

THE INFLUENCE OF DEGRADATION ON THE VISCOSITY AND MOLECULAR MASS OF POLY(LACTIDE ACID) BIOPOLYMER

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Summary

In this paper, we present a study on stability of popular biopolymer poly(lactide acid) (PLA) under degradation process. As a main objective of this study we investigate an influence of polymer decomposition on decrease of its two physicochemical parameters – dynamic viscosity and molecular mass. To include the molar mass distribution we calculate three various mass averages: the number, the weight and the viscosity molar mass. To simulate the polylactide behavior at the atomic level we use molecular dynamics method in conjunction with reactive force field ReaxFF. To provide degradation conditions similar to human interior system we operate in the MD-NVT conditions at the temperature 310K. Based on reported in literature values of polylactide density we develop computational model of its amorphous structure. We achieve full compliance with expectations – obtained values of PLA viscosity and mass are steadily dropping. Determined trends confirm progressive polymer decomposition resulting in deterioration of polymer durability. The obtained results may be use in a future to predict a lifetime of biomedical polymer implants.

Keywords: PLA, biopolymers, stability, molecular model, viscosity loss, molar mass averages

WPŁYW PROCESU DEGRADACJI NA LEPKOŚĆ I MASĘ CZĄSTECZKOWĄ POLILAKTYDU

Streszczenie

Niniejszy artykuł przedstawia badania nad stabilnością popularnego biopolimeru - polilaktydu (PLA). Celem badań była zbadanie wpływu procesu degradacji PLA na jego wybrane właściwości fizykochemiczne tj. lepkość dynamiczną i masę cząsteczkową. Aby uwzględnić zjawisko polimolekularności obliczono trzy różne średnie masowe – średnią liczbową, wagową oraz lepkościową. Symulacja zachowania polilaktydu na poziomie atomowym została wykonana z użyciem metody dynamiki molekularnej przy współpracy z reaktywnym polem siłowym ReaxFF. Narzucone, przy pomocy zespołu kanonicznego NVT, warunki degradacji były zbliżone do warunków panujących we wnętrzu ludzkiego ciała. Opierając się na wartościach gęstości polilaktydu podawanych w literaturze opracowano także atomowy model jego struktury amorficznej. Otrzymane wyniki obliczeń są całkowicie zgodne z przewidywaniami – wartości lepkości i mas spadają wraz z postępem procesu degradacji skutkując obniżoną trwałością biomateriału. Uzyskane wyniki mogą w przyszłości posłużyć do budowy modelu predykcyjnego określającego czas życia polimerowych implantów

Słowa kluczowe: PLA, biopolimery, trwałość, model atomowy, spadek lepkości, średnie masowe

1. INTRODUCTION

The health monitoring of material structure is rapidly evolving field of modern engineering research with steadily increasing number of innovative approaches [1]. The importance of health monitoring issue results from the fact that any damage of material structure may cause irreversible changes of static or dynamic behavior of the object under consideration. Therefore, the change in the material continuous mass distribution may manifest in acoustic characteristics [2], thermal response [3], FFT spectrum or BSC spectrum [4]. It is also reported that change in mass value may result in various transmissibility function [5], internal dumping force [6] and even in differences in excitation-

emission spectra [7]. As a consequence, the analysis of time-variant mass systems is much more sophisticated than the analysis for a constant mass structures [8].

An additional feature of the materials interacting with a biologically active environment like biopolymers are time-dependent physicochemical and mechanical properties [9]. The remaining fact, resulting of these changes, is that medical devices made from biomaterials may be used only as a short term implants with strictly determined lifetime. The process of implant degradation has to be proceeded in a fully controlled manner [10]. If the polymer degrades too fast, it will lose its mechanical properties. It also may cause a potential risk for a human health or life when patient's body will not be able to

expel products of implant decomposition with appropriate high speed. On the other hand, the polymer decay cannot run too slow therefore it is necessary to find an optimum time during which implant will be resorbing gradually, according to the current state of the healing tissue. Despite this inconvenience assumption popularity of biopolymers is still increasing. The reason of this is directly linked with an great opportunity to design new unique compositions with highly specific mechanical, physical and chemical properties, guarantee realization of all entrusted functions, while maintaining biocompatibility with components of living organisms at the cellular level [11].

