EGT2
ENGINEERING TRIPOS PART IIA

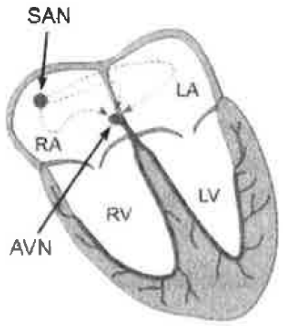
Module 3G5, BIOMATERIALS-- Cribs

---

1 (a) (i) Explain the key features of an electrocardiogram for measuring normal heart physiology.

(a) Electrocardiogram (ECG or EKG) is a test of heart electrical behaviour performed by placing a number of electrodes on the skin and monitoring the paired voltage differences between the electrodes.

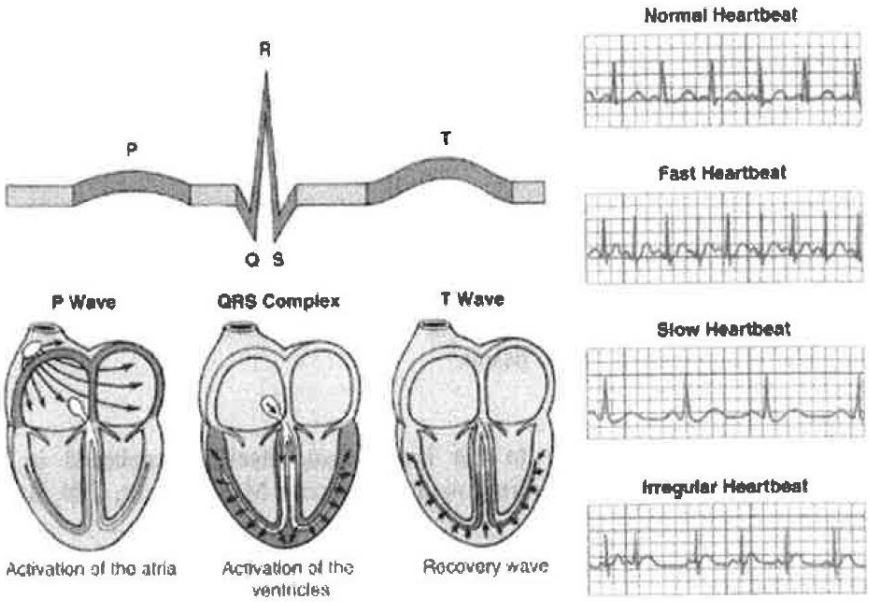
The heart has a *natural pacemaker* and it is through electrical potentials travelling through a network of electrical conduits that the muscular action (i.e. the beating of the heart) is obtained.



SAN, sinoatrial node; AVN, atrio-ventricular node; RA, right atrium; LA, left atrium, RV, right ventricle; LV, left ventricle.

The cycle starts when cells at the SAN (sinoatrial node) cause an electrical signal. The pulse travels from the SAN node to the AVN (atrioventricular node) and the atrial muscle cells contract. The pulse moves down the Bundle of His, splitting into the Left and Right bundle branches and ending in the Purkinje fibers. The ventricular muscle cells then contract and the cycle is over, ready to start again.

The output of the EKG is a voltage-versus-time plot that can indicate good or poor performance of the heart's electrical system.



The P-wave indicates the electrical activity associated with the atrial contraction, the QRS complex the electrical activity associated with the ventricular contraction and the T-wave with the ventricular repolarization and readiness to start the cycle all over again.

Because the voltage signal is plotted against time, it can be used to study the regular heart rate and also irregular heart beats that are not occurring in evenly-spaced time increments.

(a) (ii) Describe the types of pacemakers. Explain how a pacemaker restores heart function.

Pacemakers are designed to perform the function of the SAN and generate the electrical signal to cause the heart to pump. There are different types depending on the patient, those that discharge regularly and those that monitor the heart and only discharge when the heart rhythm is irregular.

