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Comparing different methods of sensitivity analysis for computational modelling of magnesium-based implant biodegradation

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Abstract: Due to increasing numbers in bone traumata, recent years have witnessed a resurgence of interest in biodegradable metallic biomaterials for temporary support of bone, e.g. in fracture healing. In particular magnesium (Mg) and Mg alloys are being investigated increasingly as temporary implant materials due to their non-toxicity, biocompatibility, and biodegradable properties. It is challenging to tailor the degradation rates of these implants so that they are appropriate for clinical use, which requires a time-consuming series of iterative experiments. A reliable computational model can accelerate the development process of these implants. In our group, we developed and calibrated a model of the *in vitro* degradation of pure Mg under physiological conditions [1], where the degradation rate is modelled as $\partial c_{Mg}/\partial t = \epsilon k_{deg}/1 + e^{-(t-t_{init})}$, meaning it depends on two key parameters the degradation rate constant (k_{deg}) and the initialization time of the reaction (t_{init}).
In general, quantifying the uncertainties in degradation models is an expensive process due to the computationally intensive and complex multiscale nature of these models. The mathematical complexity of the model is overcome by substituting the expensive model with a less expensive, compact, and faster surrogate model, which is created based on the model inputs and observations. A robust surrogate degradation model for Mg-based alloys is created using the polynomial chaos expansion (PCE) method. A major source of uncertainty in these models is the uncertainty associated with the parameter. In view of the multiscale nature of degradation models, estimation of several parameters and their influence on model prediction is necessary. Several sensitivity analysis techniques are used to rank the importance and quantify the uncertainty associated with them.To this end, several different types of sensitivity analysis techniques can be used, each of which will perform differently based on the system under consideration. Therefore, it is imperative to determine which of the sensitivity analysis techniques can be implemented most efficiently and with the greatest confidence to quantify the uncertainty in the degradation model. Accordingly, in order to achieve this goal, we are exploring three main approaches to sensitivity analysis that have been reported in the literature; the sample-based (the correlation-based method), the linearization methods (Cottor method) and the sampling methods (Sobol'indices). For a fair comparison the three methods implemented in this work are constructed with the same training samples and validated with the same experimental and optimized degradation model responses.
In Figure 1, the sensitivity analysis by the three methods is presented for the first 10 days of the reaction. The three methods are able to a certain point to detect some of the effect of varying the key parameters over the output of the model. The Cotter's method, which consists of testing the model by setting each parameter to maximum or minimum levels. In this method, the parameters' effect on the model can be estimated quickly, but some effects are undervalued and results may be misinterpreted. Depending on their importance, two factors with opposite sign effects may cancel themselves out as we can see in Figure 1a for the time period less than 5 days. Thus, this method is unreliable for our system, since it can miss important parameters. The correlation-based method is illustrated in Figure 1b. Even though the degradation model of Mg-based alloys is linear, this method is found to be unrealistic when assessing the influence of the input variables because of the interaction between the key parameters and output mapping of the system, which leads to a weak regression fit. The use of rank transformation in regression

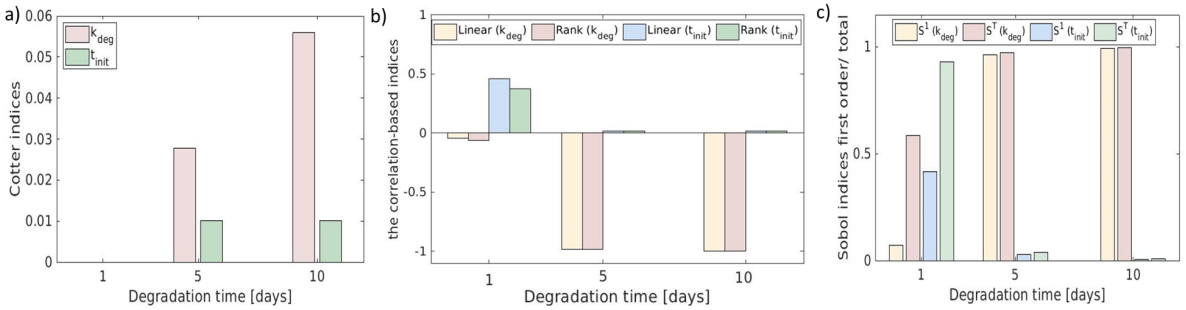

Figure 1: Sensitivity analysis of Mg degradation in SBF in terms of key parameters of the mean degradation depth; degradation rate constant kdeg and degradation time tinit. a) the correlation-based indices, b) Cotter indices and c) Sobol‘ first order (S_i) and total indices (S_{T_i}). For clarity, only three points are shown at 1, 5 and 10 days of the reaction.Total Sobol indices-calculated based on PCK metamodel for MDD

enhanced the reliability of this family of methods. Since the enhancement replaces the model outputs with the corresponding ranks, we can compare this method with other sensitivity measures. This represents a bridge between non-parametric methods (indicates as linear indices in Figure 1b) and the class of variance-based sensitivity measures (The rank indices). Signs of the indices indicate whether the model outputs are increasing or decreasing. The Sobol' indices are the most accurate tested method to capture the influence of the different variations in the degradation model response due to the fact that Soboll' indices consider the variance contribution of each individual and combination of the input parameters on the output of the degradation model through calculating two indices the first (S_i) and the total indices (S_{T_i}). However, the implementation of the Soboll' method is computationally expensive compared to other sensitivity methods since indices are evaluated using Monti-Carlo based methods. Figure 1c shows the first and total indices, where S_i represents the contribution of varying each parameter over the variance of other parameters. Where S_{T_i} measures the contribution to the output variance of each input parameter, including all variance caused by its interactions, of any order, with any other input parameter. The significant difference in the value of the two indices over the time period less than 5 days indicate a non-linear interaction between the input parameters, where the equality of the indices indicates minor to no interactions between the parameters.
In summary, we conclude that global sensitivity analyses should be implemented in order to quantify the influence of the variation in each of the input parameters k_{deg} and t_{init} on the estimations of the degradation model for magnesium-based alloys. Nevertheless, other sensitivity analyses methods may be useful for highly complex models, such as the degradation of Mg, if only an overview of the system is required or if there is limited computing power available. Furthermore, the implementation of the surrogate model reduces computation time and simplifies calculations.

References

[1] Zeller-Plumhoff, B., AlBaraghtheh, T., Höche, D., Willumeit-Römer, R. (2021). Computational modelling of magnesium degradation in simulated body fluid under physiological conditions. Journal of Magnesium and Alloys.

Short biography – My background is chemical engineering with focus on computational fluid dynamics in complex reactive system. My main PhD project is: Uncertainties in degradation models, my PhD project is funded funded through the Helmholtz Association as a pilot project in the field of information and data science, www.helmholtz-uq.de