Range of requirements for plastics aspiring to be title as a biomaterial are very broad, beginning within the manufacturing process and ending with conditions of its use and operation [9]. First of all, biopolymers have to be easily moldable, so any needed form should be feasible without causing previous material degradation. Furthermore, possible mechanisms and following effects of polymer ageing should also be carefully studied [12–16]. Every biomaterial has to be derived from a subtracts (monomers) with high chemical purity resulting in high quality of the final product. Moreover, the quality level should be reproducible regardless the batch of polymer product. Additionally, the physicochemical properties of biopolymer materials should be sufficiently enough to push them through a sterilization without risk of change of these properties or geometrical shape [17]. Finally, all biopolymeric medical products have to exhibit appropriately high reliability and durability, while operating in living tissue and physiological fluids environment without causing any advert reactions. This is also why the stability of biomaterials should be thoroughly studied and why we decided to take a deeper insight into polymer durability deterioration during its degradation process.

The objective of this work is prediction of viscosity and mass losses for polylactide (PLA) biopolymer under the degradation process. To show the time changes of this physicochemical properties we used molecular dynamics (MD) method which let us to analyze material behavior at the atomic level [18], [19], [20]. In order to include the chemical nature of polymer decomposition we employed the reactive force field *ReaxFF* which allowed us to follow reactions occurring on the polymer surface. We performed a set of MD simulation with constant temperature and volume conditions to calculate viscosity and mass values for non-degraded PLA model and for the same model after 2.5 and 5.0 ps of degradation. We also considered MD method as a great opportunity to study biopolymer implants degradation under the various conditions without no need of actual laboratory experiment at each time [21]. The simulation outputs may be a valuable start point for future prediction of biopolymer implants durability and thus may provide an extensive knowledge of the length of their life and the possi-

ble interactions within the human body. We also believed that molecular dynamics simulations might be an extremely useful tool to diagnose the estimated state of material degradation based on the molar mass averages and dynamic viscosity value.

2. BIOPOLYMERS – AN INFLUENTIAL CLASS OF BIOMATERIALS

Over the years, the definition of 'biomaterial' constantly evolved. The current formula was introduced in 1986 during a conference in Chester in the UK and today, following the IUPAC (International Union of Pure and Applied Chemistry) definition biomaterial is considered as a material used in contact with living tissues, organisms or microorganisms. It is also necessary for any biomaterial to exhibit biocompatibility and that means it has to be able to stay in contact with a living system without producing an damaging effect. From the biomedical and biotherapeutical point of view biocompatibility is also defined as material's ability to carry out an assigned task or function while the response of the host is still on an acceptable level [22].

The studies on first biomaterials have been done in the early 50s and the main research issue was focused on proving biological indifference. In practice it meant that material could not be a source or a cause of any toxicological reactions or allergies. From that time, materials fulfilling this assumption were referring as the first generation of biomaterials. The development of second generation took place in the 80s when the main goal of new designed biomaterials was shifted to from biological indifference to bioactivity. The second generation of biomaterials, by mean of unique way of tissue interaction were supposed to provoke a desired and specified response from a living matter. Since last 15 – 20 years the scientific world is dealing with biomaterials of third generation which general aim is to provide fully controlled bioactivity on a tissue at the molecular level in order to lead to their regeneration. Moreover the 3rd generation biomaterial is intended to become a temporary structure stimulating an organism to reproduce its own tissues or even entire organs [23].

