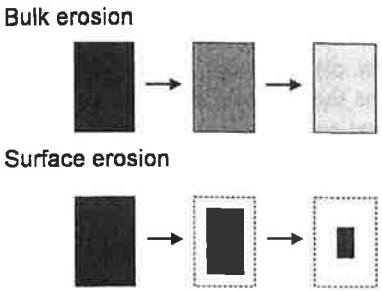
3G5 (2012)

ENGINEERING TRIPOS PART IIA, 2012
Module 3G5: Biomaterials **Principal Accessor: A.E. Markaki**

Cribs
The answers to some of the descriptive parts of questions may be longer than the candidate would have time to complete.

Question 1
(a) Bulk erosion is uniform through the sample while in surface erosion there is an erosion "front" and a degrading region of fixed thickness. In bulk erosion, the volume remains constant, there is no change of sample geometry, whereas molecular weight and density decrease linearly with time. In surface erosion, the sample shrinks and the molecular weight and density remain constant.



Bulk erosion takes place when the sample thickness W is less than a critical thickness W_c, when the time constant τ_D for water diffusion in the polymer is less than the time constant τ_E for hydrolytic bond cleavage and when the ratio of the diffusion to hydrolysis time constants, $\varepsilon = \frac{\tau_D}{\tau_E}$, is less than 1:

Bulk erosion	Surface erosion
$W < W_c$	$W > W_c$
$\tau_D < \tau_E$	$\tau_D > \tau_E$
$\varepsilon < 1$	$\varepsilon > 1$

Bulk erosion occurs when water can diffuse into the sample faster than the degradation can take place, while surface erosion is diffusion-limited.

The critical lengthscale can be found by equating the two time constants and solving for W_c:

$$\tau_D = \frac{\pi W_C^2}{4D} = \tau_E$$

$$W_C^2 = \frac{4D\tau_E}{\pi} = \frac{4 \cdot 1 \times 10^{-12} \cdot 8 \times 10^5}{\pi} \Rightarrow W_C = 1 \text{ mm}$$

NB: The diffusion constant has been converted to $m^2\ s^{-1}$ so W_c will be in m.
Thus the implant will undergo surface erosion.

While the diffusion constant for water in a polymer is roughly the same for all solid polymers, the reaction rate constant λ varies significantly and substantially. Thus, for implant design, in order to purposefully tailor whether surface or bulk erosion is occurring, the polymer material itself can be varied at fixed sample size in order to select surface or bulk erosion. This is particularly important in weight-bearing implants, where bulk erosion would be problematic and surface erosion is preferred (because the overall mechanical properties are degraded in bulk erosion whereas the remaining material in surface erosion has fixed material properties). So the current implant, at 6 mm thus greater than the critical thickness, will undergo surface erosion and the implant is suitable for load-bearing applications.

(b) (i) 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

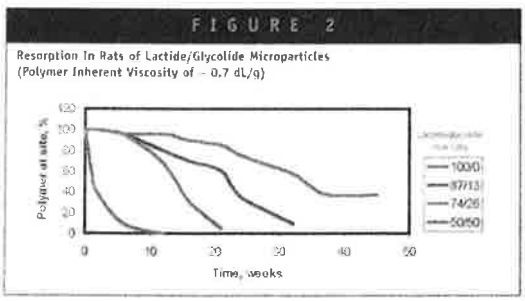
affecting chemical stability of polymers in the body is the chemical nature of the hydrolytically susceptible groups in the polymer backbone.
Additional critical factors are:

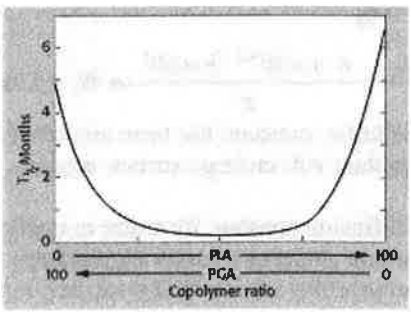
- the hydrophobic/hydrophilic character of repeat units;
- polymer crystallinity;
- glassy vs. rubbery state (faster reactions in rubbery state);
- geometry (size and surface area to volume ratio) of the device.

