

Mock exam for 3G5 Biomaterials

1

(a) How are medical devices classified? Describe the similarities and differences between medical device regulation in the US and the EU

[25%]

(b) Define and describe the following

(i) Haemostasis

(ii) Inflammation

(iii) The difference between innate and adaptive immunity

(iv) The difference between a tissue and an organ

(v) Pancreatic Islet cells

[25%]

(c) Using the following data, what is the value of the decimal reduction time if the initial bio-burden was 120 organisms per implant?

Determine an appropriate process time for sterilization of a medical implant assuming an SAL of  $10^{-6}$ .

Time in autoclave at 121°C (minutes)	Surviving organisms
1	88
3	5
8	2
11	1 per ten parts
13	2 per thousand parts
16	1 per 10,000 parts
22	3 per 100,000 parts
23	2 per million parts
27	2 per ten million parts

[25%]

(d) A cancer patient has a bone tumor that is going to be removed from the leg, and which will require a metal implant to replace the missing tissue and restore the patient's ability to walk. The surgeon asks you whether it is better to remove an entire section of the bone, or if he should leave half of the cross section intact and implant only a half cylinder adjacent to remaining bone instead of a full cylinder of metal. What do you advise, and why?

[25%]

2

(a) (i) How does corrosion affect medical implants? Give examples. How do biological entities influence corrosion? How is corrosion prevented in implant devices?

(ii) A standard electrochemical cell is formed to mimic a medical implant situation where the half cell reactions involve  $\text{Pb}^{2+}$  and  $\text{Sn}^{2+}$  at standard electrode potentials of  $-0.126\text{ V}$  and  $-0.136\text{ V}$  respectively. Which way does the reaction go? What is the cell potential? If you change the concentration of tin ions in solution by a factor of 100, what change do you expect to see? [60%]

(b) (i) Describe thrombin formation in a blood-contacting tube in terms of the relative rates of deposition and blood transport. What is the critical condition for obstruction of the tube? How is this prevented in medical implants? [40%]

3

(a) Why are polymers finding increasing use in medical implants? [25%]

(b) What is the difference between drug release from spherical capsules and from solid spheres? How would you distinguish between the two mechanisms if you were given a blinded set of experimental data in which the two mechanisms were compared? What effect would be found if the solid spheres were hydrogels undergoing substantial swelling after implantation? [50%]

(c) Discuss the ways in which finite element modelling is used to study joint replacement, including the challenges in obtaining information to generate the models. [25%]

4

(a) Identify the important mechanical performance attributes of a balloon expandable stent. Are the values of any these parameters likely to change as the stent is expanded? [30%]

(b) Figure 1 shows a side view of a NIR (New Intra-Vascular Rigid flex) cylindrical stent before expansion via an angioplasty balloon. What are the primary attractions of the NIR (New Intra-vascular Rigid flex) stent in terms of its design? Explain how they are achieved. [40%]

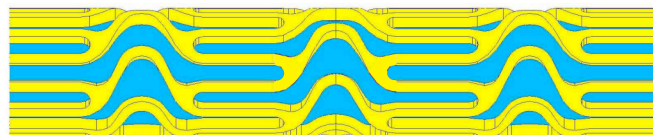


Fig. 1

(c) Why stents made of wire mesh are likely to fracture at low plastic strains? [30%]

## Crib for 3G5 Biomaterials Mock Exam

1

(a) Medical devices are classified according to risk. There are three classes of devices in the US, class I, class II, and class III. Class I devices are low risk, such as a bandage (plaster), and are also often temporary. Class III devices are high risk devices such as long term implants. Class II devices are intermediate in risk. Each class carries a different regulatory burden in terms of bringing the product to market.

In the EU, class II devices (as defined in the US) are further broken down as class 2a and 2b. The FDA reviews every medical device that is marketed in the US, whereas this does not occur in the EU where a “notified body” (independent and private organization) has authority to grant the CE mark. The EU regulatory process focuses much more on manufacturing quality control than on a requirement for establishing efficacy and safety of the device, something that is explicitly undertaken by the FDA in the US—the FDA has as part of its core mission the protection of public health, which is less emphasized in the EU compared with regulation of the “Internal Market” and standardization (including reliance on ISO). This philosophical difference is more striking than the procedural differences noted above. As a result of this, the EU relies more on voluntary standards than on federal regulations, which form the basis of the FDA procedure.

