Computational Models of Magnesium Medical Implants Degradation: A Review

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Abstract. Magnesium is attracting the attention of researchers from medical field especially implant material due to its properties, including but not limited to degradation and biocompatibility. Many chemical and physical reactions are considered to play a part in the procedure of magnesium degradation and influence the bio-tissue. To design and analyze magnesium implants, it is important to fully consider the factors that will affect the degradation and the impacts on the mechanical property as well as the in-vivo environment. Computational model gives another way to capture and analyze the in-vivo degradation behavior of the magnesium besides experiment. A review of the current computational models which could be used in study of magnesium medical implant is presented here, with the main mechanisms and accomplishments of each model highlighted.

1. Introduction
Magnesium is an important material for medical implants due to its special properties including biocompatibility, low density, high mechanical property, and biodegradability. Magnesium was first reported being used to stanch bleeding in 1878 by Huse E.C. [1]. Then Payr E. attempted to use magnesium plates in joint arthroplasties [2, 3], which could be the first reported magnesium application case in musculoskeletal surgery. Hopfner E. [4] used magnesium cylinders as vessel connectors. The early magnesium application was slightly rough because of insufficient understanding of magnesium properties. However, researchers shortly found that the biodegradability could cause unexpected problems. Groves et al. [5] reported his experiments on rabbits showing magnesium could produce abscess cavities and corrode too quickly to stabilize the fragments in fracture. The animal experiments showed that magnesium only could keep stable for 6-8 weeks in vitro. The rapid corrosion of magnesium in vitro and in vivo seemed to be insurmountable at that time. Since the late 1940s, researchers have diverted their attention to other materials such as stainless steel and Ti alloy. Studies on medical application of magnesium did not widely reemerge until the research on new alloy, surface modification, and tissue engineering, etc.

Proper alloying, such as precipitation of new phases and changing the microstructure, could improve the magnesium degradation resistance as well as mechanical properties [6]. Plenty of magnesium-based alloys were investigated by in-vivo [7-10] or in-vitro [11, 12] corrosion test, showing potential for medical use. Meanwhile, surface modification such as coating [13, 14] and surface nano-crystallization [15, 16] were proposed in order to control the degradation rate of magnesium. Then magnesium implants benefitted from the above property improvement. Since Hublein in 1998 first started the application of magnesium as a biodegradable metal stent [17], researchers have studied the potential of magnesium for medical implants, including tissue engineering [18], orthopedic implants [19, 20] and cardiovascular stents [21, 22], etc. Some specific properties are considered critical to magnesium medical implants. A moderate and homogeneous
degradation rate and adequate mechanical properties would be favorable for magnesium implants to keep integral and mechanic-functional in the in-vivo or in-vitro environment. Another important property is biocompatibility. Degradation products of magnesium includes dissolved magnesium ions, alloying elements, a mass of hydroxyl ions and hydrogen. It is believed that the degradation products could have positive or negative impacts on biological tissue, such as the hemolysis induced by high pH value [23] and the osteogenesis mediated by magnesium ion [24, 25]. Furthermore, structure design was considered playing a role in degradation rate [26-28]. These factors are all related to the degradation of magnesium, which covers mechanics, chemistry, biology, etc. Therefore, researchers are seeking computational models to capture and describe characteristics of magnesium degradation. Computational modeling could be useful and complementary tool to evaluate the performance of magnesium under multi-factor complex conditions.

This article is to summarize some magnesium degradation models that have the potentials or have been used in medical implant simulations. Their main mechanisms, accomplishments, and potentialities in this field will be illustrated.

2. Models
There are several types of magnesium corrosion degradation in biological environment, including uniform corrosion, pitting corrosion, and stress corrosion, etc., as shown in figure 1. In the uniform corrosion degradation, some of the magnesium areas play the role of anode and others play the role of cathode. When the location of anodic and cathodic areas distributed evenly in the entire material, the surface degrades uniformly. If the magnesium is immersed in neutral or slightly acid environments, pitting corrosion degradation would begin in areas where the oxide layer is weakened under the influence of aggressive ions. Stress corrosion degradation is resulted from the combination of corrosive environment and mechanical stresses. Generally, the degradation products of magnesium are hydroxide and hydrogen gas. Whereas, the degradation in biological environment would be a bit more complex, since the chemical reaction would be affected by flow speed, organic molecules, pH value, and other ions which would react with magnesium. For the magnesium degradation, modeling to date could be predominantly divided into two kinds based on different theories and assumptions, such as material damage mechanics and molecular diffusion theory. These computational models manage to describe one or more characteristics of the magnesium degradation. The first kind of models utilizes the material damage mechanics to describe the degradation procedure of magnesium. A normalized parameter will be used as an index to represent the failure degree of the material. The second kind is multiphasic models, partially based on molecular diffusion theory. Multiphasic models divide the degradation procedure into different phases according to different magnesium existing forms. Details are described in later sections. In addition, it has to be stated that some of the models are named and classified by the authors’ understanding of their characteristics.

