Noam Eliaz *Editor*

Degradation of Implant Materials

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Preface

The degradation of biomaterials is one of the major considerations in their design, processing, and use. It might be undesirable (e.g., corrosion of metallic dental implants, wear of polyethylene in artificial hip joints, or calcification of stents), but in other cases it may be desirable (e.g., absorbable sutures, biodegradable polymers for drug delivery, or tissue engineering). In both cases, the kinetics of the degradation is of paramount importance. The undesirable degradation might lower the structural integrity of the implant or release metal ions and debris that elicit an adverse biological reaction (possibly causing synovitis, periprosthetic bone loss, cytotoxicity, allergy, or even cancer).

This book summarizes the current understanding of the mechanical, chemical, and biological processes that are responsible for the degradation of a variety of implant materials. The 18 chapters were written by internationally renowned experts and address both fundamental and practical aspects. Different failure mechanisms such as corrosion, fatigue, and wear are reviewed, together with experimental techniques for monitoring them, either i*n vitro* or *in vivo*. Procedures for implant retrieval and analysis are presented. A variety of biomaterials (stainless steels, titanium and its alloys, magnesium alloys, polyethylene, polycarbonate-urethane, biodegradable polymers, calcium phosphates, etc.) and medical devices (orthopaedic and dental implants, stents, heart valves, etc.) are analyzed in detail.

In Chap. 1, *J.L. Gilbert* and *S. Mali* present the complex interactions that occur in the human body during corrosion of metallic implants. The concepts associated with oxide films and their interaction with the biological, mechanical, and electrochemical environments are discussed, as is mechanically assisted corrosion. Specific examples of biotribocorrosion are discussed. In Chap. 2, *S. Virtanen* summarizes the state-of-the-art knowledge on the degradation modes of titanium and biomedically relevant Ti-based alloys. Issues such as passivity, the effect of alloying elements, and tribocorrosion are discussed comprehensively. A short discussion on some relevant implant design-related aspects of degradation is also provided.

In Chap. 3, *T. Hanawa* reviews different aspects of the degradation of dental implants. Issues such as wear and fracture, the biological environment, corrosion,

metal ion release, biofilm formation, and contamination are discussed briefly. Materials such as titanium and its alloys, calcium phosphates, and zirconia are analyzed. In Chap. 4, *T. Eliades*, *S. Zinelis* and *W.A. Brantley* extend the discussion on dental implants—their aging, corrosion, and failure.

Chapter 5, by *F. Witte* and *A. Eliezer*, starts a series of chapters which describe positive effects and applications of controlled degradation. This chapter covers different aspects of biodegradable implants, with focus on magnesium- and iron-based alloys, and absorbable stents. In Chap. 6, *A.R. Boccaccini et al.* discuss bioactive and biodegradable scaffolds for bone tissue engineering, which are made of a synthetic biodegradable polymer matrix, such as poly(D,L-lactide) (PDLLA), and an inorganic reinforcement such as Bioglass®. In Chap. 7, *J.A. Jansen et al.* discuss different factors that influence the biodegradation of calcium phosphate cements. These cements are good candidates as bone grafts in dental, orthopaedic, and reconstructive surgery. In Chap. 8, *N. Lotan*, *R. Azhari*, and *T. Gold* present the design and performance evaluation of an implantable, degradable, drug delivery device, the function of which is controlled by the concentration and activity of a given enzyme present at the site of implantation. In Chap. 9, *J. Chevalier et al.* comprehensively review the degradation mechanisms of ceramic implants, both bioinert and bioactive, and the interactions between them and their environment. Crack propagation mechanisms are discussed, along with a variety of materials such as hydroxyapatite and other calcium phosphates, calcium sulfate, bioactive glasses, and composites of them.

Chapter 10, by *N. Eliaz* and *K. Hakshur*, starts a series of chapters which focus on the outcomes of wear and fatigue of biomaterials and implants. This chapter first gives brief introduction to the three elements of tribology—friction, lubrication, and wear. Subsequently, the principles and use of Ferrography and Bio-Ferrography in isolating wear debris and monitoring either the degradation of bone and cartilage during osteoarthritis or the degradation of hip and knee artificial joints are reviewed comprehensively. The concept of soft bearing materials such as polycarbonate-urethane (PCU) is presented. In Chap. 11, *S.H. Teoh*, *Y.L. Teo*, and *S.K. Chong* discuss fatigue failures of medical devices. First, basic fundamentals and terminologies in fatigue mechanics are presented. Subsequently, case studies of failures of hip and knee prostheses as well as of dental restoratives are discussed. In Chap. 12, *N.J. Hallab* reviews the topic of hypersensitivity to implant debris. Metal sensitivity, related tests, and case studies are presented.

Chapter 13, by *C.R. Arciola*, *D. Campoccia*, and *L. Montanaro*, discusses implant infections, historical approach to their prevention, and infection-resistant materials. In Chap. 14, *N. Vyavahare*, *F. Schoen*, and *A. Munnelly* discuss mechanisms and prevention strategies of calcification in the two classes of implants: biologically derived and synthetic. Calcification of bioprosthetic heart valves, collagen and elastin tissue engineering scaffolds, polyurethane, silicone breast implants, hydrogels and ophthalmic implants, and intrauterine devices (IUDs) is reviewed.

Chapter 15, by *L.C. Jones*, *A.K. Tsao*, and *L.D.T. Topoleski*, reviews the significance of retrieved orthopaedic implants and failure analysis to their long-term

survival. Issues such as the musculoskeletal system, orthopaedic implants, failure, preclinical and clinical testing, implant retrieval programs, the role of materials selection and implant design, and biological responses to implants are discussed comprehensively. In Chap. 16, *M. Wu* and *P. Briant* summarize the use of finite element analysis (FEA) in design, life prediction, and failure analysis of biomaterials and medical devices. Nitinol wire frame based inferior vena cava filter (IVCF) is given as a case study.

Chapters 17 and 18 discuss the biological responses to and toxicity of polymers and nanomaterials, respectively. First, in Chap. 17, *J.C. Park* and *B.J. Park* review the biological response following implantation of biodegradable polymers and some methods for biological safety evaluation of biodegradable materials recommended by the International Organization for Standardization (ISO) and the US Food and Drug Administration (FDA). Nanomaterial safety and toxicity are of great importance for nanomaterial-based medical implants. Then, in Chap.18, *T.J. Webster* and *L. Yang* introduce the host responses to implant materials and properties of nanomaterials pertinent to their altered biological responses. Next, the advances and progression of biological responses (especially concerning the toxicity of nanoscale implant materials, either after production or implantation) are summarized.

