3G5 CRIB

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1

1 (a)

(i) A cell is the smallest unit of life. Tissues are made up of cells plus nonliving extracellular matrix material (ECM). There are only four different types of tissue, nervous, epithelium, muscle, and connective tissue. Connective tissue is largely ECM, while the other three types are largely cellular. Organs are complicated structures made up of multiple different tissue types.

(ii)

(ii) Biocompatibility encompasses two things.

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

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

(iii)

(iii) Life expectancy has increased significantly since the early twentieth century, in part due to the knowledge about antibiotics and the decrease in deaths in early childhood. People who make it to adulthood also live longer. With increased life expectancy, however, comes increasing wear and tear on the tissues in the body, and an increasing need for "replacement parts" to perform various mechanical, electrical and chemical functions in the body. Thus, in the era after World War II, when biocompatibility of engineering materials was first established, implantable medical devices (medical implants whose main function is not pharmaceutical) started to be developed to help replace lost tissue/organ function.

(iv).

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.

(v)

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)

Ethical quandaries arise when two of the principles are in conflict, as in when doing good for a pregnant woman simultaneously involves doing harm to the fetus.

(vi)

Tissue engineering is trying to rebuild broken body parts by seeding a porous biomaterial scaffold with living biological cells, where necessary utilizing additional growth factors or other agents to try and encourage cell growth and development. The cell source is a key consideration: the cells can be autologous (from the person themselves), allogenic (from a donor) or xenogenic (from a donor of another species, although in practice this is rarely implemented). Cells can be from mature differentiated sources, from adult stem cells or from embryonic stem cells. Scaffolds can be made from materials that are synthetic, hybrid or natural.

(b)

(i).

Hydrolysis is the reverse reaction to condensation polymerization. For example,

$R—O—R' + H_2O \square R—OH + HO—R'$

It occurs when

1. water enters the polymer
2. there's a chemical reaction associated with bonds breaking
3. the pore size of the material increases, allowing more water to get in, such that

further hydrolysis occurs by a chain reaction

ALL polymers undergo some hydrolysis, but the rate can be very different depending on the polymer's specific chemistry/covalent backbone.

(ii

Factors affecting the hydrolysis reaction rate:

1. basic chemistry—which backbone (choice of polymer class) ** most important

2. side chains that are hydrophobic (slower) or hydrophilic (faster)

3. crystallinity: hydrolysis is slower in a crystalline structure as the water has less

access to the hydrolysable bonds

4. geometry of the implant/material: surface area to volume ratio, implant or coating

thickness. Again controls the motion of water into the material; determines

surface versus bulk erosion.

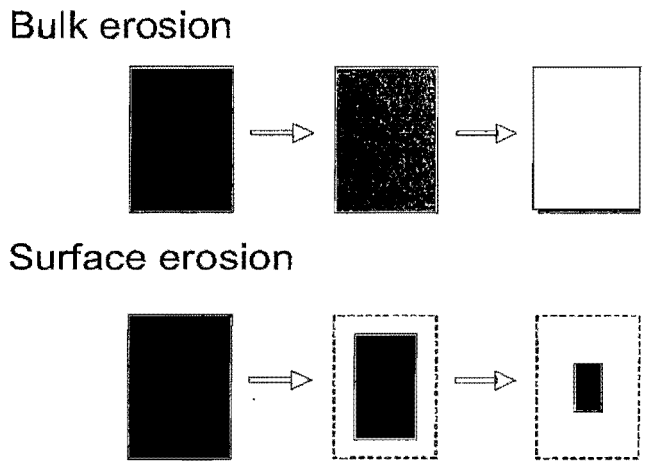
5. porosity—again due to water access

6. glassy versus rubbery state of the polymer—rubbery state, faster reaction

Aside from 1 (backbone) the others (2-6) all have to do with water access to the hydrolyzable bonds.