![Figure 1. Typical corrosion types of magnesium degradation in biological environment.](image)

Please note that the chemical reaction occurs over the entire surface of the material
2.1. Uniform Corrosion Model

The uniform corrosion model was proposed by Gastaldi et al. [29], using the continuum damage mechanics theory. A parameter is used to assess the degree of material mechanical integrity loss. This parameter is marked as D and given by the equation:

\[
D = 1 - \frac{\sigma_{ij}}{\bar{\sigma}_{ij}}
\]  

(1)

Where \(\sigma_{ij}\) is the element Cauchy stress, \(\bar{\sigma}_{ij}\) is the effective Cauchy stress. Initially D=0 implies that the material is perfectly undamaged and D increases as the corrosion progresses. When D reaches 1 the material is completely damaged and does not possess the capability of mechanic support any more. In finite element model, the element will be removed from the model when the local parameter D=1.

The uniform corrosion model is to simulate the micro-galvanic corrosion degradation, in which the corrosion degradation rate is uniform on the surface of the material. The micro-galvanic corrosion degradation is considered as one of the basic forms of magnesium degradation. For the surface elements, the damage parameter \(D_U\) is given by the following equation:

\[
\frac{d D_U}{dt} = \frac{\delta_U}{L_e} k_U
\]  

(2)

Where \(\delta_U\) is a characteristic length usually considered as the critical thickness of the corrosion degradation film, \(L_e\) is the characteristic length of the mesh to avoid the influence of the mesh size, and \(k_U\) is a material corrosion kinetic parameter.

The uniform corrosion model was first calibrated by Gastaldi et al. [29] using mass loss versus time curves obtained from immersion tests in vitro [30]. When \(k_U\), the kinetic parameter, changes in the range \(10^{-2}\text{ to }10^{-1}\text{ (h}^{-1})\), the results of the uniform corrosion model are consistent with the experiments. Grogan et al. [31] also reported that the uniform corrosion model was able to capture the mass loss rate observed in experiments. However, the experiments showed that the specimen strength with mass loss was non-linear. The uniform corrosion failed to describe the trend [31]. The uniform corrosion model is concise, whereas it may need to be added other factors to account for the non-linear evolution of strength observed in experiment. Enhanced models are summarized below.

2.2. Stress Corrosion Model

Gastaldi et al. [29] presented the stress corrosion model, which was adapted from the model used by Da Costa-Mattos et al. in simulation of stainless steel under acid environment [32], to simulate the stress modulated corrosion. The stress corrosion degradation is considered to be really dangerous because the mechanical properties would be unstable and may decrease rapidly under loadings [33, 34].

The stress corrosion model is also based on the continuum damage mechanics theory. The damage parameter \(D_S\) is given by the following equation:

\[
\frac{d D_S}{dt} = \begin{cases} 
\frac{\delta_S}{L_e} \left( \frac{S \sigma_{eq}}{1 - D_S} \right)^R & \sigma_{eq} \geq \sigma_{th} > 0 \\
0 & \sigma_{eq} < \sigma_{th}
\end{cases}
\]  

(3)

Where \(\sigma_{eq}\) is the equivalent stress affecting the whole stress corrosion degradation process, \(\sigma_{th}\) is the lowest stress value at which the stress corrosion degradation occurs. In Gastaldi’s work, \(\sigma_{th}\) was assumed to be half of the yield stress of magnesium alloy ZM21. \(L_e\), as mentioned above, is the characteristic length of the finite element mesh, \(\delta_S\) is a characteristic length of the stress corrosion process, and S and R are parameters related to the properties of corrosive environment, based on an assumption that the corrosive environment is constant over time.

In a simulation of application to the stenting procedure, Gastaldi et al. combined the stress corrosion model with the uniform corrosion model [29]. The combined model could be calibrated
based on experimental observations and well replicated the curve of global damage over corrosion time.

The stress corrosion model was further adapted by Galvin et al. [35] to plastic strain-mediated corrosion model, in order to describe the influence of permanent deformation caused by instantaneous inhomogeneous stresses, which could be observed in medical implants [36]. The damage parameter $D_e$ is given by the following equation:

$$D_e = D_{e-1} + \frac{\delta e}{l_e} k_U \varphi_e \Delta t k_e$$  \hspace{1cm} (4)

Where $D_e$ is the damage parameter for the present time step, $D_{e-1}$ is the damage parameter for the last time step, $\varphi_e$ is an index indicating the plastic deformation, $k_e$ is a scaling parameter as each element on the surface has different quantity of facets exposed to the corrosive environment.

Galvin et al. calibrated the model according to the results of experiments in his previous work [37], in which immersion tests were implemented using WE43 alloy dog-bone specimens, and further applied the model to simulation of the expansion and recoil of the stent. Results showed that the model was able to predict the non-linear influence of plastic strain on the stent radial stiffness. But both the stress corrosion model and the strain corrosion model could not account for the early rapid mass loss of magnesium.

