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Research article

Theoretical study of chitosan-graphene and other chitosan-based nanocomposites stability

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Abstract: Application of new smart materials in various areas including healthcare engineering and medicine became a very promising and urgent area of research. Chitosan has proved its uniqueness as a basis for multipurpose aims: wound dressing, tissue engineering, drug delivery, etc. Unfortunately, nowadays the smart materials are not being constructed fast enough due to complications connected with time and pricing costs of in vivo development with simultaneous constant control of desirable properties. In this paper, a simple approach is proposed for predictive, at the stage of very beginning, analysis of structure and stability of newly-developed materials, such as chitosan nanocomposites. This approach is based on molecular modeling methods, namely, on a new hybrid multiscale model of chitosan oligomers. This model has already proved its efficiency for evaluation of nanocomposites mechanical properties using only computer simulations and appropriate software. Applicability of such approach is shown here for four types of chitosan-based nanocomposites with different fillers—carbon nanotubes, graphene, graphene oxide and chitin nanoparticles. On using a simple method of predicting the stability of such composites, laws of interaction between the chitosan matrix and fillers are shown depending on the relative mass share of the fillers within the composite.

Keywords: chitosan; chitin; carbon nanotube; graphene; graphene oxide; molecular modeling; stability

1. Introduction

The so-called smart materials, especially those of nanostructured ones, nowadays became a

milestone for developing new technologies in medicine and biology [1,2,3]. Such substances could be used in many areas of healthcare services, including tissue engineering (e.g., [4,5,6]), drug delivery and targeting [7,8,9], new devices and implants [2,10,11], etc. One of the most promising materials within the area of nanotechnology application in medicine is chitosan and its derivatives. They are sustainable materials with unique biological properties, therefore they are considered very perspective for medicine. It was recently proposed that chitosan could be used for food preserving aims [12,13], tissue engineering and scaffolding [14,15], drug delivery [16,17,18], etc. Unfortunately, many researchers report on various limitations of chitosan application at the aforementioned aims due to its properties, such as high swelling at contact with water [19,20], low mechanical strength (see, e.g., [21,22]). In order to overcome these weaknesses, new smart materials based on chitosan are being developed. They include chitosan derivatives obtained by chemical alterations [16,17,19,20,23], and also by construction of nanocomposites with controlled biocompatibility [21,22,24,25,26]. The main challenge in development of these materials is the high cost of research activities related to it. This is happening due to the fact that construction of any smart material, including chitosan derivatives, is based on empirical laboratory research with consequent instrumentational study of the resulting object and its properties. If the latter do not correspond to the desired ones, all the experiment should be considered as a failure. This also leads to high duration of such procedures.

When dealing with nanomaterials, whose main features and properties depend on their molecular structure and interaction at atomistic level, a useful approach was proposed based on computer simulation, namely, molecular modeling methods. Within their framework, a material is represented as a composition of atoms and molecules with specific empirically-obtained laws of interaction (including intra- and intermolecular ones), evolution of structure in time under different conditions (temperature, pressure, external fields, deformation, etc.). Moreover, methods of molecular modeling became a comprehensive tool for study of smart materials and prediction of their properties at the very beginning of *in vivo* construction [27,28]. On using such type of computer simulation methods, one may not only visualize the structure of new material, but also characterize its stability, conditions at which it will be fully functional, and predict its mechanical, chemical, electrostatic, optical and other properties. Therefore, the main goal of this work is to present the ability of molecular modeling to theoretically propose new chitosan-based materials with desirable properties for biomedical aims such as drug delivery, tissue engineering, and wound dressing. The study will be mainly connected with the investigation of such materials stability depending on the type of the filler and their mass share. To this end, around 150 different models of composites were constructed for further simulation by means of molecular modeling, namely, molecular dynamics. In order to reduce the computational costs and time consumption of numerical experiments, a multiscale model of chitosan-based nanocomposites was used proposed in [29,30]. This model was introduced for the first time for the aims of chitosan-graphene and chitosan-carbon nanotubes composites mechanical properties evaluation [29,31] and was further developed for predictive analysis of chitosan-chitin and chitosan-graphene nanostructures composites mechanical behavior at different scales [30]. In this paper, such model will be used not as a mean for evaluation of the composites elastic moduli but as a tool for structural characterization of the matrix (chitosan) and fillers (graphene, graphene oxide, carbon nanotubes and chitin nanoparticles) behavior at interface. Also, an approach will be discussed for numerical evaluation of such composites stability (i.e., their ability to remain “as is”). Although such approach was already shown in [29], it was used there for

validation of the model and not for characterization of the composites structure, whereas in this paper it will be shown that such an approach could be of use for the aforementioned aims.