I hope that this book will become a reference source for undergraduate and graduate students, college and university professors, scientists, engineers, implant manufacturers, venture capitalists, regulatory entities, and research professionals working both in academia and industry. It may be of interest to materials, mechanical, biomedical, and corrosion engineers; biologists and medical doctors; chemists and electrochemists; surface scientists; failure analysts; etc.

I dedicate this book to my wife Billie and our three children—Ofri, Shahaf, and Shalev—for their infinite love and support.

Tel-Aviv, Israel Noam Eliaz

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Biography

Professor Noam Eliaz

Noam Eliaz is an Associate Professor at Tel-Aviv University, Israel, where he serves as the Head of the Biomaterials and Corrosion Laboratory. He also serves as a Chief Editor of the journal *Corrosion Reviews* (jointly with Ron Latanision). He received his B.Sc. and Ph.D. (direct track) in Materials Engineering, both cum laude, from Ben-Gurion University. Next, he became the first ever materials scientist to receive, simultaneously, a Fulbright postdoctoral award and a Rothschild postdoctoral fellowship and worked for 2 years in the H.H. Uhlig Corrosion Laboratory at M.I.T. To-date, he has contributed more than 230 journal and conference publications, including 31 plenary and invited talks, as well as 5 book chapters. In addition to editing this *Degradation of Implant Materials* book, he has edited a double volume entitled "Applications of Electrochemistry and Nanotechnology in Biology and Medicine" for the reputed book series *Modern Aspects of Electrochemistry* (Springer). He has garnered numerous accolades, including the T.P. Hoar Award

for the best paper published in *Corrosion Science* during 2001 (on corrosion of Ti–Ag-based alloys processed by three-dimensional printing for biomedical applications) and NACE International's Herbert H. Uhlig Award (2010) and Fellow Award (2012). His main research interests include environment-induced degradation of materials, failure analysis, Bio-Ferrography, biomaterials (with focus on electrocrystallization of hydroxyapatite and other calcium phosphates), and electrochemical processing (namely, electrodeposition, electroless deposition, and electropolishing) of materials.

Chapter 1
Medical Implant Corrosion: Electrochemistry at Metallic Biomaterial Surfaces

Jeremy L. Gilbert and Sachin A. Mali

Abstract Metallic biomaterials represent the class of materials with the largest use in medical devices in humans today. This fact will likely continue for decades to come because of the unique combination of strength, wear resistance, and corrosion resistance. However, metallic biomaterials also pose unique and specific concerns related to electrochemical behavior in the body. This chapter will focus on the elements of most importance in understanding the complex interactions present in the human body during corrosion of metallic implants. The concepts associated with oxide films and their interaction with the biological, mechanical, and electrochemical environments are discussed to provide insight into why corrosion is a critically important factor in the long-term performance of devices. Mechanically assisted corrosion in the biological system is discussed in terms of the structural, electrochemical, and biological interactions, and the idea of electrochemical history is presented to explain why such severe evidence of corrosion is observed *in vivo*. Finally, specific examples of mechanically assisted corrosion *in vivo* (or biotribocorrosion) are presented, and recent observations concerning the important role the reduction half-cell plays in the biological response to corrosion are discussed.

1 Introduction

1.1 A Short History on Metallic Biomaterials and Corrosion

Corrosion of metallic biomaterials has been an issue for as long as metals were considered for surgical repair. Early efforts at bone fracture repair, dental restoration, sutures, and other surgical applications dating back to the early twentieth

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century and earlier [1, 2] showed significant advancements in utilizing metals and alloys in the human body. With the attempts to introduce metallic biomaterials into the body came the inevitable problems associated with their use. Typically, metals were used in high-repetitive-load situations (i.e., fatigue environments), where surface wear processes take place, and where they are exposed to body fluids that led to electrochemical attack.

Early use of gold and silver alloys in applications like dental fillings and skull plates pointed to the early recognition of corrosion as a significant problem in the application of metals to the body. Silver–mercury dental amalgam usage dates back about 180 years (1833) [3], while there are early references to the assessment of steels and magnesium alloys dating back to the early 1900s [2, 4]. Dentistry pioneered the early use of metals in the body in terms of dental restorations, bridges, and crowns. One of the first uses of cobalt was in the development of base-metal alloy partial dentures. Indeed, Haynes Stellite 21, also referred to as Vitallium, was utilized as a medical/dental alloy in the late 1920s, well before it was adapted for use in high-temperature aircraft parts in 1941 [4].

Development of the currently used medical alloys accelerated in the 1920s with the application of both Co–Cr–Mo alloys and stainless steels (18% Cr–8% Ni) in the 1920s. Stainless steel was further improved by the addition of 2–3% molybdenum (Mo) to enhance pitting resistance—ultimately leading to the development of AISI 316L stainless steel and some more recent alloys. Titanium alloys were not significantly applied to biomaterials applications until the 1960s and were adapted from the aircraft industry. The work-horse alloy, Ti–6Al–4V, continues to be a primary alloy for use in orthopedic and spinal applications where high strength and high corrosion resistance are required; however, other alloys including commercially pure titanium, β titanium alloys, and alloys that eliminate vanadium are in use as well. More recently, other alloys are seeing increased use in biomaterials applications. This includes zirconium alloys, tantalum, niobium, and others. Shape memory alloys, in particular NiTi, are also seeing increased use in medical applications.

In most of the efforts to develop and use metallic biomaterials, the goal has been to have a material with suitable mechanical properties for the application while also having appropriate biocompatibility. Early studies by Laing et al. [5] looked at as many metal coupons as they could identify and implanted them into the paravertebral pocket of rabbits, allowed the tissue to heal, and then evaluated the fibrous capsule thickness. The basic finding from this work was that the more corrosion resistant the metal was, the more biocompatible the interaction (smallest fibrous capsule).

1.2 The More Corrosion Resistant, the More Biocompatible

This is the central paradigm of metallic biomaterials biocompatibility today. *The more corrosion resistant, the more biocompatible* has been the view of metals in the body for decades. Thus, the major implant alloys in use today are those that

have been shown to be highly corrosion resistant. However, corrosion resistance can result from several factors, including no or small driving force for corrosion (e.g., noble alloys: Au, Ag, Pt) and a barrier to corrosion in the form of a passive metal-oxide thin film that spontaneously forms on the surface. Alloys based on steel, Co–Cr, Ti, Zr, Nb, Ta, all owe their corrosion resistance to the development of this metal oxide thin film which acts as a kinetic barrier to corrosion. It needs to be clearly stated here that these alloys have high driving forces to corrode. Thus, if the oxide films on their surfaces are breached or disrupted, then highly energetic oxidation reactions of the underlying metal will occur, releasing ions into the environment until the oxide film reforms, which will occur within milliseconds. Thus, any discussion of corrosion of medical alloys needs to include a discussion of conjoint effects between mechanical processes that can disrupt the oxide films and the biological and electrochemical processes that arise during the repassivation processes that lead to reestablishment of the oxide film.

