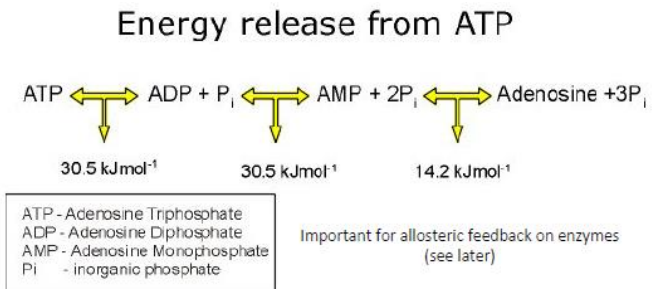
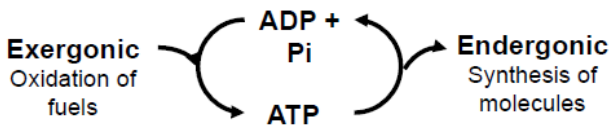
PHY3072 - MUSCLE AND EXERCISE

LECTURE 2: Introduction to Exercise Metabolism

- Learning objectives:
  - Outline sources of metabolic substrates (fuels), describe when they are used
  - Relationship between oxidative metabolism of fuels and exercise duration/intensity
  - Discuss how the RER is calculated and what it means
  - Describe the role of enzymes in metabolic reactions
- High energy phosphate bonds:
  - ATP
    - Energy released from oxidation of nutrients trapped in high energy phosphate bonds within ATP
    - ΔG = -30.5kJ/mol



  - ATP is the cell's "energy currency"
  - Hydrolysis of ATP is coupled with energy consuming processes
    - Mechanical work: muscle contraction
    - Chemical work: synthesis of cellular molecules required for growth and maintenance e.g. protein synthesis
    - Transport work: maintenance of ion gradients e.g. Na+K+ATPase

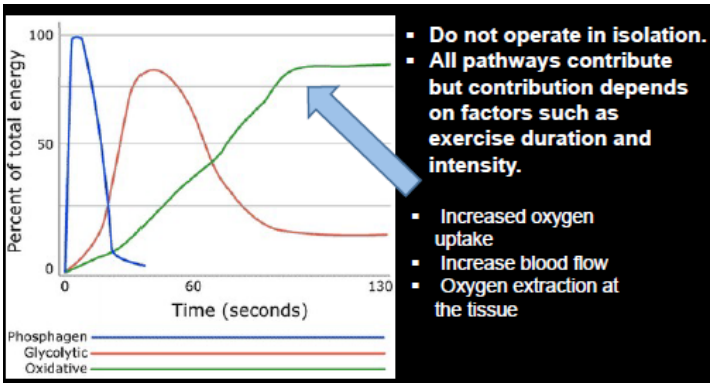


- ATP:
  - Finite amount - low levels in the body: 80-100g
  - Immediate energy source
  - All muscle ATP consumed in ~90 seconds at rest and ~2 seconds during exercise if not regenerated
  - Replenished at the rate used so [ATP] does not decrease appreciably until exercise becomes intense
  - ATP levels in the muscle are maintained quite well
  - ATP must be continuously resynthesised and replenished

- Energy for Muscle Contraction:
  - Mechanisms involved in the breakdown and resynthesis of ATP
    1. Substrate Level Metabolism (Anaerobic)
    - Phosphagen System (ATP/PCr)
    - Glycolytic System
    2. Oxidative Metabolism (Aerobic)
    - Carbohydrate, Fat and Protein

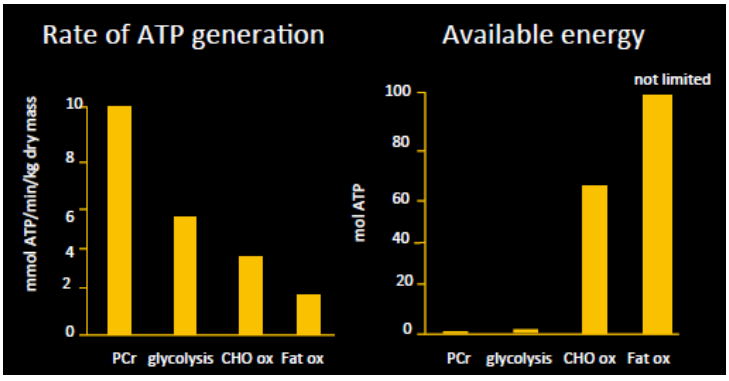
Distance	Duration[a] (min: s)	% Aerobic	% Anaerobic
100 m	9.84 (9.58)	10	90
400 m	43.29 (43.18)	30	70
800 m	1 : 41.73 (1.41.01)	60	40
1500 m	3 : 27.37 (3.26.00)	80	20
5000 m	12 : 44.39 (12.37.35)	95	5
10 000 m	26 : 38.08 (26.17.53)	97	3
42.2 km	126 : 50 (123.38)	99	1

[a] Durations given are the current men's outdoor world records at 1 April 1997.

