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Designing an AI in 3D Bioprinting: A Model that Maps Out Vascular Networks in the Heart Based on MRI Scans

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Research Question: How can an AI model pipeline automate the segmentation and mapping of vascular networks of hearts and convert cardiac MRI scans into a bioprint-ready vascular format?

Objectives: O1. Achieve clDice > 0.95 and 95% Hausdorff distance **O2.** Limit Mesh Breaks to less than 2% of total centerline length after STL conversion **O3** Generate print paths that pass "bioprintability" check

Introduction:

3D bioprinting is an emerging technology in the field of regenerative medicine that uses additive manufacturing capable of creating three-dimensional structures of organic materials, such as organs, tissues, biomaterials, and organic molecules. 3D bioprinting integrates biology and engineering to create artificial tissues and organs and presents promising solutions to various complications that occur with organ transplantations: shortage of donors, immune system rejection, and surgeries by the innovation having the potential to 3D bioprint organs on demand like the brain, heart, and liver [5], [8]. The technology can also advance the field of drug discovery to where researchers can easily manipulate and develop drugs suited to patients and even assist in the creation of synthetic prototypes of organs and tissues for research and educational purposes. Another usage that 3D bioprinting presents is to Heart diseases, which refers to conditions that affect the heart and blood vessels, such as Coronary Artery Disease, Valvular Heart Disease, Congenital Heart Disease, and more. Cardiovascular-related diseases are one of the leading causes of deaths in the US and worldwide. 3D bioprinting technology in the realm of regenerative medicine can allow for the restoration of parts of the heart, such as the myocardium and aorta, effectively tackling various complications with Heart Disease and offering a promising solution by preventing heart failure. However, many difficulties arise with 3D bioprinting complex large organs, and the AI pipeline proposed aims to help solve the issue of bioprinting vascular tissues (blood vessels), which are difficult to 3D bioprint due to their intricate structures and highly individualistic networks.

The proposed computational network, a 3D U-Net, will be trained on multiple datasets of patient heart MRI scans, converting from DICOM (typical MRI format) to NIfTI format and perform vascular segmentation (mapping out the vascular network) with the output being a binary mask of vessel/non-vessel based on the voxels (the 3D version of a pixel), which will then be converted to a STL file, 3D bioprintable format. Vascular networks are necessary for any organ to function and are especially essential for the heart, and mapping them out is an essential part of the process. The AI model, trained on supervised learning, will be employed and assessed in professional 3D bioprinting labs, where it can be further tested to be used in real-world settings. The technique used for 3D bioprinting is equally important in ensuring the success of the framework, and for the highest potential, extrusion 3D bioprinting has been the most commonly used technique with much success, especially for printing vascular tissue. Extrusion-based 3D bioprinting uses a piston and a pressure-controlled nozzle to bioprint layer by layer with main benefits including high cell density and wide variety and flexibility of possible materials [5], [6]. Extrusion-based techniques will be

mainly used for the bulk of the heart, including the myocardium and large vessels, arteries, and large vessels, and FRESH (Freeform Reversible Embedding of Suspended Hydrogels) 3d bioprinting, a type of extrusion technique that uses a watergel support bath for its base, will be implemented for the micro-vessels and capillaries [1], [2]. There are many limitations in current research and the proposed model, such as limited data with patient cardiac MRI scans with topology limited, ethical concerns and feasibility issues associated with 3D bioprinting full-fledged organs and implementing the proposed model in a real-world setting, and lack of proven and advanced bioinks with bioprinting heart applications. Research also highlights more specific issues on generalizability with lack of standards implemented across hospitals, labs, and research facilities for bioprinting applications and capturing patient cardiac MRI scans. While many previous pipelines in the past have employed deep learning in order to map vasculature networks/vascular segmentation, this novel computational model combines integrates previous models for bioprinting purposes in order to create a fully 3D bioprintable construct using vascular segmentation from MRI scans that includes producing topology-preserving masks and meshes that adhere to bioprinting guidelines before STl exports. Additionally, most cardiac MRI pipelines do not address overlapping metrics and don't enforce bioprinting requirements, such as centerline continuity or downstream printability, so outputs of these traditional models cannot be used for bioprinting purposes, which is what this proposal aims to solve.