(b)

(i) Haemostasis is blood clotting, and has two key components: primary haemostasis, given by platelet aggregation (where a platelet is a small formed element of the blood, essentially a cell fragment, which aggregates upon contact with tissue collagen during primary haemostasis) and secondary haemostasis, characterized by deposition of the protein fibrin (Coagulation factors are proteins of the coagulation cascade, which amplify or regulate the deposition of a fibrin meshwork at sites of injury for the purpose of haemostasis.).

(ii) Inflammation is a stage of response to injury concerned with removal of debris, clearance of infection, and initiation of repair. Key clinical signs are pain (Lat. dolor), warmth (calor), reddening (rubor), swelling (tumor, today would be called oedema to distinguish from malignancy), and loss of function (functio laesa).

(iii) Innate immunity is fast, the key cells are phagocytes, the key proteins are complement and it has no specific “memory” or knowledge of prior disease. Adaptive immunity is slow, key cells are the lymphocytes and key proteins are special molecules, the antibodies, that recognize specific individual antigens. The memory developed following a disease is associated with the idea that you don’t catch exactly the same cold or flu virus twice.

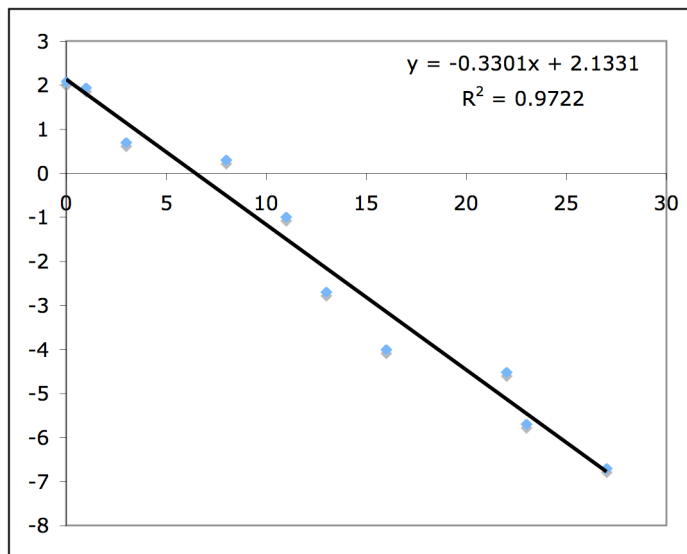
(iv) Organs are made up of tissues, typically with one dominant tissue type and the others in a supporting function. There are only 4 main tissue types in humans, nervous, muscle, epithelium and connective tissue. Epithelium is a lining tissue found on the surface of the body (skin) or the lining of tubes (blood vessels, gut) and connective tissue is dominantly acellular and forms the majority of mechanically important structures in the body. Nervous tissue is primarily electrical in function and dominates the brain and nerves; muscle can be smooth (involuntary—the heart) or skeletal (voluntary—for movement).

(v) The pancreas is an internal organ dedicated to the synthesis of gut enzymes (exocrine pancreas) and to the synthesis of hormones regulating metabolic

homoeostasis (endocrine pancreas). An Islet of Langerhans is vascularised cluster of  $\approx 1000$  or so endocrine cells in the pancreas, including insulin-producing beta cells. Senses concentrations of key metabolites (e.g., glucose) and secretes hormones to maintain blood levels of these metabolites (e.g., insulin). The disease diabetes (type 1) is a severe impairment of glucose homoeostasis, caused by auto-immune destruction of pancreatic beta cells in the islets of Langerhans.

(c) *There are several different ways to do this depending on how much of the data you would use. I will only put the simplest here.*

A rough plot and subsequent examination of the data demonstrates that it falls on a line where the approximation of the first and last points as representative would be acceptable. X-axis is time in minutes and y-axis is log of the number of organisms.



$\text{Log}_{10}$  of 120 is 2.08, of  $2e-7$  is -6.70. There is therefore a change of (in log sense) 8.78 decades in 27 minutes, the ratio of which gives 3.08 minutes per decade reduction. Note how close this is to the linear regression value (shown in the plot above) of 3 minutes exactly.

For an SAL of  $1e-6$ , the process time assuming no variation or error would fall between 23 and 27 minutes, but that does not include a factor of safety or account for variations in the measurements. Therefore an addition of around 10 minutes (just over three times the decimal reduction time) could be warranted, leading to a process time around 35 minutes.