2. Materials and Method

Chitosan is a natural polysaccharide obtained from chitin. It is proved to be non-toxic, biocompatible and biodegradable due to its structure and origins. In this work the primary material under study will be chitosan and composites made on its base.

Nanocomposites are the materials whose properties are determined by a specific mixture of their components at a level of atoms and molecules. Therefore, molecular modeling methods could be a useful tool for studying of such composites and their components *in silico* for helping of predicting their mechanical, chemical and other properties at the outcome of the final product [32]. In this work, we primarily concentrate at using of atomistic-level molecular mechanics (MM) methods with combination of coarse-grained molecular modeling (CGMM) ones by multiscale modeling. The hybrid multiscale model of chitosan used here is based on AMBER force field [33] designed for large biological molecules. The difference between the classical AMBER force field and the one used here is that within the model, the summands that classically denote electrostatic energies additives are not included. This was done to reduce the number of calculations, especially at interface of the chitosan oligomers interacting with each other. The complete description of such model was shown in [29] along with the force field parameters adjustment and explanations that the electrostatic energy additives were somehow included in van der Waals terms. Therefore, according to [29], the force field for the model is shown by the following equation (1). It should be mentioned that in order to satisfy the requirements of accounting for electrostatics effects at the interfacial stability of chitosan-based nanocomposites, the model will be further improved and electrostatics terms will be included.

$$E_{potential} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \\ + \sum_{torsions} \frac{1}{2} V_n (1 + \cos(n\vartheta - \vartheta_{eq})) + \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \varepsilon_{ij} \left(\left(\frac{r_{0ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{0ij}}{r_{ij}} \right)^{6} \right). \quad (1)$$

Chitosan-based nanocomposite structures were constructed using the following fillers: graphene flakes, graphene oxide (GO) flakes, carbon nanotubes (CNT) of various diameters and chitin nanoparticles, as they are already being used in production of biocompatible materials for purposes of medicine [21,22,26,28,34–42]. Examples of such fillers (namely, the fillers molecular structure models) are shown in Figure 1. The molecular mass of the graphene sheets varied between 1872 to 3024 a.m.u. depending on the considered composite structure (larger ones in membranes and smaller ones in ropes). Simulations of chitosan-CNT composites were performed with single-walled carbon nanotubes with molecular weight from 6048 to 18000 a.m.u..

All the simulations were performed in LAMMPS software package [43] under constant temperature of 300 K set by Berendsen thermostat algorithm [44]. Initial configurations were constructed in Argus Lab Software [45]. Visualization and numerical results were performed at VMD package [46]. It should be mentioned that in paper [30] it was shown that the composites structures

does not depend on the initial conformations (mainly in terms of their structural characteristics that tend to form the homogeneous distribution with minimal values of potential energy), therefore the author of this work believe that there is no necessity to provide the aforementioned results in the current manuscript.

