3G5 – 2025 Crib

1 (a) Briefly describe the structure of woven and lamellar bone. Explain when each type of bone would develop.

Both types of bone contain mineralised collagen fibrils (~30% dry weight) surrounded by 70 wt% calcium phosphate. In woven bone, the collagen fibres are arranged as a block of randomly oriented woven fibrils. Woven bone is found in situations of rapid growth such as in children and large animals.

In lamellar bone, the collagen fibrils are arranged in concentric cylinders known as lamellae. Several lamellae (~10-15) are bundled together to form an osteon. The osteons have a central canal called the Harvesian canal (diameter of ~200 μm) that contains blood vessels and nerves. Lamellar bone can be found in adult humans.

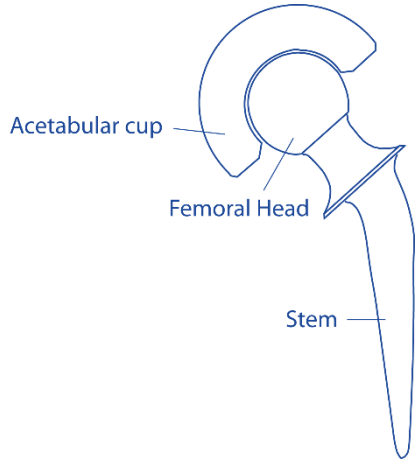
(b) State the main causes for hip replacement.

The most common cause for hip replacement is osteoarthritis. In osteoarthritis, there is a breakdown in the cartilage covering the ends of bones where they meet to form a joint. As the cartilage wears away, the bones become exposed and rub against each other. The second cause is known as avascular necrosis. In this condition, there is cellular death of the femoral head due to interruption of the blood supply. Without blood, this leads to collapse of the femoral head and degeneration of the joint. This condition has been linked to alcoholism, hip fractures, dislocations of the hip, and long term cortisone treatment for other diseases.

(c) Sketch and label the components used for hip replacement. Briefly describe the requirements for hip implants. In your answer, you should consider mechanical, biological, chemical and processing requirements.

A total hip prosthesis comprises an acetabular component (cup) and a femoral component (stem+head) – see schematic below.

- Basic mechanical properties: sufficient strength to avoid plastic deformation, brittle fracture, fatigue crack propagation and wear, preferably with a stiffness at least approximately matching that of bone, to minimise “stress shielding”. Stress shielding is the reduction of bone density adjacent to the implant because implants are stiffer than the surrounding bone, and as a result the bone surrounding the implant is inhibited from being strained.
- Biocompatible (non-toxic, non-allergenic, non-carcinogenic) and in some cases bioinert.
- Good corrosion resistance and chemical stability.
- Must be low cost and easy to manufacture into 3-D shapes.



(d) You have been contacted by an external consultant to assist in selecting a prosthetic implant for young active patients.

(i) Describe your chosen method of implant fixation. Explain the materials-selection criteria for the implant components and list the chosen materials. Discuss the surface treatments you would employ to facilitate the fixation of the implant to the surrounding bone, and the region they would be applied to. Explain your reasoning.

In terms of method for implant fixation, since the patient is young and active, the suggestion would be to use a cementless prothesis. In this case, bone-implant attachment is achieved via bone-in- or on-growth into a rough/porous surface.

The acetabular component can be made of UHMWPE (or Al2O3), both have good wear resistance. UHMWPE is sometimes backed up with a metal cup (usually Co-Cr) which provides better X-ray visibility. The femoral component (stem and femoral head) is commonly made of Ti-6Al-4V, 316L or Co-Cr alloys. They are chosen because of their mechanical properties (respectable strain tolerance, strength and toughness). However, since the boss is keen to use a surface treatment to allow bone in- or on-growth as a means of fixation, dissimilar materials must be avoided to prevent galvanic corrosion.

If the stem is coated with hydroxyapatite, galvanic corrosion is not a concern. If the stem is made of Ti alloy, then a porous Ti or hydroxyapatite coating could be employed. Hydroxyapatite allows bone on-growth, its composition is similar to calcium phosphate so it is not only biocompatible but also bioactive.

Femoral heads can be made of Al2O3 and ZrO2. They need to have high wear resistance. An advantage of using a ceramic instead of metal for the head is that it is harder and hence more wear resistant.

A Co-Cr stem can be combined with porous Co-Cr (bead-sintered or fibre/wire based) or hydroxyapatite coating or a 316L stem with a porous 316L fibrous coating or hydroxyapatite, however, the modulus of both stem alloys is about twice than that of titanium alloys, hence the stress shielding effect is stronger so are less preferable.

