EGT2
ENGINEERING TRIPOS PART IIA

Module 3G5, BIOMATERIALS Crib YYS Huang

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, 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 for water diffusion in the polymer is less than the time constant for hydrolytic bond cleavage and when the ratio of the diffusion to hydrolysis time constants, epsilon, is less than 1. Surface erosion is for the opposite case. Expressions need to be given for the diffusion and hydrolysis time constants and a means for establishing the critical thickness should be provided. Full details from the notes are provided below.

Surface vs bulk erosion

Two competing time-scales:

(1) Diffusion time scale: characteristic for water to diffuse into the implant

$$\tau_D = \frac{\langle x \rangle^2 \pi}{4 D_{eff}}$$

D = diffusion constant for water in that polymer, cm^2/s

<x> is the mean distance the water has to travel

(2) Hydrolysis reaction rate time scale

Assume Poisson kinetics for hydrolysis reactions.

The likelihood that a bond has been cleaved at time t is

$$f(t) = \lambda \exp(-\lambda t)$$

where lambda is a rate constant related to the half-life of a polymer bond.

the volume of polymer containing one degradable bond is

$$V = \frac{\bar{M}_n}{N_A \rho (DP - 1)}$$

N_A is Avogadro's number

Rho is the polymer density

DP = degree of polymerization, the number of monomers in the polymer chain (note DP can be found from M_n/M_0 where M_0 is the molecular weight of one monomer)

DP – 1 because there are N-1 bonds between N monomers (above 3 and 4, respectively)

The number of polymer bonds in distance <x> is
$n = \langle x \rangle / V^{1/3}$

The amount of time needed to degrade n bonds is
$$\tau_E = \frac{1}{\lambda} \ln n = \frac{1}{\lambda} \{\ln \langle x \rangle - \ln (V^{1/3})\}$$

Make a non-dimensional function to compare the two time frames:
$$\varepsilon = \frac{\tau_D}{\tau_E}$$
Where a trade-off is seen (i.e. from one rate-limiting case to another) for $\varepsilon = 1$

or solve for <x> by setting $\varepsilon = 1$ *to define a critical sample size,* W_c

The critical specimen thickness is proportional to the diffusion constant and inversely proportional to the hydrolysis reaction rate $W_c \propto D/\lambda$

For $W < W_c$ bulk erosion (also $\tau_D < \tau_E$ and $\varepsilon < 1$)
For $W > W_c$ surface erosion (also $\tau_E < \tau_D$ and $\varepsilon > 1$)

(b) Definitions of number average molecular weight, $\overline{M}_n$, weight average molecular weight, $\overline{M}_w$, and molecular weight polydispersity index, *PDI* (with values for Sample A and B, using tables below):

$$\bar{M}_n = \frac{\sum M_i n_i}{\sum n_i} = 3106 \qquad \bar{M}_n = \frac{\sum M_i n_i}{\sum n_i} = 1353$$

$$\bar{M}_w = \frac{\sum M_i^2 n_i}{\sum M_i n_i} = 3360 \qquad \bar{M}_w = \frac{\sum M_i^2 n_i}{\sum M_i n_i} = 2094$$

$$PDI = \bar{M}_w / \bar{M}_n = 1.08 \qquad PDI = \bar{M}_w / \bar{M}_n = 1.55$$

where M_i = molecular weight of polymer (in *i*th range of distribution)
n_i = number of chains in *i*th range of distribution.

Sample A

M_i	n_i	$M_i n_i$	$M_i^2 n_i$
500	840	4.2e5	2.1e8
1500	620	9.3e5	1.4e9

Sample B

M_i	n_i	$M_i n_i$	$M_i^2 n_i$
500	6050	3e6	1.5e9
1500	3320	5e6	7.5e9

2500	730	1.8e6	4.6e9
3500	9200	3.2e7	1.1e11
sum	11390	3.5e7	1.2e11

2500	1820	4.6e6	1.1e10
3500	1205	4.2e6	1.5e10
sum	12395	1.7e7	3.5e10

(c) Distribution B is a step-polymerization (condensation polymerization) and distribution A is for chain-polymerization (free radical polymerization).