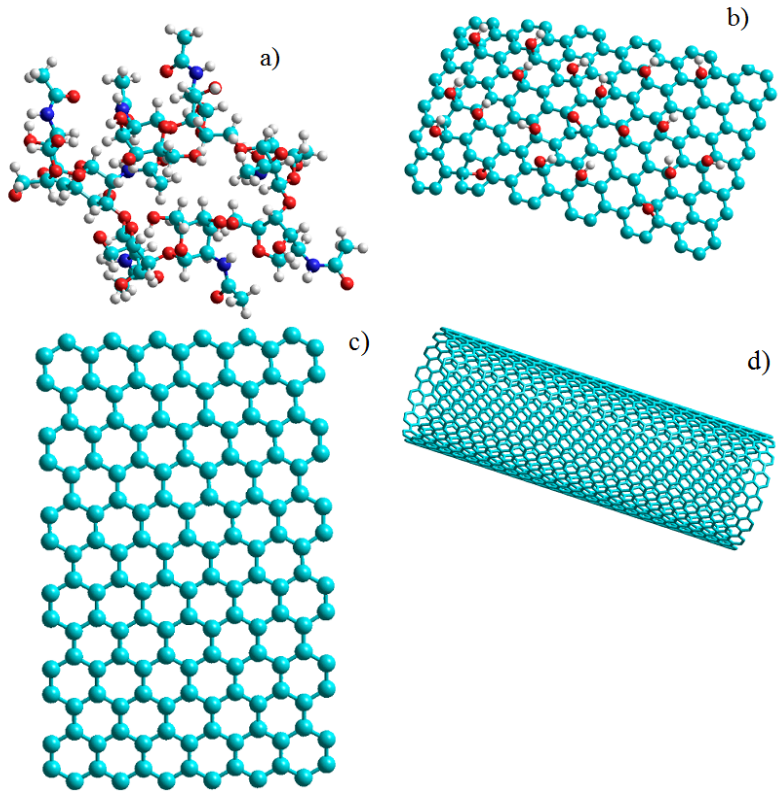

Figure 1. Graphical representation of chitosan nanocomposite fillers: a) chitin nanoparticle; b) graphene oxide nanoparticle; c) graphene flake; d) carbon nanotube. Red color: Oxygen atoms; Blue: Carbon; White: Hydrogen; Dark blue: Nitrogen.

In the current manuscript, we provide information on pure energy stability characteristics without considering the solvents effects. Therefore, all the composites were constructed and simulated in vacuum, (i.e., without water molecules and other solvents) in order to also reduce the calculations time and costs. This assumption was based on the previous researches data where it was shown that at temperatures closer to ambient ones, the water environment does not play an important role in attraction of chitosan to the carbon nanotubes, whereas the latter increases [47].

Unfortunately, this study has some limitations connected with the fact that we consider new or existing materials at atomic and molecular level. The number of atoms is restricted by the molecular modeling software and the computational characteristics of the PC at which all the analysis activities are performed. For example, depending on software, at an average Core i5 CPU and 4 GB of memory, one may study a system with up to 2,000,000 atoms within 1–2 days of molecular mechanics and molecular dynamics simulations (e.g., minimization procedures).

The sought-for characteristics for such composites in this work are to be: stability of composite at molecular level. This characteristic could be explained as follows: if, at the molecular level, the

composite components weakly interact with each other, or tend to form non-stable complexes, then the final substance could separate into pure phases and will not form a composite. Otherwise, if the components tend to strongly bind to each other (e.g., by non-bonded interactions—van der Waals, etc.), then the final substance will be stable. This information could be obtained by MM methods of energy minimization of molecular structure representation with help of a simple procedure described fully in [29] for the adsorption energy ΔE (called a stability parameter) calculated as a difference of total potential energies of equilibrated complex and sum for energies of its components located infinitely far away from each other. If such difference is negative, then the structure could be considered as stable one. Moreover, the larger the absolute value of the difference, the more stable the structure is. An example of the stability parameter evolution with simulation time is shown in Figure 2 for the chitosan-graphene composite with graphene mass share of 0.5 wt%.

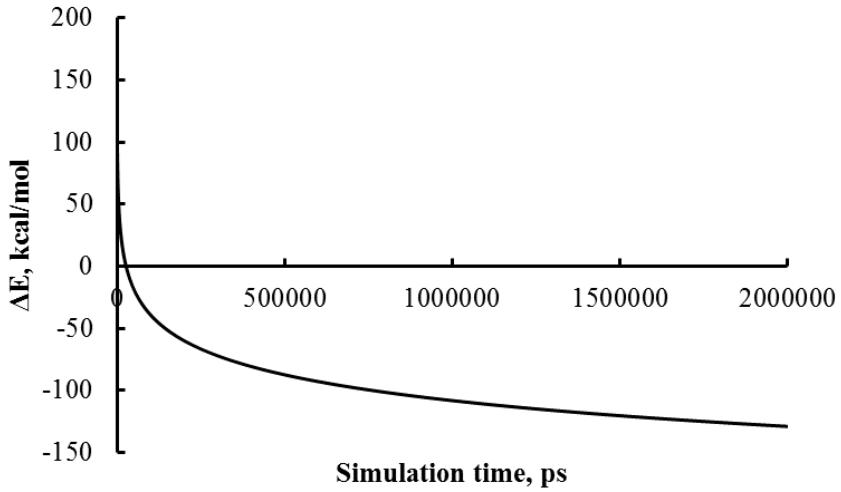

Figure 2. Dependence of the stability parameter on the simulation time.

