**A Model of Polymer Degradation and Erosion for Finite Element Analysis of Bioresorbable Implants**

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**Abstract** – Finite element analysis is an essential tool for the design of bioresorbable medical implants such as bioresorbable vascular scaffolds. However polymer erosion has been traditionally modelled using empirical rules rather than differential equations. The rule-based models are difficult to implement in a finite element analysis. Consequently, these models have been limited to simple geometries such as plates or spheres. This paper presents a set of differential equations that govern the hydrolytic chain scission and bulk erosion of bioresorbable implants where polymer erosion is modelled using a differential equation replacing the empirical rules. These differential equations can be conveniently solved using a commercial finite element package to calculate the molecular weight and mass loss as functions of time for a bioresorbable implant. A case study of Absorb bioresorbable vascular scaffolds (BVSs) is presented using data obtained from the literature, where 98 Absorb BVSs were implanted in 40 porcine coronary arteries. It is demonstrated that the finite element model can fit the experimental data of both the molecular weight and mass loss as functions of time to an accuracy of approximately 5%.

**Keywords:** bioresorbable implants, finite element analysis, polymer degradation, polymer erosion, mathematical model.

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1. **Introduction**

A bioresorbable implant can combine the functions of structural support and drug delivery and start to break down when no longer required, without leaving any permanent material behind after a period of time. Bioresorbable pins and screws made of polyglycolides (PGAs) and polylactides (PLAs) have been used in orthopaedics for internal fixations. Following the orthopaedic applications, a huge effort has made over the last decade or so to develop bioresorbable drug-eluting stent to treat blocked coronary arteries. Metal stents coated with a thin layer of polymer containing anti-restenotic drugs such as taxus or sirolimus are being widely used clinically. However the drugs also inhibit arterial re-endothelialisation as a side effect to its beneficial effects on restenosis. As a result of the reduced re-endothelialisation, stent remains exposed leading to increased risk of stent thrombosis. To attenuate this risk, bioresorbable stents, often referred to as bioresorbable vascular scaffolds (BVS), have been developed. BVSs are made of biodegradable polymers such as PLAs. The polymer chains start to break down through hydrolysis reaction as soon as water penetrates the device and there is no permanent implant left behind after 3-5 years, hence removing the risk of further device thrombosis. Unfortunately several large randomised trials indicated a significant increased risk of very late scaffold thrombosis ([Ali, Gao et al. 2017](#_ENREF_1); [Ali, Serruys et al. 2017](#_ENREF_2)) compared with best-in-class metal drug eluting stents. The dominating mechanism, revealed by recent OCT studies by Yamaji et al ([Yamaji, Y et al. 2017](#_ENREF_20)), is that randomly disintegrated struts penetrating the neointima and suspend themselves in the lumen. This is essentially a biomechanical issue which requires fundamental understanding of the polymer degradation and bulk erosion that lead to the mechanical failure. Finite element analysis of this process requires a multi-physics model of polymer degradation, bulk erosion and mechanical failure. It is apparent that mechanical stresses play a key role in the disintegration of the implant. This paper focuses on the polymer degradation and bulk erosion aspects of the multi-physics model. Integration of the effect of mechanical stresses in the model is an ongoing work.