Step	**Chain**
Any two potentially reactive end groups can react	only species with active centers add monomer units
monomer depletion occurs rapidly	monomer concentration decreases steadily
polymer MW increases slowly with time	high molecular weight polymer forms at once
any size species can react with another, and many chains are reacting at one time	concentration of reacting chains is low compared with the non-reacting monomer and polymer

(d) (i) Elastic modulus increases with MW up to a point, then plateaus.

(ii) Strength increases with MW up to a point then continues to increase but significantly more slowly. This can be described by:

$$\sigma_f = \sigma_f^{\infty} - \frac{K}{M_n}$$

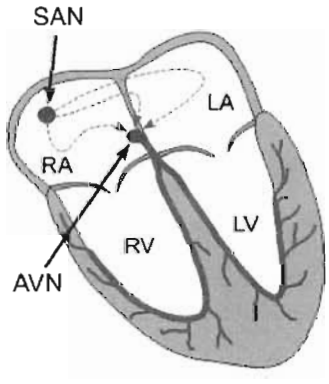
(iii) Melt viscosity increases with MW and does not saturate, which means that it is a good mechanism for actually estimating the MW.

2

(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.

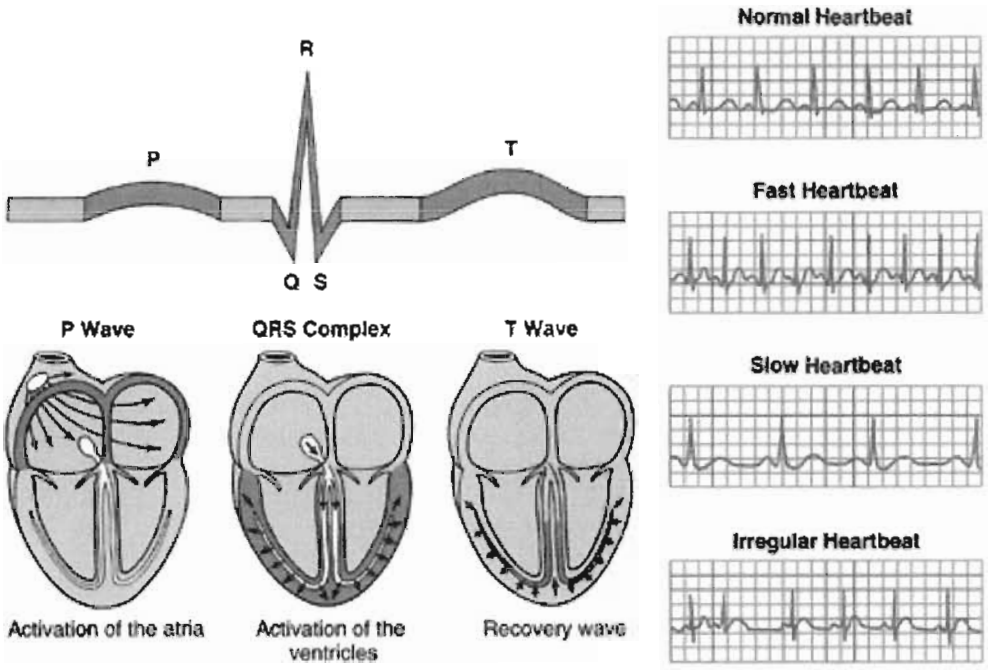


SAN, sinoatrial node; AVN, atrioventricular node; RA, right atrium; LA, left atrium, RV, right ventricle; LV, left ventricle.

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 system is—as is often the case in physiology—remarkably redundant. Any bunch of electrical tissue in the heart can act as the pacemaker if the SAN node is not working. The SAN node cells are faster than the others, so if the SAN node fails the overall process is slowed and this is one reason for artificial pacemakers.

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)

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 heart muscle, porous or non-porous for tissue-ingrowth. Electrode Materials: Pt, TiN, RuO_2, IrO_2, Nb_2O_5

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.