The existing range of biomaterials is classified into following classes [24]: metal, ceramic, polymer and composite biomaterials. Each group represent different mechanical and physicochemical properties therefore they could be used to form medical implants with various utilities i.e. heart valves, bones fragments, orthopedic screws and plates or dental implants. It is also important that selection of biomaterial suitable for potential implant should include all its functional characteristics [25].

2.1. Biopolymers

Over the years it turned out that plastics could be a promising alternative for metal and ceramic biomaterials, and just like them were able to successfully fulfilled given tasks and activities. Although plastics were initially used only as a disposable medical products, now are working as self-dependent implants able to maintain some functions of human body system [26].

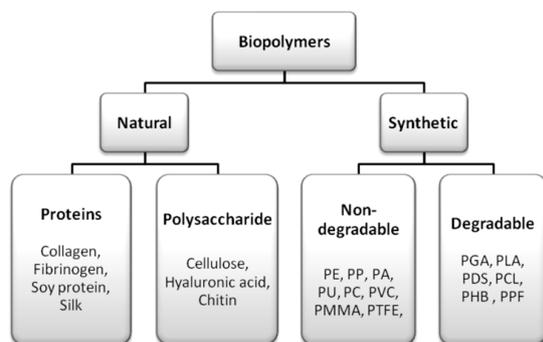


Fig. 1. Biopolymers classification (explanation of abbreviations are located in the text)

Biopolymers are roughly divided into two sections: polymers with natural origin and polymers produced by chemical synthesis (Fig. 1). Polymers from both groups are widely used in medical applications but their particular utilities are determined by specific properties and possibilities of shaping the final products [27].

Natural biopolymers are produced within living organisms as structural components of tissues. These include mainly proteins and polysaccharides. From all biopolymeric proteins the most popular in medicine is collagen, less frequently fibrinogen and elastin. Recently, the soy and silk are also tested for bioengineering applications [28]. Commonly used polysaccharides include cellulose, hyalu-ronate, chitin, chitosan, alginic acid with its salts and heparin [29].

Synthetic biopolymers classification emphasize the fact, that plastics are more or less susceptible to active biological environment. Those of them which are highly resistant to this activity are called non-degradable biopolymers, remaining one belong to the degradable group. The non-degradable synthetics are willingly used in various type of surgeries (i.e.: plastic, reconstructive, vascular or trauma), and the most popular are: silicones, polyethylene (PE), polypropylene (PP), polyamide (PA), polyurethane (PU), polymethacrylates (PMA), polytetrafluoroethylene (PTFE), polycarbonates (PC), acrylic resins and polyvinyl chloride (PVC). Currently use biodegradable polymers include: polylactide (PLA), polyglycolide (PGA) and its copolymers with lactides, polycaprolactone (PCL), polydioxanone (PDS), polyhydroxybutyrate (PHB), polypro-

pylene fumigates (PPF), polyorthoesters, polyesters, polyamides and polyanhydrides. Medical applications for degradable biopolymers are focused on tissue engineering, orthopedics, drug delivery and short term implants [23], [25], [30].

2.2. Poly(lactide acid)

One of the recently popular biopolymer is polylactide acid (PLA). Besides the fact it belongs to a group of biodegradable materials it is also fully resorbable. It means that under active biological environment (like an interior of the human body) they degrade only to harmless by-products which are components of the tissue or are present in the body in a natural manner and can be excreted from it. In fact, PLA is resolvable to water and carbon dioxide and total time of its degradation is varies from 6 months to over 4 years [31]. In general, PLA is obtained from the synthesis of lactide of lactic acid obtained by glucose combustion with oxygen deficiency. PLA is an environmentally friendly material and thus may be prepared from natural raw materials i.e. corn flour, potatoes or sugar beets.

Based on polymer stereochemical composition we may distinguish [32]:

- L-PLA and D-PLA – homochiral, stereoregular and isotactic variety,
- DL-PLA – heterochiral, atactic variety,
- D-PLA/L-PLA – stereocomplex of pure L-PLA and D-PLA varieties.