The oxide films on these surfaces, while referred to as passive films, are not, in fact, passive but are highly dynamic in their response and interaction with the biological environment [6–9]. The oxides are responsive to the prior electrochemical history of the surface and can change their structure and properties (e.g., impedance [10]) with exposure to different solutions and voltage conditions on their surface. That is, the electrochemical history of the passive oxide film is very important in determining subsequent behavior. Electrochemical history can be thought of as the time course of solution and voltage conditions to which the surface is exposed. The behavior of a surface will depend on this prior history, sometimes in very profoundly different ways than is typically expected for an alloy surface. This is important since one consequence of mechanical disruption of the oxide films and their repassivation is the large transient shift in voltage across the interface that results from the burst repassivation and slow reduction-coupled reactions that result. Prolonged exposure to cathodic potentials that results from triboelectrochemical interactions of the surface may result in dramatically altered corrosion resistance of the entire oxide-film covered surface, even in locations not exposed to mechanical abrasion.

The consequences of corrosion in the biological system have, for the most part, focused on the effects of the ions and particles released from the metal surface on the adjacent biological system. Ion toxicity and local particulate burden have significant effects on the body and need to be carefully considered [11]; however, these are not the only factors and effects worth noting. Recently, the metallic biomaterials biocompatibility paradigm has come under some pressure to be modified. For example, recent studies of Mg alloys *in vivo* have shown that highly corroding alloys can induce high rates of bone formation [2, 12]. Interestingly, this effect was noted as early as 1910 [1]. Second, other work has shown that titanium and Co–Cr–Mo can be induced to cause cell death *in vitro* with relatively small impressed cathodic voltages [13–15]. Also, published work has shown that protein adsorption and conformation on metallic surfaces can be affected by substrate electrochemical state [16]. With these recent developments, it is clear that metallic biomaterials can have profound effects on the biological system, beyond the effects

of ions and particles, and the biological system can also profoundly influence the electrochemical behavior.

Indeed, corrosion of metallic biomaterials is mostly a story of conjoint effects. That is, corrosion, in and of itself, in most of the alloys used is not a significant problem when no other effects are at play. However, when combined with mechanics, restricted crevice-like geometries, inflammation, or any combination thereof, significantly increased corrosion rates can occur that may lead to adverse biological process or failure of the device.

This chapter will discuss metallic biomaterials corrosion from the materials science perspective and will also provide insight into some of the biological consequences and interactions that are possible. This chapter will not focus on the consequences of metal ion release or particle generation on the local and systemic tissues of the body. There are several good reviews of this in the literature [11].

2 Basics of Corrosion

2.1 Oxidation and Reduction

Corrosion processes are electrochemical reactions that take place at electrode surfaces which include charge transfer across the electrode–electrolyte interface [17]. Two basic types of electrode reactions can occur: oxidation and reduction [see (1.1) and (1.2)]. In oxidation, a chemical species reacts to raise its valence state by releasing electrons, while reduction processes reduce the valence state of other species by taking on an electron. The convention used here is that when positive charge moves from electrode to electrolyte (i.e., metal atom in the metal surface going to metal ion in solution), this represents a positive (or anodic, or oxidation) current. Similarly, when positive charge moves from electrolyte to electrode, it is a negative (or cathodic, or reduction) current. In all electrochemical systems that are closed systems (i.e., no external source or sink for charge), a fundamental rule of electrode reactions is that the sum of all anodic currents must balance out (averaged over time) with the sum of all cathodic currents. That is, the electrode–electrolyte interface will adjust its voltage to arrive at the conditions where both anodic and cathodic currents are equal. Or, put another way, there can be no long-term net accumulation of charge. This is called the "Mixed Potential Theory" [17], and a clear understanding of this concept is essential for understanding how corrosion processes work.

$$\begin{aligned} \mathrm{Co} &\rightarrow \mathrm{Co}^{2+} + 2\mathrm{e}^{-} \\ 2\mathrm{Cr} + 3\mathrm{H_2O} &\rightarrow \mathrm{Cr_2O_3} + 6\mathrm{H}^{+} + 6\mathrm{e}^{-} \end{aligned} \quad \text{(Oxidation reactions)} \qquad (1.1)$$

$$\begin{aligned} &O_2 + H_2O + e^- \rightarrow HO_2^{\bullet} + OH^- \\ &HO_2^{\bullet} + H_2O \rightarrow H_2O_2 + OH^{\bullet} \quad \text{(Reduction reactions involving oxygen)} \\ &H_2O_2 + 2e^- \rightarrow 2OH^- \end{aligned} \tag{1.2}$$

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$$

$$O_2 + 2H_2O + 2e^- \rightarrow H_2O_2 + 2OH^-$$

Note the two oxidation reactions (1.1) represent ionic dissolution and oxide formation reactions. Both liberate electrons into the metal which will act to lower the potential of the implant (i.e., make more negative) until the reduction reactions can remove these electrons. The reduction reactions listed are a limited subset of possible reduction reactions that may be present at implant surfaces. They involve mostly oxygen, water, and their reactive oxygen by-products, including hydroxide radicals and hydrogen peroxide. These are listed to emphasize that there are intermediate species that may arise from reduction processes which are known to have significant effects on the biological system and can induce oxidative stress in cells [18]. These oxidation and reduction reactions are not meant to be an exhaustive listing, but rather a representative list of possible reactions. In particular, there are numerous other potential reduction reactions possible in the biological system, including reduction of disulfide bonds [19] and other protein-like molecules. The effect of redox reactions at implant surfaces on the biological system has received very little in-depth study and much is still unknown about the interactions that may arise. Indeed, the redox state of cells is highly dependent on numerous redox processes across the cell membrane, within the cell and outside of the cell. The redox state of the cell is known, for example, to influence adhesion sites, actin cytoskeletal formation, membrane potential, permeability, etc. [20–24]. Thus, the redox state of cells is likely affected by the local redox environment presented by a metallic implant alloy which can serve as a source or sink for oxidation or reduction equivalents.