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)

Galvanic corrosion

This can take place whenever two different metals are placed in contact with an electrolyte, in this case, blood and body fluid. (*NB* need not be two large metal components, can be two regions within an inhomogeneous microstructure of an alloy such as bronze). Titanium, aluminium and chromium are common problematic ions in medical implants.

Anode reaction

oxidation reaction

$M \rightarrow M^{n+} + ne^-$

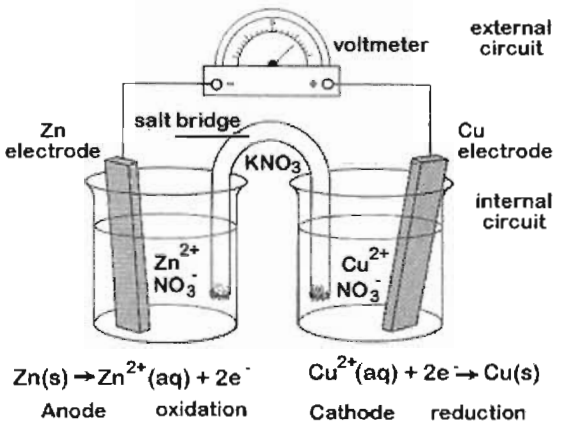
Cathode reaction

reduction reaction

$M^{n+} + ne^- \rightarrow M^{(n-1)+}$ (a more noble metal)

Standard Electrochemical cell

The overall reaction is made up of at least one anode and one cathode reaction.



The galvanic couple consists of two metals electrically connected in a liquid electrolyte. The standard conditions are for pure metal electrodes, in a 1M solution of metal ions and at room temperature. The two solutions must be in contact to allow for movement of ions between the two sides of the cell, as shown here with the "salt bridge," in order to maintain charge balance via motion of counterions.

In this case, you get the dissolution of zinc and the deposition of copper

$$Zn \rightarrow Zn^{2+} + 2e^-$$

$$Cu^{2+} + 2e^- \rightarrow Cu$$

The overall voltage is positive so this is a spontaneous reaction; if these were reversed the overall voltage would be negative and the reaction would not be spontaneous in this direction.

Critically, the standard electrochemical cell is for equilibrium conditions, and it says absolutely nothing about corrosion rates!!!!!

4 ways biological entities affect corrosion

NB: two of these deal with biological molecules (proteins) and two with living cell activity

1. Proteins can interfere with the galvanic reaction balance. Proteins bind metal ions and remove them from the surface, leading to more metal dissolution
2. Cells can affect oxide layers (which normally promote passivation) because their formation depends on local potential and local pH, both of which can be changed by cell activity
3. Proteins adsorbed on surfaces can physically block oxygen diffusion, again limiting passivation layer formation
4. Bacterial cells can "steal" hydrogen from the cathode reaction, encouraging further corrosive action

(c)

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".

Seconds to minutes: Haemostasis ("plug")

- platelet aggregation (seconds), fibrin deposition (minutes) combining to seal off the wound and entrapping microbes
- Triggered by disruption of endothelial cells lining blood vessel walls

Minutes to hours: Acute inflammation ("clean")

- Rubor (redness), tumor (swelling), calor (heat), dolor (pain)
- Phagocyte activation (monocytes become macrophages, polymorphonuclear neutrophils migrate)
- Further activation of endothelial cells triggering increased vascular permeability, vasodilatation
- Complement assists in phagocytosis and can kill bacteria directly by membrane disruption/pore formation

Hours to days or weeks: Termination of acute inflammation and initiation of wound healing followed by resolution ("repair")

- Bacteria being cleared
- Initiation of fibrosis (scarring/collagen deposition) through fibroblast activation by macrophages
- Contraction of wound, restoration of normal tissue architecture and epithelial cell barrier
- Angiogenesis (blood vessel formation)

This is related to implantation because implantation almost inevitably involves the disruption of normal tissue at the implantation site (skin disruption); the body interprets the insertion of an implant as an injury and mounts a wound-healing response directly to it. Long-term problems with implants include chronic inflammation due to incomplete wound healing processes and/or bacterial infection.

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.

3 (a)

The equilibrium concentration is the horizontal dotted line asymptote.