Literature Review:

Recent Advances in Vascular and Heart 3D Bioprinting: Research has noted that 3D bioprinting technology is an emerging field that promises various implications to transplantation limitations and integration in addressing heart and cardiovascular disease and in accelerating drug testing and disease modeling. The heart is one of the most studied organs for 3D bioprinting, and while many miniature models and prototypes have been successfully printed, a fully functional heart has yet to be successfully bioprinted. Feinberg *et. al* and his colleagues in 2020 were able to develop FRESH, a new bioprinting technique discussed earlier in the paper and then were able to bioprint collagen-based trileaflet heart valves and beating ventricles and used hierarchical machine learning to optimize the printing parameters of FRESH for printing fidelity [1]. In 2022, a Boston University Team were able to successfully complete a project on creating a miniaturized heart with organon chip, where they were able to print a tiny miniPUMP heart chamber using a mix of stem-cell-derived cardiac tissue and microfabricated polymer parts but however without the help of machine learning [6]. Finally, in a study led by Noor *et. al*, they were able to 3D bioprint miniature patient-specific hearts using the patient's omentum tissue, the tissue lining up the abdominal cavity that connects the stomach to other nearby organs, and using iPSCs (induced pluripotent stem cells) with the extracellular matrix to create a bioink, they were able to develop a cellularized human heart [3].

Research in Recent Deep Learning Models for Vascularization and Gaps: Many deep learning models have been developed in the past for segmenting vascular tissue from cardiac MRI images, but very few have focused on generating vessel segmentation for bioprinting purposes and converting into STL files, a friendly platform for bioprinting. One of the more recent deep learning models for vascular segmentation of the heart based on cardiac MRI images was from Bustamante *et. al* , where they were able to develop a 3D deep-learning model to segment the full heart, mainly the four cardiac chambers and vessels on 4D flow cardiac MRI of real patient data and were able to achieve a high dice score of 0.908 across testing but the limitations in the research present were low dice scores in the right atrium and branch vessels and the training data labels were derived from atlas and manual edits [7]. The model proposed in this paper however focuses on a pipeline that covers from patient cardiac MRI images to blueprints for bioprinting and is able to use topology preservation of particularly thinner vessel structures not already highlighted in MRI images. Prior studies only segment prominent and the main cardiac structures and rarely preserve vascular topology or evaluate printability, which disconnects the image segmentation and bioprinting applications, which is addressed in this research proposal.

Current Limitations: However, many limitations exist and have been highlighted within current research in deep learning models and the technology, which hinders models abilities before it can be set and used in the real world. Data limitation is a pressing issue, with not that many publicly available datasets for the algorithm to train on, which can inhibit the accuracy. Within the public datasets, such as HVSMR 2.0, a significant portion of the data is unlabeled and doesn't include fine topology labeling, again reducing the amount of available data that the system can train on. Another challenge that needs to be addressed is the ethical concerns associated with 3D bioprinting. Before the computational model can be employed, regulatory certifications and approvals would need to be administered by the FDA and to be used in lab settings, the Institutional Review Board (IRB) approval would also be needed, due to the use of patient data. For use in hospital settings, the model would need to follow certain technical requirements, rigorous guidelines, and testing along with validation requirements outlined in the model training. Bias and Generalizability also presents another issue, where performance from one vendor of a 3D bioprinter may degrade and change in another vendor, and new protocols with specific sequences and parameters will have to be implemented to achieve similar results. Another challenge with the 3D bioprinting framework are bioinks, as many current bioinks developed today adhere to challenges to support the bioprinting of a functional heart, specifically for blood vessels. Bioinks present today for bioprinting cardiac tissue are mainly made up of naturally occurring biopolymers such as collagen, gelatin, fibrin, alginate, and decellularized ECM hydrogels [8]. Many advancements for an optimized bioink are underway and will need to be fully developed before bioprinting of the full heart takes place. Maintaining the heart in condition also presents issues and still requires advanced technology, such as keeping the heart beating and making sure the heart receives proper oxygen diffusion, but advancements have been made, such as in new techniques in organ transplantations of the heart that are able to utilize warm and cold perfusion technology, that extend the recovery-to-transplant timeframe to 12 hours from just 3-4 hours [9].

Implications of proposed model: Once employed and modified to fit the majority of hospital and lab settings, the algorithm will be able to solve the issue of mapping out vascular networks of the heart, and after training on other datasets, it can expand into other vital organs, such as the brain and liver, allowing improvements to be made and getting closer to be able to fully 3D bioprint organs on demand. With the ability to 3D bioprint these large organs, organ transplantation difficulties, such as immune system rejection, complications with surgeries, side effects of immunosuppressant drugs, and even infections will be minimized. The innovation can also help eliminate the organ transplantation waitlist, where 13 people die each day on the waitlist in the US according to the Health Resources and Services Administration. Other areas the framework can help advance include drug discovery, as researchers can easily manipulate and test drugs on 3D bioprinted organ or tissue models, such as organ-on-chip models, a new and aspiring field that presents itself as an alternative to traditional 2D and 3D cell cultures. Organ-on-chip models are detailed vitro models that can be used to better model diseases, such as tumors and cancers, helping researchers to better modulate treatment plans and for drug testing.