The coatings above could be applied in the proximal region of the stem to provide a surface for bone on-growth (hydroxyapatite) or in-growth (Ti coating). Below the proximal third, the stem can be grit blasted. This is less rigid fixation than in the proximal, but still allows a good surface for on-growth. The distal tip of the stem should be polished, which allows no-growth.

(ii) One of the consultants suggested that the main reason for hip implant failure is wear. Briefly comment on whether you agree with this suggestion.

While wear can be a cause of hip implant failure, it's not the main reason. Loosening is the main reason for failure. Ensuring that the interfacial bond remains strong, so that interfacial shear displacements do not occur and wear debris does not form at the interface, is an important objective. In cementless implants, wear occurs due to friction between implant components (implant-bone interface), particularly at the articulating surfaces. In cemented prosthesis, bone cement (space filler not a glue) deteriorates through fatigue and biological processes, producing wear debris.

2 A firm is designing a new active implantable medical device, called a neurostimulator. This is a device that is implanted in the skull to measure brain activity for identifying seizure events. Seizure detection then triggers the delivery of an electrical current to the tissue that stops the seizure. The firm plans on making and selling the device in the EU first and then expanding to the US in the future.

(a) The firm believes this is probably a Class III medical device under both EU and US regulations. Explain how they would confirm if this classification were correct in both cases.

The key concepts to get across here are that in the US, medical device classification is based on precedence. There is a database that can be accessed online by the firm and they can check for similar devices to confirm this is a Class III device. If there are no approved neurostimulators on the market, then they will have to go through a more detailed process applying to have it assessed. In the EU, there are guideline documents to support the regulation documents and enable the firm to self-assess the classification.

A basic answer will not there is a database in US to check and it is self-assessed in EU.

A good answer will provide a clear description of the concept of precedence in the US and that there is a separate process for new devices. A good answer will also note that there are guideline documents that support the EU regulations to help firms check the classification by following a series of questions (>20 questions) that are based on the potential for human harm.

A strong answer would note all of the above and highlight that in the EU, while it is self-assessed, the documentation and assessment is checked as part of the audit / regulatory approval process. A strong answer may also note that in the EU, if you are still unsure, then you can ask the country's Competent Authority for help (i.e. the MHRA in UK).

(b) Explain what is meant by the term *biocompatible*, in relation to medical devices.

A strong answer will explain that there are two aspects, biofunctionality (an appropriate response of a material in a specific application, e.g. resistance to clotting), and biosafety (no negative effects of the biomaterial on the organism/tissue/etc., e.g. no issues with cytotoxicity). A basic answer will only note one of these aspects or will mention the terms without any explanation.

(c) Describe how the firm would ensure this new device is biocompatible.

When the firm is designing the device, they will select materials where the literature, clinical experience, animal studies or previously approved Class 3 devices provide evidence that they are appropriate in terms of biocompatibility.

The answer will also note there is an international standard for biological evaluation of medical devices, to assess biocompatibility and it is critical that the firm follow the standard and all its relevant parts for their device. For example, as this is an implantable in the brain, it will be critical to understand what is leaching from the device and its effect on surrounding tissue. A complete answer will indicate that there are many aspects of biocompatibility other than only cytotoxicity, and give a couple of examples (e.g. sensitisation, irritation), but it will only give a detailed explanation of assessing cytotoxicity, as that was explained in the lectures.

Biocompatibility is not only assessed on the individual materials and components, but on the completed device after it has been manufactured, packaged and sterilised. This is because these are all processes that could lead to changes in surface chemistry or introduction of contamination that will change the biocompatibility. As this is a Class III device, the biocompatibility will very likely need to be assessed in vivo also.

A basic answer will note the fact there are international standards and give some details about cytotoxicity. A good answer will include further details regarding other sources of information and clearly indicate that it is important to consider both the materials at the design stage and the final product. A very strong answer will note a selection of additional points as noted above.

(d) The firm must provide a sterilised, packaged product to their customers. The firm is going to try ethylene oxide and gamma radiation sterilisation techniques to test if they are suitable for their device. Describe any two benefits and any two challenges for each of these techniques.

Any two challenges and any two benefits will be considered. In each case, a basic answer will note the challenge or benefit briefly, a good answer will describe why this is particular to the sterilisation technique and a strong answer will make sure the challenge is clearly explained, linked to the mechanism of sterilisation and also make sure the answer is somewhere linked back to the device (whether in terms of material considerations or other). A strong answer may also be one that provides a clear link to how the challenge or benefit links to the key considerations when selecting a sterilisation technique in general.

