JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 2 (1991) 125–128

A way to improve understanding of the physiological response of tissue to implant bioceramics: the thermodynamics of irreversible processes

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The concept of thermodynamics of irreversible processes is introduced in order to understand the interaction of bioceramics with living tissue. It is considered that a disturbance is brought about in the open system of the living body when a bioceramic is implanted. While the system is reaching its new steady state, interfacial reactions occur, resulting in a new interfacial structure. It is suggested that the tissue response to implant is governed by the thermodynamic forces caused by the different characteristics of the implant and its host tissue. It is expected that the interface between implant and surrounding tissue is unstable because of a continuous remodelling of the steady state. Thus improvements in the long-term performance of bioceramics are not easily achieved.

1. Introduction

Bioceramics are ceramic materials with a specific physiological behaviour. The first studies of ceramics for use in men were undertaken about 20 years ago. After two decades of development, bioceramics now receive world-wide attention in solving challenging medical problems. In clinical practice they are applied for minuscule middle-ear implants, hip implants, heart valves and tooth implants.

Bioceramics are classified into two major types in terms of the interfacial response to them of tissue [1]. These are inert bioceramics such as Al_2O_3- and calcium phosphate-containing bioactive bioceramics. The last group can be subdivided further: surface reactive bioceramics such as bioactive glass Na_2O–CaO–CaF_2–P_2O_5–SiO_2, and resorbable bioceramics such as calcium phosphate bioceramics.

Inert bioceramics undergo little or no chemical change during long-term exposure to the physiological environment. A very thin (several μm or less) fibrous capsule forms on the interface between implant and tissue, and isolates the implant from the surrounding tissue. For surface reactive bioceramics, a chemical reaction of the material with the physiological environment occurs. A bony interface is developed, resulting in a chemical bond between the tissue and the implant surface. Resorbable calcium phosphate ceramics appear to function as a mineralized framework for bony remodelling similar to autogenous grafts, because their compositions contain only elements that are easily processed through normal metabolic pathways.

It has been shown [2, 3] that the stability of the interface between living and non-living substances determines the success or failure of a bioceramic and its device. The formation of either a fibrous capsule or a stable adherent bond is the primary determinant in the long-term performance of a bioceramic. Although impressive progress in the development of bioceramics has been made in the last two decades, there are still many problems puzzling researchers in this area. It has been found [3] that the long-term success rate of bioceramics is much less certain than in the short term, because the interface is unstable under functional stimuli over long periods of time. There is wide variation in the reported success rates of implants: they depend on animal species, age of patient, implanting site, mechanical loading and other factors [4–6]. To find the mechanism that causes biomaterials to be compatible with the body is the aim of many biomaterial scientists [3, 5, 7]. However, their results have not yet led to a unified theory [2].

The main object of this paper is to introduce the thermodynamics of irreversible processes to obtain a better understanding of the physiological responses of living tissue to non-living implants.

2. Irreversible process thermodynamics in open systems

A system is said to be open when it can exchange matter and energy with its surroundings. In an open system, entropy change dS during a time interval dt

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can be decomposed into the sum of two contributions

$$dS = d_eS + d_iS \tag{1}$$

where d_eS is the entropy flux due to exchange with the environment, and d_iS is the entropy production corresponding to the irreversible process caused by the non-equilibrium state. Taking time derivatives of Equation 1, we obtain

$$\frac{dS}{dt} = \frac{d_eS}{dt} + \frac{d_iS}{dt} \tag{2}$$

where the entropy flux term $\frac{d_eS}{dt}$ is related to the constraints exerted by the outside world, and does not have a definite sign. In contrast, the second law of thermodynamics stipulates that the entropy produced inside the system can never be negative

$$\frac{d_iS}{dt} \geqslant 0 \quad (= 0 \text{ at equilibrium}) \tag{3}$$

Entropy production density is defined as

$$\frac{d}{dV}\left(\frac{d_iS}{dt}\right) \equiv \sigma \tag{4}$$

Then we may deduce

$\sigma > 0$; irreversible process (5a)

$\sigma = 0$; reversible process connecting two equilibrium states (5b)

Obviously any restriction can be imposed on the part of d_eS/dt. However, the system can arrive at the state with:

$$\frac{dS}{dt} \leqslant 0 \tag{6a}$$

as long as

$$\frac{d_eS}{dt} \leqslant -\frac{d_iS}{dt} \tag{6b}$$

As a result, a system may attain a state of lower entropy than the initial state, or the thermodynamic entropy of the system remains constant provided that a sufficient amount of negative entropy flow is injected into the system.

The state corresponding to

$$\frac{dS}{dt} = 0 \tag{7}$$

is called a steady non-equilibrium state. Since the system is not in equilibrium, this state is not stable but steady. At steady non-equilibrium, variables do not evolve with time and entropy production density σ is also time independent, while internal entropy production continues from irreversible processes such as diffusion, heat conduct and chemical reactions.