(iii)

Bulk erosion is when water enters a polymer uniformly and erosion occurs throughout the sample. The properties of the sample degrade uniformly with time. Surface erosion is when water can only gain access to a limited depth of the implant, and the erosion only takes place along this limited (fixed width) front. The properties of the core material do not change. This is illustrated below:



The trade-off between the two erosion mechanisms has to do with the competition between the diffusion time for water into the polymer, which is related to the diffusivity (diffusion constant) of water in the polymer, and the erosion time of the implant, which is related to the hydrolysis reaction rate constant. If the water can diffuse into the polymer faster than the hydrolysis can occur, the bulk erosion mechanism occurs. If the hydrolysis reaction is much faster than the diffusion of water into the polymer, then surface erosion will occur. NB for most polymers the diffusivity of water in the polymer is about the same, and the tunable parameter for device design is via choice of polymer with different hydrolysis reaction rate constants.

(iv)

For use of erodible polymers in drug delivery, we have the two tunable parameters as in the comparison between bulk and surface erosion above, the diffusion time constant for water in the polymer and the hydrolysis reaction time. But now we have a third additional critical parameter, the diffusivity of the drug in the polymer. For a bulk eroding polymer, the drug is released via the increase in porosity in the material as it degrades. For a surface eroding polymer, the drug is released from the surface of the implant as the material is removed.

2

(a)

The body is an extremely harsh environment for medical implant materials.

→ Specialized mechanisms for degradation are related to the evolutionarily-derived defenses against foreign invaders and attackers. The aqueous, ionic environment is passively an issue in addition to active attack from biological entities.

Physiological solutions are highly corrosive to metal materials, containing 0.9% salt (roughly a third of the concentration of sea-water) at a pH of 7.35-7.45 and a temperature of 37°. Charged ions are present, such as Na+, K+, Ca++ and Mg++ plus Cl−, phosphate and carbonate. The environment is not constant either!

Degradation is thus further accelerated by active biological effects. As a result, microbiologically-influenced corrosion is faster than passive corrosion.

4 ways biological entities affect corrosion (metals) and degradation (polymers)

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

1. 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 provide 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

(b)

Consequence 1: increase risk of aseptic loosening of implants

One trigger for inflammation may come from a foreign body reaction in response to wear particles, which are generated by friction on the plastic and metal surfaces of the joint prosthesis. Macrophages are able to phagocytose not only bacteria, but also artificial particles, such as latex beads. Upon histological analysis of fibrotic capsules from many loosened implants, wear particles generated from the prosthesis may be found inside macrophages. Other wear particles are seen inside multinucleated giant cells, which are thought to arise by the fusion of a number of macrophages attempting to phagocytose particulate matter that is too large for an individual cell to engulf. In this kind of implant failure, there is no evidence of bacterial infection. In individuals with this histologic appearance, loosening appears to be a slow process, with a mean time of 10 years between the original implant and the revision surgery. This process, referred to as aseptic loosening, appears to be the most common source of implant failure. Analyses of this sort have been employed to explore the links between inflammation and osteolysis, and the results have been used to propose models for how the two are linked in aseptic loosening (Fig. 11). It is thought that activation of macrophages by wear particles (or, in septic loosening, by bacteria) triggers the release of soluble small messenger proteins, called proinflammatory cytokines, which

bind to cytokine receptors on tissue cells to signal inflammation. One consequence is the activation of synovial lining cells, which go on to proliferate, accounting for the increased content of synoviocytes in the osteolytic tissue. In addition, these cytokines alter the balance between bone formation and destruction.

Consequence 2: dissolved metal ions in tissues

Even in a well-functioning TJR with a titanium implant there is a three-fold increase in Ti ions found in the blood compared with non-implanted controls. In a failed TJR there can be a 50 fold increase in blood serum Ti ions. This is extremely serious since the implant itself is local, but ions in the blood are now systemic! They can also cause serious allergic reactions, which are part of the adaptive (as opposed to innate) immune response, associated with lymphocytes and antibody-antigen interactions. Adaptive immune responses matter in the design of implant biomaterials for several reasons:

n They generally worsen inflammation and intensify the innate response to bacterial infection.

n They may cause allergies – i.e., inflammation in response to foreign but otherwise innocuous substances, which intensifies upon repeated or prolonged exposure. Allergic responses to implant materials can cause loss of function of the implant, and in extreme cases may cause death.