For ethylene oxide: A common benefit is its excellent compatibility with a very wide range of materials and so it is likely going to sterilise without damaging the function of the device or changing its biocompatibility. Another benefit is that it can occur after the product is in sealed packaging, and so will remain sterile. There are additional benefits, such as its very good efficacy across a wide range of targets. As this device has a range of materials, including metals, electronics and likely polymers, a technique with broad material compatibility is good. It is also a very common technique with easy accessibility. It has a number of challenges, including the pressure on the technique to be reduced, due to environmental impact. This may be expanded to highlight the toxicity and dangers associated with the technique. The main challenge often noted is the quarantine required, so products have to wait 1-2 weeks to be ready to ensure toxic residues have left surfaces. This can be challenging to manage. It may also be noted how complex this method is to control.

Gamma radiation has even greater benefits in terms of in-packaging sterilisation. It will penetrate through multiple levels of packaging and so can be completely wrapped and ready to ship prior to sterilisation, which makes it easier to manage. Another benefit is that the product is immediately sterilise and ready to ship. This can also be economical because it is normally a third party managing many different devices for sterilisation. There are some challenges, mainly that it is extremely expensive to build and manage due to the safety and use of cobalt 60. This essentially means you will have to manage the manufacturing very carefully. Another challenge is that some plastics degrade under gamma radiation and as this is for implanting into the brain, there will have to be very tight controls over the material properties and behaviours.

In general, efficacy, compliance, compatibility, penetration depth, safety, cycle time, monitoring and economics are the most common topics to consider when comparing techniques.

(e) Describe any two trends in the medical devices market that may influence the design of this new technology.

There are a range of trends that can be drawn upon and any valid trend will be considered, including those beyond the lecture content. A basic answer will note a valid trend that could be considered relevant to this device. A good answer will clearly link a valid trend to the device. A strong answer will explain the trend in detail and provide details about the link to and influence on the design of the neurostimulator device in the question.

For example, the growth of remote monitoring of patients may be explained, linking to the increased adoption of remote healthtech since the covid pandemic, with both providers

and consumers more willing to participate. It may influence the design as it could enable recording and transmitting of data linked to when seizures occur and their level of severity, to inform healthcare professionals and enable better treatment. This would likely link also to a trend in increasing numbers of connected devices, sending data to healthcare providers. The answer may refer to AI and machine learning, provide a definition and note that the collection of data from all the patients may enable better interpretation about when a seizure is going to happen and enable signals to prevent them, rather than relying on stopping them.

There may be a trend noticed more focused on design, where the design is specifically created to support implantation through surgical robotics.

Option #1. Cognitive computing, artificial intelligence, machine learning: AI is revolutionizing healthcare by enhancing data analysis, predictive modelling, and personalized treatment plans. For neural implants, AI can improve signal processing, adaptive learning, and personalised design of stimulation parameters.

Option #2. The growth and adoption of telehealth, remote healthtech, wearables: Post Covid-19 pandemic increased consumer willingness, provider willingness, and regulatory changes enabling greater access and reimbursement for wearables. Thus, the design of the neural implant can become a wearable and remote monitoring solution.

Option #3. Surgical robotics for minimally invasive implantation: There is a growing emphasis on minimally invasive surgical techniques. For neural implants, this means developing devices that can be implanted with minimal disruption to surrounding tissues, reducing recovery times and improving patient outcomes.

(f) Explain how medical device regulations ensure safety throughout the lifespan of the device.

A basic answer will demonstrate an understanding of the lifetime of the medical device, running from conception and development through to manufacturing and packaging, then to sales, use, possibly multiple uses and finally end-of-life (which may be disposal or remanufacturing). A basic answer will also note that medical device regulations cover this full journey to ensure safety.

A good answer will also note more detail that there are international standards that need to be adhered to at every stage and provide a bit more detail. For example, noting that the

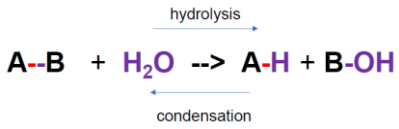
design and concept stage has specific standards and information that needs to be recorded, and the emphasis is not only on the manufacturing.

A strong answer will give more details about the manufacturer's role of post-market surveillance. This involves recording and taking action on all adverse events that occur linked to the device, tracking challenges with labelling, any activities that may require a device recall, etc. These are reported to the competent authorities in the countries where the device is available and they ensure the manufacturers take the appropriate actions. A very strong answer will also note that regulations dictate when devices can be reused or remanufactured for sustainability reasons, rather than used one time. This extends the life of the device but then the third party that remanufactured the device becomes the main entity responsible for the product lifetime.