Thermodynamic non-equilibrium systems have a tendency to seek equilibrium. The tendency of processes to evolve to this time-independent state is governed by so-called thermodynamic forces. These are special forces linked with the distance from equilibrium. Thermodynamics forces are responsible for various irreversible processes. For diffusion processes due to the inhomogeneity of constituents in a system, the thermodynamic force (χ_j^{diff}) is proportional to the chemical potential (U_j) gradient

$$\chi_j^{\text{diff}} = -\nabla(U_j/T) \tag{8}$$

Thermodynamic forces corresponding to chemical reaction are contributed by chemical affinity (A) whose value is equal to zero at equilibrium

$$\chi_j^{\text{react}} = A/T \tag{9}$$

It has been shown that the entropy production density is determined by the thermodynamic forces χ_j and the flows J_j associated with the various irreversible process

$$0 = \sum_j \chi_j \times J_j \tag{10}$$

In the range of the linear nonequilibrium system

$$J_j = \sum_k L_{jk} \times \chi_k \tag{11}$$

where L_{jk} are the phenomenological coefficients obeying Onsager's reciprocity relation

$$L_{jk} = L_{kj} \tag{12}$$

Generally speaking, systems in the linear region are near equilibrium where the thermodynamic forces of irreversible process are weak. It can be deduced that during the evolution of linear systems towards steady nonequilibrium states the entropy production decreases and takes its lowest value compatible with external constraints when this steady state has been reached. This is the theorem of minimum entropy production and is illustrated in mathematics as

$$\frac{dP}{dt} < 0 \quad \text{away from the steady state} \tag{13a}$$

and

$$\frac{dP}{dt} = 0 \quad \text{at the steady state} \tag{13b}$$

where P is entropy production per unit time

$$P = \frac{d_iS}{dt} \tag{14}$$

From the viewpoint of the theorem of minimum entropy production, the steady state in a linear system is stable with respect to perturbation from exterior and internal fluctuations. In such a system the spontaneous emergence of order in the form of spatial or temporal parts differing qualitatively from equilibrium-like behaviour is ruled out. However, if the system is extended very far from equilibrium to the non-linear range, its steady non-equilibrium state does not have this stability property. Even small perturbations may be amplified by the intrinsic dynamics of the system and have a sizeable influence on the evolution of the state. An interesting or unexpected new structure, namely a dissipative structure beyond the equilibrium structure, may appear. It should be emphasized that matter and energy exchange between the system and the outside world are necessary to maintain this structure.

3. Physiological response of tissue to implant bioceramics

A living organism is an open system far from equilibrium. Its processes are irreversible and in the non-linear range. The maintenance of life is responsible for the exchange of energy and matter with the surroundings. The steady non-equilibrium state of this system of functional and structural order in the living body is supported by the negative entropy flow contributed by food in, and waste out, of the living body.

For a normal living organism it is reasonable to assume that the entropy change of the system is zero

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{\mathrm{d_i}S}{\mathrm{d}t} + \frac{\mathrm{d_e}S}{\mathrm{d}t} = 0 \tag{15}$$

and that entropy production P changes slowly with ageing and is compensated by a negative flow of entropy in such a way that the total time variation of the entropy is zero.

Consider a living organism, L, as consisting of many subsystems (L_j) (Fig. 1a). Every subsystem is also an open system. Its entropy change obeys Equation 2

$$\frac{\mathrm{d}S_\mathrm{j}}{\mathrm{d}t} = \frac{\mathrm{d_i}S_\mathrm{j}}{\mathrm{d}t} + \frac{\mathrm{d_e}S_\mathrm{j}}{\mathrm{d}t}$$
$$= P_\mathrm{j} + Q_\mathrm{j} = 0 \text{ (at steady state)} \tag{16}$$

where $Q_\mathrm{j} = \mathrm{d_e}S_\mathrm{j}/\mathrm{d}t$ is entropy flow into every subsystem. The entropy production of system L in the irreversible process can be formed as

$$P = \sum_\mathrm{j} P_\mathrm{j} \tag{17}$$

and entropy flow from the exterior can be represented as

$$Q = \sum_\mathrm{j} Q_\mathrm{j} \tag{18}$$

When the system L arrives at steady state, each subsystem L_j is itself in a steady state, and the distribution of entropy production and flow of entropy is then fixed in every subsystem.

After bioceramics are implanted in a subsystem L_j, additional thermodynamic forces appear in this subsystem due to non-equilibrium between the implant and its surroundings (Fig. 1b). These forces bring about additional entropy production and can be considered as disturbance ΔP_j exerted in the subsystem L_j. According to Equation 16, the entropy change of subsystem L_j containing an implant is

$$\frac{\mathrm{d}S_\mathrm{j}}{\mathrm{d}t} = P'_\mathrm{j} + Q'_\mathrm{j} + \Delta P_\mathrm{j} \tag{19}$$

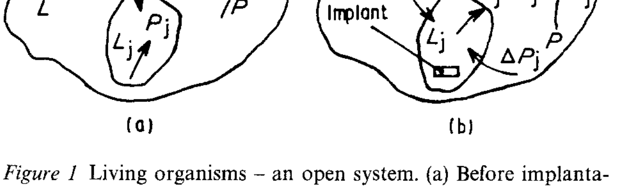

Figure 1 Living organisms – an open system. (a) Before implantation of bioceramics; (b) bioceramics are implanted in subsystem j, injecting an additional entropy production ΔP_j in it.