Note that such curve (with clearly defined logarhythmic trend) was obtained by applying of the sliding average processing of the original experimental data in order to show the main tendency of the stability parameter to a more or less constant value throughout the numerical experiment.

The similar trends were found for all the other nanocomposites energy stability parameters.

3. Results and Discussion

Chitosan-carbon nanotubes (CNT) composites were constructed and studied for various shapes of the outcomes: membranes, fibers and nanoparticles. In all the cases the mass share of CNT did not exceed 1% in order to prevent (or minimize) potential toxic effects of such fillers [21]. Examples of structures are shown in Figure 3 where the effect of chitosan chains twisting around the filler is observed [35].

Study of stability of constructed chitosan-CNT nanocomposites demonstrated that interactions within such structures are preferable for the molecules. Dependence of the aforementioned energy difference on mass share of CNT in composite is shown in Figure 4, where one could observe that with mass share growth the structure becomes more and more stable with a good logarhythmic trend.

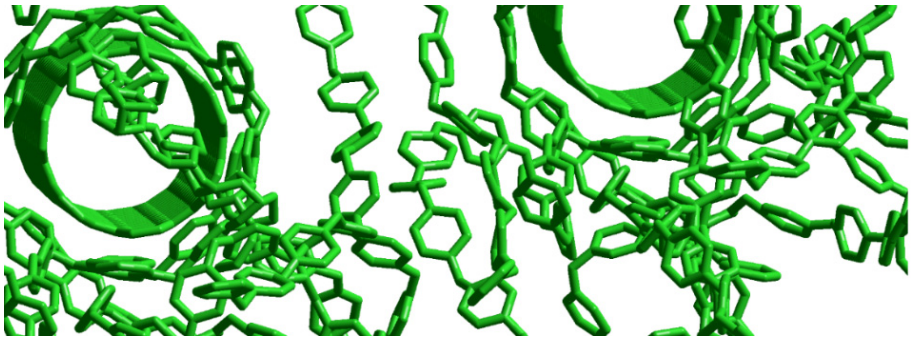

Figure 3. Structure of chitosan-CNT nanocomposites. All the atom types are shown in one color in order to demonstrate only structural features of chitosan chains interactions and spatial distribution.

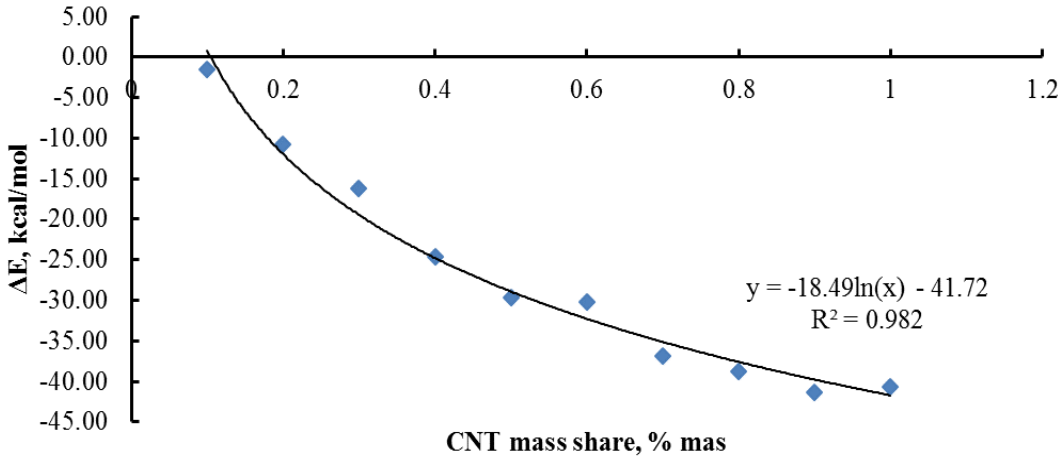

Figure 4. Dependence of stability parameter on CNT mass share in chitosan-based nanocomposites.