3 Many polymer-based biomaterials are subjected to hydrolysis as part of the biodegradation process.

(a) State what a hydrolysis reaction is.

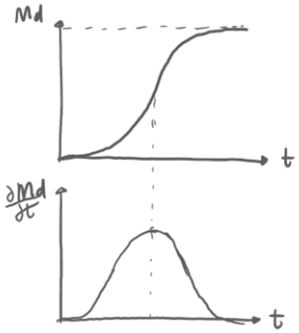
A hydrolysis reaction is a chemical process in which a molecule is broken down into smaller components by the addition of water.



(b) A new hydrolysable polymer is synthesised to be potentially used for localised delivery of cancer drugs. This new co-polymer was measured to exhibit a critical thickness (W_c) for bulk versus surface erosion of 1 mm.

(i) The hydrolysable polymer is made into a suture with a diameter of 300 µm. Sketch the likely delivery profiles for this suture, i.e. rate of drug release versus time, and total mass of drug release versus time. State your assumptions.

The diameter of the suture 300µm is smaller than Wc=1mm. Thus bulk erosion will take place.



Md: total mass of drug release; dMd/dt: rate of drug release. Assumptions: the hydrolysable polymer is used as the carrier for cancer drugs, where the drugs are homogenously dispersed into the matrix. The polymer undergoes matrix erosion resulting in drug release, and the rate of drug release is directly related to the rate of matrix erosion due to hydrolysis.

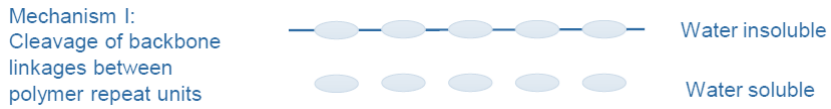
(ii) Based on (b)(i), suggest whether this drug releasing suture could be suitable for localised cancer drug delivery in the brain. Briefly state your reasoning.

Not suitable for cancer drug delivery in the brain. The release profile is burst release, thus that the level of drugs release is hard to control in both dosage and the time point of burst release. The cancer drugs released can much exceed the safety level becoming dangerous to the patient, or not effective for the treatment.

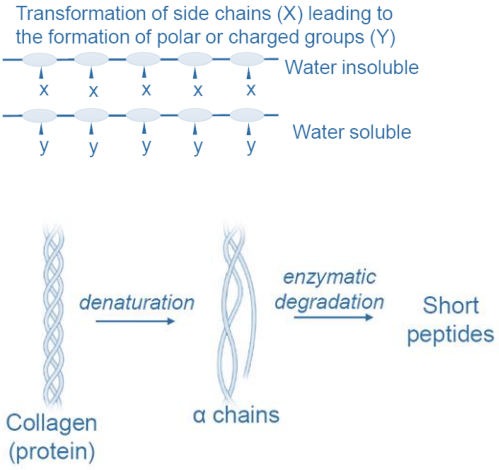
(c) Both poly(lactic-co-glycolic acid) (PLGA) and collagen can be used as suture materials.

(i) Compare the hydrolysis reactions associated with a PLGA suture versus a collagen suture when interfaced with body fluids. You may support your answer with a sketch.

For the PLGA suture, the hydrolysis reaction breaks down the main chain bonding, i.e. the polyester bond.

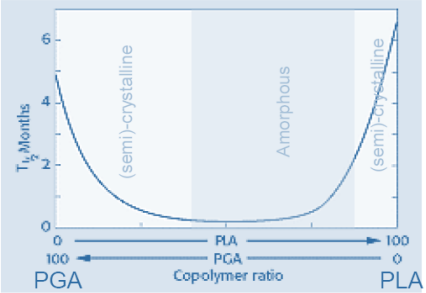


For the collagen suture, the hydrolysis reaction transforms the side chains of collagen fibres to polar or charged groups, this leads the originally water-insoluble tertiary collagen structure to dissociate, making the collagen 'denatured' and water soluble. Subsequently, enzymatic reaction helps to accelerate the hydrolysis reaction of the individual collagen alpha chains, breaking down the main chain peptide bonding.



(ii) State how co-polymerisation affects the properties of a PLGA suture. You may support your answer with a sketch.

Hydrophobicity and crystallinity depends on PLA/PGA ratio. This then influences the degradation rate (half-life, $T_{1/2}$) and the corresponding mechanical response with time.