2.3. Pitting Corrosion Model

Grogan et al. [31] proposed the pitting corrosion model, which is also based on the continuum damage mechanics theory. It was used to capture the effects of localized or pitting corrosion degradation. The damage parameter $D_p$ is given by the following equation:

$$\frac{dD_p}{dt} = \frac{\delta u}{l_e} \lambda_e k_U$$  \hspace{1cm} (5)

Where $\lambda_e$ is a pitting parameter randomly assigned at every element of the surface in the finite element mesh according to Weibull distribution. Weibull distribution is widely used in material reliability analysis. An element that is assigned a larger magnitude of $\lambda_e$ will degrade faster than those assigned smaller ones, and it will be removed from the mesh when it is totally degraded. Then its adjacent elements will be assigned pitting parameters $\lambda_e$ given by:

$$\lambda_e = \beta \lambda_n$$  \hspace{1cm} (6)

Where $\lambda_n$ is the pitting parameter of the recently degraded element, and $\beta$ is a dimensionless coefficient related to the speed of pit growth.

Boland et al. [38] further calibrated the pitting corrosion model by comparison with data obtained in the experiments, in which the WE43 alloy was immersed in the Hank solution. Results showed that the combination of the uniform corrosion model and the pitting corrosion model could well replicate the mass loss over time and the decrease trend of strength over mass loss.

In addition, Boland et al. indicated that factors such as pulsatile blood flow, dynamic loading and arterial remodeling, etc. are influential when considering the degradation rate and the mechanical integrity of the magnesium implants, though these factors have not been described in the pitting corrosion model.

2.4. Gurson-Tvergaard-Needleman (GTN) Model

The models presented above are all based on the continuum damage mechanics theory. From another perspective, Vijayaraghavan et al. [39] presented the GTN model based on meso-damage mechanics theory, in which the damage of material is resulted from the formation of mild cracks and voids. The yield function of the GTN model is as follow:

$$\phi = \left( \frac{\sigma_{eq}}{\sigma_m} \right)^2 + 2q_1 f^* \cosh \left( \frac{3q_2 \sigma_{eq}}{2\sigma_m} \right) - 1 - (q_3f^*)^2 = 0$$  \hspace{1cm} (7)
Where $\sigma_{eq}$ is the effective stress, $\sigma_h$ is the hydrostatic stress, $q_1$, $q_2$ and $q_3$ are fitting parameters, and $f^*$ is the damage parameter calculated as a function of void volume fraction $f$. $f^*$ is given by:

$$f^* = \begin{cases} f & (f_0 \leq f \leq f_c) \\ f_c + k(f - f_c) & (f_c < f \leq f_F) \end{cases}$$

(8)

Where $f_0$ is the initial void volume fraction, $f_c$ is the critical fraction at which the voids begin to aggregate, and $f_F$ is the failure fraction at which the macroscopic cracks appear. For $f^*=0$, the yield condition becomes the normal yield condition, and $f^*=1$ means the material is totally damaged. The detailed computational framework could be found in a previous work [40]. Applying this GTN model and genetic programming, Vijayaraghavan et al. developed an FE simulation framework in order to predict the mechanical properties of AZ31 alloy under different working conditions combined by parameters including the strain rate, and temperature. Especially, different magnesium alloys could be distinguished in this model according to the Pilling Bedworth ratio. And because the analyzed temperature range is 300K to 450K, this model is also suitable for analyzing high temperature conditions.

The material damage mechanics models presented above capture the overall long-term corrosion degradation of magnesium implants, whereas they do not account for the multiphasic processes, such as the formation of corrosion film on the interface between magnesium implants and biological tissue and the increase of film thickness over time. The degradation of the interface between the implant and the biological tissue is believed to have a strong influence on the bonding strength of the two. A new approach for capturing the details is a kind of models that could be classified as multiphasic models. Multiphasic models separate the corrosion degradation process over time into different phases according to the existence forms of magnesium, including the origin material, intermediate, and final products. A detailed description is provided in the following sections.

2.5. Transport Model

Grogan et al. [41] proposed a transport model using adaptive meshing and molecular diffusion theory to capture the changing surface of magnesium during corrosion degradation. A basic assumption is that the metallic ion diffusion rate is slower than the electrochemical reaction rate since the implants are surrounded by films of corrosion products.

The model could be described as the following equation:

$$\frac{\partial [\text{Mg}]}{\partial t} = \nabla (D_{Mg} \nabla [\text{Mg}])$$

(9)

Where $[\text{Mg}]$ represents the concentration of magnesium ions, and $D_{Mg}$ is the diffusion coefficient associated with the degradation rate. As the degradation develops, the surface of magnesium moves, and the mass must obey the law of conservation. Thus according to the Rankine-Hugoniot condition, the velocity of the magnesium surface is given by:

$$\{-D_{Mg} \nabla c - (c_{sol} - c_{sat}) \psi \} \cdot n = 0$$

(10)

Where $c_{sol}$ is the concentration of magnesium ions in the solid, $c_{sat}$ is the saturation concentration of magnesium ions in solution, $\psi$ is the surface velocity vector, and $n$ is the normal vector.