It should be mentioned that in the current work we did not specifically considered the stacking interactions between chitosan and CNT or graphene flakes due to the fact that their mass share in composites was too small to provide any significant effects at the energy characteristics of such structures stability.

Features of interaction between chitosan and graphene flakes were previously shown in [48], where it was observed that chitosan chain tends to mimic the flat shape of graphene platelet. Moreover, similar was found for chitosan-graphene and chitosan-graphene oxide composites (see [29,30,31] and in current research). Stability of chitosan-graphene nanostructures was found to be even larger in comparison with chitosan-CNT nanocomposites (see Figure 5a), whereas chitosan-graphene oxide ones were slightly less stable (Figure 5b). The specific features of the model utilized in this work did not allow to consider electrostatics effects of interaction between graphene oxide and chitosan matrix. Perhaps it was a reason for smaller values of the stability parameters for such composites. Therefore, we believe that further investigation should be done. But due to the fact that the fillers mass share is quite small in comparison with the total composites mass, we believe that the trends of decrease of the stability parameter (i.e., stability increase) will remain, especially in

the view of the previous researches that demonstrate that in such cases, the electrostatic terms provide only minor additions into total structure potential energy and binding energy [49].

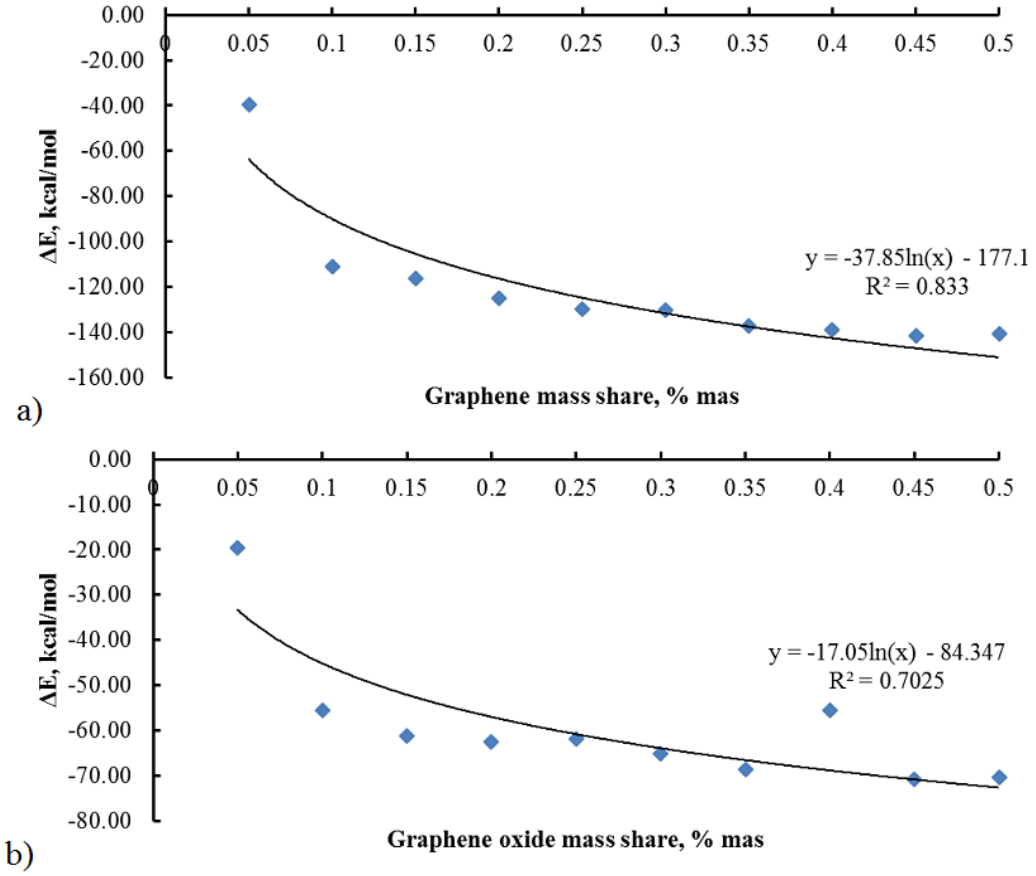

Figure 5. Stability parameter dependence to mass share of a) graphene; b) graphene oxide.