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.

(ii) PGA and PLA have the same backbone chemistry (ester), but devices made of PGA erode faster than those made of PLA since PLA side chains are more hydrophobic. PLA-PGA blends in the 50:50 composition range are amorphous, while the pure polymers are semi-crystalline. The degradation rates for PLA-PGA blends depend on the crystallinity, polymer molecular weight and specimen porosity. Some additional details are in the image below, the key point of which is that amorphous 50:50 blends erode significantly faster than either polymer alone (either of the bottom two plots would satisfy the question in terms of a sketch of the time-scales of co-polymer erosion, either showing the percentage of polymer remaining as a function of time, on the left, or the half-life as a function of composition, on the right). Because this is a continuum, the PGA:PLA ratio can be used to optimize the composition to target a specific degradation rate.

PGA	PLA	Morphology
0-25 mol%	75-100%	Crystalline
25-65%	35-75%	Amorphous
65-100%	0-35%	Crystalline





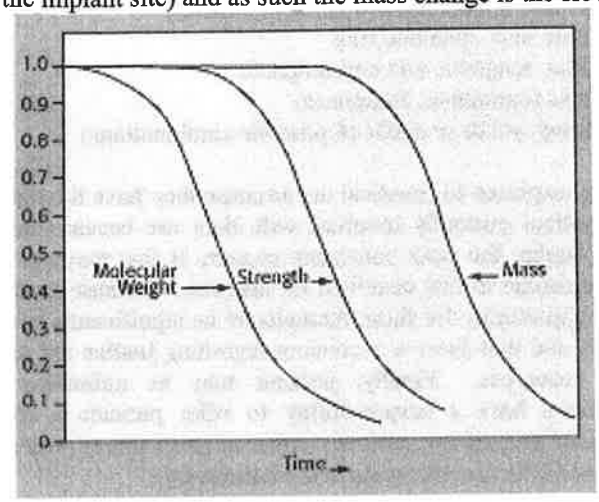
This is critical in the context of tissue engineering, in which there is a trade-off between the degradation of the scaffold material and the in-growth of new tissue (extracellular matrix). If the polymer scaffold degrades either too slowly or too quickly compared with the growth of new tissue, full functioning of the organ is unlikely.

(iii) The following plot illustrates how the molecular weight, strength and mass decrease with time. The molecular weight decrease is the fastest, because long polymer chains cut in the centre or near the centre will have a rapid effect on the molecular weight. The strength

decrease lags the molecular weight decrease slightly because the strength-molecular weight relationship goes as

$$\sigma_f = \sigma_f^{\infty} - \frac{C}{MW}$$

where σ_f^{∞} is the plateau value and C is a constant. In other words, strength reaches a plateau at large molecular weights, so at first the molecular weight changes are not reflected directly in the strength. The mass changes most slowly, because although the chains are cut by hydrolysis, until they get quite short they remain in place (i.e. are not cleared by the body or diffuse away from the implant site) and as such the mass change is the slowest overall.



Question 2

(a) Morals are defined as relative goodness or badness in the context of a singular human action or character. Ethics is defined as a theory or system of moral values, for a population, not for single persons, "a set of principles for right conduct".

The modern framework for bioethics arose after a number of atrocious acts were committed by medical doctors where they did not keep the patients' interests to heart but instead conducted experiments using human guinea pigs, most importantly the experimentation on Jews by Nazi doctors during World War II but also the later Tuskeegee syphilis trials. The Nazi doctors were implicated in the Nuremberg Trials after which the first codification of bioethical principles took place, but the principles did not get coded into law (at least in the US) until the late 1970s-early 1980s at which point they became more important and more generally well-adopted. These principles are now also the (non-binding) governing rules of the World Health Organization.