This model simplified the degradation process of magnesium as a Stefan problem. Obviously, the mass loss rate is associated with the concentration of magnesium ions in solution, which could predict degradation rates in various chemical environments.

Based on the transport model, Bajger et al. [42] further took the corrosion film and the chloride ions into consideration. It is a model using level set method to capture the topology of the material during the corrosion.

The model takes the following form:
Where \( k_1 \) and \( k_2 \) are the reaction rates of the Mg(OH)\(_2\) film formation and dissolution, respectively, \( D^e \) is the effective diffusion coefficient, \( F \) is the film concentration, and \( \text{max} \) indicates maximum.

The model in this study explicitly emphasizes the evolution of the corrosion film and its potential effects on the degradation rate. And it is also worth mentioning that the transport model can analyze the influence of the surrounding fluid flow (e.g., blood flow) on the degradation rate. Besides, although the mass loss is explicit, the transport model could not directly calculate the evolution of mechanical strength. Grogan et al. [41] believed that the implant strength predictions of the transport model and the uniform corrosion model are basically consistent. This view may be based on the assumption that mechanical strength is linearly related to mass.

2.6. Empirical Model

This model was proposed by Dahms et al. [43] based on mainly three assumptions in order to use fewer parameters to describe the materials failure process. The first assumption is that the magnesium flux going into the solution is time-constant. The second one is that a porous continuum film will be formed during degradation, which will control the transport of the magnesium ions. The third one is that the concentration of magnesium in the film is constant. According to the above assumptions, the model is described by an empirical equation as follow:

\[
\frac{\partial [Mg]}{\partial t} = \nabla(D^e_{Mg} \nabla[Mg]) - k_1 [Mg] \left(1 - \frac{F}{F_{\text{max}}} \right) + k_2 F [Cl]^2
\]

\[
\frac{\partial F}{\partial t} = k_1 [Mg] \left(1 - \frac{F}{F_{\text{max}}} \right) - k_2 F [Cl]^2
\]

\[
\frac{\partial [Cl]}{\partial t} = \nabla(D^e_{Cl} \nabla[Cl])
\]

(11)

Where \( k_1 \) and \( k_2 \) are the reaction rates of the Mg(OH)\(_2\) film formation and dissolution, respectively, \( D^e \) is the effective diffusion coefficient, \( F \) is the film concentration, and \( \text{max} \) indicates maximum.

The model in this study explicitly emphasizes the evolution of the corrosion film and its potential effects on the degradation rate. And it is also worth mentioning that the transport model can analyze the influence of the surrounding fluid flow (e.g., blood flow) on the degradation rate. Besides, although the mass loss is explicit, the transport model could not directly calculate the evolution of mechanical strength. Grogan et al. [41] believed that the implant strength predictions of the transport model and the uniform corrosion model are basically consistent. This view may be based on the assumption that mechanical strength is linearly related to mass.

2.7. Triphasic Model

Ahmed et al. [44] proposed the triphasic model, which was once used to describe the corrosion of copper block in atmosphere [45]. In this model, magnesium degrades into magnesium hydroxide, and then carbon dioxide induces magnesium hydroxide to grow into porous magnesium carbonate. Fluid runs through the porous film, contacts with the magnesium, and then further dissolves the inside magnesium. The thickness of the porous film was considered to be important to the degradation evolution. As shown in figure 2, using \( r \) as spatial coordinate, region where \( a < r < \beta \) is the magnesium hydroxide, and region where \( r > \beta \) is magnesium carbonate.
The conservation of mass implies
\[ \frac{1}{r^d} \frac{\partial}{\partial r} (r^d \epsilon_1 v_{s1}) = 0 \quad r \in (\alpha, \beta) \]
\[ \frac{1}{r^d} \frac{\partial}{\partial r} (r^d \epsilon_2 v_{s2}) = 0 \quad r \in (\beta, S) \]  
\( (13) \)

The conservation of total material volume implies
\[ \frac{1}{r^d} \frac{\partial}{\partial r} (r^d (\epsilon_i v_{si} + (1 - \epsilon_i) v_{fi})) = 0 \]
\( (14) \)

And transport equations for water and carbon dioxide are
\[ \frac{\partial((1-\epsilon_i)W_i)}{\partial t} = -\frac{1}{r^d} \frac{\partial}{\partial r} (r^d (1 - \epsilon_i)J_{W1}) \quad r \in (\alpha, \beta) \]
\[ \frac{\partial((1-\epsilon_i)W_i)}{\partial t} = -\frac{1}{r^d} \frac{\partial}{\partial r} (r^d (1 - \epsilon_i)J_{W2}) \quad r \in (\beta, S) \]
\[ \frac{\partial((1-\epsilon_i)C_2)}{\partial t} = -\frac{1}{r^d} \frac{\partial}{\partial r} (r^d (1 - \epsilon_i)J_{C2}) \quad r \in (\beta, S) \]  
\( (15) \)