(c)

(i)

$V_1 = -0.277$ V $\quad 3Co^{2+} + 6e^- \rightarrow 3Co$

$V_2 = +0.744$ V $\quad 2\,Cr \rightarrow 2Cr^{3+} + 6e^-$

$V_{total} = 0.467$ V

Chromium is the anode and thus is corroded.

(ii)

$V_1 = -1.662$ V $\quad 2Al^{3+} + 6e^- \rightarrow 3Al$

$V_2 = +2.363$ V $\quad 3\,Mg \rightarrow 3Mg^{2+} + 6e^-$

$V_{total} = 0.701$ V

The aluminium/magnesium system is more corrosive overall, which helps explain why cobalt-chrome alloys are used in medical devices but aluminium and magnesium are less likely to be found in this context.

Avoiding implant corrosion? (metal implants)

- Use a sacrificial coating, something that corrodes in lieu of the underlying implant material due to its greater activity
- use noble metals such as platinum, silver, and gold or noble metal coatings
- avoid junctions between dis-similar metals
- use more corrosion resistant metals and alloys (Ti alloys are the least corrosion resistant, followed by Co-Cr, NiTi and the most corrosion resistant are stainless steels)
- perform surface modification aimed at purposeful oxide passivation layer formation, using surface melting, alloying, or plasma etching
- avoid metals! Use ceramics, polymer composites, and tissue-engineering approaches instead of metals.

3

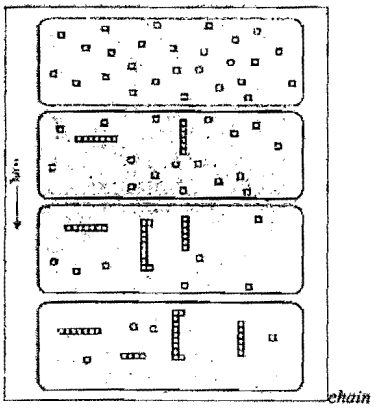
(a)

Polymeric Materials

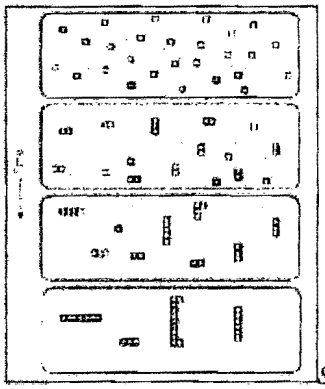
A polymer is a large molecule (macromolecule) composed of repeating structural units (mers) typically connected by covalent chemical bonds. While polymer in popular usage suggests commercial plastics, the term refers more generally to a large class of natural and synthetic materials with a variety of properties and purposes.

Making polymers: Step vs Chain polymerization

Step (condensation)	Chain (addition)
Any two potentially reactive end groups can react	only species with active centers add monomer units—an initiator is required
monomer depletion occurs rapidly	monomer concentration decreases steadily
polymer MW increases slowly with time	high molecular weight polymer forms quickly
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
$O_i + O_j \rightarrow O_{i+j}$	$O_i + O \rightarrow O_{i+1}$



chain



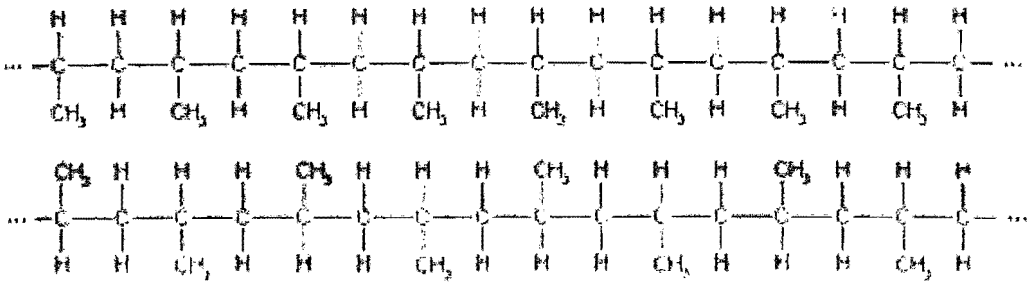
Step

(b) (i)

Coiled length: $\bar{L} = l\sqrt{2n} = 0.154 * \sqrt{2 * 750} = 5.96$ nm This is the size of the polymer in its random walk configuration.