There are three types of pacemakers:

- *Demand pacemakers*, which monitor the heart rate and discharge electricity only when the heart rate falls below a programmed minimum or misses a beat. Used in cases where the heart works most of the time, and in younger, healthier patients.
- *Fixed-rate pacemakers*, which discharge a steady stream of electrical impulses, regardless of the underlying heart rate.
- *Rate-responsive pacemakers*, which monitor various physical changes in the body (e.g., respiration, physical activity) and change the rate of discharge accordingly.

Irregular heart rhythms associated with poor natural pacing can be associated with disturbances of electrical *impulse generation* or of electrical *impulse conduction*. (So roughly to the engineer that means either a bad battery/spark system or faulty wiring!)

Generation problems include when the generating is starting somewhere other than the SAN or other failures of operation of the SAN.

Conduction problems include complete blockages in the regular conduction pathways or "re-entry loops" where firing occurs independent of/without any further signal coming from the SAN.

(b) (i) Describe the key features of the disease type I diabetes mellitus. Describe the current medical device technologies used in the treatment of diabetes and their operating principles.

Diabetes type I or juvenile diabetes occurs when there is autoimmune (i.e. self-inflicted) destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood glucose (hyperglycaemia). The classical symptoms are frequent urination, increased thirst, and increased hunger but simultaneous weight loss. It is fatal if not treated with exogenous insulin.

Currently there are two critical technologies used in diabetes care. The first is glucose sensing devices, either external or implanted, to measure the current blood sugar, and the second is insulin pumps for drug delivery.

Glucose sensing has dominated the biosensor literature and has delivered huge commercial successes to the field. The deceptively simple combination of a fungal enzyme (glucose oxidase) with an electrochemical detector: oxidation of the glucose in a blood sample is catalyzed by an enzyme (glucose oxidase) and the hydrogen peroxide H_2O_2 is the target of either electrical or colorimetric quantification.

Although the development of more convenient hand-held glucose biosensors for one-shot measurements of glucose in a pin prick of blood have been of enormous help to diabetic patients, it is clear that further improvements in the technology are essential. There are two principal avenues of potential improvement compared with having to keep pricking the finger to measure blood glucose: implantable subcutaneous glucose electrodes, that allow for continuous monitoring, and minimally invasive or noninvasive instruments for glucose measurement. For implanted glucose sensors, Microfabrication technology has aided in the design of enzyme electrodes that can be inserted under the skin, typically in the abdominal area. A monitor attached to the patient receives a measurement from the biosensor every ten seconds and stores an average glucose value in its memory once every five minutes. This implantable sensor has a lifetime of up to three days. An alternative non-invasive approach uses reverse iontophoresis to extract glucose

from skin tissue and to measure amperometrically the hydrogen peroxide resulting from oxidation of the glucose in the presence of glucose oxidase. In this case, the instrument is in the form of a wrist watch providing automatic readings up to three times per hour for as long as twelve hours.

Insulin pumps have been introduced as an alternative to multiple daily injections of insulin and have been growing in use, especially in people who exhibit poor compliance with blood monitoring and injections, such as diabetic children. The modern pumps are the size of a pager, controlled by microprocessors and pump different insulin concentrations for daytime, night-time and mealtime. Although one commercially available pump has a continuous glucose monitor on the same device, the two components are not currently allowed to communicate and thus current insulin pumps are open loop.

(b)(ii) How do biological responses create obstacles to the function of engineered diabetes implants?

The tip of the finger can become callous and sensitive following repeated pricking with a lancet for measurements using an external glucose-monitoring device, potentially requiring the use of a different device that can use blood sampled from another location. Subcutaneously implanted glucose sensors trigger a local inflammatory and wound healing response, which results in a fibrotic layer that walls of the implant and impairs diffusion of glucose to the sensor after a few days, thus rendering the implant non-functional. A similar fibrotic response over a similar time-span impairs the subcutaneous delivery of insulin from an implanted insulin pump.