Where d=0, 1, 2 represents Cartesian, cylindrical and spherical geometry, respectively, \( \epsilon_i \) is the volume fraction of the material \( i \), \( v_{si} \) is the movement velocity of interface of material \( i \), \( v_{fi} \) is the speed of flow of water and carbon dioxide, and \( J_{Xi} = -D_X \frac{\partial X_i}{\partial r} + v_{fi} X_i \). \( D_X \) is the diffusion coefficient, and \( X \) represents the mark of water, W, or carbon dioxide, C. Through rigorous analysis of boundary conditions, the evolution of the interfaces of different phases under advection diffusion can be calculated. The novel feature of this model is the explicit consideration of the flow of liquid phases in porous media and the explicit consideration of MgCO$_3$ and Mg(OH)$_2$ that would hinder degradation. According to the calculation results, Ahmed et al. believed that decreasing the porosity of hydroxide layer could hinder contact between water and material to slow down the degradation. Notably, due to the fact that the constituents of the media that an orthopedic implant will be exposed to are more complex, the boundary conditions need to be considered more carefully when using this model for simulation.
2.8. Multicomponent Model

Multicomponent model was proposed by Sanz-Herrera et al. [46]. This model takes lots of particles into account including magnesium, magnesium ions, Cl⁻, Mg(OH)²⁺, water, MgCl₂, and OH⁻, etc. The proportion among the particles is determined by the chemical equations. A set of 14 equations and corresponding 14 unknowns were listed according to the chemical reaction among all particles. For brief description, only the key equations are introduced here:

\[
\begin{align*}
\dot{\rho}_{aq} &= -\nabla(-\nabla \rho_{aq}) + \dot{\rho}_{H_2O}^r + \dot{\rho}_{H_2}^r + \dot{\rho}_{OH^-}^r + \dot{\rho}_{Cl^-}^r \quad \text{in} \quad \Omega(x,t) \\
\dot{\rho}_{Mg} &= -k_d \ast \rho_{Mg} \quad \text{in} \quad \Omega(x,t)
\end{align*}
\]

Where \( \Omega(x,t) \) is the biomaterial domain, \( x \) is the vector position of a point of the domain, \( \rho_{aq} \) is the concentration of aqueous species, \( \dot{\rho}^r \) is reactive rate, and \( k_d \) is the kinetic constant related to the magnesium reaction rate. Subscripts indicate the corresponding substance respectively. The parameters are mostly adapted from a previous work [47].

The author succeeded in simulating the degradation process of a magnesium screw in vivo [48] regarding mass loss and degradation rate. This model allows the analysis of pH evolution and hydrogen production, which could be an important factor to the magnesium degradation rate and the activity of surrounded tissue. However, it has to be stated that some of the boundary conditions may need to be considered carefully, as the transportation of substances in the organism would cause changes in concentration.

3. Discussion

Magnesium medical implant degradation is a complex process covering mechanics, chemistry, biology, etc., and it includes several degradation types such as uniform corrosion, pitting corrosion, and stress corrosion. At the same time, the chemical reaction within the degradation would be affected by body fluid flow speed, organic molecules, pH value, and other ions. The reaction products including hydrogen gas and magnesium ions, etc. will be emitted to the surrounding tissue. Degradation film will occur on the surface. Then the structure and mechanical stability of magnesium medical implant change due to mass loss.

At present, computational modeling could partially replicate the degradation process of magnesium based on theory such as material damage theory and molecular diffusion. A brief overview and key equations of degradation models is shown in Table 1. In the application of magnesium medical implants, some properties are attracting the most attention, such as the mechanical properties after implanted, the effect of hydrogen gas and dissolved molecules of the degradation products, and the evolution of pH value over time. The mechanical properties could be explicitly expressed in the models based on material damage mechanics. The distribution of the degradation products could be simulated in the multiphasic models. Most of the models could replicate the production of hydrogen gas. But only the multi-component model manages to simulate the evolution of pH value. It is noteworthy that none of the models could describe all the mentioned characteristics.
Multi-phasic model