The physical, chemical and mechanical properties of PLA are strictly related to given stereochemical variety. The range of material parameters possible to obtained for PLA is very broad thus it will not be discussed here. Readers interested in this issue may find a detailed summary of PLA properties in [30].

The applications of PLA are concerned into two fields. The first one are biomedical applications associated with production of biodegradable implants or other medical devices and also the use of PLA as a carrier for sustained release pharmaceuticals. The second one might be generally understood as industrial applications. PLA is used in the food and packaging industry (production of containers, bottles, cups, cutlery and other disposable items in contact with food), in textile industry (light sportswear with low water absorption) and in the horticultural industry (production of biodegradable flower pots, films and garden UV-proof furniture) [33].

3. POLY(LACTIDE ACID) STABILITY STUDIES

3.1. Molecular model

At the first step of polylactic acid (PLA) model construction we developed a single lactide ring. Properly combined atoms were subjected to energy minimization algorithm with a conjugate gradient

method in the presence of a universal force field [34]. As a result, we obtained an optimized lactide ring geometry as shown in a Fig. 2.

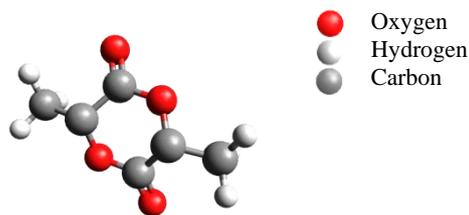


Fig. 2. A single lactide ring in the arrangement corresponding with the minimum value of molecule energy

As a lactide polymerisation runs as a ring-opening type, it was required to distinct a mer unit from the lactide ring structure. We isolated repeating unit (Fig. 3) which clearly showed so-called head and tail atoms used as a connectors for subsequent joined mer units.

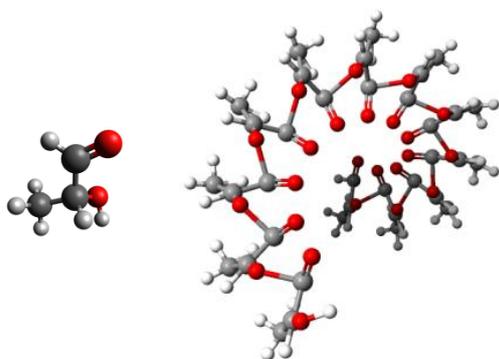


Fig. 3. PLA monomer unit (left) and homopolymer structure (right)

Based on developed monomer unit we defined a polymerisation with degree equals 12. As a result we obtained a single homopolymer chain (Fig. 3), which geometry was resubjected to energy minimization process. A number data for a single PLA chain are presented in Table 1.

At the final step we combined 8 previous optimized chains to create an actual simulation box containing an amorphous structure (Fig. 4). Selected conformation provided the most uniform and consistent spatial distribution maintaining density of matter at the constant level $\rho=1.27 \text{ g/cm}^3$. The density value was determined based on information available in [30]. Owing to the fact that atactic mixture of L-PLA/D-PLA is significantly more amorphous than homochiral isotactic L-PLA and D-PLA chains, we considered only the values concerned with DL-PLA. The final structure was exported to chemical text format supporting partial charges (.mol2) for use in further simulation.

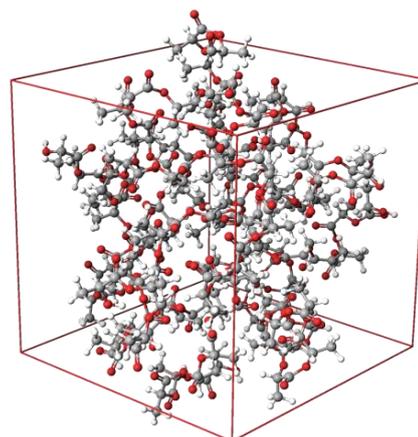


Fig. 4. An amorphous structure within a cubic simulation box. The edge length was about 20.8 \AA