Mathematical models for hydrolytic chain scission of aliphatic polyesters have been developed by various authors. Early models vary from simple analytical expressions of molecular weight as a function of time ([Lyu, Schley et al. 2007](#_ENREF_8); [Chen, Zhou et al. 2011](#_ENREF_3)) to differential equations for temporal evolution of molecular weight distribution ([Staggs 2002](#_ENREF_16); [Perale, Arosio et al. 2009](#_ENREF_12)). Pan and his co-workers developed a set of partial differential equations for the hydrolytic degradation taking into account of the full interplay between autocatalytic effect, diffusion of oligomers, chain-cleavage induced crystallization and buffering effect of embedded calcium phosphate phase ([Wang, Pan et al.](#_ENREF_19) ; [Han and Pan 2009](#_ENREF_6); [Pan, Han et al. 2011](#_ENREF_11); [Pan 2015](#_ENREF_10)). In the later stage of the degradation, once the molecular weight reduces to a critical level, bulk erosion occurs leading to accelerated mass loss. The bulk erosion has been traditionally modelled using rule-based discrete approach rather than differential equations ([Siepmann, Faisant et al. 2002](#_ENREF_15)) ([Zhang, Zhou et al. 2017](#_ENREF_21)). A simple example of the erosion rules is that a small cell of the polymer is removed if its average molecular weight reduces to a critical value ([Sevim and Pan 2018](#_ENREF_14)). A major disadvantage of these rule-based models is that they cannot be directly implemented in a finite element analysis, making them difficult to use in the design of any medical implant of a sophisticated geometry. All the bulk erosion models in the literature are limited to very simple geometries such as spheres or plates. The purpose of this paper is to present a unified mathematical model for polymer erosion and hydrolytic chain cleavage by using only differential equations. These governing equations are solved using a commercial finite element package to predict the molecular weight and mass loss as functions of time for a BVS. It is demonstrated that the finite element model can fit a set of porcine data obtained from literature very well for the entire process of degradation.

1. **A model for hydrolytic chain scission and bulk erosion**

In the hydrolytic degradation model by Pan and his co-workers ([Pan 2015](#_ENREF_10)), the state of an aliphatic polyester is represented using three variables: which is the molar concentration of polymer chain scissions due to hydrolysis reaction, which is the molar concentration of short polymer chains and which is the degree of crystallization (for semi-crystalline polymers such as the poly (L-lactide used to make the Absorb BVS). The short chains are mobile and catalyse the hydrolysis reaction through acid disassociation. The rate of polymer chain cleavage is governed by equation (4.9) presented in the work by Pan ([Pan 2015](#_ENREF_10)), which can be rewritten as:

|  |  |
| --- | --- |
|  | (1) |

In equation (1), is the molar concentration of ester bonds in the amorphous phase of the polymer at the beginning of degradation, and are constants indicating the nature of the polymer chain scissions (random or end scissions), is the molar concentration of ester bonds of the crystalline phase, and and arereaction rate constants for non-catalytic and autocatalytic hydrolysis reactions respectively.

The degree of crystallization, , of the polymer increases as cleaved polymer chains gain extra degrees of freedom and can be calculated as ([Pan 2015](#_ENREF_10))

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| --- | --- |
| , | (2) |

in which and are the initial and maximum degrees of crystallization respectively, and is the crystallization rate.

The concentration of the short chains, , is governed by

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| --- | --- | --- |
|  |  | (3) |

The first term on the right-hand side of the equation represents the production rate of the short chains due to polymer chain scission. is the molar concentration of ester bonds of all the short chains given by

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| --- | --- | --- |
|  | . | (4) |

The second terms of Eqn. (3) represents Fickian diffusion where *D* is the diffusion coefficient of the short chains in the polymer body.

In the current paper, in order to model bulk erosion an erosion index *S* is introduced to represent the volume fraction of eroded polymer. In a rule-based model, it can be assumed that *S* of a small cell of the polymer bodyjumps from 0 to 1 if the molecular weight of the cell reduces to a critical level . Despite of its simplicity, such a rule-based model is difficult to implement in a finite element analysis. In this paper, it is proposed that the rule is replaced by a differential equation:

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| --- | --- |
|  | (5) |

Here represents the erosion rate and has a unit of 1/*t*, and is a given function that kicks start the change in *S* as approaches ,

|  |  |  |
| --- | --- | --- |
|  |  | (6) |

in which is the initial molecular weight and is a non-dimensional numerical constant. The solution of Eqn. (5) is an *S*-shaped function which changes its value from 0 to 1 as approaches *.*