Material damage model

Table 1. The evaluation of analytical capability is listed in Table 1. It is marked as \( Y \) when the model do have the analytical capability, otherwise it is marked as \( N \).
There could be several directions to further develop the simulation of magnesium medical implant degradation. The first one is to develop a multi-physical and multi-scale modeling framework. A multi-physical framework, viz., a combination of different degradation models, could be more favorable to simulation of magnesium medical implants. The properties of magnesium implants, such as mechanical properties, structural properties, and chemical properties, would change over time during degradation. Whereas few of the multiphasic models discussed previously put forward an explicit representation of how the morphological changes affect the mechanical response of magnesium. At the same time, the material damage models are difficult to discuss the distribution of degradation products. Thus in the case of simulation of magnesium medical implants, for example, simulation of orthopedic implants, just one model cannot well simultaneously capture plural properties. Besides, the framework should also be multi-scale. As shown in figure 3, the size of magnesium medical implants is usually between 1-100 mm, whereas the thickness of degradation film is usually less than 100μm. When the evolution of the degradation film has to be considered in the simulation framework, the local corrosion needs to be related to changes in the mechanical and structural characteristics of the overall implant in an appropriate way. At the same time, since the computing resource must be limited, the thickness of degradation film is also far less than the average length of finite element mesh, which means mechanical simulation and degradation simulation must be performed at different scales. Therefore, further investigation is necessary to develop comprehensive multi-physical and multi-scale frameworks in order to capture the realistic behavior of medical magnesium implants.

Another important direction is to match magnesium implants in terms of mechanical properties and biodegradation properties with medical requirements such as stents and orthopedic implants. As shown in figure 3, as the process of magnesium degradation progresses, the magnesium or its alloy would be replaced by the surrounding tissue. The mechanical load will then be shared by the implant and the newly grown tissue. Obviously, if the magnesium degrades too quickly, too high a load will have a negative impact on tissue growth, and the product of magnesium degradation also has an effect on tissue growth. Method to achieve matching would possibly be to combine the models of magnesium degradation with the models of biological tissue growth, and to consider biological factors to simulate physiological conditions in vivo. Capturing the interactions between magnesium implants and biological tissue would be beneficial to design of magnesium medical implants. For example, the local concentrations of magnesium ions, hydrogen etc. might play great roles in the activity of biological tissue. Zhang et al. [24] reported the formation of new bone after intramedullary implantation of a pin containing ultrapure magnesium and proposed the potential of magnesium ions in promoting CGRP-mediated (calcitonin gene-related polypeptide-a) osteogenic differentiation.
Besides, the porosity of magnesium implants was reported having effect on bone growth [28] and vascularization [49]. Furthermore, in the process of magnesium degradation in-vivo, the activities of surrounding biological tissue such as growth and apoptosis would probably change the mechanical and chemical boundary conditions. In the past few decades, modeling of bone regeneration has also been frequently studied and discussed. Bone regeneration models could simulate the healing process of bone fracture, distributions of cells and tissue, and the mechanical properties evolution of bone, etc. The detailed description could be found in Isaksson’s work [50]. With the development of bio-factor-mediated models [51-54] and mechano-mediated models of bone regeneration [50], the combination of magnesium degradation and bone regeneration modeling would be a significant challenge and greatly improve the performance in simulating the biological tissue response to the changes of material properties.

In addition, it would also be a potential direction taking other factors such as surface treatment and alloying into consideration in computational modeling, as we all know that pure magnesium implants are not suitable for most medical applications. New craftsmanship like alloying [7-12] and surface modification such as coating [13, 14] and surface nano-crystallization [15, 16] were proposed in order to control the degradation rate of magnesium. However, in the foregoing review, most material damage models are calibrated according to specific experimental data, and multiphasic models assume the magnesium is pure. A model that could account for the degradation modification techniques would be hugely beneficial in simulating the performance of various magnesium materials to enhance future design and development.

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5. Conflict of Interest
There is no conflict of interest.

6. References
[1] EC H. A new ligature? Chicago Med J Exam 2(172) (1878).
[2] E. P. Beiträge zur Technik der Blutfäss- und Nervennaht nebst Mittheilungen über die Verwendung eines resorbirbaren Metalles in der Chirurgie. Arch Klin Chir 62: 67-93 (1900).
[3] E. P. Blutfäss- und Nervennaht (nebst Mittheilung über die Verwendung eines resorbirbaren Metalles in der Chirurgie). Centralblatt für Chirurgie (28) (1901).
[4] E. H. Ueber Gefäsnaht, fässtransplantation und Replantation von amputirten Extremitäten. Arch Klin Chir 70(417): 71 (1903).
[5] Groves E. An experimental study of the operative treatment of fractures. BRIT J SURG 1(3): 438-501 (1914).
[6] Gusieva K, Davies CHJ, Scully JR, Birbilis N. Corrosion of magnesium alloys: the role of alloying. INT MATER REV 60(3): 169-194 (2015).
[7] Miura C et al. In vivo corrosion behaviour of magnesium alloy in association with surrounding tissue response in rats. BIOMED MATER 11(2): 25001 (2016).
[8] Witte F, Kaeve V, Haferkamp H, Switzer E, Meyer-Lindenberg A, Wirth CJ, Windhagen H. In vivo corrosion of four magnesium alloys and the associated bone response. BIOMATERIALS 26(17): 3557-3563 (2005).
[9] Kraus T, Fischerauer SF, Hänzi AC, Uggowitzer PJ, Löffler JF, Weinberg AM. Magnesium alloys for temporary implants in osteosynthesis: In vivo studies of their degradation and interaction with bone. ACTA BIOMATER 8(3): 1230-1238 (2012).
[10] Amerstorfer F et al. Long-term in vivo degradation behavior and near-implant distribution of resorbed elements for magnesium alloys WZ21 and ZX50. ACTA BIOMATER 42: 440-450 (2016).
[11] Liu D, Hu S, Yin X, Liu J, Jia Z, Li Q. Degradation mechanism of magnesium alloy stent under simulated human micro-stress environment. Materials Science and Engineering: C 84: 263-270 (2018).