Removal of the drug from the system at the rate -b as above
input (drip, pump) at a constant rate a (independent of either t or y or C)

$$\frac{dy}{dt} = a - by$$

Initial concentration of 0: y(0) = 0
Equilibrium concentration for

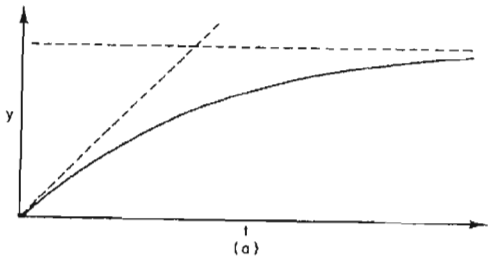
$$\frac{dy}{dt} = a - by = 0$$

$$y = \frac{a}{b}$$

(note that b can be person specific, while a is set by the delivery method)

Full solution:

$$y(t) = \frac{a}{b}\left[1 - \exp(-bt)\right]$$



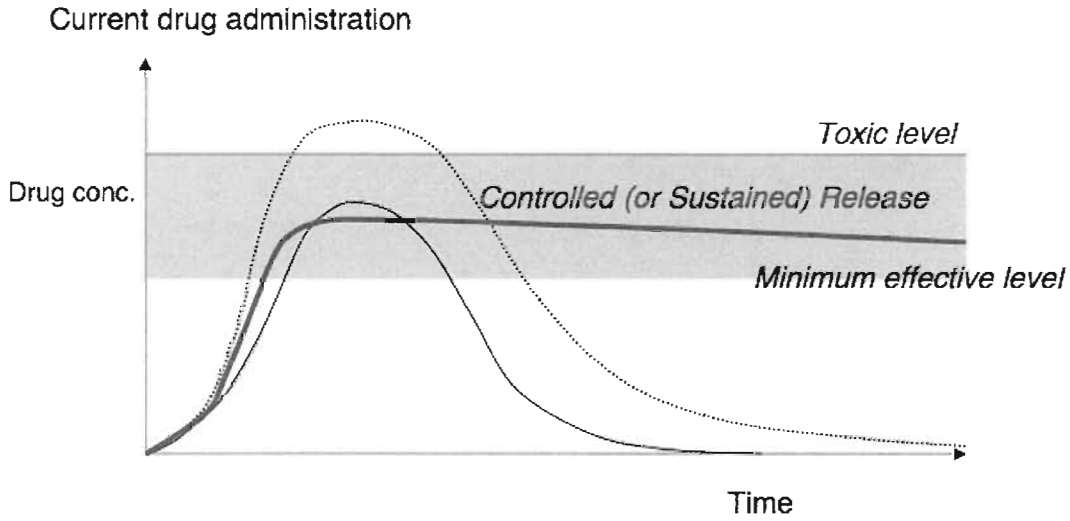
The initial slope is *a*.

In general there is a minimum effective level and a toxic level (maximum tolerable dose) for a drug. A controlled release mechanism involves the use of a physical or chemical principle engineered into a device such that the drug is released into the body in a sustained manner designed to keep the body concentration of the drug approximately constant (and between the minimum effective level and maximum tolerable dose) over much longer time-scales than that for clearance of a drug after a single or multiple injection(s). Single or multiple injections are the traditional

mechanisms of delivery compared with a controlled release or constant infusion mechanism due to either a pump or a new technology (i.e. drug released from polymer microspheres or a patch).