3.2. A molecular dynamics simulation

To investigate the stability of the chosen bi-polymer (PLA), time changes for dynamic viscosity were obtained by mean of molecular dynamics (MD) simulations. The values were calculated for following cases:

- for non-degraded PLA model
- for PLA model with previous degradation with length 2.5ps
- for PLA model with previous degradation with length 5.0ps

Besides the viscosity the polymer molecular mass was also determined. Due to the molar mass distribution it was necessary to obtained three different 'types' of molecular mass averages i.e.: number average molar mass M_n , weight average molar mass M_w and viscosity average molar mass M_η [35].

Tab. 1. Parameters for single PLA chain

Molecular formula	$C_{36} H_{50} O_{24}$
Number of atoms	110
Atomic mass	867 u
Number of monomer units	12
Number of bond (total)	109
including	
single order	97
double order	12

Tab. 2. Parameters for final PLA model

Molecular formula	$C_{288} H_{400} O_{192}$
Number of atoms	880
Atomic mass	6934 u
Number of single chains	8
Number of bond (total)	872
including	
single order	776
double order	96

3.2.1. Non-degraded model

For initial model (without degradation) all mass averages are equal to each other and equal to molecular weight of single twelve-mer PLA chain shown in Table 2 thus there was no need to obtain this value by MD simulations. To calculate the value of dynamic viscosity a standard MD simulation in the presence of a universal force field was performed. A run was preceded by the polymer relaxation at a temperature of absolute zero. MD conditions were set up as canonical ensemble (NVT) with constant temperature 298K and total simulation length was 10000 steps, 0.01fs each one.

3.2.2. Degraded model

Calculations for further cases required prior simulation of polymer degradation with duration time equals to 2.5ps and 5.0ps. PLA decomposition was studied as an isothermal process in aquatic environment where the number of water molecules was determined as a 17% of the total system volume. The temperature regime was inspired by the conditions within the human body and was established at 310K (37°C). In order to include the reactive nature of degradation process a *ReaxFF* force field was applied [36], [37]. One of the ideas used in *ReaxFF* is bond order calculation based on the interatomic distances. The duration of MD simulation of two degradation cases took 10 000 and 20 000 steps, which considering a single step length as a 0,25 fs gave respectively 2.5 and 5.0 ps.

The main objective of this study it means mass and viscosity calculations were performed based on degraded PLA structure with the same MD procedure as for the non-degraded model (NVT ensemble with temperature 298K).

4. RESULTS AND DISCUSSION

According to imposed condition all MD simulation had to be run as an isothermal processes. To verify if the constant temperature regime is satisfied we plotted temperature curve for chosen NVT simulation (Fig. 5). Except the initial steps of simulation, where system is pursuing to achieve the desired temperature, the course of temperature curve remains flat. Although a slight temperature fluctuations throughout examined period of time were also observed, they are consider as a result of unavoidable numerical errors and stochastic nature of MD method. Therefore, it may be concluded that during discussed simulations the atomic system was at a steady state.