(d) A half-implant in this case would be detrimental (potentially do “more harm than good” and thus be unethical!) as the bone in parallel with the implant would be stress-shielded. Stress shielding of bone—due to the absence of mechanical forces to provide homeostasis—leads to bone resorption and bone loss near the metal implant would increase the likelihood of implant failure due to loosening. On this basis, assuming a metal implant, it would be best to remove the full cross-section. However, this is mechanically not ideal, nor is it biologically ideal since it would interrupt the bone marrow cavity in the centre of the bone. As such, a far better scenario would be to replace only half the section with a material with more bone like mechanical properties, particularly the elastic stiffness. A bone-like biomimetic composite or other polymer-ceramic composite with properties optimized to be similar to bone—much less stiff than most implant metals—would increase the

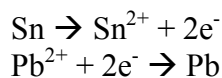
potential for good implant performance. Therefore I advise exploring all options, including potential clinical trials of new materials, before proceeding with the metal cylinder implant scenario.

2

(a) (i) All implants eventually fail. However, corrosion leads to rapid (earlier than expected) failure of implants by accelerated material degradation leading to a loss of functional performance. Examples include failure of pacemaker leads due to both metal (lead) corrosion and oxidative corrosion of the polymer lead insulation.

Biological entities influence corrosion in different ways, depending on whether proteins or cells are being considered. The reaction balance can be disturbed (e.g. not enough of a species present to keep the reaction balanced, thus encouraging further corrosion) by bacteria “stealing” free Hydrogen or proteins binding free metal ions. This mechanism affects the corrosive action directly, while a second effect can be if biological entities prevent formation of a passivated oxide layer on a metal implant, by proteins blocking oxygen diffusion or cells influencing the local pH. Corrosion prevention strategies include use of noble metals, use of more corrosion-resistant alloys like Ti-alloys, or surface modification to encourage a more substantial passivation layer.

(ii) Lead is the cathode reaction and tin is the anode, such that overall



And the cell potential is

$$\Delta V = -0.126 + 0.136 = 0.01$$

As such the cell is only slightly favoured for the reaction to go forward. This can be influenced by changing the ion concentration in the baths from that in the standard cell, and then the Nernst equation must be used. This would give

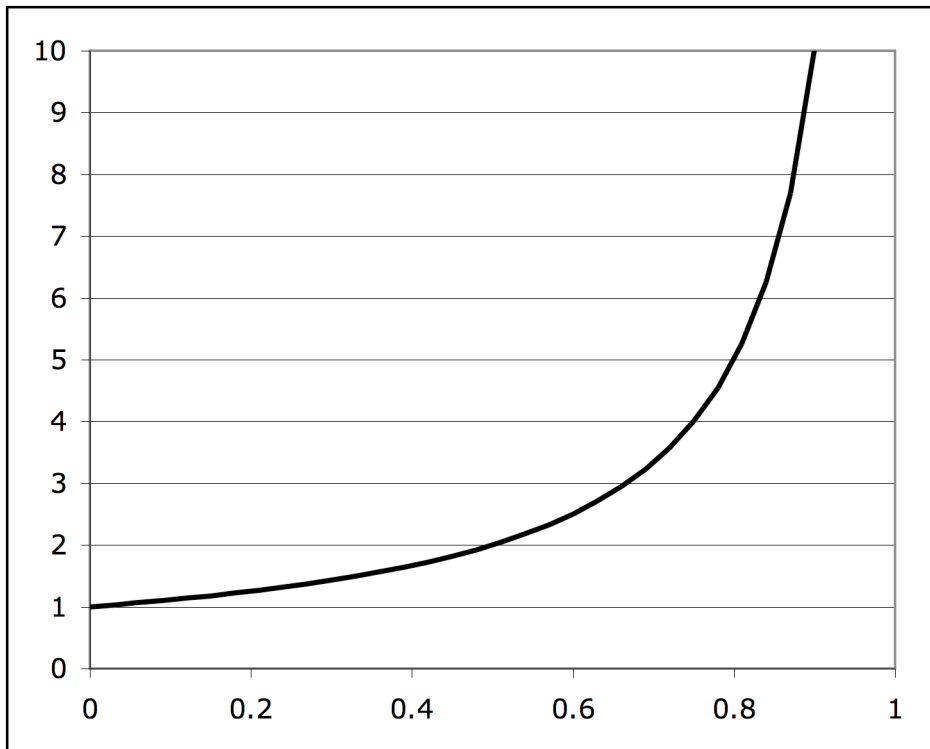
$$\Delta V = 0.01 - \frac{RT}{n\mathfrak{F}} \ln \left[ \frac{[\text{Sn}^{2+}]}{[\text{Pb}^{2+}]} \right]$$

If you decrease the tin ions by a factor of 100,  $\ln 0.01$  is largely negative and the reaction direction is unlikely to change. However if you increase the tin ions by a factor of 100,  $\ln 100$  is positive and the direction of the overall reaction could reverse such that the anode and cathode reactions flip due to the large presence of  $\text{Sn}^{2+}$  (currently on the RHS of the overall reaction).