In ruled-based models, eroded elements are simply removed leaving empty cells filled up with liquid. In fact the eroded polymer chains still need to diffuse out of the device although this is a rather fast process. Another diffusion equation for the eroded polymer chains can be added to the model. However the erosion only occurs at the later stage of the degradation process by which time the mass loss by the diffusion of the short chains is overwhelmed by the diffusion of the eroded polymer chains. For the sake of simplicity, it is proposed to modify Eqn. (4) such that it reflects diffusion of the short chains before significant erosion occurs and switches to that of the eroded chains once erosion starts. This is achieved by firstly extending the source term of Eqn. (4) to include the eroded polymers such that

|  |  |
| --- | --- |
|  | (7) |

and secondly making the diffusion coefficient *D* in Eqn. (3) dependent on the erosion index *S* such that

|  |  |
| --- | --- |
|  | (8) |

in which is the diffusion coefficient of the short chains in degraded polymer and is the diffusion coefficient in the liquid filled phase. Eqn. (8) combines the effective diffusion coefficient for short chain diffusion in the early stage of degradation and that of the eroded polymer chains once erosion starts.

To complete the model, the following expression for due to Pan *et. al.* ([Pan 2015](#_ENREF_10)) is used

|  |  |  |
| --- | --- | --- |
|  |  | (9) |

in which is the diffusion coefficient of short chains in the non-degraded polymer and is the porosity cause by the leaving of the short chains given by

|  |  |
| --- | --- |
|  | (10) |

The leaving of the short chains and eroded polymers from the device leads to mass loss which can be calculated by the volume integration of

|  |  |
| --- | --- |
|  | (11) |

over the entire device at any given time, in which is given by Eqn. (7) instead of Eqn. (4). Finally, the number-averaged molecular weight of the polymer is calculated using

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| --- | --- | --- |
|  |  | (12) |

in which and are the initial molecular weight and degree of polymerization respectively.

Eqns. (1-3) and (5) together with expressions (6) – (12) can be implemented in a commercial finite element software such as COMSOL Multiphysics by users. Chapter 7 of the book edited by Pan ([Pan 2015](#_ENREF_10)) presented a step by step guide for the implementation. Although the book did not consider Eqns. (5-8), it is straightforward to make the extension in the implementation. The commercial software allows users to select from different types of finite elements. The second order triangle elements were used in this study. Mesh convergence study was performed to ensure that the selected mesh size was small enough to give converged results. COMSOL does not allow users to interfere with its time discretization and numerical methods for time marching. Typical outputs of the model include spatial distributions and time evolutions of the average molecular weight , erosion index *S* and mass loss. Proper initial and boundary conditions need to be applied. For example, for an implant that is free from any residual monomers, the initial conditions are that = 0, 0 and *S* = 0 at *t* = 0. Perfect sink conditions for the oligomer can be assumed at the interface between the implant and its surrounding medium, i.e. 0 at the interface.

The model contains a set of parameters that need to be obtained. The initial molecular weight , the initial molar concentration of ester bonds , the initial degree of polymerization , the molar concentration of ester bonds of the crystalline phase , and the initial degree of crystallization are properties of a given polymer and can be obtained from the literature or polymer manufacturers. and are constants that reflect the nature of polymer chain scissions and have been determined previously (see Chapter 3 of the book edited by Pan ([Pan 2015](#_ENREF_10))) for different biodegradable polymers. The critical molecular weight for erosion, , can be obtained by taking the value of at which a sudden increase in mass loss occurs in a degradation experiment. The maximum degrees of crystallization can be obtained from crystallization data. The diffusion coefficient in liquid-filled pores is simply taken as a much larger value than to reflect the very fast diffusion. in expression (5) is taken as an empirical constant which is fixed for all polymers. This leaves five model parameters to be determined, which reflect the kinetic rates of the hydrolysis, erosion and crystallization processes including

* , – rate constants for non-catalytic and autocatalytic hydrolysis
* – the erosion rate
* – diffusion coefficient of short chains in non-degraded polymer
* - the crystallization rate

These five kinetic parameters can be measured independently using degradation experiment for a given polymer. Alternatively, they can be obtained by best fitting the model prediction with experimental data for a given implant, which is effectively back calculation for the parameter identification. In practice the back calculation is more realistic considering that the degradation experiment for PLAs used in these implants can take up to five years. This approach also naturally takes into account of any in-vivo effect on the degradation when in-vivo data are used. In the next section, this approach is used for a case study of the Absorb BVS.