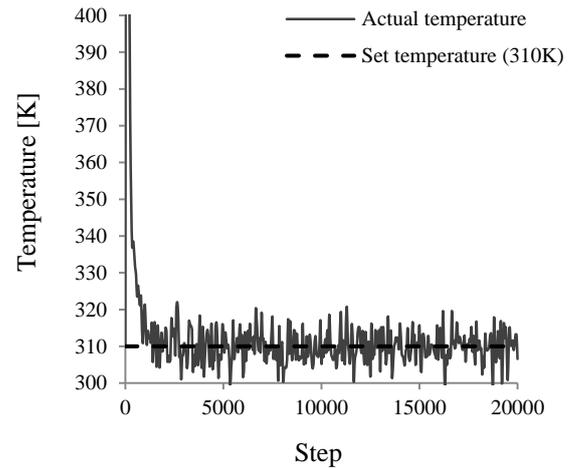


Fig. 5. Temperature setting for NVT simulation of PLA degradation

To check whether the further condition of NVT process is fulfilled we checked two additional parameters i.e. simulation box volume and its internal density of matter. The volume remaining in a line with expectation at the constant level approximately $V=9070 \text{ \AA}^3$ and consequently invariant box dimensions keep the density at desired value $\rho=1.27 \text{ g/cm}^3$. The progressive PLA decomposition was additionally confirmed by variable number of independent molecules inside the simulation box and increasing number of hydrogen bonds as it is shown on the Fig. 6.

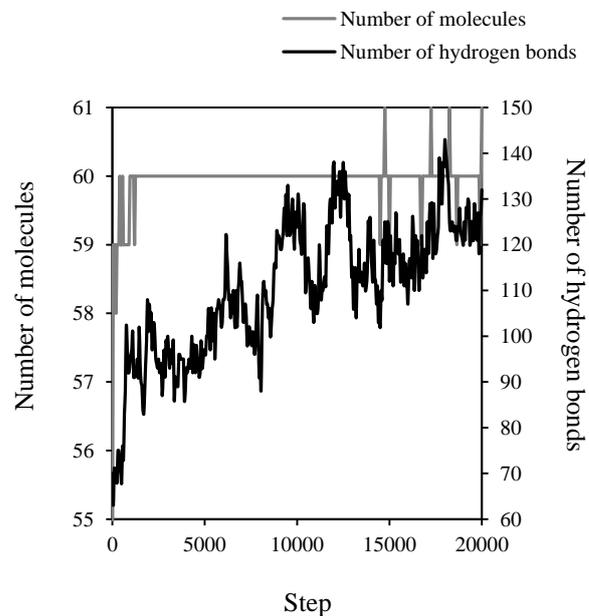


Fig. 6. Number of molecules and hydrogen bonds during PLA degradation (simulation 5.0 ps)

4.1. Dynamic viscosity

The initial value of PLA dynamic viscosity calculated by MD – NVT simulations was equal to $\bar{\eta}_0 \approx 0.42cP$ and for following performed degradation runs this value dropped to $\bar{\eta}_{10\,000} \approx 0.24cP$ and $\bar{\eta}_{20\,000} \approx 0.19cP$ (Fig. 7). Therefore the relative decreases between 0 and 2.5 ps and between 2.5 and 5.0 ps of simulation were, respectively, 43.3% and 20.2%. Although the viscosity drop during the first considered period is the quite significant it should not be confusing as long as the overall tendency is still decreasing within explainable limits.

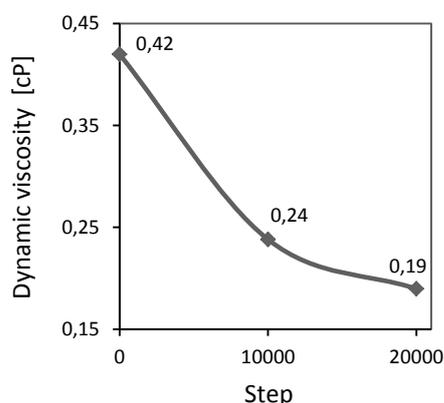


Fig. 7. Changes of dynamic viscosity during the degradation process

4.2. Molecular mass averages

For the initial PLA structure all mass averages are equal to each other ($M_n = M_w = M_z = 866,768u$). During the degradation all mass values are steadily decreasing with the length of simulation. The steepest decline was observed for number average – for subsequent examined periods of time (2.5 and 5.0 ps) the relative decline was, respectively, 52.6% and 19.9%. The relative changes in the value of weight averages was registered as 16.1% and 4.0%, and for the viscosity average: 40.3% and 12.2%. Therefore the lowest rate of mass losses was found for weight average molar mass M_w which results from invert impact of polymer chain length to estimated mass average. Because weight average directly refers to the longest chains, formed during the polymer degradation, this value for every examined point will be higher than for averages including most of the impact from the shortest chains (number average). The influence of middle-long chains on the molecular mass is expressed by viscosity average which values (at every step of simulation) supposed to be between the number and the weight average value (Fig. 8). Regardless the mutual relation between particular averages, the general downward trend for all mass curves is sustained.