(b) An expression for thrombin concentration at the implant (tube) wall,  $C_w$ , relative to that in the blood,  $C_b^0$ , is

$$\frac{C_w}{C_b^0} = \frac{1}{1 - \frac{k_p}{k_L(x)}}$$

where  $k_p$  is the rate of thrombin generation on the material wall and  $k_L$  is the local mass transport coefficient for thrombin in the blood, as a function of position in the tube,  $x$ . This roughly plotted is as follows:



Thus all is well if

$$k_p \ll k_L$$

but for some materials  $k_p \approx k_L$

and the critical obstruction criteria for the tube is met. To prevent this, the surface of implants can be treated to try and reduce  $k_p$ . One such treatment is heparinization, which can reduce the  $k_p$  of a plastic tube by an order of magnitude.

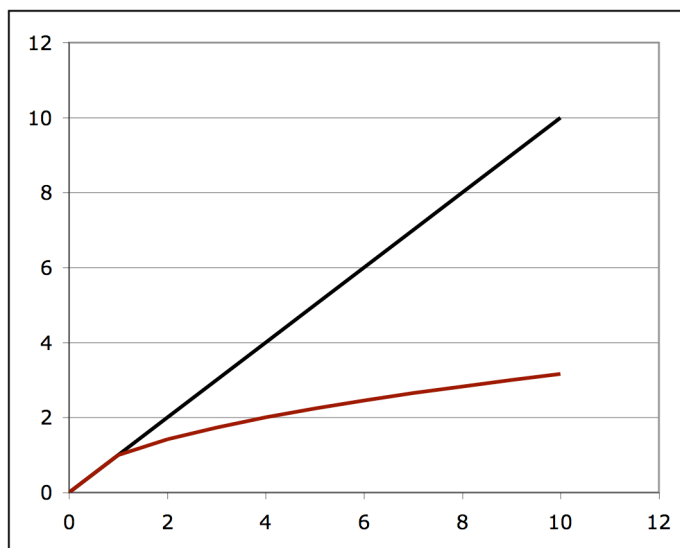
3

(a) Polymers are finding increasing use in medical implants for a number of reasons. First, their mechanical properties are far more comparable to tissues in the body, such that they are better for mechanical implants (either alone or as the basis of composite materials) than much stiffer metals or ceramics. Second, the natural tendency for polymers to undergo hydrolysis and subsequent degradation and erosion in the body has led to development of new medical technologies based on this controlled degradation behaviour. Examples include drug delivery applications and tissue engineering, in terms of emerging fields, and resorbable sutures as a long-time existing technology based on controlled polymer degradation. Because of their chemistry, and the similarity to the body's chemistry (proteins are just biopolymers) it is also easy to add biological functionality to polymers by binding biological molecules directly to them in surface modification applications. Finally, hydrogel materials mimic most directly the natural condition in the body (which is 70% water!) and are finding more and more use for their tissue matching profiles, although hydrogel mechanical properties are poor and this is a weakness.

(b) Drug release from spherical capsules and from solid spheres are both diffusion-controlled drug delivery systems. In diffusion controlled systems, all modelling is based on Fick's second law and there is only a single variable controlling the overall behaviour, in this case the diffusion constant for the drug within the polymer.

However, in reservoir systems the drug release profile is approximately linear in time, while in a monolithic matrix system the drug release profile has a complicated, nonlinear functional form. To distinguish between the two systems, data for the drug released (normalized by the total amount of drug) would be plotted against time, and the functional form compared with the two extremes noted above. It may prove useful to numerically differentiate the data to see more clearly the differences in functional form. In making this examination, it is critical to exclude very late time data, for especially in the reservoir case the linear profile assumption is likely to be invalidated when the amount of drug runs out and the steady-state diffusion assumption begins to fail.