Extended length: $L_{ext} = 2nl\sin\frac{109.5°}{2} = 2(750)(0.154)\sin\frac{109.5°}{2} = 189$ nm This is the size of the polymer when the backbone is extended but still kinked at the standard bond angle.

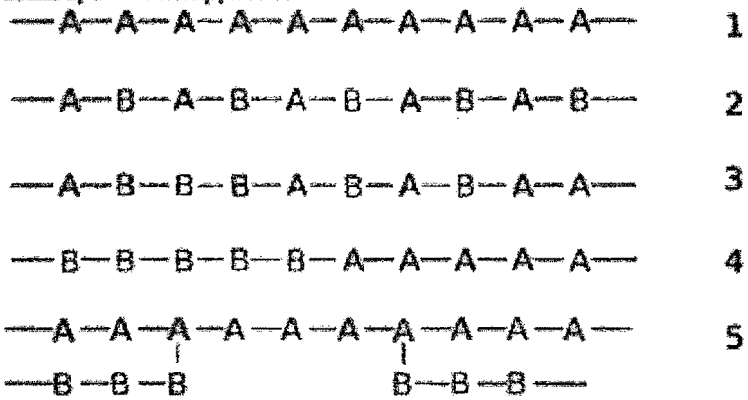
(ii)



Structure as in PE but with one in every four H atoms replaced with a methyl group.
Upper form: isotactic (all substituted groups on the same side)
Lower form: syndiotactic (substituted groups on alternating sides)
Polymers can also be atactic, where the substituted groups are placed randomly.

(iii)

Co-Polymers and Block Co-polymers
Polymers consisting of more than one monomer. These can be organized (i.e. alternating ABAB) or random. If the monomers of each type are grouped together, they are called "block co-polymers" and these have some specialized applications.



1. homopolymer
2. alternating co-polymer
3. random co-polymer
4. block co-polymer
5. grafted block co-polymer

(c)

Number average

Mean Mi	Xi	xiMi
12,000	0.05	600
20,000	0.16	3200
28,000	0.24	6720
36,000	0.28	10,080

44,000	0.20	8800
52,000	0.07	3640
	Sum	33,040 g/mol

Weight average

Mean Mi	wi	wiMi
12,000	0.02	240
20,000	0.10	2000
28,000	0.20	5600
36,000	0.30	10800
44,000	0.27	11880
52,000	0.11	5720
	Sum	36,240 g/mol

PDI = Mw/Mn = 36240/33040= 1.097

(d)

$$\%crystallinity = \frac{\rho_c(\rho_s - \rho_a)}{\rho_s(\rho_c - \rho_a)}$$

s = sample
c = fully crystalline
a = fully amorphous

Solve for ρ_c and ρ_a

(A) For ρ_s = 2.144 and % crystallinity = 51.3

$$51.3 = \frac{\rho_c(2.144-\rho_a)}{2.144(\rho_c-\rho_a)} * 100$$

$$\Rightarrow 51.3*2.144/100 = \frac{\rho_c(2.144-\rho_a)}{(\rho_c-\rho_a)} \quad \ldots(2)$$

(B) For ρ_s = 2.215 and % crystallinity = 74.2

$$74.2 = \frac{\rho_c(2.215-\rho_a)}{2.215(\rho_c-\rho_a)} * 100$$

$$\Rightarrow 74.2 * 2.215 / 100 = \frac{\rho_c(2.215-\rho_a)}{(\rho_c-\rho_a)} \quad \ldots(3)$$