Recent studies have focused on the consequences of reduction of disulfide bonds in terms of protein structure and properties, membrane transport, and intracellular behavior (e.g., redox sensitive chaperones, NAD/H and NADPH behavior, ROS and oxidative stress, etc.). Indeed, some of these studies have shown the importance of disulfide bonds, present primarily in cysteine and methionine amino acids, which are highly susceptible to redox processes [20], and which are involved in the oxidative stress response and in intracellular chaperoning. Thiol and disulfide redox status also affects the ease of uptake of cell-penetrating peptides (CPPs) [21] including transmembrane transport of prions and other short peptides [22]. The redox status of a cell is critical to its oxidative stress state. It seems very likely that when cells are adjacent to a half-space (metal surface), actively reducing species available at their surface, including disulfide-containing molecules, will affect their redox balance.

Additional work in the redox biology of cells has involved reactive oxygen species (primarily, NO and H_2O_2) and their role on a variety of biological systems.

Oxidative stress and the generation of H_2O_2 by the cell have been shown to be able to depolymerize actin [23] and alter cellular adhesion [24].

All half-cell reactions (i.e., those reactions that are either oxidation or reduction reactions) establish a potential at the electrode interface, called the equilibrium potential, to balance the forward and reverse reactions for that half-cell. Note the forward reaction for a half-cell can be defined as the reduction reaction. Running this reaction in reverse results in an oxidation reaction. That is, a half-cell reaction is a reduction reaction in one direction and an oxidation reaction in the other. Which reaction occurs depends on the potential of the electrode relative to the equilibrium potential for the half-cell. When multiple half-cell reactions are present on the same surface with different half-cell equilibrium potentials, then the electrode cannot satisfy the equilibrium potential for all simultaneously. Therefore, the electrode potential will change until all oxidation processes balance with all of the reduction half-cell reactions. This potential is called the Open-Circuit Potential (OCP) and it is the potential that defines where all half-cell reactions balance out to net zero current. If the OCP is above a particular half-cell equilibrium potential, then that half-cell reaction will be an oxidation reaction. Whereas if the OCP is below the half-cell potential, the reaction will be a reduction reaction. The rate of the specific reaction will be governed by the magnitude of the voltage difference between OCP and the equilibrium potential, the availability of the species, and the voltage–current characteristic behavior governing the kinetics of the reaction. For nonoxide film covered electrodes, the Butler–Volmer equation [25] governs this behavior and shows that currents rise exponentially with voltage away from the half-cell potential. However, with passive films, other kinetic factors alter the electrode behavior and give more complex behavior.

It is important to note that on real metallic biomaterial surfaces, the OCP of the surface can undergo significant changes depending on what reactive species are present and how they affect the overall balance of reactions. For example, increasing concentrations of hydrogen peroxide (a by-product of inflammation) typically results in a more positive OCP for a particular alloy surface, while additions of proteins to the electrolyte will typically decrease the OCP of the surface. Because most of these surfaces are oxide film covered, and these oxide films are sensitive to voltage and solution conditions [6, 9], OCP shifts can occur not only due to the presence of a new half-cell reaction, but also because of alterations in the film's kinetic barrier behavior. That is, the oxide film's charge transfer characteristics and how they are affected by the surrounding species is an important element in the overall balance that is present.

2.2 Oxide Film Kinetic Effects and Disruption

Oxide film charge transfer behavior is highly complex and is comprised of both the mechanisms of ionic transport across the film and the electronic charge transfer [26]. Ionic transport is a function of the process of migration where the high electric field that develops across this oxide will drive cations (i.e., metal ions) to move in one

direction (usually from metal to electrolyte), while also driving anions (e.g., oxygen ions) from the electrolyte to the metal. The process of migration involves movement due to the presence of an electric field and the atomistic mechanisms by which ions jump through these thin film oxides (e.g., vacancy motion, boundary transport, etc.). Also important in the movement of charge through the oxide is the transport of electrons and electronic holes (regions of positive charge) through the oxide. This involves adoption of the concepts from the semiconducting field, including electron tunneling, Schottky barriers, charge carrier densities, Fermi energy levels, and flat band potentials. Basically, electron (or electronic charge) movement through oxide films can be dramatically altered by the electronic nature of the oxide film present. For a more detailed discussion, please look at the following reference [27].

Thus, the nature of the oxide thin film on these surfaces is highly influential in terms of the severity and extent of corrosion reactions that can occur. For example, when the oxide film is mechanically removed from the surface such that bare metal is exposed directly to electrolyte, several events transpire at very high rates. Within the first nanosecond or two, the surface metal atoms begin to oxidize and either leave the metal surface as ions, or remain as oxidized ions on the surface. Electrons are liberated from the atoms and attach themselves, typically to oxygen atoms at the surface, and an intense electric field forms that can reach the order of 10^7 V/cm. Within one to two milliseconds this electric field will provide the driving force for repassivation as metal oxidation results in oxide film formation by interaction with water molecules [i.e., metal plus water goes to metal oxide plus hydrogen ion plus electrons, see (1.1)].

This burst reaction will reform the oxide film within milliseconds, according to the low-temperature, high-field growth models first proposed by Cabrerra and Mott, and Gunthershultze and Betz [28, 29], but will also accumulate a large number of electrons in the metal that will result in an overall shift in the surface potential to more negative values. That is, an oxide film covered surface that is abraded will see its OCP shift to more cathodic potentials. As the potential shifts to more negative values, the corresponding reduction reactions will increase until the excess electrons are removed and the potential slowly moves more positive back to its starting OCP. These shifts in OCP are important to understand because as mentioned, they (1) change the structure of the oxide film, (2) alter the reactions that are taking place, and (3) can result in propagating electric fields that may affect biological processes in the adjacent tissue [30].

3 The Electrochemical, Biological, and Mechanical Environment

3.1 Conjoint Effects in Biomaterials Corrosion

To understand medical alloy corrosion and its impact on the use of alloys in the human body, it is useful to have a clear understanding of the environments in which

these alloys operate. This includes the chemical/electrochemical environment, the biological environment, and the mechanical environment. Additionally, a detailed understanding of the nature of the surface of alloys and the interfacial zone of the biological system is crucial for an understanding of the complex processes related to corrosion. The role of the biological system on the corrosion process, as well as the effect of the corrosion processes on the biological system, is also necessary to be able to design and utilize metals in the body.

Also, virtually all corrosion testing takes place in *in vitro* tests that try to simulate, in a simplified fashion, the electrochemical conditions of the body. Moving to simplified environments may make control and interpretation of experiments more feasible, but they also remove important potential interactions that may dominate particular metal–body behavior. As a result of the fact that most corrosion testing is done in simplified physiological solutions (e.g., pH 7.4 buffered isotonic saline solutions), very little systematic assessment of how complex "real" biological systems affect corrosion behavior has been explored. This includes assessment of restricted crevice-like geometries associated with, for example, bone cement–metal interfaces [31], modular tapers, and deep implant locations like diaphyseal intramedullary canals.