In swelling-controlled systems, such as a hydrogel loaded with a drug, there are two critical parameters. As in the case of diffusion-controlled systems, the diffusion constant for the drug in the polymer is important, but here an additional diffusion constant, that for the diffusion of water into the polymer, is important. The increasing water content as hydrogels swell results in enhanced diffusion of the drug as the swelling results in pore spaces being opened up. This can be detected as a change in the functional form of the drug release profile from depending on the square root of time (similar to the profile for the non-swelling monolithic matrix system above) to a linear dependence on time, illustrating the accelerated diffusion. (a sketch might be useful here: plot of cumulative drug release as a function of time)



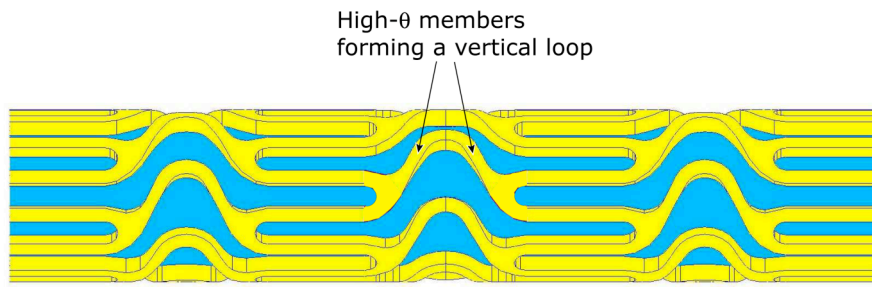
(c) Finite element modelling is extremely useful and well-used in joint replacement studies. Examples include cemented versus cementless simulations, optimization of design of implants by trying to reduce stress concentrations, and sophisticated models in which an “adaptive remodelling” approach is used to simulate the way that living bone responds to mechanical loading by deposition or resorption of bone, and the associated changes in local bone stiffness. This field has expanded recently with the use of patient-specific geometrical data—3D datasets identifying the tissues from medical imaging such as CT or MRI scanning, where the images are used to generate the finite element mesh. The mechanical properties and geometry of the implant are well-known.

There are many challenges, however, in making these simulations clinically relevant and this is the subject of much current research. Challenges in information gathering for model development include the necessity for determination of appropriate mechanical properties for tissues in the body, which is typically done by *ex vivo* testing, including both healthy and diseased tissues. For adaptive remodelling models, a functional form of the bone tissue's response to loads is needed and used for the iterative models, but this is an assumption. Also needed for simulations are approximations for implant-interface boundary conditions and identification of loading conditions that approximate *in vivo* loading. Again these are normally approximated with the best information available, including the use of cadaveric specimens with instrumentation (i.e. strain gages on the bone, pressure transducers in the soft tissue) to try and identify appropriate loading conditions.

4

(a) The important mechanical performance attributes of a balloon expandable stent are the axial beam stiffness ("flexibility"), the internal pressure needed to induce plastic deformation ("yielding pressure"), the axial contraction ratio and the expansion ratio at fracture. The values of all of these parameters (except the expansion ratio at fracture) are likely to change as the stent is expanded. For a specified material, these characteristics are dependent on the geometrical shape and orientation of the structural members making up the wall of the stent.

(b) The NIR stent has a low axial beam stiffness (high flexibility) in the unexpanded form. This is highly desirable since this eases passage of the stent through tortuous vessels. The high flexibility of the NIR stent is obtained by the introduction of pairs of members forming vertical loops. These members, marked in Figure, are oriented at high orientation angles to the horizontal ( $\sim 70^\circ$ ). The beam stiffness of these sections is therefore low, allowing for high flexibility upon insertion. In the deployed form, the two oppositely-inclined high- $\theta$  members rotate to smaller  $\theta$ , forming part of the expanded lattice and allowing for high beam stiffness and resistance to radial collapse. Furthermore, by connecting together two oppositely-inclined high- $\theta$  members in the "vertical loop" pair, a further benefit has been obtained from the rotation of these two to smaller  $\theta$  on expansion of the stent, because this generates an axial expansion which partly offsets the normal contraction caused by the "horizontal loop" members rotating to larger  $\theta$ .



(c) Wire joints are likely to cause premature fracture. These joints, particularly if they are formed by a means such as soldering or welding, will tend to have a different microstructure from that of the wires themselves. For example, they might have a coarser grain structure and strong segregation of certain elements to the grain boundaries. Such joints are likely to fracture at low plastic strains.