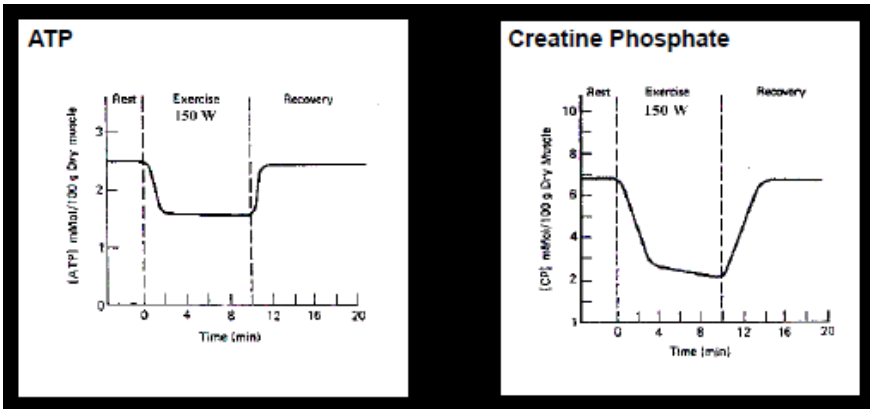


- Do not operate in isolation
- All pathways contribute, but contribution depends on factors such as exercise duration and intensity

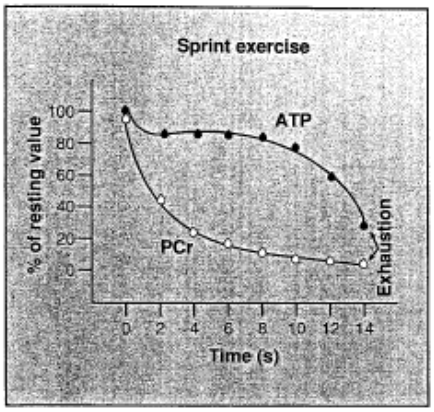
- Capacity of energy systems:



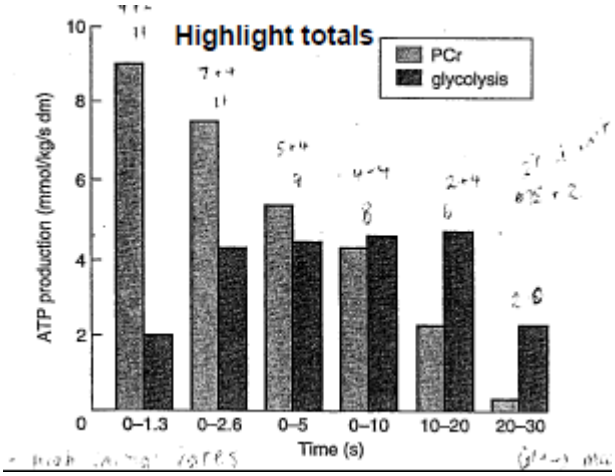
- Substrate levels metabolism: Phosphocreatine
  - PC + ADP → ATP + creatine (enzyme = creatine kinase)
    - Relatively modest store (70-80mmol/kg dm)
    - Immediate (0-1.3s)
    - Major role is to buffer ADP accumulation
    - Time course of utilisation
- Substrate level metabolism during "moderate" exercise and recovery