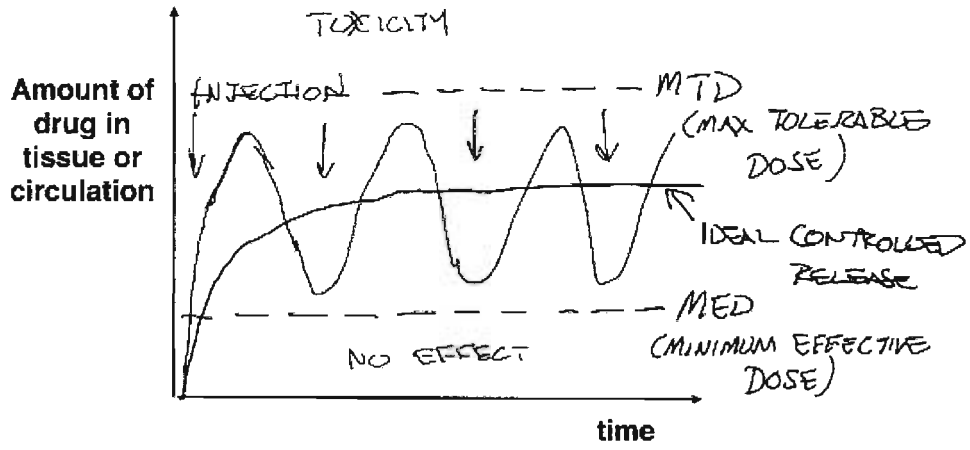
A single injection aims to reach a moderate dosing level (between the minimum effective level and maximum tolerable dose) but the drug's effect diminishes with time and dips below the minimum effective dose as the drug is cleared from the body. To achieve a sustained effect, multiple injections are used by which a periodic increase in the drug is delivered, with the timing of this delivery attempting to occur before the drug concentration falls below the minimum effective dose. This is very difficult to control, especially in light of patient variability in clearance rates. This paradigm of multiple injections is generally not seen as an ideal or sustainable model for patient autonomy and medical independence.

Controlled release versus single dose:



Controlled release versus multiple injections:

Bolus drug injection:



(b) Higuchi equation and associated assumptions:

Switch to Planar, not radial, system with a disbursed drug in a patch; this is a classic solution.

$$M_t = A\sqrt{(2C_0 - C_s)C_s Dt}$$

Higuchi 1961

i.e. square root of time behavior
Spherical solution for this case much more complicated.

This is a very useful expression but contains many assumptions that are often neglected (and this expression is over-ly used due to its simplicity); requires

1. $C_0 >> C_s$
2. *thin film with negligible edge effects (large patch)*
3. *size of drug particles << film thickness*
4. *carrier material does not swell or dissolve*
5. *diffusivity of the drug is constant (depends neither on drug concentration, time or position)*

M_t = amount of drug released

A = device (patch) surface area

C_0 = initial drug loading

C_s = drug solubility in polymer

D = diffusion constant for drug through polymer

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

(c) (i)

Nanoparticles are things 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)

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)

(ii)

Nanoparticles are difficult to characterize due to their small size. Physical measurements of nanoparticles rely on indirect measurements or measurements based not on light microscopy, which is impossible at these size scales. Common nanoparticle size measurement techniques include:

- Atomic Force Microscopy (AFM)

- Scanning Electron Microscopy (SEM)
- Transmission Electron Microscopy (TEM)
- Dynamic Light Scattering (DLS) (indirect)
- Small-Angle X-ray Scattering (SAXS) (indirect)

	10 nm NP	30 nm NP	60 nm NP
AFM	8.5 ± 0.3	24.9 ± 1.1	55.4 ± 0.3
SEM	9.9 ± 0.1	26.9 ± 0.1	54.9 ± 0.4
TEM	8.9 ± 0.1	27.6 ± 2.1	56.0 ± 0.5
SAXS	9.1 ± 1.8	24.9 ± 1.2	53.2 ± 5.3
DLS	13.5 ± 0.1	28.6 ± 0.9	56.6 ± 1.4

The resulting measurements agree relatively well for larger (60 nm) particles and less well for smaller (10 nm) particles. In nearly all cases the measured diameters are smaller than the prescribed size of the particles. Yes, this is critical because a decrease in particle size gives a geometrical increase in surface area per unit mass and a corresponding increase in surface reactivity.

(iii)

Prior to sale of any implant, there is a process of regulatory control that varies depending on the country, although the general conditions of the process are similar. The implant is typically developed in a research environment, where studies are done in vitro and in animal models to assess the biocompatibility and efficacy of the implant. The implant is then brought into limited clinical trials, to test the performance of the implant in a human context. This is regulated closely, for example, in the US, the FDA has to authorize an "investigational device exemption" allowing the device to be implanted into humans without it having been fully approved yet. There is an important review of ethical issues to do with any implant before it is used in the human body. Success in limited clinical trials leads to more extensive clinical trials, and eventually an application to the appropriate regulatory authorities in the US and EU prior to clearance for sale.