[12] Tian Q et al. Development of a novel loading device for studying magnesium degradation under compressive load for implant applications. MATER LETT 217: 27-32 (2018).

[13] Oosterbeek RN, Seal CK, Seitz J, Hyland MM. Polymer-bioceramic composite coatings on magnesium for biomaterial applications. SURF COAT TECH 236: 420-428 (2013).

[14] Wan P, Tan L, Yang K. Surface Modification on Biodegradable Magnesium Alloys as Orthopedic Implant Materials to Improve the Bio-adaptability: A Review. J MATER SCI TECHNOL 32(9): 827-834 (2016).

[15] Laleh M, Kargar F. Effect of surface nanocrystallization on the microstructural and corrosion characteristics of AZ91D magnesium alloy. J ALLOY COMPD 509(37): 9150-9156 (2011).

[16] Sealy MP, Guo YB, Caslaru RC, Sharksins J, Feldman D. Fatigue performance of biodegradable magnesium-calcium alloy processed by laser shock peening for orthopedic implants. INT J FATIGUE 82(3): 428-436 (2016).

[17] Hermawan H, Dube D, Mantovani D. Developments in metallic biodegradable stents. ACTA BIOMATER 6(5): 1693-1697 (2010).

[18] Yazdimamaghani M, Razavi M, Vashaee D, Moharamzadeh K, Boccaccini AR, Tayebi L. Porous magnesium-based scaffolds for tissue engineering. Materials Science and Engineering: C 71: 1253-1266 (2017).

[19] Windhagen H et al. Biodegradable magnesium-screw clinically equivalent to titanium screw in hallux valgus surgery: short term results of the first prospective, randomized, controlled clinical pilot study. BIOMED ENG ONLINE 12(62) (2013).

[20] Cha P et al. Biodegradability engineering of biodegradable Mg alloys: Tailoring the electrochemical properties and microstructure of constituent phases. SCI REP-UK 3(2367) (2013).

[21] Erbel R et al. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. LANCET 369(9576): 1869-1875 (2007).

[22] Haude M et al. Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial. LANCET 381(9869): 836-844 (2013).

[23] Zhen Z, Liu X, Huang T, Xi T, Zheng Y. Hemolysis and cytotoxicity mechanisms of biodegradable magnesium and its alloys. Materials Science and Engineering: C 46: 202-206 (2015).

[24] Zhang Y et al. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. {NATURE MEDICINE} 22(10): 1160-1169 (2016).

[25] Vormann J. Magnesium: nutrition and metabolism. 24(1): 27-37 (2003).

[26] Zhuang H, Han Y, Feng A. Preparation, mechanical properties and in vitro biodegradation of porous magnesium scaffolds. Materials Science and Engineering: C 28(8): 1462-1466 (2008).

[27] Gu XN, Zhou WR, Zheng YF, Liu Y, Li YX. Degradation and cytotoxicity of lotus-type porous pure magnesium as potential tissue engineering scaffold material. MATER LETT 64(17): 1871-1874 (2010).

[28] Jasmawati N, Fatihhi SJ, Putra A, Syahrom A, Harun MN, Öchsner A, Abdul Kadir MR. Mg-based porous metals as cancellous bone analogous material: A review. Proceedings of the Institution of Mechanical Engineers, Part L: Journal of Materials: Design and Applications 231(6): 544-556 (2015).

[29] Gastaldi D, Sassi V, Petriti L, Vedani M, Trasatti S, Migliavacca F. Continuum damage model for bioresorbable magnesium alloy devices — Application to coronary stents. J MECH BEHAV BIOMED 4(3): 352-365 (2011).

[30] Pardo A, Merino MC, Coy AE, Arrabal R, Viejo F, Matykina E. Corrosion behaviour of magnesium/aluminium alloys in 3.5 wt.% NaCl. CORROS SCI 50(3): 823-834 (2008).

[31] Grogan JA, O Brien BJ, Leen SB, McHugh PE. A corrosion model for bioabsorbable metallic stents. ACTA BIOMATER 7(9): 3523-3533 (2011).
[32] Da Costa-Mattos HS, Bastos IN, Gomes JACP. A simple model for slow strain rate and constant load corrosion tests of austenitic stainless steel in acid aqueous solution containing sodium chloride. CORROS SCI 50(10): 2858-2866 (2008).