(d) For the following polymer characteristics, briefly discuss their effects on the rate of hydrolysis degradation of a hydrolysable polymer.

(i) Degree of crystallinity;

Increased degree of crystallinity limits the possibility of water accessibility, thus decreases the rate of hydrolysis degradation.

(ii) Molecular weight distribution;

Widening the molecular weight distribution would reduce the optimal possible crystallinity of the polymer, and thus increase the rate of hydrolysis degradation. It could also make the rate of hydrolysis less controllable.

(iii) Degree of polymerisation.

Increase the degree of polymerisation, thus the chain length of the polymer, would decrease the rate of degradation.

4 (a) Mechanical valve and biological valve are two different types of heart valve replacements.

(i) In a mechanical valve, state the material that is typically used for forming the flap structure which regulates blood flow.

Pyrolite® Carbon (or amorphous carbon)

(ii) The flap structure in a biological valve is currently made from sterilised, cell-free biological tissues. Discuss how the material properties associated with a biological tissue flap determine its performance and usage, as compared to a mechanical valve.

Heart valve is a permanent implant subjected to constant rapid blood flow. The material surface could induce thrombosis, and/or undergo wear due to the blood flow.

Biological valves: The cell-free animal or human tissue constitutes material surfaces that are intrinsically blood compatible (i.e. thrombo-resistant). However, the biological materials are soft (with modulus below 1MPa) and undergo wear and erosion due the blood flow. Hence, these valves typically do not require long-term blood-thinning medication but may need to be replaced after ~10 years.

Mechanical valves: With high Young's modulus (>10 GPa) and hardness, the valve materials are durable can last a lifetime. However, materials such as Pyrolite® Carbon do not offer blood compatible surfaces, and thus patients would require lifelong blood-thinning medication to prevent clots.

(iii) Ongoing research proposes to incorporate cells into the biological flap structure in order to produce a tissue engineered valve. Suggest the motivation behind this research proposal. Discuss major considerations associated with the cell component of such a tissue engineered valve.

In the case of the biological flap, the motivation is to harness the intrinsic generative ability of the cells to synthesize and repair the biological tissues and extracellular matrices when they degrade during the implant's operation. Hence, the tissue engineered valve could be both blood compatible and long-lasting (without needing revision surgery).

Consideration 1: The choice of cells;
Cell sources can be differentiated or stem cell based.

1) Differentiated cells
• Autologous (self)
• Allogeneic (transplant)
• Xenogeneic (another species)
2) Stem cells (undifferentiated or partially differentiated cells that can differentiate into various types of cells and proliferate indefinitely to produce more of the same stem cell.)
• Embryonic (ethical issues)
• Adult (potentially self, e.g. mesenchymal stem cells)
• Induced pluripotent stem cells (iPSC)

Consideration 2: The scalable manufacturing of cells: A large number of cells is needed for TE application, ~ 5x10^8 cells per cm^3 of tissues. Differentiated cells quickly lose their characteristics during culture and cannot produce at large quantity. Stem cells can be cultured at large quantities but may lack the exact functions of differentiated cells.

Consideration 3: The length of time for cell culturing in vitro to mature with the entire scaffold, versus to mature in vivo.

(b) Describe the different states of water present in a hydrogel.
• Free water – water that is not intimately bound to the polymer chain and behaves like bulk/pure water, i.e. undergoes thermal transition at temperature analogous to bulk water (at 0˚C)
• Freezing bound water – water that is weakly bound to the polymer chain and undergoes a thermal phase transition at a temperature lower than 0˚C
• Bound water (non-freezing water) – water tightly bound to the polymer, which does not exhibit a first order transition over the temperature range from -70 to 0˚C.

(c) In early designs of total hip implants, high-density polyethylene (HDPE) was commonly used as the plastic liner.

(i) What is the most likely degradation mechanism of a HDPE liner? State the consequences of such degradation on the implant host.

The high-density polyethylene acts as a load-bearing surface, and subjected to friction and wear. The wear process releases small wear particles, which can trigger foreign body response, leading to inflammation of the surround tissues. This in turn can cause aseptic implant loosening, which requires revision surgery of the implant (typical mean time to revision surgery of about 10 years).

(ii) To upgrade the plastic liner material, a designer suggests replacing HDPE with polyurethane. Comment on the suitability of this upgrade.

The wear performance of a material is determined by hardness and coefficient of friction. Polyurethane has a lower young's modulus (softer) and higher coefficient of friction than HDPE, thus the upgrade to polyurethane will result in worse performance than HDPE