The process is different in the US and the UK in both philosophy and in details of execution. The duration and rigor of the examination process for the implant depends on the risk it presents to humans, and the existence of a comparable product in the approved implant market. In the US there are three categories of risk in order of increasing risk: class I, class II and class III. In the EU, class II is subdivided into class 2a and class 2b. Long term implants, as would be expected for this tissue engineered replacement, are high risk and considered class III; further, there is little precedent for the approval of such implants such that the approval process will be more rigorous than that for an established class of medical device.

The philosophical difference between the US and EU is that in the US the implant must be proven to be efficacious (beneficent) while in the EU the emphasis is on safety and process control (non-malificence). The governmental body, the FDA, in the US must approve all implants for sale, while in the EU authority is not centralized but is delegated to a "notified body" which is an independent and private organization with authority to grant the CE mark, which approves the device for sale. The FDA procedure is based in federal regulation while the EU process relates to voluntary standards.

Further, and this is critical, this gets complicated fast with nanoparticle based drug delivery! We have here:

- PEG polymer coating
- PLGA biodegradable core, or perhaps magnetic core elements as well
- Biological antibody molecules
- Drug being delivered

So we have multiple engineering materials PLUS biologically-derived entities PLUS a chemical/pharmaceutical drug.

There is currently no regulatory framework that can handle all of this, and as a result such systems are being handled on a case-by-case basis.

This is an evolving area of medical device regulation and we can expect that things will be changing as the next generation of devices and products comes to market.

4.

(a) Bone is a composite material. It is composed of around 30% (dry weight) mineralised collagen fibrils surrounded by approximately 70% calcium phosphate. Calcium phosphate is ceramic crystalline mineral.

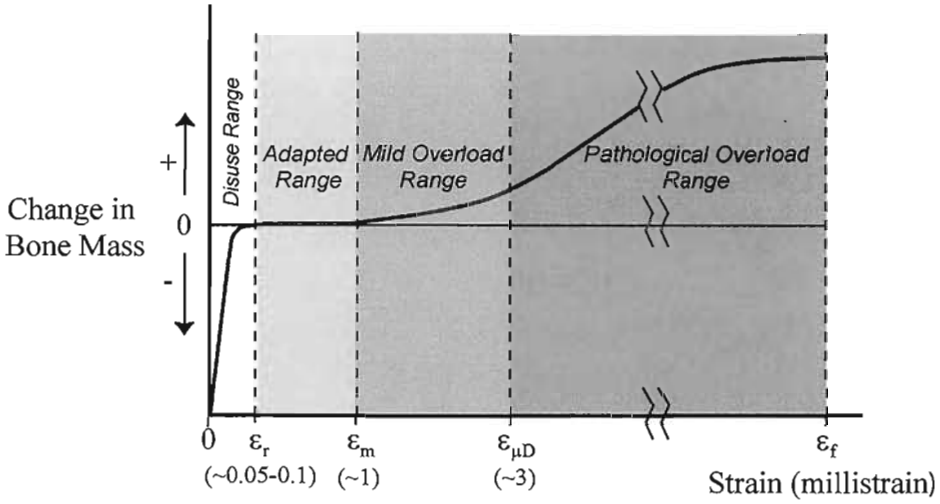


Fig1 : Threshold strains and regions of mechanical usage according to the "Mechanostat". Subscripts: r (remodeling), m (modeling), μD (micro-damage) and f (fracture).