The most interesting structures were of chitosan-chitin nanoparticles composites. Due to the large number of atoms in such macromolecules, the hybrid model was utilized proposed in [30]. All the main characteristics of interaction of chitin and chitosan are discussed also in [30], along with the structure of such composites. It should be mentioned that due to similarity of chitin and chitosan macromolecules, their mixture becomes quite homogeneous at molecular level of simulation, unless we consider chitosan-chitin nanoparticles, where the filler looks as an inhomogeneous inclusion in the polysaccharide matrix. Due to biocompatibility of both chitin and chitosan, in this work the composites were considered with up to 30% mass share of chitin nanoparticles.

One of the most interesting results was obtained for evaluation of stability parameter for chitosan-chitin nanocomposites. It was found (see Figure 6) that ΔE almost does not depend on the mass share of such filler, although at approximately 20% mas it slightly grows and then demonstrates a sustainable but very slow increase. This might be reasoned by mutual effects of similar molecular structures of chitin and chitosan. Further investigations are planned to be made in order to characterize the effects of polar cites interaction between chitin and chitosan, or chitosan and graphene oxide. To do so, the hybrid model used in this research will be updated to account for such effects.

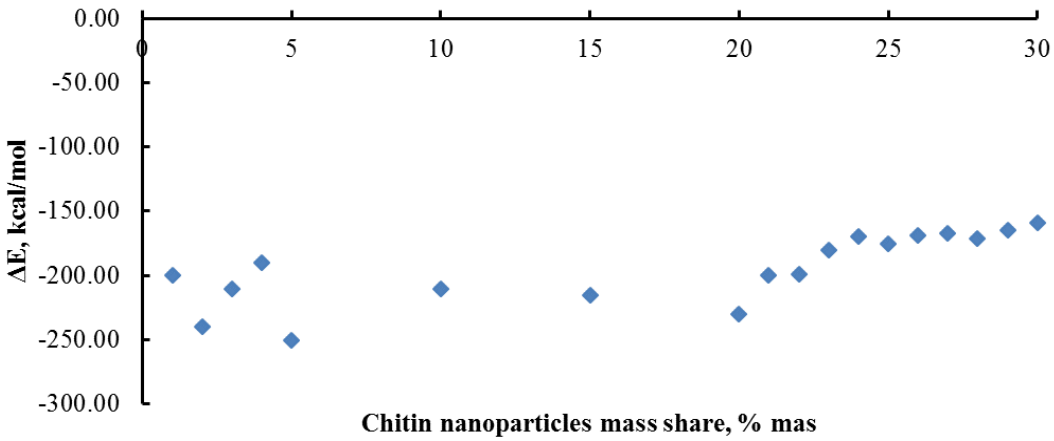

Figure 6. Change of stability parameter of chitosan-chitin nanocomposites with filler mass share growth.

4. Conclusion

In the current research, an approach is discussed for theoretical in silico study of biocompatible chitosan-based nanocomposites stability. Such approach could be useful for predictive analysis of new smart materials, urgent for needs of modern healthcare activities (for example, wound healing or guided drug delivery, tissue engineering and grafting, etc.). Knowing the structure features and stability of the materials that are only at the stage of developing will definitely allow the researchers to minimize the costs and wasted efforts at empirical construction of the sought-for new nanocomposite.

In this paper, four types of composites were studied, namely chitosan with addition of CNT, graphene, graphene oxide and chitin nanoparticles. All such materials demonstrated a good stability. A parameter for numerical evaluation of composite stability (i.e., tendency to remain "as is") was introduced: value ΔE, and its dependency on fillers mass share was discussed. For chitosan-graphene, chitosan-CNT and chitosan-graphene oxide, such dependencies were quite similar, with logarithmic decay, whereas composites with chitin nanoparticles showed a completely different character.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this manuscript.

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