. There are core emergent inflammatory response.

→ Emergent evasion/defense strategies in bakteria — build thick cell wall so they're hard to digest. But this will invoke greater digesting power. This trajectory forces the bakteria to become intracellular, facultative, reside-resident parasite — recreated in metazoan body. This can be kept up through more activation of phagocytes, so if can spread. To avoid parasitic infestation, the phagocyte has to become hyper-active so if can digest & undergo cell death.

Another strategy — changing the recognition site so the host cells don't recognise it. This is a coevolution driven diversification in extracellular niche parasite pathogen.

# There also exist Damage AMPs. so inflammatory response is wired to respond to both mechanical injury and pathogen

This in turn pushes the metazoan recognition receptors to diversify. But how much?

So there are Pattern Recognition Receptors (PRR) that efficiently bind to Pathogen Associated Molecular Patterns (PAMPs)# that are molecular motifs.

Another solution is to solubilize the receptors that when bound to pathogen recognition site, transduce the signal to immunocytes. This will be a constant domain whose function is to trigger a macrophage upon allosteric change

This is the complement system that is used to amplify recognition. Another function is to neutralize the pathogen — by creating pores or other enzymes. But the drawback is this would require huge concentrations of the complement chemicals. Hence, calling out for phagocytes is still necessary.

There is a coevolution driven diversification of infection / defence strategies. But the generational time of pathogen is ~hours whereas that of humans / larger metazoans is ~years. How then do we 'win'?

This is linked to the evolution of ap adaptive immunity. There is a clear, dichotomous split in invertebrates vs vertebrates that wrt antibodies and molecular mechanisms of adaptive immunity.

Agnatha — unusual — no antibodies in structural sense but yes in the functional sense

Lecture 37 25/5

3 ecological niches in metazoan body - extracellular fluid, vascular blood flow (causes shear problems) and intracellular niche — cytosolic and intravesicular

Cytosolic niche — how does cell deal with viruses in the cytosome?

Time optimisation for detecting viruses — receptors in the cytosome

Metazoans have 3D supracellular organisation.

Its possible for organism to isolate the infection by triggering an inflammatory response in the local region. Plants are very modular, this way — tissues can be shed easily.

In metazoans, cell death can impede the spread of infection.

So immune cells recognize putatively infected cells and signal them to die. Cell death (apoptosis) through extracellular microenvironmental cues is a design of multicellular animal development.

Thus, like phagocytic immunocytes, for this we have killer immunocytes which identify virus infected cell and stimulate it to die

Some molecular signal must be shown on the infected cell (at an early stage) which can be detected

Proteome sampling is not very effective because there could be v. complex, unique proteins in the body that would be 'foreign' to the immunocyte.

Viruses essentially takes over the protein synthesis machinery of the cell and using it for itself.

Because of this, cellular protein turnover is reduced which changes the distribution of proteins

on the cell membrane. So the killer immunocyte has a set of receptors that recognize proteins on the membrane. Some trigger the cell to kill, while other signals dominantly inhibit the signal. Unless the inhibitory signals are present.

Recall microbes have shorter generation time — so they can diversify much faster. If the receptor diversity was linked to the host's generation time, that puts host at a disadvantage Vertebrates have done something radical to overcome this — make an infinite (practically) number of different receptor repertoire so any incoming foreign body is recognised. This requires some kind of mutagenesis.

Thus VDJ recombination

But just creating a diversity of receptor repertoire in the immunocytes is not enough.

*"Somatic diversification of receptor repertoire" *

Because of this shift in functional anatomy, there are significant ramifications — lymph nodes to collect all possible antigen and expose it to the library of receptors.

One a receptor recognizes a pathogen, it clones itself and creates a lineage of immunocytes that secrete antibodies which neutralize pathogen and help phagocytes engulf them.

Another complexity: A system of proteome sampling so the cell presents its internal proteins on the surface — so formed protien turnover?

(?)
43 min