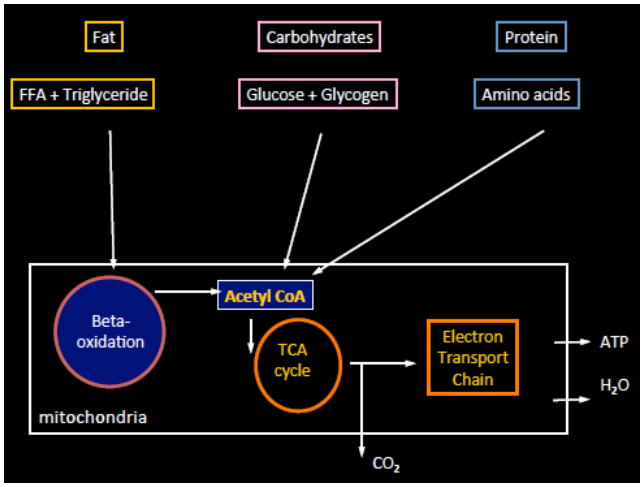
- Substrate level metabolism during "all-out" exercise:



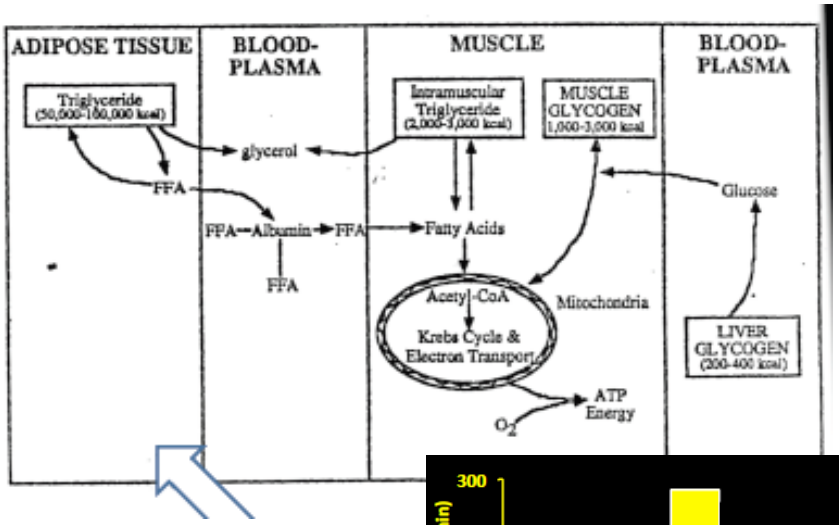
- Substrate level metabolism: Glycolysis
  - Large muscle glycogen stores (500 mmol/kg dm)
  - Occurs rapidly (<2sec)

- Oxidative 

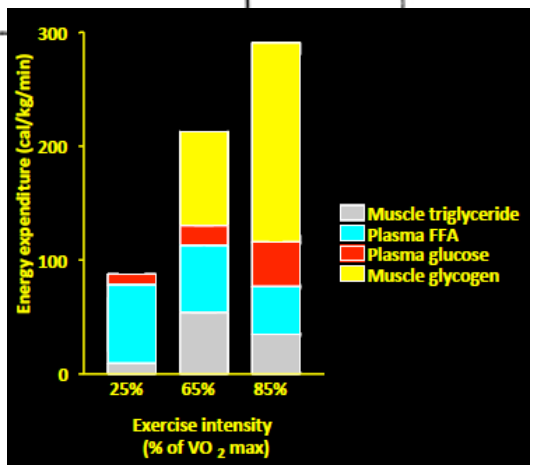
Metabolism:
    1. <u>Carbohydrate</u>
    - Stored as glycogen in muscle and liver
    - Circulates in blood/plasma as glucose
    2. <u>Fat/Lipids</u>
    - FFA released from adipose tissue triacylglycerol stores
    - Intramuscular triacylglycerol
    3. <u>Protein</u>
    - Amino acids (long duration exercise, not addressed herein)
- Metabolic Fuels
    - Liver glucose (0.8-1.6 MJ)
    - Muscle glycogen (8-15 MJ)
    - Adipose-derived FA (essentially unlimited)
    - Intramuscular FA (12-20MJ

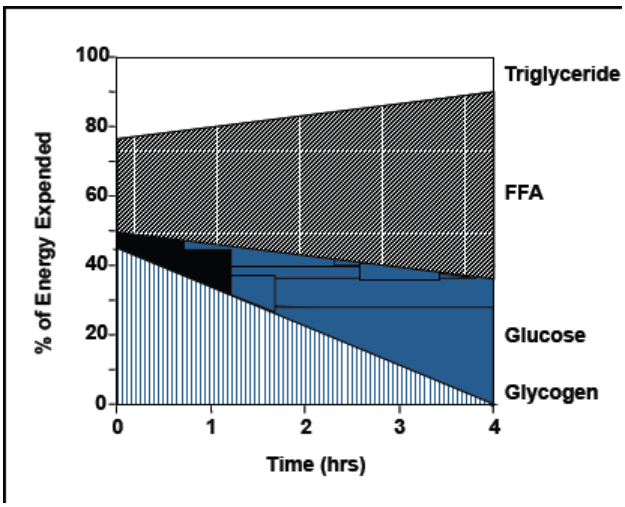


- Oxidative metabolism:



- Carbohydrate and Fat are the primary energy substrates for oxidative metabolism
- Protein is usually a relatively minor source of energy (<5% of total energy)
- Carbohydrate and fat utilisation is determined primarily by EXERCISE INTENSITY and DURATION





- Oxidative metabolism:
  - Other factors affecting fuel selection:
    - Substrate availability
    - Diet or nutritional status
    - Prior exercise
    - Muscle fibre type composition
    - Physical fitness or training status
    - Environmental factors - e.g. temperature and altitude

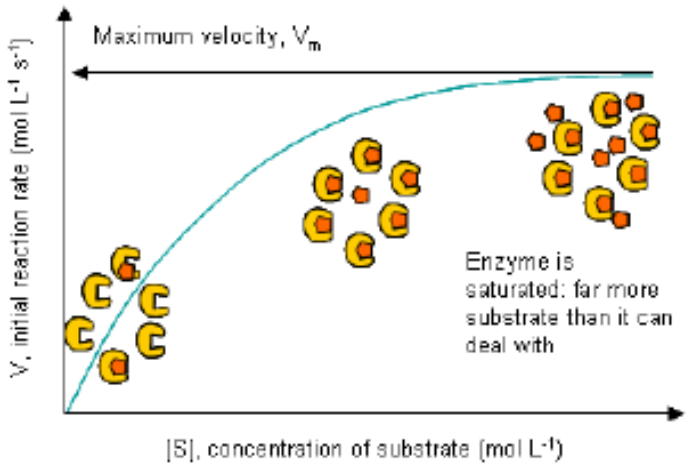
    - Gender (male/female)
    - Hormones
- Assessing metabolism:
  - Whole body metabolism:
    - Calorimetry (heat)
    - Indirect calorimetry (O_2 use)
  - Substrate use:
    - Tissue biopsies and biochemical evaluation
    - Substrate tracers

- Calculating substrate oxidation
  - Calorimetry is the science of measuring the heat of chemical reactions or physical changes as well as heat capacity
    - Thermometer attached to an insulated container
  - Expensive and practically difficult to measure heat production during exercise
  - Why is indirect calorimetry possible?
  - Fuel + O_2 → Heat + CO_2 + H_2O
  - Measurements of O_2 consumption and CO_2 production can give information on type and rate of fuel oxidation
  - **RER = respiratory exchange ratio**
  - **RER = V_{CO_2}/ V_{O_2}**
- Calculating substrate oxidation (RER):
  - Glucose ($C_6H_{12}O_6$) + $6O_2$ → $6H_2O$ + $6CO_2$ + Heat
    - RER = V_{CO_2}/V_{O_2} … 6mol/6mol = 1.0
  - Fat ($C_{55}H_{104}O_6$) + $78O_2$ → $55CO_2$ + $52H_2O$ + Heat
    - RER = V_{CO_2}/V_{O_2}… 55mol/78mol = 0.7
  - So based on the V_{O_2} and V_{CO_2} measured at the mouth, one can calculate the amount of CHO and fat being oxidised
- Calculating substrate oxidation:
  - Caveats/Warnings?
    - Intermediate metabolic processes do not occur (e.g. lipogenesis, gluconeogenesis, ketogenesis)
    - No protein oxidation (usually very low)
- Enzyme control of metabolism:

Enzyme + Substrate ⇌ Enzyme-substrate (transition) complex → Enzyme + Product

  - Speeds up reaction - reduces activation energy

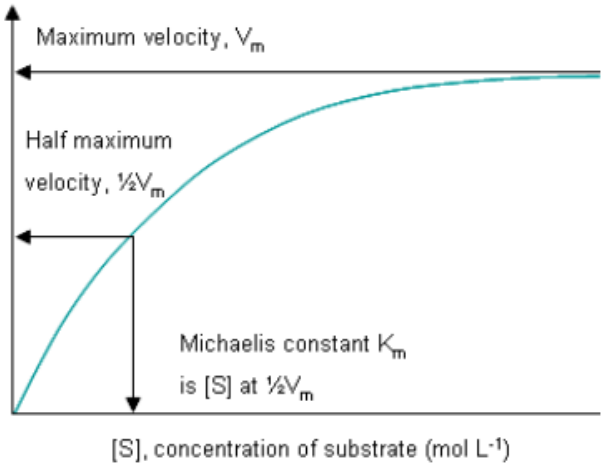
- Highly specific



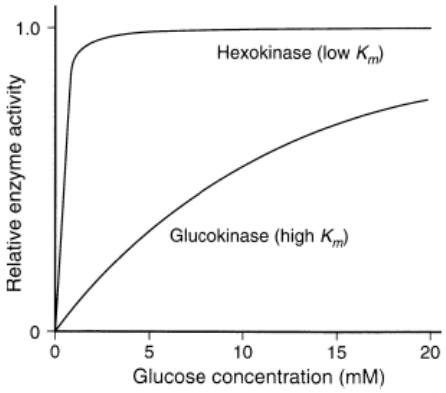
- This is important because enzymes control the flux of metabolic pathways

- Regulation of enzyme activity:
  - Enzyme activity is regulated by:
    - Substrate availability
    - Product inhibition
    - Enzyme concentration
    - Temperature
    - pH
    - Allosteric regulation
    - Covalent modification
- Regulation of enzyme activity: Substrate Concentration
  - At low [substrate] velocity increases
  - Maximum velocity = Vmax, Enzyme saturated
  - Km - [substrate] needed to produce half Vmax
  - Km reflects affinity for substrate
    - Smaller Km = greater affinity
  - In cells [substrate] equal or less than Km

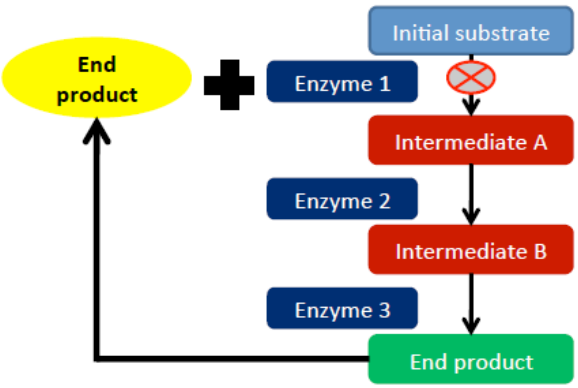
- Respond to changes in [substrate] as is on the steep slope of curve



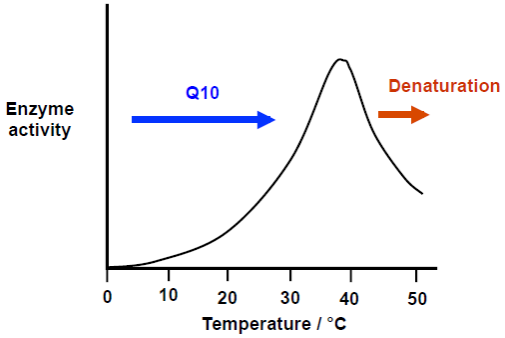
- Example: Glucose phosphorylation to glucose-6-phosphate
- <u>Muscle and brain:</u> hexokinase Km = 20-120uM. Phosphorylates glucose even when blood glucose is low. Important in brain which relies solely on glucose
- <u>Liver:</u> glucokinase Km=5mM. Responds when blood glucose elevated (i.e. after meal) to minimise hyperglycaemia. Doesn't compromise glucose supply to other organs when glucose is low



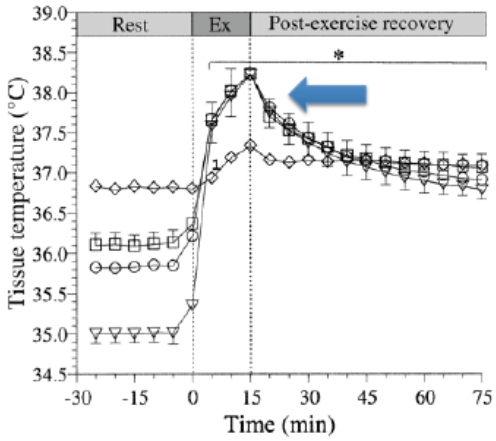
- Regulation of enzyme activity: Product Inhibition
  - Product binds to enzyme and inhibits its activity
  - When levels of product are high it is energetically favourable to inhibit product formation
  - Advantageous if end product of pathway can bind to initial enzyme, inhibit activity allowing pathway to be inhibited