The four key principles are:

1. Respect for Autonomy

the patient (or a medical research study subject including someone in a medical implant clinical trial) is a participant in the process (anti-paternalism, the doctor does not act God-like because of his or her education and training in medicine)

2. Justice

there is a fair distribution of scarce healthcare resources, which means that public health systems such as the NHS do not have the option to deprive the many of basic care for specialist care of the few

3. Beneficence

"do good"

4. Non-maleficence
"don't do bad"; a restatement of the Hippocratic canon principle to "first do no harm"

The last two play out against each other in a fifth principle not always listed with the primary four, that of "Double Effect" which is when two competing interests are involved, most often encountered when harm must be done to a fetus in order to save the life of a mother.

(b) (i) Nanoparticles are on the order of 1-100 nm in size, and they can be a range of materials and geometries:
- Liposomes (like cells, fatty membrane containing contents)
- Nanoshells and quantum dots, quantum rods
- Metals and metal oxides, magnetic and non-magnetic
- Carbon-based structures (nanotubes, fullerenes)
- Polymer or protein based, solids or shells (4 possible combinations)

Nanoparticles are being explored for medical use because they have the potential to **do good**. However, there are cautions currently involved with their use because there is some worry that they may also **do harm**; the most consistent concern is that they can be irritants in the lungs via a mechanism similar to that observed for asbestos. Because nanotechnology is still emerging, there is the opportunity for these therapies to be significantly more expensive than traditional therapeutics, and thus there is a concern regarding **justice** and the fair distribution of scarce healthcare resources. Finally, patients may be unfamiliar with these new technologies, and doctors have a responsibility to offer patients a choice of the new technology and traditional technology, with the unbiased provision of pros and cons allowing for the informed consent of the patient (**respect for autonomy**).

Examples of nanoparticle applications in drug delivery:
- Drug on surface (TNF on Au with PEG)
- Drug inside a polymer capsule (reservoir system) (Pt, others in PLGA)
- Drug inside, distributed evenly throughout an erodible polymer (PLGA)

(c) ***Swelling controlled systems*** are particularly useful when the diffusivity of the drug in the polymer is very low. Water enters the pore spaces in the polymer, opening them up (causing swelling) and the swelling enhances drug diffusion.

Overall the behavior is controlled by two competing diffusivities:
(1) Diffusivity of drug in the polymer (as in diffusion controlled systems, above)
(2) Diffusivity of water in the polymer (to give rise to swelling)

A semi-empirical expression for the drug release shows this to be enhanced drug release compared with pure diffusion-controlled systems: cumulative drug released M_t = constant*t^n

In pure Fickian diffusion, $n = 0.5$ as noted above if swelling enhanced diffusion, $n = 0.5$ to as high as 1 for the case where the effective diffusivity of the drug in the polymer increases linearly with time, $D = D_0 + constant*t$

The governing law can be found from the two unknowns and two data points using $M_t = C\ t^n$ where M_t is the amount of drug released at time t, C is a constant, and n is between 0.5 and 1 for swelling-controlled systems.

By taking one data point and solving for C and substituting.

$$C = \frac{M_2}{t_2^n}$$

$$M_1 = M_2\left(\frac{t_1}{t_2}\right)^n$$

$$\ln\left(\frac{M_1}{M_2}\right) = n\ln\left(\frac{t_1}{t_2}\right)$$

$$n = \ln\left(\frac{M_1}{M_2}\right)\Big/\ln\left(\frac{t_1}{t_2}\right) = 0.8$$

$$C = \frac{M_2}{t_2^{0.8}} = 100$$

$M_t = 100\ t^{0.8}$

This is an empirical power law that shows a larger exponent than would be expected for diffusion alone, so there is some effect of swelling-enhanced diffusion. Pure diffusion would have $n = 0.5$ so this is a significant acceleration in drug release, but not the maximum swelling-induced effect, which would be found for n = 1.