Dividing (2) by (3) :

$$51.3*2.144 / (74.2*2.215) = \frac{(2.144-\rho_a)}{(2.215-\rho_a)}$$

$$\Rightarrow 0.669 = \frac{(2.144-\rho_a)}{(2.215-\rho_a)} \Rightarrow 1.482 - 0.669\rho_a = 2.144 - \rho_a \Rightarrow 0.331\ \rho_a = 0.662$$

$$\Rightarrow \rho_a = 2.000\ g/cm^3$$

Substituting the value of ρ_a in (2) :

$$51.3*2.144/100 = \frac{\rho_c(2.144-2.000)}{(\rho_c-2.000)}$$

$$\Rightarrow 1.1 = \frac{\rho_c(0.144)}{(\rho_c-2.000)} \Rightarrow 1.1\ \rho_c - 2.2 = 0.144\ \rho_c \Rightarrow 0.956\ \rho_c = 2.2$$

$$\Rightarrow \rho_c = 2.301\ g/cm^3$$

(b) Substituting the values of ρ_c and ρ_a in (1) for $\rho_s = 2.26\ g/cm^3$:

$$\% \text{ Crystallinity} = \frac{(2.301\ g/cm^3)(2.260\ g/cm^3 - 2.000\ g/cm^3)}{(2.260\ g/cm^3)(2.301\ g/cm^3 - 2.000\ g/cm^3)} \times 100 = 87.9$$

4 (a) A total hip prosthesis comprises an acetabular component and a femoral component. The acetabular component is usually made of UHMWPE (or Al_2O_3) 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 (strain tolerance, strength and toughness). Often the stem is coated with HA or porous Ti, Co-Cr coatings (bead-sintered or fibre/wire based ones) to allow bone in-growth as a means of fixation. 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. A hip implant is mainly used to treat osteoarthritis. In osteoarthritis, there is a breakdown in the cartilage covering the ends of bones where they meet to form a joint. As the cartilage wears away, the bones become exposed and rub against each other. The second cause is known as avascular necrosis. In this condition, there is cellular death of the femoral head due to interruption of the blood supply. Without blood, this leads to collapse of the femoral head and degeneration of the joint.

An endovascular stent is an expandable perforated tube used to widen blocked or occluded vessel. Balloon expandable stents, are manufactured primarily from austenitic stainless steel (316L) which has very high ductility (~50% in the annealed condition). Tantalum (Ta), cobalt–chromium (Co–Cr), cobalt-platinum (Co-Pt) alloys have also been used. Ta and Pt have good radiopacity, which facilitates precise positioning of the stent. Co alloys allow thinner stent struts without sacrificing strength. Self-expanding stents are made from an equi-atomic alloy of nickel and titanium (NiTi) which exhibits superelasticity and shape memory effects. The latter allow very large recoverable strains. (as high as ~8%).

An endovascular stent graft is an expandable tube composed of an impervious fabric (ePTFE, PET etc) supported by a stent. The choice of the fabric is driven by the need to prevent any cell adhesion. Stent grafts are used to treat aneurisms.

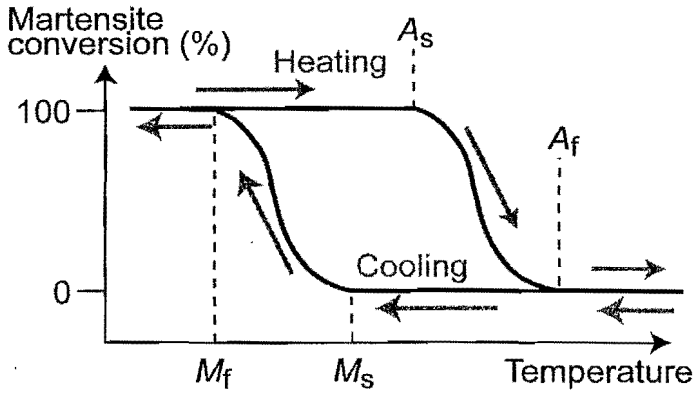
(b) In orthopaedic implants, cell attachment is required to increase the lifetime of the implant. This is in contrast to cardiovascular stents, in which case cell attachment may lead to vessel renarrowing (restenosis) known as neointimal hyperplasia. To overcome this problem, metallic stent surfaces are smoothen, passivated to improve corrosion resistance, polymeric coatings (degradable and non-degradable), drug eluting coating