(The complete plot is not required for obtaining full marks, the regions which are of interest are "the disuse range", "the adapted range", and the "mild overload range". No need to quote the values of the threshold strains)

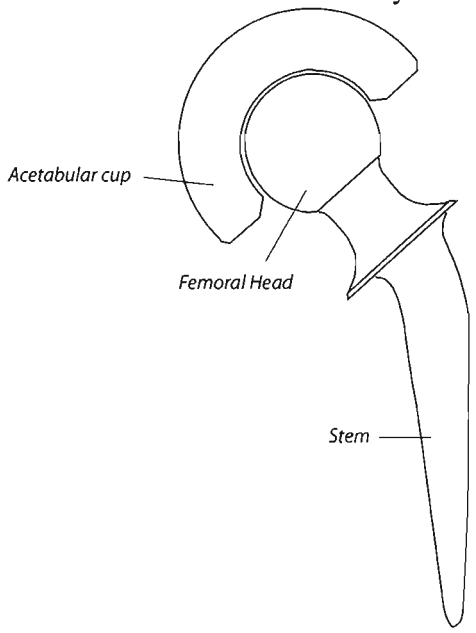
Bone responds to loading. Wolff first proposed this in 1892. The Mechanostat proposes that bone formation (modelling) and bone resorption (remodelling) are triggered at threshold strains. According to Mechanostat, bone formation (modelling) and bone resorption (remodelling) are in equilibrium in the adapted range. If bone strains fall below a lower remodelling threshold ε_r, bone mass is removed in order to bring the strains back within the adapted range. Conversely, if strains exceed a modelling threshold ε_m, bone mass is added to bring the strains back to the adapted range.

(b) The components of a total hip replacement are shown schematically below; femoral (stem+femoral head) and the acetabular cup.

Acetabular cup is usually made of UHMWPE and fixed in place with PMMA cement. UHMWPE is sometimes backed up with a metal cup (usually Co-Cr) to provide 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). Often the stem is coated with hydroxyapatite, bead-sintered coatings (Co-Cr, Ti) or fibre/wire meshes (Ti). Hydroxyapatite allows bone on-growth while bead-sintered coatings or fibre/wire meshes encourage bone in-growth. Femoral heads can also be made of Al_2O_3 and ZrO_2. Femoral heads need to have a low coefficient of friction and high wear resistance.

Selection criteria for a total hip replacement:

- Basic mechanical properties: sufficient strength to avoid plastic deformation, and resistant to brittle fracture, fatigue crack propagation and wear, preferably with a elastic modulus at least approximately matching that of bone, to minimise "stress shielding". An implant with a elastic modulus much higher than that of bone will reduce the physiological load below that normally experienced with the result that the equilibrium between bone-making and bone-removal is displaced towards the latter, producing bone loss around the implant.
- 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.



(c)

(i) The difference between the two coatings is that the plasma-sprayed coating encourages bone on-growth whereas the fibre/wire mesh coating promotes bone in-growth.

(ii) In thermal sprayed coatings, the coating material is projected against a substrate in molten form, where it impacts and solidifies, thus coating the substrate. When the coating impinges onto the substrate, thermal contraction is inhibited by the underlying substrate. The temperature differential ΔT generates a biaxial tensile stress σ in the plane of the coating, which is given by

$$\sigma = \frac{\alpha\ \Delta T\ E}{1-\nu} = \frac{13\times10^{-6}\cdot(550-25)\cdot165}{1-0.3} = 1.6\ \text{GPa}$$

Such high (quenching) stresses (in the GPa range) may promote debonding and spallation of the coating. However, in practice, the quenching stress values are in the MPa range. There are two reasons for this. The elastic modulus of sprayed material is often appreciably low because of the presence of porosity, micro-cracks etc, in practice, the elastic modulus of thermal sprayed hydroxyapatite is ~30 GPa. Furthermore, it is common for stress relaxation processes to come into operation during splat quenching. These may include microcracking, plastic flow, creep, interfacial sliding etc.

(iii) Using E_f = 200 GPa (Materials Data Book), f = 0.15 (=1-0.85), L = 0.5 mm and D = 0.1 mm, the Young's modulus E of this material is estimated to be 0.33 GPa.
This material has a very low elastic modulus, much lower than that of (cortical) bone (~15 GPa). Therefore, it would not be feasible to make the stem entirely out of this material since it won't be able to support loads encountered at the implant site. Conversely, a stiff implant can cause a "stress shielding" effect.