where P'_j and Q'_j are, respectively, entropy production and entropy flow of tissue in the subsystem after implantation. Supposing the change of entropy production of tissue in subsystem due to the implantation of bioceramics is $\Delta P'_\mathrm{j}$, then

$$P'_\mathrm{j} = \Delta P'_\mathrm{j} + P_\mathrm{j} \tag{20}$$

In relation to implantation of biomaterials there are two possible responses. One is that the distribution of entropy flow in subsystem Q'_j seems not to be disturbed. In this case, bioceramics can be thought of as ideally compatible with the tissue. The other response is just the opposite. Under the former conditions using Equations 16, 19 and 20

$$\frac{\mathrm{d}S_\mathrm{j}}{\mathrm{d}t} = \Delta P'_\mathrm{j} + P_\mathrm{j} + Q_\mathrm{j} + \Delta P_\mathrm{j} = \Delta P'_\mathrm{j} + \Delta P_\mathrm{j} \tag{21}$$

When a new steady state is reached in a subsystem with an implant, the change of entropy is zero

$$\frac{\mathrm{d}S_\mathrm{j}}{\mathrm{d}t} = \Delta P'_\mathrm{j} + \Delta P_\mathrm{j} = 0 \tag{22a}$$

and thus

$$\Delta P'_\mathrm{j} = -\Delta P_\mathrm{j} \leqslant 0 \tag{22b}$$

The conclusion is that self organization may occur in this subsystem. A new order of structure can appear around the implant ceramics, bringing about negative entropy production $\Delta P'_\mathrm{j}$ to compensate for the perturbation from implant materials. A new steady-non-equilibrium state arrives in this system. It has been shown in the preceding section that some organized tissue is formed around the implant. A fibrous capsule is found on alumina implants, and bony tissue on bioactive glasses and on calcium phosphate ceramics.

Equations 10 and 11 show that additional entropy production ΔP_j depends on thermodynamic forces of irreversible process between implant and tissue. When thermodynamic forces increase to the extent that the change in entropy flow into subsystem Q'_j affects the whole physiological process, the biomaterials can be considered as incompatible with the tissue. Therefore the less the thermodynamic force, the less the additional entropy production ΔP_j and the better the compatibility of implant materials with tissue. According to Equations 8 and 9, it is found that thermodynamic forces are associated with the gradient of element composition between bioceramic and surrounding tissue. Bioceramics composed of ions commonly found in the physiological environment have much less steep gradients and hence lower thermodynamic forces than those consisting of constituents never found in living tissue. Therefore the former disturbance on the subsystem is smaller and biocompatibility is better. This is shown by the experimental results that bioactive glass has better biocompatibility than alumina ceramic. In our model excellent biocompatibility requires little thermodynamic force. This conclusion by no means contradicts with the assumption of Hench [2, 3] that an ideal implant material performs as if it were equivalent to the host tissue.

According to the assumption mentioned above that negative entropy flow is related to ageing, the entropy flow in every subsystem is also age-dependent. This means that the steady non-equilibrium state established in the system containing implant and living tissue is not stable. Steady states are continuously replaced by new ones, thus the implant and tissue interface is unstable and uncontrollable. It is difficult to increase the long-term success rate because remodelling of the steady state occurs in biological systems. Special attention should be paid to variation of the interface with the steady state in order to improve the reliability of long-term performance. The thermodynamics of irreversible processes in the bioceramic–tissue system can guide us to increase the long-term success rate of bioceramics.

It is obvious that testing *in vivo* is an effective and economic way to predict the behaviour of bioceramics. But the information obtained from *in vivo* tests may deviate from the *in vitro* situation, as suggested by de Groot [8]. It can be demonstrated that the steady non-equilibrium state of the system *in vivo* is different from that *in vitro*. Entropy flow seems to be zero under the *in vivo* conditions. Using Equation 6, $P = 0$ at steady state, showing that this steady state is at equilibrium. But the steady state of an *in vitro* system is far from equilibrium. The shift of steady state from equilibrium to non-equilibrium influences the interaction between ceramic implants and physiological solutions, showing that results from *in vivo* testing may not be in agreement with those from *in vitro* tests.

4. Summary

The living body is an open system far from equilibrium; a system which can be divided into many subsystems. Each subsystem is at its steady non-equilibrium state once the living system reaches the steady state. When a bioceramic is implanted, an additional thermodynamic force is exerted on the system and a disturbance is brought about. The newly organized tissue is induced and a new steady state appears. It is suggested that the tissue response to an implant is likely to be associated with thermodynamic forces, dominated by the difference in their innate characteristics, such as composition. A better biocompatibility of bioceramics is then associated with low thermodynamic force. Because remodelling of the steady state occurs in biological systems, the interface between the bioceramic and its host tissue is also unstable in the long term.

It is necessary to take into account that *in vitro* systems are closed but *in vivo* ones are open. Therefore, the behaviour of bioceramics *in vitro* is likely to be different from that *in vivo*.

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Received 21 January
and accepted 31 October 1990