Q1. Examiner's Comment:

This question consisted of two parts of assay-type questions and it was relatively popular. Top marks were achieved for completeness, with single line answers failing to give the full definition or answer compared with longer and more thoughtful answers.

2 (a) Write brief notes to explain the following:

(i) cytotoxicity and biocompatibility; [10%]

Cytotoxicity, "cell toxicity" falls into 4 categories:

(i) Cell death
(ii) Cell damage
(iii) Cell population growth slowed (dead/damaged cells don't proliferate)
(iv) Cell metabolism altered

Biocompatibility encompasses two aspects:

Biosafety: the exclusion of severe deleterious effects of a biomaterial on an organism. Includes cytotoxicity and mutagenicity/carcinogenity (ability to form cancerous tumors). Usually associated with a low-level immune response to the implant.

Biofunctionality: ability to perform with an appropriate host response in a specific application

(ii) the classification of medical devices according to risk; [10%]

Medical devices are classes according to risk, with class I being the lowest risk and class III being the highest risk, for long-term implantable devices. Class II or moderate risk devices are further divided into class IIa and class IIb devices in the European system, but not in the US system where there is a single class II. Low risk class I devices are relatively easy to get to market, but class II and III devices require increasing levels of scrutiny in terms of regulatory oversight at all stages of design and development.

(iii) the principles of bioethics; [10%]

There are four principles of bioethics:

(i) Respect for patient autonomy (the patient is a participant in the medical process)
(ii) Justice (there is a fair distribution of scarce healthcare resources)
(iii) Beneficence (do good)
(iv) Non-maleficence (do no harm)

(iv) how are nanoparticles characterized for drug delivery applications? Define 'targeting' in the context of nanoparticle drug delivery; [10%]

Nanoparticles are characterized according to their physicochemical properties (particle size and size distribution, surface area and surface area to volume ratio, surface electrical charge, shape, surface functionality, and aggregation state); their toxicity and immune response in *in vitro* (literally "in glass" such as in culture dishes in an incubator) biocompatibility assays, and their toxicity and immune response in *in vivo* (in the body, as in an animal) biocompatibility assays.

Targeting is the process of delivering a drug locally instead of systemically. Targeting can be passive or active. In passive targeting, nanoparticles accumulate near tumours due to their size: tumour tissue has greater permeability and these particles would be excluded from normal tissue. In active targeting, molecules are conjugated to the

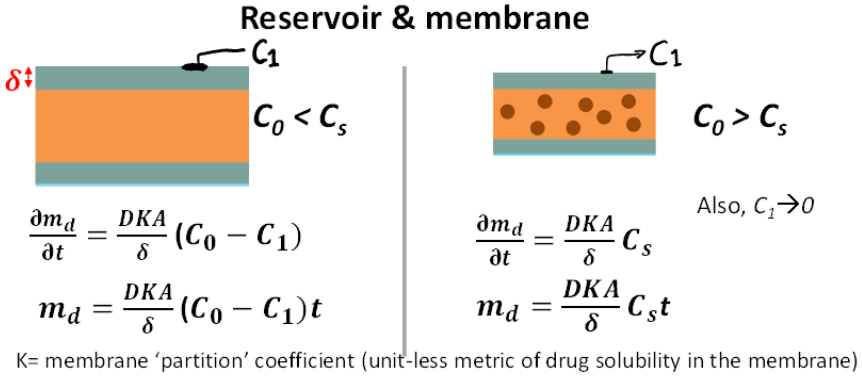
nanoparticles, such as antibodies seeking antigens that are only expressed in the tumour tissue.