(d) In general, a Monte Carlo simulation follows a set of generic guiding principles:
1. Define a domain of possible inputs.
2. Generate inputs randomly from the domain.
3. Perform a deterministic computation using the inputs.
4. Aggregate the results of the individual computations into the final result.

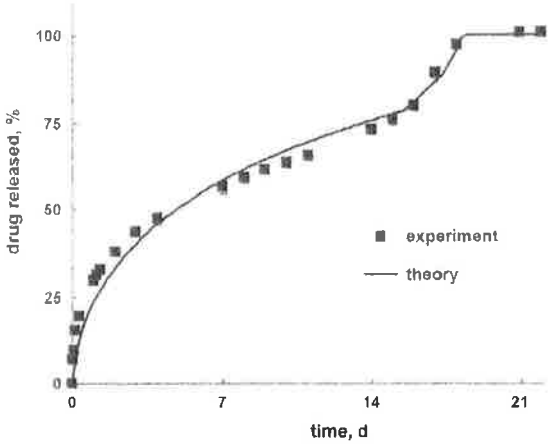
For this specific case, a Monte Carlo simulation could follow the following steps:

a. Create a set of equal-volume, axisymmetric domains.

b. Assign each domain randomly as "drug" or "polymer" and initially assign all "polymer" as intact. Generate random lifetimes for each polymer cell: Assume that the lifetimes of each cell will be exponentially distributed and independent. A random exponential variable can be generated using the formula Lifetime = $\frac{-\ln(1-p)}{\lambda}$ where p is a random number between 0 and 1 and λ is the hydrolysis reaction rate constant.

c. Start the simulation from time t = 0 and increment the time in small discrete steps, stopping each time one additional cell has eroded.

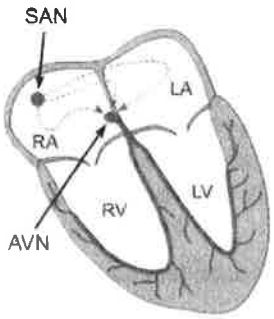
d. For each time step determine whether each cell is in contact with water. Any cells in water contact can start to diffuse (drug) or start to hydrolyze (polymer). Check at each time step if any polymer cell has fully eroded (elapsed time t is greater than the cell lifetime) and whether this erosion has created a path for more cells to be in contact with water. Calculate at each time step, based on the drug diffusion coefficient, at which time the drug will escape the boundary of the initial device when it has a free path for escape. At each time step, calculate the volume of the drug that has been released compared with the total initial volume and plot as a function of time. This will be a complicated, nonlinear, non-monotonic function of the approximate shape:



Question 3

(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.

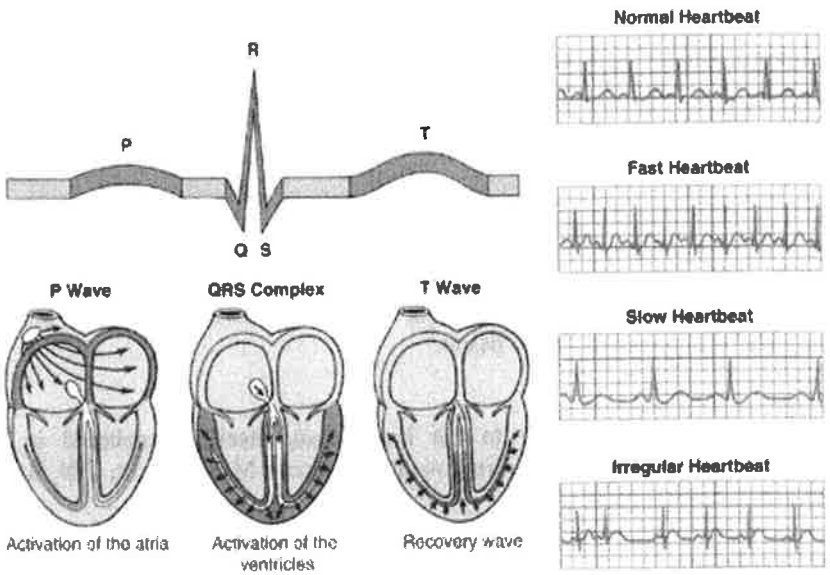
The heart has a *natural pacemaker* and it is through electrical potentials travelling through a network of electrical conduits that the muscular action (i.e. the beating of the heart) is obtained.