3.2 The Electrochemical Environment

In most *in vitro* tests assessing the corrosion performance of metallic biomaterials, the solutions used are highly approximate substitutes for the real biological environment. To first-order approximation, the body is a pH 7.4, 0.9% (0.154 M) NaCl solution. This is the most simplified solution used to evaluate corrosion. More complex solutions used *in vitro* include phosphate buffered saline (PBS), Ringer's solution, Hank's solution, simulated biological fluid (SBF), and several others. All of these are inorganic salt solutions that approximate the inorganic constituents in body solutions. In some cases additional constituents are included that are typically organic components like amino acids, single protein solutions (e.g., albumin), cell culture medium, and medium with serum additions. These combined solutions again attempt to get more representative of the actual body environment, yet do not come close. They also raise the complexity of the possible electrochemical reactions present and make interpretation of experiments more difficult, yet they also give better insight into how complex biological systems may interact with metal surfaces.

Some general comments can be made about *in vitro* electrochemical environments. These are typically aqueous salt solutions that provide the electrolyte to complete the electrochemical circuit (to allow both oxidation and reduction processes). Typical redox-active species in these solutions are dissolved oxygen and water. The ionic salts are not thought to participate in reduction reactions. When additional species are added, depending on the redox potential and the ease of the reaction, these additional species may participate in the processes. Examples of

additions include hydrogen peroxide. If the added species do not participate in redox processes, but do adsorb to surfaces, that may (or may not) significantly alter the overall redox balance of the surface.

3.3 The Biological Environment

The biological environment into which metallic biomaterials are placed is highly complex, time and spatially varying, and can result in very severe corrosion conditions. It is important to understand, in any evaluation of metallic biomaterials corrosion, that metal implants are placed into a wound site. That is, the surgical intervention creates a zone of damage around the metal where the wound healing process must occur. Thus, the environment adjacent to the metal, at least initially (during acute inflammation) or chronically, can be dramatically altered in terms of its electrochemical effects. Many of the cellular and biochemical constituents in a wound site can produce redox processes. As mentioned, species like hydrogen peroxide, hypochlorous acid, peroxynitrite, and other enzymes are redox active and can create conditions locally that are very different than the *in vitro* solutions used in corrosion testing [32].

Researchers have shown that hydrogen peroxide can, for example, alter the oxide film on titanium alloys [33]. Indeed, significant alterations in corrosion behavior of titanium alloys can be induced by a combination of hydrogen peroxide and voltage history. Chandrasekaran et al. showed, for example, that cathodic polarization of Ti–6Al–4V in the presence of 0.03 M hydrogen peroxide in PBS to −1 V for 10 min followed by anodic polarization can selectively dissolve the β-phase regions of the surface [34]. Selective dissolution did not occur when the potential was not held cathodically prior to anodic polarization. This implies that cathodic voltages result in alterations of the oxide film, lowering its resistance to electrochemical transport processes and ultimately allowing the oxide film on the β-phase to lose its passive character, resulting in β-phase dissolution. Ehrensberger et al. [10] followed up on these studies with electrochemical impedance spectroscopy (EIS) studies on the voltage-dependent oxide film resistance and showed that titanium oxides can undergo three orders of magnitude decrease in oxide resistance over the voltage range of 0 V to −1 V vs. Ag/AgCl.

This combination of increased inflammatory oxidizing agents and negative voltage excursions that can arise from mechanical factors (oxide film abrasion) may lead to the kinds of severe corrosion attack seen in the selective dissolution processes discussed earlier. Indeed, in a recent retrieval study, Rodrigues et al. showed severe corrosion attack of Ti–6Al–4V modular body hip replacement junctions where the microstructure appeared to be attacked preferentially at the β-phase regions (i.e., selective dissolution) [35], and showed extensive pitting corrosion attack and hydrogen embrittlement of the Ti–6Al–4V alloy in the human body.

Additionally, it is important to remember that metal surfaces in the body may be adjacent to highly restricted crevice-like solution conditions. This is particularly

true in metal-on-metal (MoM) interfaces including modular tapers and MoM hip replacements. When such restricted crevices arise, the local solution conditions can be dramatically altered from the commonly assumed pH 7.4, 0.154 M saline environment [26]. Indeed, early work on the corrosion of modular taper interfaces showed that the pH and Cl^- concentration within the modular taper deviate significantly from the physiological level. There are indications from retrieval analyses and other experiments that the pH within taper crevices can, under certain conditions, reach below one [26]. Additionally, the cationic concentrations within tapers can be orders of magnitude higher than those seen in the peri-implant tissues. The role of cation concentrations in solutions adjacent to corroding implant surfaces remains a mostly unexplored area of study.

3.4 The Mechanical Environment

The mechanical environment for metallic biomaterials typically consists of high cyclic loads associated with the activities of daily living and can also include significant surface interactions that include wear against a counter face. The general processes of wear can be further classified into large cyclic motion (wear) and small cyclic motion (fretting) processes. Typically, wear processes are thought to occur at occlusal surfaces (in dentistry) and joint surfaces for total joint prostheses. Fretting, on the other hand, is thought to primarily occur at screw–countersink junctions in fracture fixation devices [36], dental implants, and modular taper interfaces of total joint prostheses [37, 38]. While these are important areas where fretting occurs, others are also present and likely to be influencing the corrosion behavior of devices. These additional locations include back-side contacts in joint prostheses, bone-implant contact regions, overlapping cardiovascular stent contact points [39], and other locations where surface contact and small cyclic motion takes place.

4 Biotribocorrosion Fundamentals

4.1 Wear and Corrosion in the Biological System

For wear of, for example, MoM implants, much of the research on the longevity of these devices has focused entirely on wear (ignoring the corrosion aspects). However, recently, researchers [40] have realized the importance of corrosion processes during wear in these and other devices. It is important to state that in the biological system one cannot have wear of a metal device and NOT have corrosion reactions taking place as well. That is, wear of metals in the body is a tribocorrosion (wear and corrosion) process. The phrase tribocorrosion does not

fully and adequately describe the full range of what is more appropriately called mechanically assisted corrosion, where other mechanical mechanisms like elastic straining, plastic deformation, etc., which can affect the oxide film covered surfaces, are included.

Tribocorrosion (i.e., mechanically assisted corrosion) is a conjoint failure mechanism that is highly complex and comprised of surface mechanical processes and surface electrochemical processes. Tribocorrosion in the biological system (biotribocorrosion) has the additional factors of biological processes at play. Thus, biotribocorrosion is the process of corrosion, modified and assisted by the processes of wear (wear and fretting) occurring in and influenced by the adjacent biological environment.