1. **A finite element model for Absorb BVS**

Otsuka *et al.* ([Otsuka, Pacheco et al. 2014](#_ENREF_9)) presented experimental data of number averaged molecular weight and mass loss as the functions of time for Absorb BVS implanted in porcine coronary arteries. A total number of 98 BVSs were implanted in 40 pigs and examined at 9 time intervals over a period of 42 months. The molecular weight were measured using gel permeation chromatography (GPC). This molecular weight data are directly used to test our model. The degraded polymer were recovered to calculate the mass loss. Examination of their mass loss data reveals that there was a sudden mass loss of about 7% at the very early stage (within 3 months) of the degradation. Detailed examination of the histological images of the degraded scaffolds presented in their paper indicates that the initial mass loss was most likely due to the fast degradation of the coated Poly (DL-lactide) layer that contains everolimus. In this paper we focus on modelling degradation of the main support structure of the scaffold. Consequently the initial mass loss is deducted from the experimental data, i.e. each of their data points is scaled using: (mass loss – initial mass loss)/(100-intial mass loss)\*100.

The poly (L-lactide) that was used to make the Absorb BVS was semi-crystalline. This polymer might experience significant recrystallization which was induced by polymer chain cleavage during the hydrolysis degradation. However no information was provided for the change in degree of crystallinity in the work by Otsuka *et al.* ([Otsuka, Pacheco et al. 2014](#_ENREF_9)). In this section it is assumed that the degree of crystallinity remains constant. The effect of chain-cleavage induced crystallization will be considered in the next section. If remains constant, i.e. and then Eqn. (1) can be simplified. The rate constant and in Eqn. (1) can be regarded as an set of effective values standing for , and .

The best fit between the model predictions and the experimental data are shown in Fig. 1 for the volume-averaged molecular weight and in Fig. 2 for mass loss as functions of time respectively. Table 1 provides all the parameters used to obtain the model prediction. It is worth to report that a large range of values of the four kinetic parameters were searched manually in our study to best fit the experimental data, and that the values provided in Table 1 are unique to give the best fit. A sensitivity study was performed in which an overall “error” of least squares between the model predictions and the experimental data was defined. The error was plotted against individual variations in the values of the four kinetic parameters respectively. The results show sharp increase in the error for any small variation from the values presented in Table 1. Fig. 3 shows the finite element model used in this study. Fig. 3(a) shows the local image of the Absorb BVS taken from Otsuka *et* al. ([Otsuka, Pacheco et al. 2014](#_ENREF_9)). The image was directly transformed into the three-dimensional finite element model shown in Fig. 3(b). Due to symmetry of the scaffold structure the finite element model is for a representative unit of the scaffold. From the images provided by Otsuka *et* al. ([Otsuka, Pacheco et al. 2014](#_ENREF_9)), the thickness of the strut in the radial direction was estimated as 0.2 mm and the width of the strut along A-A shown in Fig. 3(a) was estimated as 0.176 mm. All other dimensions were scaled to these two values. The radial curvature of the representative unit has little effect on the degradation process and ignored in the finite element model. At the scaffold surface, perfect sink condition, i.e. 0, is assumed. At the four rectangular cross-sections of the strut (exampled by A-A indicated in Fig. 3(a)), zero flux condition, i.e. 0, is used to reflect symmetry, where *n* represents the normal vector to the cross-section. The molecular weight presented in Fig. 1 is the volume averaged value of given by Eqn. (12) over the entire representative unit. The mass loss in Fig. 2 is calculated as the volume integration of given by Eqn. (11). The results presented in Figs 1 and 2 were tested by a mesh convergence study, i.e. further refined mesh led to no change in the fitting accuracy.