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.

(b) (i)
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.

(ii) A standard pacemaker has three parts:
Generator
Small box containing a battery. Acts as the natural SA node in that it generates a regular 2-4 mA electrical current. The least taxing component of a pacemaker from a pure biomaterials perspective.

Leads
Wires for conducting the electrical signal to the heart. Typically made of a noble metal, such as Platinum, for corrosion resistance, and coated with silicone rubber or polyurethane (or polyether-urethane) rubber. The leads are quite complicated in that they must contain both the anode and the cathode in a single casing with insulation between the wires plus an external packaging element that contacts the tissue.

Electrodes
Mechanism of electrical signal delivery to the heart tissue itself. Anchored in the heartmuscle, porous or non-porous for tissue-ingrowth. Electrode Materials: Pt, TiN, RuO2, IrO2, Nb2O5

Sources of pacemaker failure:
- infection (most rapid failures)
- electrode dislodgement
- myocardial perforation (hole in the heart)
- electrode corrosion
- lead fracture
- insulation failure (polymer corrosion)
- thrombosis/thromboembolism (a general problem in any implant that is blood contacting)

Thrombosis: the formation of a blood clot (thrombus) inside blood vessels, obstructing the normal flow of blood.
Thromboembolism: a thrombus moving from one part of the body to another via the vessels.

(iii) Health of the implant relates to the performance of the electrodes at the electrode-tissue interface. A key failure mode is fibrosis at the electrode-tissue interface, such that ECM tissue that is not electrically active is deposited near where the electrical signals are being transmitted. This can then interfere with the electrical signal transmission and cause serious problems requiring surgery and perhaps electrode replacement.

The normal wound healing response involves three stages, "plug" "clean" and "repair". Collagen production and fibrosis are a natural part of the normal wound-healing response in the "repair" phase: new tissue needs to be filled in to replace that lost to the injury. Fibroblasts secrete copious amounts of ***collagen*** and other matrix proteins. Collagen is the most abundant structural protein of the extracellular matrix of connective tissue, on account of its ability to assemble into fibrils and higher-order structures and to give mechanical strength to tissues such as bone and cartilage. The production of collagen may be excessive and leave the repaired tissue looking different and functioning less well than healthy tissue, forming a ***scar***. The overproduction of collagen in response to injury is referred to as ***fibrosis***, and occurs frequently not only in mechanical injuries, but also in chronic diseases that lead to tissue damage or in this case forming a capsule around the electrode, interfering with the implant function.
Fibrosis, the replacement of normal tissue by scar tissue with excess collagen and few functional cells, has already been mentioned. It may arise either due to imperfections during the attempts of the tissue to repair the initial injury; the scar tissue may then continue to be re-

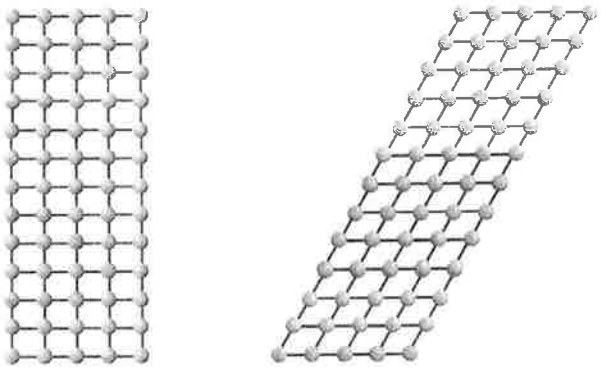
modelled by macrophages and fibroblasts and a more nearly normal tissue structure restored gradually over weeks and months. Alternatively, fibrosis may accompany chronic inflammation or wall off an abscess or foreign material persisting at the site of injury. If the regenerative capacity of the tissue becomes sufficiently exhausted, fibrotic changes may become irreversible, and the normal function of the tissue lost permanently.