There are several research programs studying the fretting corrosion behavior of medical alloys. Mischler et al. [40–43] have developed several interesting methods for systematic evaluation of fretting corrosion of Ti alloys (amongst others) in physiological solutions and have investigated the effects of potential and proteins (amongst other factors).

To understand biotribocorrosion, the following sections will lay out the basic factors, processes, and mechanisms at play in each aspect of the process. There are three basic aspects (mechanical, electrochemical, biological) at play; however, in each of these primary areas highly complex processes are ongoing. Additionally, the materials in contact and engaged in the processes play an important role. Thus, the materials science of the surface of the metallic biomaterials is critical.

Below is a short, and incomplete, listing of the materials factors, the mechanical factors, and the electrochemical factors that are important in biotribocorrosion. Within each of these broader categories, more specific information of the structure, properties, and processes present during biotribocorrosion is provided. This is meant to help the reader understand the wide range of factors that interact to give rise to mechanical-assisted corrosion in the biological system.

4.2 Materials Factors

4.2.1 Structural Factors

Surface Oxide

Thickness, chemistry (e.g., chemistry and oxidation states of cations), structure, e.g., suboxides present, defect density (vacancy distribution, pipe-diffusion paths, amorphous vs. crystalline), residual stresses (volumetric mismatch with substrate), growth mechanism (high-field growth with electromigration transport), electronic states, semiconducting behavior, ionic transport behavior.

Substrate Alloy

Crystal structure and orientation to the surface, volumetric mismatch with oxide, chemistry of near-surface alloy, transport processes (diffusion) within metal, dislocation structure (cold-working state), precipitate and defect inclusions.

Biological Environment

Proteins adsorbed and their conformation, pH and ion levels (in crevices and restricted geometry environments), oxidizing agents present (ROS, enzymes, proteins, cations, etc.), electrical double layer, surface water structure.

4.2.2 Properties

Surface oxide

Semiconducting properties (flatband potential, Fermi level, work function, defect density), ionic transport properties (vacancies, oxide boundaries for pipe diffusion and migration, etc.), oxide modulus, oxide fracture strain/stress, coefficient of friction with opposing surface, interfacial fracture strain (stress), electric field generated.

Substrate alloy

Yield stress, work hardening sensitivity, hardness, diffusion coefficients, redox sensitivity of alloy constituents.

4.3 Mechanical Factors

Contact asperity geometry, contact stresses, coefficient of friction, fracture strain, interfacial strain to failure, modulus, yielding, fracture mechanics of thin films, relative sliding distances, elastic displacements, structural rigidity of constructs.

4.4 Electrochemical Factors

Thermodynamic condition (potential), active redox processes, surface oxide and electric field, relative anodic and cathodic areas, impedance characteristics (kinetic barriers to oxidation and reduction charge transport processes), solubility of cations, oxide forming tendencies and stability, solution chemistry.

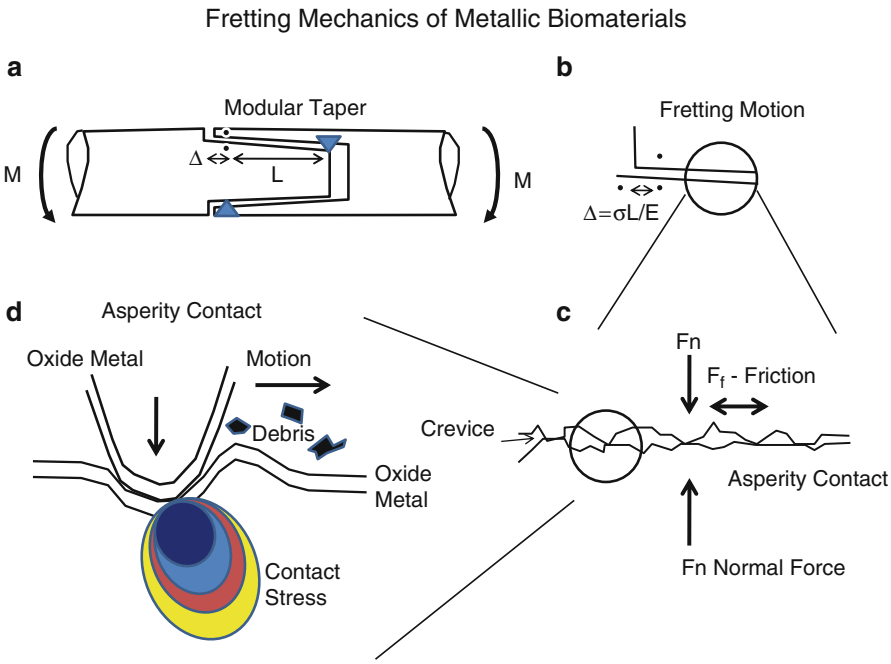

Fig. 1.1 Schematic representations across spatial scale of the mechanics of fretting. (**a**) Elastic bending strains, in conjunction with rigidly connected contact point (*triangles*) can give rise to elastically based displacements, (**d**), in the taper. This does not require rigid body sliding to occur. (**b**) Zoom-in of elastic fretting strains with the displacement depends on the bending stress, modulus, and distance from rigid contact. (**c**) Schematic of a zoom-in on the contact region within a modular taper. Crevice solution can fit within the contacts and the interface will consist of asperity–asperity contact and normal and frictional stresses. (**d**) Close up of metal–oxide surfaces in asperity contact and causing contact stresses, local surface deformation, and oxide debris

One can see from the above listing of factors, that these interfaces and the processes associated with mechanically assisted corrosion *in vivo* are highly complex and interactive and span several different physical, chemical, and biological disciplines.

To understand mechanically assisted corrosion, a series of figures are presented to provide insight into the mechanical and electrochemical elements. Figure 1.1 is a series of schematics of a modular taper interface. In Fig. 1.1a, there is a representative modular taper where an applied bending moment, M, is shown. If one assumes that there are two points within the taper (triangle regions) that can be considered rigidly connected to the opposing surface, then the elastic strain associated with cyclic bending will give rise to a displacement, Δ, within the taper interface (see Fig. 1.1b), which results from taking the flexure formula for stress, assuming this stress is constant along the length, L, of the taper from the fixed point to the point of interest. One can see from this that the displacement, Δ, will be given by:

$$\Delta = \varepsilon L = \frac{\sigma L}{E} = \frac{MyL}{EI}$$

Inputting appropriate values for M, L, y, E, and I yields Δ in the range of 20–40 μm for typical tapers in use today. This equation shows, first, that fretting displacements can arise solely from elastic deformation and do not require rigid body displacements of the implant. Simply considering elastic deformation behavior, fretting displacements are within the range observed in these tapers. Additionally, this equation gives insight into the mechanical design features that may affect fretting motion. That is, the flexural rigidity (EI) of the modular cross-section will be important. Higher modulus materials (e.g., Co–Cr alloys) will have less elastic-based fretting motion. Larger diameter tapers will also have smaller fretting motions. This analysis is highly simplified, but none-the-less provides insight into the macroscopic stress and design issues that may be important.