In cementless prosthesis, bone-implant attachment is achieved via bone-in-growth into a rough/porous surface. In this case a number of surface engineering approaches are employed to secure the implant. This involves the use of rough coatings such as thermally-sprayed HA and Ti, bead-sintered coatings (Co-Cr, Ti) and wire/fibre meshes (Ti and Stainless Steel).

(c) The difference between diffusive and martensitic phase transformations is that the latter does not involve any diffusion. In martensitic transformations, each atom moves a small distance relative to its neighbours in a well-defined way. This homogeneous shearing of the parent phase creates a new crystal structure, without any compositional change (no diffusion). The key to such a process is that it is

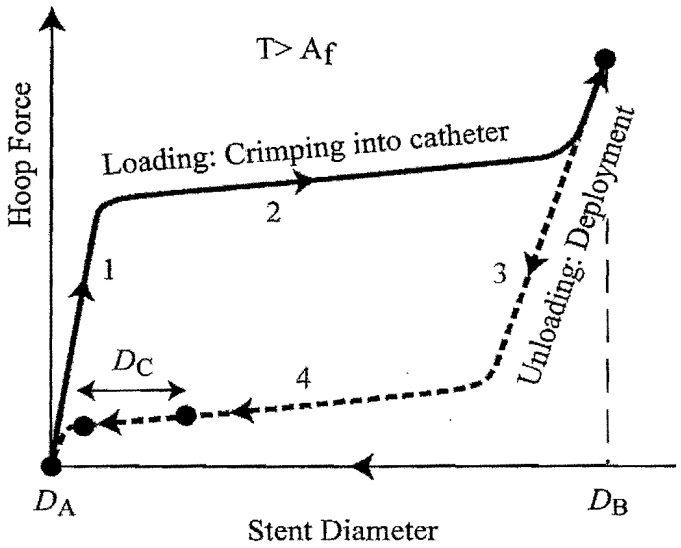
diffusionless, and consequently can happen extremely rapidly. This allows very large recoverable strains, strains as high as ~8%, which are much higher than normally expected during conventional elastic deformation. Such effects involve martensitic transformations induced by an applied external strain or a temperature variation.

There is generally a temperature hysteresis associated with the martensitic transformation – see Figure below. On cooling, the parent phase starts to transform into the martensite at a temperature M_s, ending at a second, lower temperature M_f. The reverse transformation commences at some temperature A_s, ending at a final temperature A_f.



(d) 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 (region 1), which is then followed by a superelastic plateau whereby the austenite transforms to martensite (region 2). The crimped stent is then inserted into a catheter for implantation in the body. When deployed from the catheter *in vivo*, initially the stent gets elastically unloaded (Region 3) followed then by reversal of the phase transformation (region 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).

For superelasticity to be possible, T must be above A_f (so the austenitic phase is initially predominant), but also the stress required to form the martensite must be below that needed to induce plastic deformation.



At $T < M_f$, the stent is compressed from an initially large diameter to a small diameter to fit within a catheter, where it is being kept cool (e.g. cold saline). The catheter is then threaded through the vessel and, once in the desired location, retraction of the sheath allows the stent to expand and warm up to body temperature. The material then transforms to its parent phase and reverts to its "trained" shape. As in the case of the superelastic stent, the stent exerts an outward force on the vessel and, conversely, the vessel exerts a constrictive force on the stent. The net effect of this force balance will determine the equilibrium diameter of the stent.

For shape memory to be possible, T must be below M_f (so the martensitic phase is initially predominant), but also the temperature A_f at which austenite finishes forming, on heating, needs to be smaller or equal to 37°C (body temperature).