Question 4

(a) Stents can be divided into two main groups on the basis of the method of expansion. *Balloon expandable stents* arrive premounted on a balloon anglioplasty catheter. While mounted the stent is moved into place and the balloon is inflated to expand the stent to the desired diameter. *Self-expanding stents* come premounted or sheathed. Once deployed to the treatment area, the sheath is pulled back, allowing the stent to expand to its predetermined diameter.

Balloon expandable stents expand by plastic deformation by an angioplasty balloon while self-expanding ones use the "superelastictity" or the "shape memory" effects.

(b) Martensitic transformations occur by means of a phase change from a "parent phase" (frequently referred to as austenite) to a "martensitic" phase. The process involves co-operative shearing of the lattice i.e. each atom moves a small distance relative to its neighbours in a well-defined way– see schematic below. This homogeneous shearing of the parent phase creates a new crystal structure, without any compositional change (no diffusion).



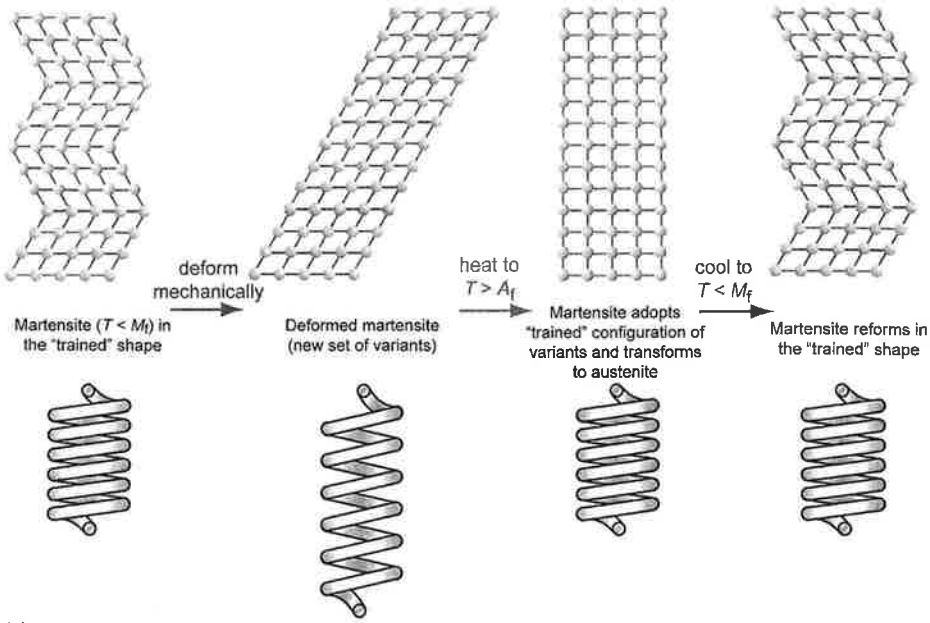
Parent phase (austenite)

Martensitic phase

The shape memory effect involves martensitic transformations stimulated by changes of temperature. It also involves a new concept - that of material being "trained" to have a preferred shape. This involves heating the specimen (while constrained into a certain shape) to high temperature (well above A_f), holding it at this temperature for a short period and then cooling it quickly to ambient temperature. Stress relaxation occurs during holding and then, during cooling (in the constrained shape), the austenite-martensite transformation takes place in such a way as to minimise the overall shape change. There is subsequently a tendency for the specimen to adopt its "trained" shape, in which transformation between parent and martensitic phases takes place readily.