If one now looks more closely at the interfacial mechanics, there is asperity–asperity contact that initially takes place between metal and oxide surfaces (Fig. 1.1c, d). Within this asperity contact region, there is enough space for a crevice and solution to fill the space. Contact stresses and frictional interactions will arise within these regions, and if the stresses and deformation mechanisms are large enough, oxide disruption will occur and oxide debris will be generated. Figure 1.2 shows a little more detail of those factors identified above as being important to the surface mechanical processes. This includes (Fig. 1.2a) the dislocation structure, the surface oxide structure (including the film and dome-like shape of passive oxide films), and the properties (e.g., moduli, fracture strains, hardness, etc.) that will impact on the mechanical disruption of the oxide. The nominal contact stresses needed to induce oxide disruption sufficient to cause enhanced corrosion is an important property and is likely to be very low for Co–Cr alloy and even lower for Ti alloys. The local asperity–asperity contact stresses are likely much higher; however, it is also likely that only relatively low contact stresses are necessary for oxide abrasion processes.

Also shown in Fig. 1.2b is what transpires electrochemically just behind a moving asperity that is scraping oxide film from the metal surface. Oxide debris is released and two basic oxidation reactions occur just behind the moving asperity: ion dissolution and oxide repassivation. The first of these releases cations into the crevice solution, while the second regenerates the oxide and releases hydrogen ions into solution. Both oxidation reactions shown result in the accumulation of positive charge in the crevice solution and electrons accumulating in the metal (causing a drop in potential of the surface). The electrons will move to any other location on the metal surface where reduction reactions are present (and still, in electrical contact with the solution) and will be consumed in those reactions. Additionally, anions (Cl^-, PO_4^{3-}, etc.) will be drawn into the crevice in order to maintain charge neutrality and balance the cation release. This combination results in lowering of pH and phosphate and chloride ion levels (among others) in the crevice. These reactions, if they continue within the crevice and are slow to clear from there, will result in a highly aggressive acidic solution that may result in continued corrosion processes after the fretting motion ceases. Indeed, in *in vitro* testing of modular tapers, one can detect this continuing process by the increased currents that remain after loading is stopped [44].

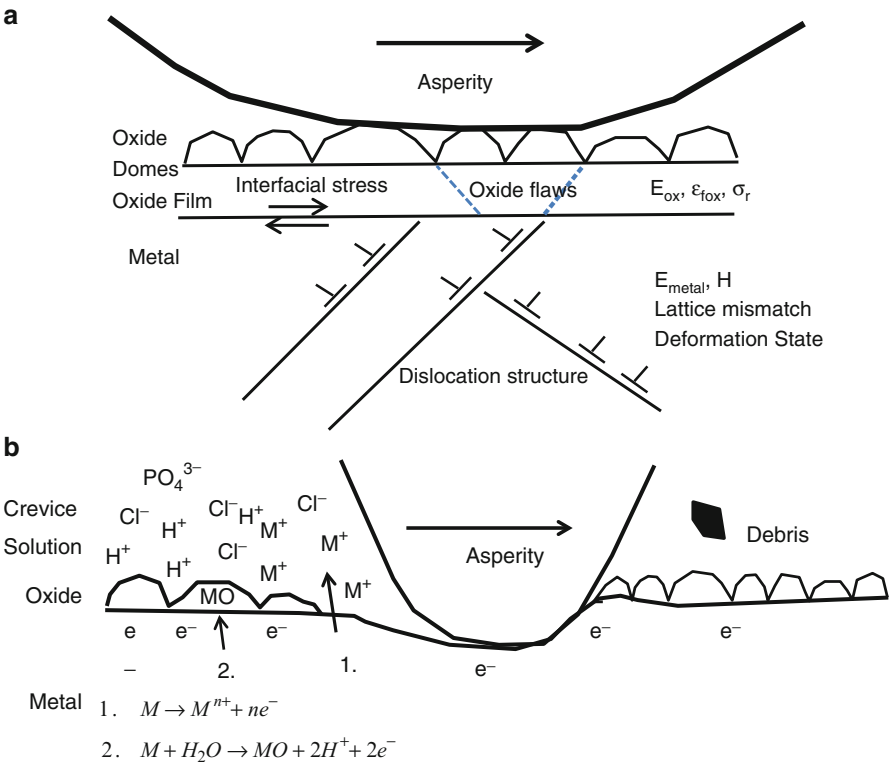

Fig. 1.2 Schematic views of asperity–oxide–metal interfaces showing some of the factors associated with fretting corrosion processes. (**a**) The surface oxide film in contact with an opposing asperity has a structure that typically consists of an oxide film–oxide dome morphology with specific properties of modulus, fracture strain, and residual stresses present in the oxide. A lattice mismatch between oxide and metal gives rise to residual stresses and interfacial stresses as does the asperity interaction. Metal substrate structure and chemistry is also important including the dislocation structure (amount of cold working, hardness, etc.). (**b**) A second schematic of an asperity moving across a metal–oxide surface where contact stresses and motion scrape oxide from the metal surface, creating oxide debris while behind the moving asperity are electrochemical reactions reforming oxide and dissolving metal ions into the crevice solution. Hydrogen ions are generated as well and anions (Cl^-, PO_4^{3-}, etc.) migrate into the crevice to maintain charge neutrality and result in pH drops

Figure 1.3 schematically represents the atomic-scale view of the metal–oxide–solution crevice interface (Fig. 1.3a). Also shown are two scanning electron micrographs taken of the cross-section of a retrieved Ti–6Al–4V alloy (Fig. 1.3b) [35]. These images are from a pitted region of the interface where severe pitting attack of the alloy had taken place while inside the human body. This is the first documented case of pitting corrosion attack of Ti alloys in the human body. What is interesting to note in this figure is that there are a network of tunnels and microsized crevices between the alloy and the oxide where the highly aggressive solution

