Advances in Additive Manufacturing of Materials: Current status and emerging opportunities

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Let me continue with this discussion on challenges and opportunities in additive manufacturing. we have discussed about this. We are discussing about the bioink development cell viability and material properties that we have covered in the last lecture. We started the resolution and precision. printing resolution is important and placement accuracy is equally important. Placement accuracy means how precisely you are able to place the cells within the 3D printed structure with the 3D printed scaffolds that is important.

And large volume 3D, 4D bioprinting like manufacture constructs with reproducible property and large volume means this has to also to what extent you are compromising other printing resolution. Because if you remember in one of the earlier slide, if you see that millimeter cube per hour that is the volume that you can be printing and what is the minimum feature size. So, there is almost a linear kind of a relationship. Those things can be needs to be assured.

Then post-printing maturation like tissue maturation like what is the post-printing culture timescale that you want, that you need to involve so that the tissues that are constructed, they also have good functionality. And integration with host tissues like ensuring that how the bioprinted tissues integrated with the host tissues when implanted that is also challenging. Then comes complex tissue architecture in terms of vascularization and multicellular architecture. vascularization means whether this complex intricate vascular network within the 3D, 4D printed constructs that needs to be ensured and multicellular structures that replicating complex tissue physiology is also challenging. Regulatory hurdles and accessibility, regulatory challenges like navigating such landscape is a time consuming and uncertain like regulatory challenges and accessibility.

Now, why regulatory challenges are important? Any materials which are used as an implants, let us say titanium, stainless steel or cobalt chrome alloys, these are time tested implants. These are being used for the reconstruction of the different anatomical parts in the human body, whether it is a hip or knee or ankle or shoulder. It has been clinically used for years and decades, clinicians they have a significant trust and confidence on these

implants. But when you go to some of the tissue engineer scaffolds, clinicians simply they do not have much experience in handling these tissues. before and they need to gain their confidence before they can allow the patients to be treated with this kind of tissue engineer scaffolds.

therefore, if the clinicians are not confident, then these scaffolds cannot be used in the patients. That is number 1. Number 2 is that these are the time-consuming and uncertain because it is large kind of significant time is being spent depending on the existing regulatory landscape in that particular country. For example, European Union they started with MDR 2017 that medical device regulation rule. In India, we have a DCGI and depending on which country you are doing research and you are trying to do this translational research, one has to first follow the rule of the land and if you want to go international, then you have to go either for the CE marking or for the FDA approval and all.

all those things takes lot of time. Last one is the scalability and clinical studies like scalable production like critical size tissue constructs with targeted biocompatibility. Industry engagement like GMP compliant manufacturing facility and clinical study like stronger engagement of clinicians to translate it into patient's bedside. these things are equally important that you know that industry engagement, now industry needs to be strongly involved in making this tissue engineered or 3D printed scaffolds in a reproducible manner. As I mentioned you earlier that reproducibility is also important in the bio ink development.

If the bio ink itself cannot be reproduced with a precise set of properties from every batch, then how industry can take up this product to the market, that reproducibility needs to be first established. And then industry must have GMP compliant facility. I have seen in countries like Germany and other countries also industries really struggling to produce the different batches of these different kind of bio-inks in a reproducible manner. And scalable production like for critical size tissues constructs with targeted biocompatibility you have to go to that large volume of the hydrogel to be printed in a reproducible manner. let us start now with some more examples of this exploiting AI-ML approaches to accelerate AM processes, AM process optimization.

this is the topic with kind of you know that I will continue also in this slide. biomaterial science essentially produces lot of data related to the chemical, surface topography, electrical, biocompatibility, mechanical properties and toxicity study. On the biological omics structure that ionomics, fluxomics, metabolomics, genomics, transcriptomics and microbiomics and proteomics, these are like different sets of properties. The different set of properties one investigate and then you also generate lot of data. Now, you have seen or

you have been exposed to the concepts of data science in the earlier lectures.

And in the data science essentially involves metadata management, artificial intelligence and statistical approach and biomaterial science. And biomaterial science it comes, data science it comes and converges. it essentially makes this kind of biomaterial mix. biomaterial mix essentially converges both the biomaterial science and data science together. It starts with the lab-scale development, in vitro testing like you know physiologically, simulated environment testing, preclinical studies in the animal body, device prototype you fabricate, clinical studies you essentially do in the human subjects.

Then you scale up the manufacturing and get the regulatory approval before you go to the market. One of the things that is very important like this biometeoromics is not only related to the biomaterials but also ceramicomics. Ceramicomics like you know ceramics as a material class has been introduced earlier in one of the earlier lectures and there you have seen some of the basic ceramics like you know whether it is alumina or zirconia, there also ceramic processing is important, ceramic microstructure is important. and ceramic properties like you know for example, strength reliability is one of the important properties. Now, what are the modelling approaches these are important like multi-scale simulation like DFT, MD and FEA, data curation and mining of the published datasets.