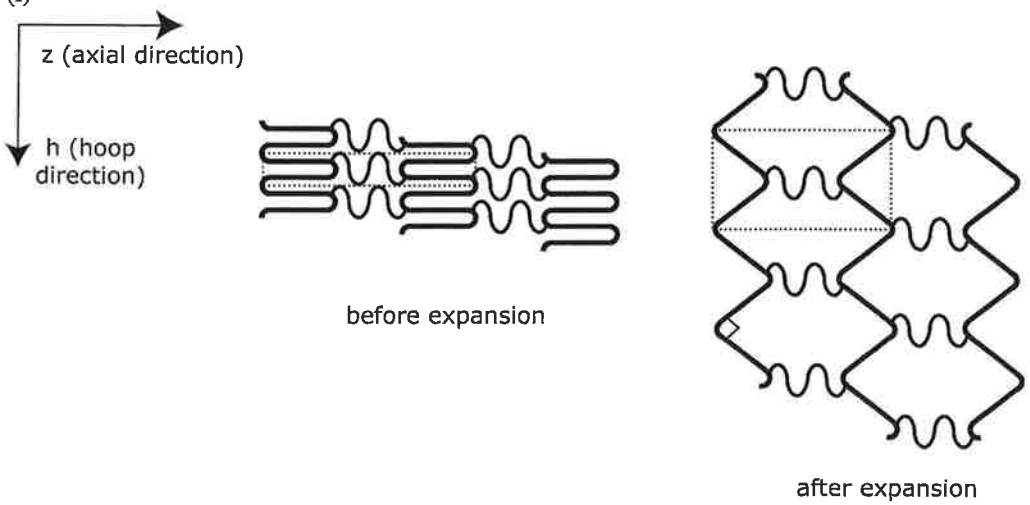
The schematic below shows how a shape memory alloy can recover a "trained" shape, after being subjected to a large (apparently plastic) strain while in the martensitic state. This is done by simply heating the specimen, so as to stimulate transformation of the martensite to

austenite. This takes place (in the absence of applied stress) by the martensite first reverting to its "trained" set of variants and then transforming.



(c)

(i)



(ii) The disadvantage of this design is its axial contraction (i.e. reduction in its length), which prevents precise positioning of the stent. Another disadvantage of this particular stent design is its high axial beam stiffness before deployment because the members lie at low orientation angles (horizontal loop members – the arrangement of the vertical loop members remains unchanged during expansion). This is highly undesirable since stents must often be pushed through vessels that may exhibit relatively high curvature.

The desirable mechanical characteristics for a stent are:
- a low axial beam stiffness (high flexibility) before expansion, because this allows the stent to curve around corners;

- a relatively high yielding pressure, particularly after expansion, to retain the vessel in an expanded condition;
- a low axial contraction ratio (ratio of relative decrease in length divided by the relative increase in radius) to allow precise positioning of the stent.
- a high expansion ratio at fracture.

Preferred functional characteristics include biocompatibility that minimises short and long term complications, plus durability in the stressful, corrosive environment of the human body.

(iii) The reason for developing drug-eluting coatings is to treat in-stent restenosis, which is due solely to "Neointimal Hyperplasia". This is excessive tissue proliferation due to post-implant arterial injury (roughly analogous to a scar forming over an injury) and foreign body response. To overcome this problem, approaches have included both degradable and non-degradable polymeric coatings, and drug-eluting coatings.

In drug-eluting stents, drugs are embedded in a polymer matrix that is coated onto the stent. The drug is released into the vessel by diffusion and/or polymer degradation over varying periods of time that can be engineered by the specifics of the polymer-drug system.

The main advantages of drug-eluting stents include: targeted drug delivery to precise area requiring treatment; ongoing delivery through phases of healing; no additional material or procedures required and ongoing delivery through phases of healing.

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Numerical Answers

1. (a) Critical thickness 1 mm

3. (c) $M_t=100\ t^{0.8}$