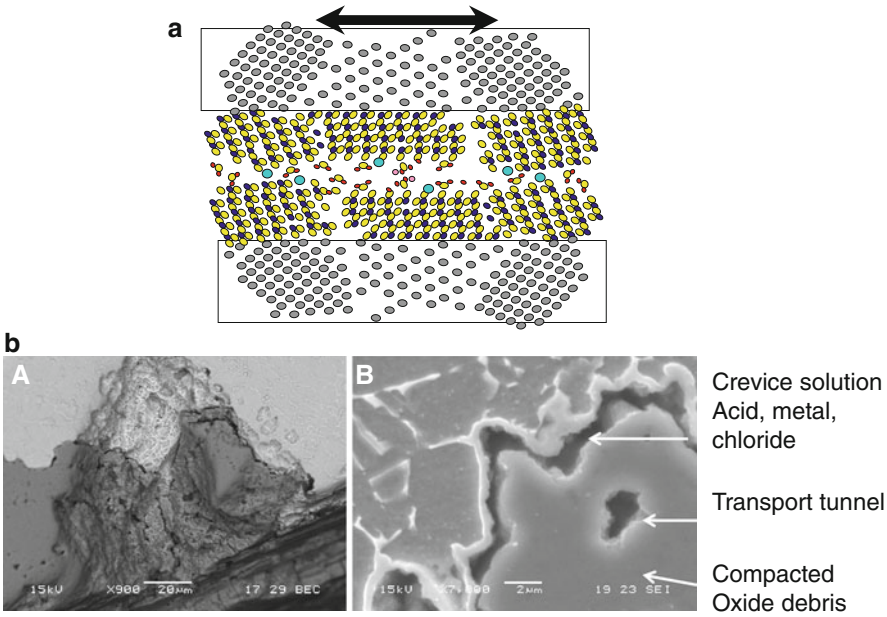

Fig. 1.3 (**a**) Atomic scale schematic of metal–oxide–crevice solution interface. (**b**) Scanning electron micrograph images of Ti–6Al–4V cross-sections from modular body implant tapers. *Gray regions* (*lower parts*) are oxide regions within a pit on the Ti alloy surface. This pitting penetrated up to 200 μm in to the taper surface. The high magnification image shows some interesting and important structural details at the interface between the metal and the oxide. There are small (1–2 mm) channels and tunnels for crevice solution transport. It appears that dissolution of the alloy occurs with subsequent precipitation of the oxide and enrichment of the Ti alloy surface of a precipitated layer (*light line* along the interface). This oxide debris structure likely affects solution chemistry and helps drive the pitting attack (images in (**b**) are reprinted with permission from Wiley [35], all rights reserved)

accumulates and proceeds to corrode the metal. It appears, based on these images, that there is a dissolution process of the metal into the crevice solution and then a precipitation back out of the debris on the oxide side. Also, there appears to be about a 1 μm thick zone on the alloy surface which has precipitated from the reactions taking place (bright line on alloy surface). Thus, the alloy dissolves while the oxide front grows and this process continues, leading to a penetrating pitting-like corrosion attack. The exact details of this process are not known; however, it is clear that because the pits are up to 300 μm deep, fretting is not likely a part of the process ongoing in these pits.

Electrochemically, abrasion of surface oxides dramatically raises the current density and alters the overall polarization behavior, as can be seen in Fig. 1.4 [45]. In this work, a Co–Cr–Mo surface was subject to potentiostatic conditions (from −1 V to +1 V vs. Ag/AgCl) and abraded with 600 grit emery paper for 15 s, followed by a recovery period. The abrasion current density and recovered current

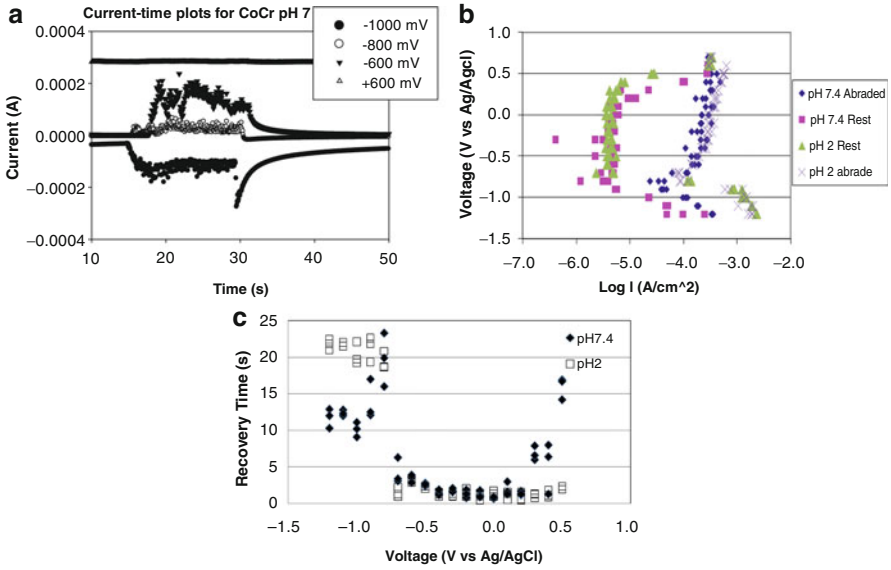

Fig. 1.4 Results of polarization testing of Co–Cr–Mo alloy in pH 7.4 and pH 2 PBS solutions. Alloy surfaces were potentiostatically held and abraded with 600 grit emery paper and then allowed to recover. (**a**) Current versus time plots for abrasion results at four different potentials (−1000, −800, −600, and 600 mV vs. Ag/AgCl). (**b**) Polarization plot of the resulting data over the range of potentials from −1,000 mV to +700 mV. Note that the current density is about 50 times larger during abrasion and that pH did not have a significant effect over most of the range. (**c**) Time constant for recovery of the current after abrasion is stopped. Note the voltage dependence of the recovery that reflects both the presence of the oxide film and the predominant electrochemical reaction being affected. (Images reprinted by permission of ASM International, all rights reserved [42])

levels were tested at pH 7 and pH 2 in PBS, and the time constant for the recovery curves was determined (Fig. 1.4b, c respectively). Clearly (Fig. 1.4b), the abrasion currents are about 50 times greater than the recovered current densities, and there are systematic changes in the time constant for recovery with voltage. These abrasion currents are unlikely to be the maximum possible since the abrasion was not uniform and complete at any time point.

5 Electrochemical History Effects

An element of corrosion behavior that is often poorly understood, especially when it comes to oxide-film covered alloys, is the concept of electrochemical history. That is, how the prior voltage–time solution conditions affect present and future behavior of the surface. For example, oxide films (e.g., TiO_2) are known to have an anodization rate of about 2 nm/V [46], which is not fully irreversible. That is, oxide films can