Proposed Methodology:

Datasets/Preprocessing: The neural network will be trained on cardiac MRI segmented images from the HVSMR 2.0 dataset that will have labeled vessel labels, and these images will be converted from DICOM to NIfTI using the Python library, Nibabel, and will be preprocessed for normalization, resizing, denoising, and augmentation. For uniform data across for the model to train on, various libraries from the Python Library, MONAI, will be used for preprocessing, mainly MONAI.transforms and MONAI.data, which serve to normalize and adjust the data and allow the model to continue training after checkpoints and split into training and testing datasets.

Model Structure: The algorithm includes a 3D U-Net CNN (Convolutional Neural Network), which is specialized for image segmentation of medical images and will contain an encoder, bottleneck, decoder, and finally the output layer. The input of the engine will be the patient cardiac MRI images that highlights the myocardium and larger vessels. The output will be a segmentation mask, highlighting the vascular structures into a highly detailed map of vessel and non-vessel using the frameworks, PyTorch and MONAI.

Model Training: Supervised learning will be the method employed with 70% of the dataset for training, 15% for testing, and 15% validation. Due to the large size of 3D MRI scans, batch sizes will range from 1–4. The network will be trained for approximately 100 epochs using the Adam optimizer. For model evaluation, the Dice coefficient, specifically clDice, will be used to measure the accuracy and precision between the prediction of the AI and the ground truth, and Hausdorff distance to measure the distance between the predicted and the actual vessel boundaries. The model will aim for 95% Hausdorff distance and ~95% clDice.To display the results of the model, the Python Library, Matplotlib will be used to display the dice metric, the accuracy of the model, and the training loss, essentially the quantity of error of a model based on the training data, with the epoch number. A patient parameter (early stopping) will also be implemented, where after a certain number of epochs if improvement in dice score is not made, the model will stop training and will include checkpoints to save the best version of the model based on the best dice score.

Post-processing and STL File Conversion: After segmentation is complete, steps will be taken to clean up the mask, the output, and then converted into 3D meshes and then exported as a STL file with smoothing algorithms and even a constraint reinforcement to set the parameters using tools such as 3D Slicer and Blender to convert it into a 3D bioprintable format.

Project Timeline: Data collection will happen for around 1 month and primarily employ the HVSMR 2.0 Dataset and a hospital dataset using set standards that is split into testing and training, followed by model training on the datasets that will take around 2 months. After an accuracy of ~95% is achieved, a testing cycle of 2 weeks will occur, which will be followed by data analysis that determines real-world fit. The machine learning model over a course of a month will be proposed to various laboratories, research facilities, and hospitals for further testing and evaluation. The study will adhere to standards and ethical guidelines that the IRB has outlined, which includes privacy of patient data. For feasibility, requirements include a time frame from around 10-12 weeks using public and private datasets acquired from hospitals and a GPU with around 24 GB of VRAM is required for the computational aspect, and the use of open source models and tools (MONAI, PyTorch, Blender, etc.) supports the pipeline from start to finish.

Conclusion:

While 3D bioprinting technology continues to evolve, the central issue of mapping out and bioprinting vascular tissue and blood vessels remains a significant challenge and barrier to bioprinting a fully functioning heart. The review highlights all of the implementations of bioprinting in various fields, including in organ-on-chip, heart diseases, and replacing organ transplantations. This research proposal was able to outline a 3D U-Net pipeline that utilizes deep learning techniques, which takes in patient MRI heart scans and then uses segmentation to map out the vascular networks ready for 3D bioprinting in order to address this central problem. With the integration of machine learning and advancing bioprinting techniques, FRESH and extrusion-based bioprinting, the framework is equipped with the potential for the most optimized and efficient way towards bioprinting organs while being the most practical.

With much effort going into improving the capacity and potential of bioprinting technology, the framework cannot still bioprint such large organs in a reasonable amount of time and contains limitations, including data limitations and concerns, lack of optimized bioinks, and ethical concerns,

but with the assistance of machine learning and other AI tools as well as research focused on expanding the model to a wide variety of organs and expanding datasets, many of these challenges may be overcome as done similarly with this proposed computational model in the upcoming years, leading bioprinting technology in the future to be a life-saving tool widely used everywhere.

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