(v) What are PEG and PEGylation? Why is PEG used with nanoparticles in drug delivery? [10%]

PEG is polyethylene glycol, a non-ionic polymer with a repeating CH_2-O-CH_2 backbone, and it is extremely hydrophilic. PEGylation is the process of attaching PEG molecules to something else, to take advantage of the unique properties of PEG. Because it is so hydrophilic, attaching PEG to an otherwise less-biocompatible moiety such as a nanoparticle, can make the entire complex more biocompatible and more efficient in terms of drug delivery.

(b) A drug delivery patch is employed for transdermal drug delivery.

(i) Considering the patch as a diffusion controlled delivery device, sketch a suitable patch design which will result in a constant rate of drug delivery. Based on your stretched design, state and label the key geometrical factors and the boundary conditions which will affect the rate of delivery. [15%]



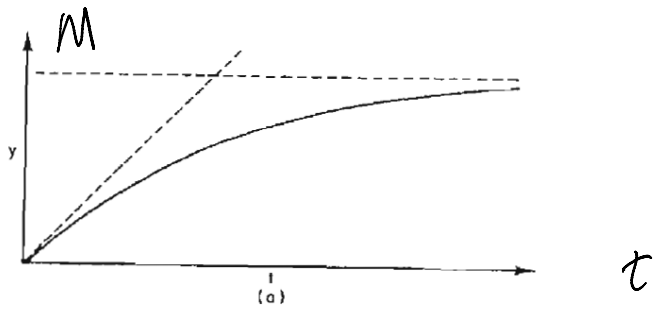
Approximately constant release rate (* for a slab geometry).

NB. The detailed form of the equation is not required. Answer either case is sufficient.
The reservoir and membrane configuration as shown above can provide a constant rate of delivery, for both the conditions of $C_0 > C_s$ or $C_0 \leq C_s$, where C_0 is the drug concentration in the reservoir, and C_s is the solubility limit of the drug in the reservoir. To establish a constant rate of delivery, the reservoir drug concentration C_0 and the surface drug concentration C_1 should stay constant.
The geometrical factors which will affect the delivery rate are the slab surface area A, and the thickness of the membrane δ. The concentration boundary conditions of C_1, and C_0 (or C_s in the case of $C_0 \leq C_s$) across the membrane will also affect the rate of delivery.
(For the above answer, the display of full equations are not required).

(ii) Assuming a constant rate of drug delivery *a* is sustained overtime, sketch a graph describing the amount of drug released into the skin as a function of time. Clearly label any asymptotic limits and state your assumptions [15%]

Take λ as the rate of drug clearance in the body, the mass of drug in the body is represented as:

$$M = \frac{a}{\lambda}(1 - exp(-\lambda t))$$



Initial slope is *a* (*i.e.* evaluate dM/dt at t=0).
The steady state mass of drug in the body is a/λ (*i.e.* evaluate M for $t \rightarrow \infty$)

(iii) A drug loaded in the patch has an exponential decay characteristic with a half-life of five day clearance in the body. The toxic level for the drug in the body is 100mg, and the minimum effective level is 10mg. Calculate the range of delivery rates which should be designed for this drug. [20%]

The rate of drug clearance:
$\lambda = \ln 2 / T_{1/2} = 0.69/5 = 0.138\ day^{-1}$

Since at the steady state, $M_{ss} = a/\lambda$
The upper delivery rate: $a_{max} = M_{toxic} \times \lambda = 100 \times 0.138 = 13.8$ mg/day
The lower delivery rate: $a_{min} = M_{eff} \times \lambda = 10 \times 0.138 = 1.38$ mg/day

Q2. Examiner's Comment:

This question consists of two parts, where part (a) consists of a list of short descriptive questions; and part (b) involves both the understanding of a concept, as well as some calculations. The mark variation is significant, where the lowest mark obtained was 5/20, and the top mark achieved was 19.5/20. In part (a), students could either answer all key points well, or fail to address any. In part (b), most mistakes occur in (iii) where students may have failed to distinguish the concept between the mass of the drug remain in the patch, or the actual amount of drug being released and distributed into the body.