And then third one is the data science approaches like machine learning, deep learning and uncertainty qualifications like predicted values and the true value that has been used like training data and test data. this is essentially a framework that integrates the multi-scale physics based models, experimental data in processing microstructure property space of ceramic materials, data science approaches including metadata management, machine learning algorithms and uncertainty predictions to accelerate the development of new ceramics and glass. essentially similar efforts have been made by John Mauro, one of my close colleagues from Penn State, United States and then he mentioned is that Glassomics that is published in Acta Materialia in 2022. Ceramicomics is one of the new things. That is essentially bringing the ceramics fabrication and ceramics actually can be also manufactured in the 3D printing.

here again 3D printing technique plays an important role in manufacturing the design ceramic implants. what are the major elements of the biomaterialomics? This is the biomaterials development, biocompatibility, then it is biocompatibility structure, mechanical cell responses, performance assessment, preclinical and clinical studies, then you have the modeling approaches like multiscale simulation like DFT, MD and FEA approaches. Data mining like metadata management, machine learning and deep learning and e-platform like you know that is the database and online platforms like you know the top 0 and python and cell net and so on and so forth. biocompatibility is important that we

have introduced you in one of the earlier lecture when I have introduced you to the introduction to the biological system. what happens when these biomaterials are being developed in the first generation biometrics, they are essentially bioinert materials.

Like it is a minimal foreign body reactions. Then comes second generation biomaterials like bioactive materials and bioreservable materials. Then comes third generation biomaterials, functional tissue engineered scaffolds. And then comes fourth generation biomaterials like biometrics driven accelerated development of these materials. Now, when you have a 4-generation biomaterials like digital twins, like properties of performance to be predicted by digital twins that is also important.

Like fusion of high throughput experiments, multi-physics models and data science approaches all are important in this particular case. Now I will give you some examples where we can implement the biometrics approaches in the context of additive manufacturing or 3D printing as well. this work was published in Acta Biomaterialia a few years ago in 2022 or so. what are the things that are important? The things that are important also clinical data because clinical data is important otherwise how the clinical performance can be predicted for this set of materials and here there are challenges in the clinical data collection like availability of anonymized patient data like 2018 is 4000 clinical trial data sets. These are all publicly and privately sponsored clinical datasets.

There is different clinical trial organization like Vivli, clinicaltrials.org and Yoda project on clinicalstudydatarequest.com. Like summer it is 3200 patient datasets, it is 414 clinical datasets and here is the 4000 clinical trial datasets. What is the limitation? The limitation is that these are very less number of datasets which are publicly available for biomedical devices or implants.

we need to essentially adapt AI-ML tools to classify and analyze the available clinical study results in order to predict the clinical study outcome with reasonable confidence. one of these approach is that integrated computational materials engineering approach which is also used some of the statistical approaches. For example, there is something called response surface modeling approach, RSM approach which is used for the PSP to establish PSP linkage of zirconia, toughened alumina process structure property linkages. And here we have used the process parameters sintering temperature, sintering time, materials parameters zirconia content and magnesium oxide content. And in this particular case is the RSM approaches, you have a sintered density which is a function of either coded values like Xi, Xi is that A, B, C, D and A is the sintering temperature, B is sintering time, C is zirconia content, D is the magnesium oxide content.

And there is also epsilon is your error term. And there are other things is that is the average

of responses and multivariate regression coefficient. Now, if you plot sinter density which is experimental which is predicted, so same way you can also use the machine learning algorithms like one side is the same parameter what is predicted and one parameter what is experimental. same things you can see sinter density and sinter and same thing you can do this for grain size experiment or grain size predicted. essentially response surface modelling was utilized to predict sinter density and grain size based on limited number of datasets and this particular case actually is less than 100 datasets were utilized.

maximum up to 30-31 datasets which are utilized in this particular case. Now, you can see that this particular line the 45 degree line is essentially followed in this particular case and you can clearly see both the sinter density and grain size they are kind of scale with each other both between experiment are predicted. What is the beauty of the sintering parameters is that that you can do these kind of zirconia toughened alumina, small cylindrical sample, 2 femoral head, 2 acetabular socket, 4 different type of samples. You can use based on the optimized parameters which is used here for the parametric based on this RSM variation or RSM based analysis. You can also use femoral head and then also 3D structures of using ICME approaches and all.