Obtained results are in agreement with experimental results [38], [39]. Numerical differences

between the outputs from computer simulations and results of real experiment resulting from limitations of MD method (i.e. much shorter time of simulation than duration of actual process) or from molecular model size (real samples of polylactide implants

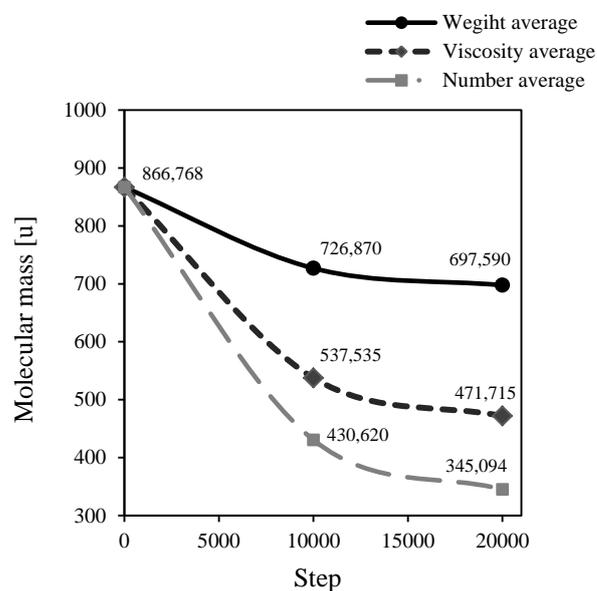


Fig. 8. Number, viscosity and weight mass averages changes in function of MD simulation length

have significantly higher degree of polymerization thus the homopolymer chains are longer). Nevertheless, viscosity and mass drops prediction, as the main purpose of this study, stays consistent with above-mentioned examples with respect to general decreasing tendency.

5. CONCLUSION

Materials stability studies are extremely important issue. From the biomaterials point of view it is also connected with knowledge of predicted material lifetime and this information may be unnecessary when we consider biomaterials for a medical application.

To present one of the ways of biopolymer stability studies we have created a polylactide acid (PLA) computational model suitable for molecular dynamics (MD) simulation in a presence of reactive force field *ReaxFF*. The main objective of this study was prediction of selected PLA physicochemical properties (dynamic viscosity and molecular mass) during degradation process. We have examined three cases of developed PLA model (2 degraded model with different time of decomposition and 1 non-degraded) for mass and viscosity calculations. As we have proofed during the polymer degradation all observed parameters have been dropping as expected. Although the general trend for mass and viscosity is always decreasing, depending on the considered issue it may be identi-

fied as a negative or positive phenomena. Furthermore, for biopolymers used for medical applications (i.e. resorbable polymer implants, surgical sutures) or in food industry (i.e. eco-packaging) this drop and consequently the loss of stability of entire material is even desired. Moreover, the change in material viscosity directly influences the material damping therefore developed viscosity prediction may be also use in the future to determinate the value of material damping factors.

As we have taken under consideration that ReaxFF (used for reflect the chemical nature of degradation process) does take into account only processes occurring at the polymer surface we advise to compared computational outcomes with experimental studies in order to obtained reliable results. It also remains an open research issue: how the size of simulated model corresponds with the actual samples of material? It seems to be obvious that direct transfer of simulation outcomes to real macroscopic objects has to be preceded by adequate scale graduation and finding this appropriate scale may be the powerful ground for future scientific theory. Nevertheless, MD method in conjunction with reactive force field provides a useful insight into the degradation and thus allows to study its influence on biomaterials stability.

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