3 Polylactic acid (PLA) – polyglycolide (PGA) co-polymers are one of the most widely used hydrolysable implant materials for tissue engineering scaffolds. Figure 1 below shows how the degradation half-life and the crystallinity of the co-polymer vary with the constituent PLA and PGA composition.

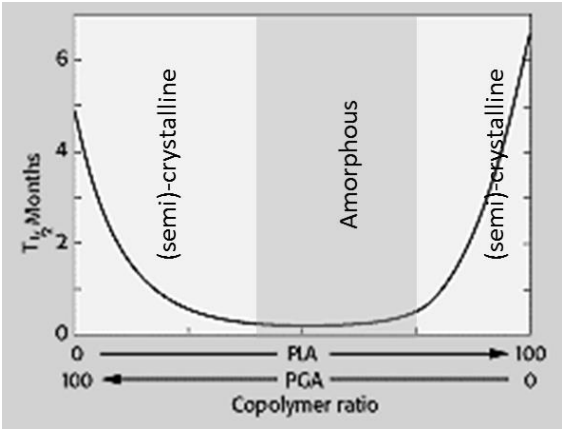


Figure 1

(a) Define hydrolysis. What are the common factors influence hydrolysis? Explain how these factors can account for the shape of the curve seen in Figure 1. [20%]

PLA and PGA are both polymers (polyesters) that undergo hydrolysis, the breakdown of polymer chain covalent chemical bonds on exposure to water. The most important factor affecting chemical stability of polymers in the body is the chemical nature of the hydrolytically susceptible groups in the polymer backbone.

Additional critical factors are:

- the hydrophobic/hydrophilic character of repeat units;
- polymer crystallinity;
- glassy vs. rubbery state (faster reactions in rubbery state);
- geometry (size and surface area to volume ratio) of the device.

These are all important because of the relative ease of water reaching the hydrolytically susceptible groups in the backbone. Water motion through the material is by diffusion and is slowed by hydrophobic units, high crystallinity/low porosity and large diffusion distances in the case of large parts with small surface/volume ratios. Also affecting the degradation rates are the outward diffusion of hydrolysis by-products; if trapped, they can create pH gradients that accelerate hydrolysis in the center of the sample, leading to gradients in the specimen.

PLA and PGA have the same backbone chemistry (ester), but implants made of pure PGA erode faster than those made of pure PLA since PLA side chains are more hydrophobic. In addition to the side chain chemistry, the crystallinity of the co-polymer also contributes the hydrolysis rate. Co-polymers in the composition range of about 35%-75% of PLA are amorphous and therefore exhibit shorter half-lives (or, fast degradation) compared to the semi-crystalline ones.

(b) Based on Figure 1, suggest what PLA-PGA co-polymer ratio or composition you will use for the following applications. State the reasons for your choice.

(i) resorbable sutures [10%]

9:1 PGA to PLA ratio is commonly used (other ratios close to this value also accepted with supporting explanation). The resulting material is semi-crystalline and has a degradation half-life of approximately one and half months. The semi-crystallinity gives the material adequate tensile strength which enhances the filament fracture resistance over the course of wound healing. In addition, the degradation half-life of one and half months matches the times commonly needed for complete wound closure.

(ii) resorbable capsules for drug delivery [10%]

Co-polymers which have compositions resulting in an amorphous structure is used. Therefore, co-polymers in composition range of about 40%-70% of PLA are used (answers are accepted as long as the quoted ratio falls within this range with supporting explanation). This is because, an amorphous structure provides a homogenous phase for drug dissolution and release. The exact composition of choice will be determined by the length of delivery time required, and also by the drug solubility in the co-polymer.

(iii) resorbable screws for bone graft [10%]

A composition with close to pure PGA is used. This is because pure PGA has a good mechanical strength compared to the co-polymers. A longer healing time is also required for recovering from bone defects, thus the degradation half-life of five months associated with pure PGA is also adequate.