And then after that we have done a lot of this, this work is essentially in collaboration with NIT Rourkela Debasish Sarkar's group, we have patented this particular, this work and then also we have published a few papers here. And then you can see this wear debris particles like how this wear debris particles they cause proliferation, cell compatibility and histological analysis after that they are injected into the mice model for 8 weeks histocompatibility. these are all more on the biological sites, but on the 3D printing sites I will explain to you more. it is like a multivariate regression analysis was done essentially to establish PSP linkages. Your output is Y is the matrix is a function of beta matrix multiplied by X matrix plus epsilon is a vector of errors.

this is a vector of regression coefficients and multivariate regression analysis was done. This is a full factorial design. response surface method is one of the multivariate regression analysis. when artificial machine learning was not utilized the way it is being utilized currently in the present generation by the present generation scientist across the different scientific domains. people used to use the different multivariate regression models like either full factorial design or fractional factorial design or box van Koehn design or response surface methods or Taguchi statistical model.

in this particular case, the examples that I have shown you, it was more in the RSM approach it is used and this particular work is also published in Advanced Health Engineering Materials or Journal of American Ceramics Society. this is process structure biocompatibility or process structure property. Property here essentially is the

biocompatibility PSP linkages which were established using this particular approach. now if you look at that additive manufacturing of biometric implants, now how it will be used? Now, you have seen some of the laser based techniques like whether it is SLM or whether it is a DED, whether it is a DMLS or whether it is LENS. These are like different kind of techniques that you have learnt in the past.

in the several lectures that I have presented before in this as part of this course. what are the different parameters which are important like laser power, scan speed, hatch spacing, layer thickness and material properties, material parameters, out of these things your microstructure development is important, strength and fracture resistance and defects are also important. this defects analysis what we have learnt that is the classification algorithms that is important. Strength and fracture resistance more it is like a regression analysis that would be important. one case is the regression based ML models that will be useful and another is a classification based ML models that will be used for defects analysis.

Now, process, modeling and output. process is your process parameters and material properties, output is your microstructure, defects and properties these are also important. And modeling is your process physics, mechanistic models and data-driven models like machine learning and deep learning that will also be utilized. Now, how this AI-ML can be also used for metal 3D printing? For example, if you remember single track analysis or multi-track analysis of the metal 3D printing that I have discussed before. you can do the single track analysis, then you can do the 3D model of the melt pool, then you can see the different parameters like melt pool width, melt pool depth and then melt pool height and so on and what is the area of the melt pool, what is the area of the weld pool and so on. these three that if you utilize this optical microscopy and arrange profilometry analysis information, then you can get the 3D melt pool.

During the process itself in-situ, you can essentially utilize process camera to get the melt pool features and then you can input IR image features and then you can utilize it into machine learning and deep learning approaches. And then when you plot it, for example, you can train that multiclass SVM models and to classify the melt pools. And from there you can essentially say that whether this particular combination of parameters will lead to printed constructs without any defect. essentially you get that in-situ data, that process camera data, you get the 3D model of the melt pool and you combine both the things for the rapid monitoring and then for the rapid diagnostics of the metal 3D printed structures. This is what I was trying to refer from this particular slide.

what are the future predictions, directions in terms of predictability or printability of AI-ML? This is the last slide, it was more for metal 3D printing. Here, this is more for let us

say extrusion 3D or 4D printing, 4D bioprinting or 4D printing. what you see the first generation is autologous transplantation, second generation is cell and tissue engineering, third generation is 3D bioprinting and fourth generation is the 3D bioprinting, then you give the external stimulation, you change the shape of the materials or tissue 3D printed structures and functionality of the structures and fifth generation But that what we believe that will essentially revolutionize the field is that when you utilize or when you incorporate AIML approaches or when you implement AIML approaches. to predict the safe fidelity, to predict the tissue maturation, to predict the biophysical properties of the 3D bioprinted scaffolds. And here you can see that is the predicted mechanical properties of Gelma and this is the actual mechanical strength of the Gelma and you can see that what is the level of predictions here.

this is the fifth generation AI-based bioprinting approaches, AI-based bioprinting that can revolutionize that particular field. this particular case what we believe that 3D and 4D bioprinting that we still did not see that much exploration of AI-ML approaches in this particular domain, but hopefully in the days to come that AI-ML approaches will be developed. implemented very strongly in the field because otherwise you know that you vary the different parameters like extrusion pressure, that is what is the layer spacing or build speed and so on, then you intuitively vary all these parameters. You essentially do large number of experiments before you can successfully predict that you know what is the kind of properties and shape, fidelity and tissue material and biophysical properties of this scaffold it will be. With this, I want to close this particular lecture.

But before I close, I would like to mention that we need to develop more clear understanding on the different data science approaches and then how to handle low volume of experimental data because many of the extrusion bioprinting for one specific set of material systems it can generate 100 datasets or 120 datasets and all. Whether this kind of small volume datasets, what are the specific algorithms, how the different algorithms whether tree based algorithms they will perform better, their performance matrix like R square value, RMSE values or error analysis or error distribution whether it will follow Gaussian type of distribution those things will value or not that you need to do it these particular cases need to be carefully understood. before you can essentially apply the AIML approaches for many of these extrusion 3D printing or other printing approaches. For example, once in this last series of lectures I have described in details about melt electro writing. For example, melt electro writing there is materials related parameters and there is also melt electro writing related parameters and then if you combine all these parameters to generate a critical amount of datasets and then whether this critical amount of datasets is good enough for the artificial machine learning algorithms to be implemented and to be applied that needs to be kind of investigated very, very clearly here before we can essentially utilize this AIML approaches in much more details. Thank you very much.