Fig. 4 presents the distributions of molecular weight calculated using the finite element model over the cross-section *A-A* as indicated in Fig. 3(a) at four different times. Difference between the distribution patterns of the molecular weight at the four different times can be identified by observing the images together with the value bars. At week 20, Fig. 4(a) shows that the molecular weight is almost uniform in the section. The irregular color pattern in Fig. 4(a) is an exaggeration of the very small differences. At week 60 Fig. 4(b) shows that a small differentiation appears between the inside and the surface of the strut. At week 100, Fig. 4(c) shows that the molecular weight at the surface is almost 3 times higher than that inside the strut. This level of surface/bulk differentiation remains until week 180 as shown in Fig. 4(d). This surface/bulk differentiation was firstly reported by Li *et al.* ([Li, Garreau et al. 1990](#_ENREF_7)). The underlying reason is that short chains near the surface can diffuse out and reduce the local acidity, leading to slower rate of polymer degradation. This feature is well captured by the finite element model. The patterns are representative to all cross-sections. This is because the dominating directions of short chain diffusion out of the strut are in the plane of the cross-section. The surface and bulk differentiation in the local acidity is therefore similar at all the cross-sections.

**4. Effect of cleavage-induced crystallization on BVS degradation**

In order to demonstrate the effect of chain-cleavage induced crystallisation, the finite element analysis was repeated by using a set of assumed values of the crystallization rate and due to lack of experimental data. The initial degree of crystallisation was set as = 0, 0.2, 0.4 and 0.6 respectively. The maximum degree of crystallinitywas set at 0.8. The concentration of ester bonds of the crystalline phase was taken as the same as that of the amorphous phase, i.e. , despite that it should be slightly higher. The crystallization rate was taken as 1060 (no unit) which ensures to reach at the end of the 180 weeks. The poly (L-lactide) for the Absorb BVS should have a relatively high initial degree of crystallinity. For consistency in the comparison, it is assumed that in the case presented in Figs 1 and 2, which leads to a set of values of =2.375x10-5 week-1 and = 4.11x10-6 (mol m-3)-0.5 week-1.

Fig. 5 shows the volume-averaged degree of crystallinity over the entire device as a function of time for the four different initial values of . The trend shown in the figure is typical for those observed in experiment for semicrystalline PLAs and PGAs ([Han and Pan 2009](#_ENREF_6); [Gleadall, Pan et al. 2012](#_ENREF_4)). Fig. 6 shows the effect of initial degree of crystallinity on the molecular weight change with time. For the case of (the line marked by circles) it can be observed that the prediction is very similar to that of the previous section (the line without any symbols) ask well as to the experimental data (the black squares). In this case the change in degree of crystallinity during degradation is relatively small (0.6 to 0.8). Hence the change in crystallinity has a small impact on the molecular weight. However it can be further observed from Fig. 6 that smaller values of can have a major impact on the reduction rate of the molecular weight. The smaller the initial degree of crystallinity, the faster the degradation becomes which is consistent with the general experimental observation that the crystalline phase is more difficult to degrade ([Zong, Wang et al. 1999](#_ENREF_22); [Tsuji and Ikada 2000](#_ENREF_17); [Tsuji and Muramatsu 2001](#_ENREF_18)). Fig. 7 shows the effect of initial degree of crystallinity on the mass loss during degradation. The model predicts that the mass loss is rather sensitive to the initial value of . The highly crystalized polymers have stronger resistance to the mass loss, which is consistent to the common sense that the crystalized phase is more resistant to polymer dissolution.

1. **Discussion**

In order to obtain the kinetic parameters in the model using independent experiment, one could imagine implanting a large set of simple plats of different thicknesses in animal coronary arteries and measuring the molecular weight and mass loss by scarifying the animals at different times over the entire degradation period (42 months in the case study of this paper). This approach has obvious difficulties in multiple dimensions. Development of the next generation of bioresorbable implants can benefit hugely by learning from existing degradation data such as those obtained through the animal trials for bioresorbable coronary stents ([Otsuka, Pacheco et al. 2014](#_ENREF_9)). These long-term data are extremely valuable due to the time and cost taken by such trials and measurement. The mathematical model presented in this paper provides an effective tool to bridge the existing data with any new implants made of same or similar bioresorbable polymers. This is achieved by firstly back-calculating the model parameters using a finite element model for the existing implant (i.e. by using the approach presented in section 3), and secondly applying the model parameters in finite element models for any newly designed implants. The porcine data used in section 3 are in fact 18 sets of data points. The data points at different stage of the degradation play different roles in determining the kinetic parameters. The rate constants for non-catalytic and autocatalytic hydrolysis, and , are heavily controlled by the molecular weight data throughout the entire degradation test while the diffusion coefficient, , is heavily controlled by the mass loss data in the early stage (before erosion starts) of the degradation test. On the other hand, the erosion rate, , is almost uniquely determined from the mass loss data in the erosion stage of the degradation test. The degradation data shown in Figs. 1 and 2 can therefore be considered as the next best information to the imaginary but almost impossible standard experiment to measure the kinetic parameters.