(c) When implanted, a PLA-PGA co-polymer will undergo erosion in the body. Assume a hydrolysis rate constant of $\lambda=5\times10^{-6}$ s^{-1}, a diffusion coefficient of $D=10^{-8}$ cm^2, and the volume containing one degradable bond to be $V=3\times10^{-22}$ cm^3:

(i) Determine the critical thickness W_c for bulk *vs.* surface erosion, to the millimetre accuracy. [25%]

$$\tau_D = \frac{\pi < x >^2}{4D_{eff}}$$

$$\tau_E = \frac{1}{\lambda}\ln(n) = \frac{1}{\lambda}(ln < x > -ln(V^{1/3}))$$

$$\xi = \frac{\tau_D}{\tau_E}, \quad <x>|_{\xi=1} = W_c$$

$$\xi = \frac{\frac{\pi <x>^2}{4D_{eff}}}{\frac{1}{\lambda}(\ln <x> - \ln V^{\frac{1}{3}})}$$

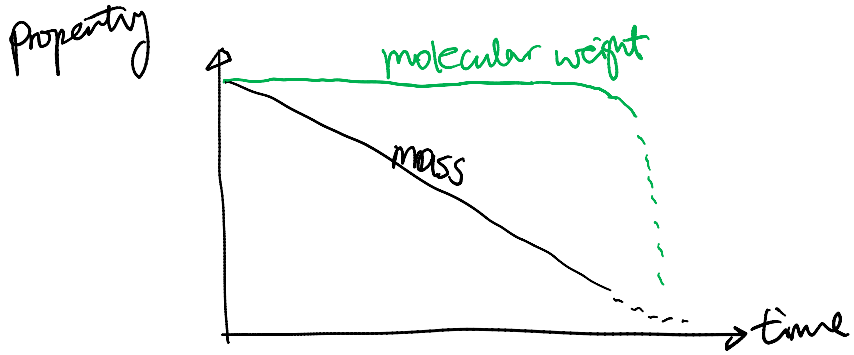
$$1 = \frac{\frac{\pi W_c^2}{4 D_{eff}}}{\frac{1}{\lambda}(\ln W_c - \ln V^{\frac{1}{3}})}$$

$\lambda=5\times10^{-6}$ s^{-1}, $D=10^{-8}$ cm^2, $V=3\times10^{-22}$ cm^3
$W_c \sim 0.2$ cm = 2mm

(ii) Consider the implant to be a slab of 2cm thick, suggest the dominating erosion mechanism. [10%]

$W > Wc$, surface erosion.

(iii) Based on your erosion mechanism suggested in (ii), sketch how the mass and molecular weight of the slab implant will change over time. Give brief explanations on the key features. [15%]



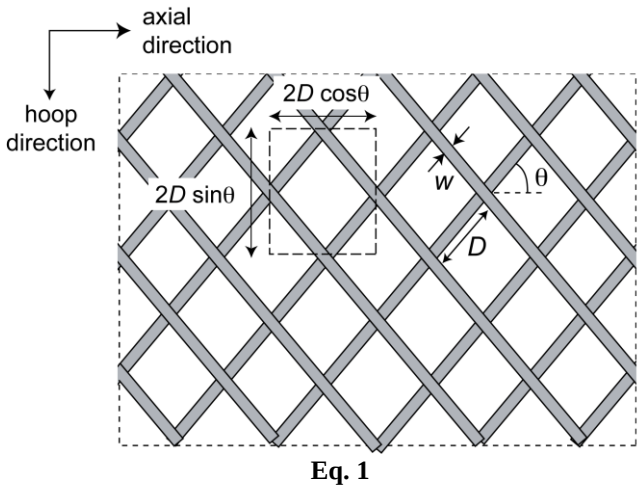
Since the erosion mechanism is surface dominant, the molecular weight of the material stays constant until the final stages where the implant disintegrates. For a slab geometry, one can assume erosion dominates at the two surfaces of the largest area. With a constant rate of water penetration, the mass of the slab thus decreases approximately linearly until the implant disintegrates.