[33] Atrens A, Song G, Liu M, Shi Z, Cao F, Dargusch MS. Review of Recent Developments in the Field of Magnesium Corrosion. ADV ENG MATER 17(4): 400-453 (2015).

[34] Peron M, Torgersen J, Berto F. Mg and Its Alloys for Biomedical Applications: Exploring Corrosion and Its Interplay with Mechanical Failure. METALS-BASEL 7(2527) (2017).

[35] Galvin E, O’Brien D, Cummins C, Mac Donald BJ, Lally C. A strain-mediated corrosion model for bioabsorbable metallic stents. ACTA BIOMATER 55: 505-517 (2017).

[36] Murphy BP, Savage P, McHugh PE, Quinn DF. The stress-strain behavior of coronary stent struts is size dependent. ANN BIOMED ENG 31(6): 686-691 (2003).

[37] Galvin E, Cummins C, Yoshihara S, Mac Donald BJ, Lally C. Plastic strains during stent deployment have a critical influence on the rate of corrosion in absorbable magnesium stents. MED BIOL ENG COMPUT 55(8): 1261-1275 (2017).

[38] Boland EL, Shirazi RN, Grogan JA, McHugh PE. Mechanical and Corrosion Testing of Magnesium WE43 Specimens for Pitting Corrosion Model Calibration. ADV ENG MATER 20(10): 1800656 (2018).

[39] Vijayaraghavan V, Garg A, Gao L, Vijayaraghavan R. Finite Element Based Physical Chemical Modeling of Corrosion in Magnesium Alloys. METALS-BASEL 7(3): 83 (2017).

[40] Zhao PJ, Chen ZH, Dong CF. Damage and Failure Analysis of AZ31 Alloy Sheet in Warm Stamping Processes. J MATER ENG PERFORM 25(7): 2702-2710 (2016).

[41] Grogan JA, Leen SB, McHugh PE. A physical corrosion model for bioabsorbable metal stents. ACTA BIOMATER 10(5): 2313-2322 (2014).

[42] Bajger P, Ashbourn JMA, Manhas V, Guyot Y, Lietaert K, Geris L. Mathematical modelling of the degradation behaviour of biodegradable metals. BIOMECH MODEL MECHAN 16(1): 227-238 (2017).

[43] Dahms M, Höche D, Ahmad Agha N, Feyerabend F, Willumeit-Römer R. A simple model for long-time degradation of magnesium under physiological conditions. Materials and Corrosion 69(2): 191-196 (2018).

[44] Ahmed S, Ward J, Liu Y. Numerical Modelling of Effects of Biphasic Layers of Corrosion Products to the Degradation of Magnesium Metal In Vitro. MATERIALS 11(1): 1 (2018).

[45] Clarelli F, De Filippo B, Natalini R. Mathematical model of copper corrosion. APPL MATH MODEL 38(19-20): 4804-4816 (2014).

[46] Sanz-Herrera JA, Reina-Romo E, Boccaccini AR. In silico design of magnesium implants: Macroscopic modeling. J MECH BEHAV BIOMED 79: 181-188 (2018).

[47] Sun W, Liu G, Wang L, Li Y. A mathematical model for modeling the formation of calcareous deposits on cathodically protected steel in seawater. ELECTROCHIM ACTA 78: 597-608 (2012).

[48] Li Z, Sun S, Chen M, Fahlman BD, Liu D, Bi H. In vitro and in vivo corrosion, mechanical properties and biocompatibility evaluation of MgF2-coated Mg-Zn-Zr alloy as cancellous screws. MAT SCI ENG C-MATER 75: 1268-1280 (2017).

[49] KARAGEORGIOU V, KAPLAN D. Porosity of 3D biomaterial scaffolds and osteogenesis. BIOMATERIALS 26(27): 5474-5491 (2005).

[50] Isaksson H. Recent advances in mechanobiological modeling of bone regeneration. MECH RES COMMUN 42: 22-31 (2012).

[51] Geris L, Gerisch A, Sloten JV, Weiner R, Oosterwyck HV. Angiogenesis in bone fracture healing: A bioregulatory model. J THEOR BIOL 251(1): 137-158 (2008).

[52] Burke DP, Kelly DJ. Substrate Stiffness and Oxygen as Regulators of Stem Cell Differentiation during Skeletal Tissue Regeneration: A Mechanobiological Model. PLOS ONE 7(7): e40737 (2012).

[53] Bailon-Plaza A, Van der Meulen M. A Mathematical Framework to Study the Effects of Growth Factor Influences on Fracture Healing. J THEOR BIOL 212(2): 191-209 (2001).
[54] Chen G, Niemeyer F, Wehner T, Simon U, Schuetz MA, Pearcy MJ, Claes LE. Simulation of the nutrient supply in fracture healing. J BIOMECH 42(15): 2575-2583 (2009).