- Regulation of enzyme activity: Temperature
  - Velocity increases with increasing temperature
  - Q10 (the temperature coefficient): reaction rate doubles with every 10°C rise in temperature
  - BUT at high temperatures proteins denature

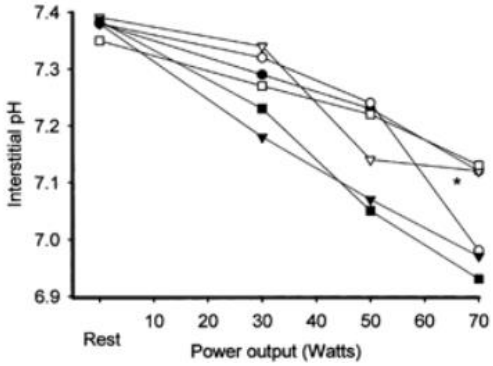


  - Muscle temperature increases during exercise
  - Exacerbated when exercising in hot environments and alters muscle metabolism

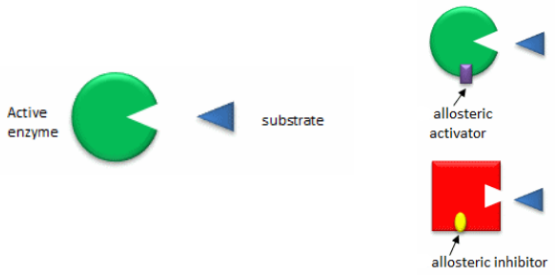


- Regulation of enzyme activity: pH
  - Enzymes have an optimum pH
  - Activity is reduced outside optimum range
  - Structure of the enzyme may be changed
  - Active site is distorted and the substrate no longer fits

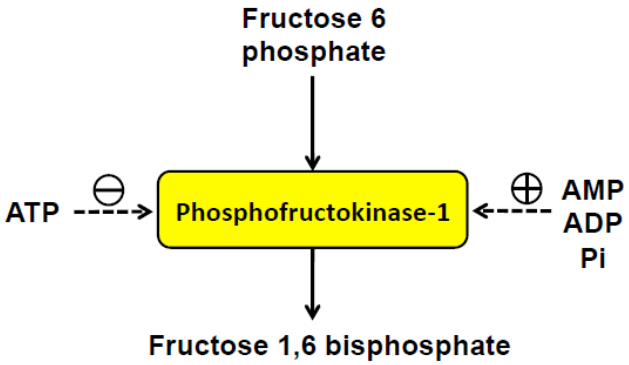
- Extreme pH levels will produce denaturation
- Muscle pH is reduced during exercise in an intensity dependent matter
- Implications for metabolism:
  - E.g. pH drop inhibits fatty acid oxidation enzymes and may cause the decrease in fat metabolism seen during intense aerobic exercise



- Regulation of enzyme activity: Allosteric Regulation
  - Effector molecules bind to sites on enzymes other than the active site (allosteric sites) and regulate activity
  - Effectors that enhance enzyme activity are referred to as allosteric activators
  - Those that decrease enzyme activity are called allosteric inhibitors



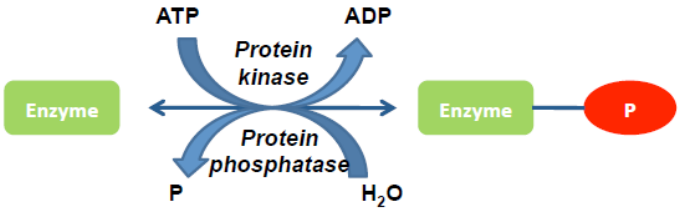
e.g. Phosphofructokinase 1: regulatory enzyme of glycolysis



- Regulation of enzyme activity: Covalent Modification
  - Post-translational modifications effect enzyme activity by:

- Changes in shape
- Promote or inhibit interaction of substrates and allosteric regulators
- Alter cellular location (i.e. cytosol to membrane)

- Regulation by phosphorylation events common
  - Phosphorylated by protein kinases
  - Dephosphorylated by protein phosphatases
  - Phosphorylation status mediated via signalling pathways



e.g. Glycogen phosphorylase: regulatory enzyme of glycogen degradation