4 **(a) When diagram in Figure 2 shows part of the tubular wall structure of an unexpanded cylindrical stent, unwrapped so that it is planar. The individual members all lie at angles of $\pm\theta$ to the axial direction – see Figure 1. They all have both a width and a thickness of w (=0.2 mm), and a spacing between crossover points of D (=2 mm).**

(i) Sketch a "unit cell" of the wall structure, which has its sides parallel to the axial and hoop directions. Estimate the metal volume fraction in the wall of the unexpanded stent if the inclination angle θ is 20°. [15%]

A unit cell is identified of sides $2D\cos\theta$, $2D\sin\theta$ and w. Each cell contains 4 metal segments. The metal volume fraction is thus given by

$$f = \frac{4\,Dw^2}{(2D\cos\theta)(2D\sin\theta)w} = \frac{w}{D\cos\theta\sin\theta} = \frac{(0.2\times10^{-3})}{(2\times10^{-3})\cdot\cos 20^\circ\cdot\sin 20^\circ} = 0.31$$



Eq. 1

(ii) Estimate the relative increase in the radius, and the relative decrease in length, hence the axial contraction ratio of the stent, when the inclination angle θ is 50°. [15%]

relative decrease in length $= \dfrac{2D\cos 50^o - 2D\cos 20^o}{2D\cos 20^o}$; 0.31

relative increase in radius $= \dfrac{2D\sin 50^o - 2D\sin 20^o}{2D\sin 20^o}$; 1.24

axial contraction ratio ; 0.25

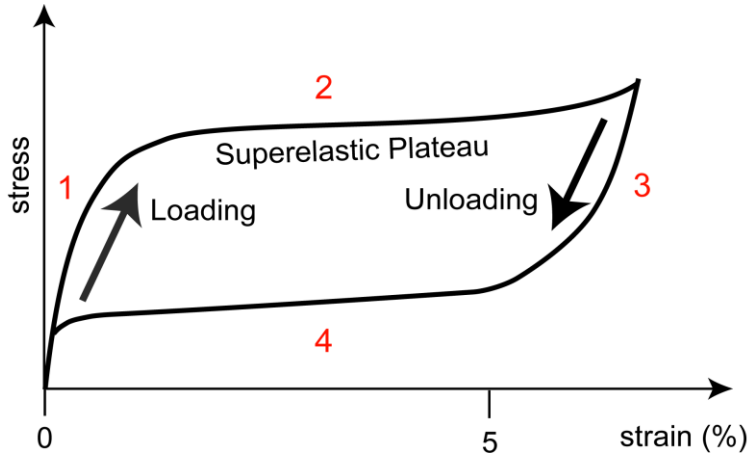
(iii) Explain the disadvantage of this stent wall design in terms of its mechanical properties and how these maybe undesirable from a surgical point of view. [20%]

This particular stent design has high axial beam stiffness before expansion because the members lie at low orientation angles to the horizontal. This is highly undesirable since stents must often be pushed through vessels, which may exhibit relatively high curvature. Stents with high axial beam stiffness before expansion may apply excessive local pressures causing serious damage to the vessel wall. The subsequent repair process is complex with inflammatory and thrombotic pathways being activated. Platelets become adherent to the damaged vessel wall due to loss of the protective endothelium (inner layer of the blood vessels). These changes culminate in recurrence of restenosis, and the need, because of luminal renarrowing, for further intervention. Another disadvantage of this design is its axial contraction (i.e. reduction in its length), which prevents precise positioning of the stent. Nowadays, stent wall designs incorporate features that tend to reduce the axial contraction ratio.