1. **Conclusion**

It is shown that the bulk polymer erosion can be modelled using a differential equation replacing empirical rules. The differential equation can be conveniently implemented in a commercial finite element package together with the governing equations that were developed previously by Pan and his co-workers. The finite element model takes into account of the full interplay between hydrolytic chains scission, autocatalytic effect, short chain diffusion, chain-cleavage induced crystallization and bulk erosion. It is further shown that the finite element model is able to fit the porcine data ([Otsuka, Pacheco et al. 2014](#_ENREF_9)) of Absorb BVS very well.

Using the same finite element method, these parameters can be used in future to virtually design new coronary stents or other bioresorbable implants of any geometry and dimensions made of the same or similar poly (L-lactide). Furthermore, using the relationship between the mechanical properties and degradation state of these polymers developed in our previous work ([Gleadall, Pan et al. 2015](#_ENREF_5); [Samami and Pan 2016](#_ENREF_13)), it is possible to design the implants in order to achieve desired mechanical performance during the degradation process.

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| --- | --- | --- |
| Material parameters | | Kinetic parameters |
| 102000 Da  (Pan, J., Ed. 2015) | = 2  (Pan, J., Ed. 2015) | , = 9.5x10-6 week-1 |
| = 17300 mol m-3  (Pan, J., Ed. 2015) | = 1000\*  (Pan, J., Ed. 2015) | = 2.6x10-6 (mol m-3)-0.5 week-1 |
| = 1417  (Pan, J., Ed. 2015) | = 19 | =0.07967 week-1 |
| = 28  (Pan, J., Ed. 2015) | = 20000 Da | = 1.0x10-13 m2 week-1 |
| Xc = Xc0 |  | *k*c = 0 |

Table 1. Parameters used to obtain model predictions in Figs 1 to 4

Chart, scatter chart

Description automatically generated

Fig. 1 Comparison between model prediction (solid line) of this paper and experimental data (discrete symbols) of ([Otsuka, Pacheco et al. 2014](#_ENREF_9)) for volume averaged molecular weight over the device as a function of time for Absorb BVSs implanted in pigs.

Diagram

Description automatically generated

Fig. 2 Comparison between model prediction (solid line) of this paper and experimental data (discrete symbols) of ([Otsuka, Pacheco et al. 2014](#_ENREF_9)) for mass loss as function of time for Absorb BVSs implanted in pigs. Initial mass loss in the first 3 months was deducted from the experimental data for this comparison.

Diagram

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Fig. 3 A finite element model for the Absorb BVS (a) scanned local image and (b) a representative unit used in the finite element analysis.

A picture containing shape

Description automatically generated

Fig. 4 Distribution of molecular weight calculated using the finite element model over the cross-section *A-A* as indicated in Fig. 3(a) at four different times.

Diagram

Description automatically generated

Fig. 5 Volume-averaged degree of crystallinity over the BVS as a function of time for different initial degrees of crystallinity.

Diagram

Description automatically generated

Fig. 6 Volume-averaged molecular weight as a function of time for different initial degrees of crystallinity. The model prediction and experimental data in Fig. 1 are reproduced here for comparison.

Diagram

Description automatically generated

Fig. 7 Mass loss as a function of time for different initial degrees of crystallinity. The model prediction and experimental data in Fig. 3 are reproduced here for comparison.