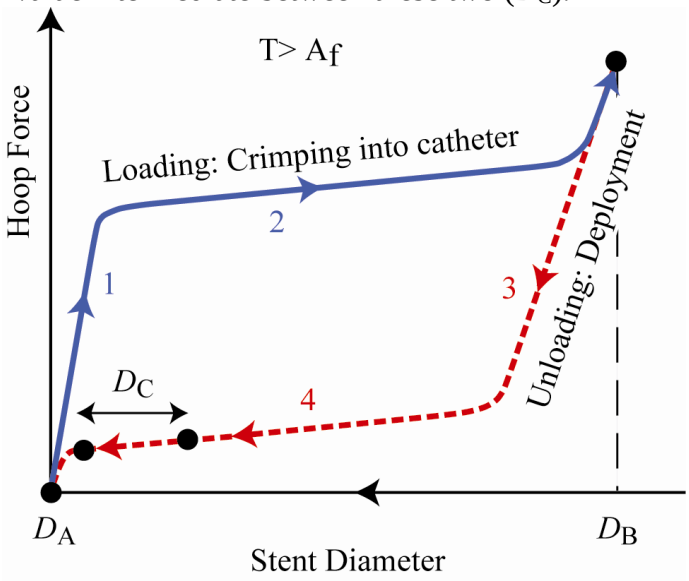
(b) Consider an endovascular stent made of a superelastic alloy. Describe the superelastic effect by sketching the form of the stress-strain curve typically exhibited by such a material and explain why it has this form. Using a hoop force – stent diameter diagram, explain how the superelastic effect is utilised in stents. [50%]

Superelasticity involves martensitic transformations stimulated by imposed mechanical strain. When mechanically loaded in a certain temperature range, relatively large strains can be generated, which are recoverable on unloading.

A typical stress-strain curve is illustrated below. At $T > A_f$, if deformed in the parent phase, initially the material undergoes normal elastic deformation (regime 1). Once the applied stress exceeds a critical value, the parent phase starts transforming to martensite. Increases in the proportion of the parent phase transformed are stimulated without much increase in the applied stress, giving rise to the characteristic “superelastic plateau” (regime 2). When the stress is released, there is conventional elastic unloading of the strained material (regime 3). In regime 4, the phase transformation spontaneously reverses (although there is some hysteresis), and the original shape is recovered.



At $T > A_f$, the stent in the parent phase (austenite) with an original diameter D_A (higher than the relaxed diameter of the vessel) is collapsed to a small diameter D_B. Initially, there is conventional elastic straining (Regime 1), which is then followed by a superelastic plateau whereby the austenite transforms to martensite (Regime 2). The crimped stent is then inserted into a catheter. When deployed from the catheter *in vivo*, initially the stent gets elastically unloaded (Regime 3) followed then by reversal of the phase transformation (Regime 4). The stent is trying to recover its original shape but is constrained from full recovery to D_A by the lumen walls. The stent exerts an outward force on the vessel (trying to expand to its relaxed diameter) and, conversely, the vessel exerts a constrictive force on the stent. A suitable equilibrium diameter is then established with a value intermediate between these two (D_C).



Q3. Examiner's Comment:

This question was about biodegradable polymers, which involves some short descriptions questions and a calculation of the erosion mechanism. All 29 students have attempted this question, despite of the fact that this is a new question compared to the previous TRIPOS papers. Since the materials have been covered in details in class, most students have answered the question well (as reflected by the high average mark obtained). The top raw mark obtained is 20/20, while the lowest is 6/20.

Q4. Examiner's Comment:

This question is on the description and calculation of a stent structure. The top raw mark obtained is 14/20, while the lowest is 5/20. Notable mistakes associated with the calculations included putting down the wrong formula, and/ or mis-calculated the geometry. In the part which requires to explain the superelastic effect used in stent, many students failed to demonstrate the correct hoop force – stent diameter diagram.