Model credibility plan mid-year update for

**Systems modeling guided bone regeneration**

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PIs: Xiaobo Zhou (UTHealth), Yunzhi Yang (Stanford)

**Summary:** The ultimate goal of this project is to optimize the geometrical and biophysical properties of the pre-vascularized and cytokine preloaded scaffold for optimal bone regeneration, by integrating mathematical modeling, bioinformatics approaches and wet-lab experiments. For more information, refer to <https://www.imagwiki.nibib.nih.gov/Systems%20Modeling%20Guided%20Bone%20Regeneration>

**Details regarding model credibility plan**

* 1. List of planned actions outlined in Model Credibility plan

1. We have outlined strategies and metrics for evaluating the credibility of the proposed multiscale models to address the bone regeneration in vitro and in vivo. This includes performing verification, validation, uncertainty quantification and sensitivity analysis, as well as documenting model limitations.

2. The credibility assessment methods and metrics used will be both qualitative and/or quantitative; and will be accessible for use by a third party not on our team.

3. Criteria for evaluation for our models will also include adequacy, trustworthiness, authenticity, integrity, availability, documentation, and transparency.

* 1. Brief description of information gained by each credibility action

1. We have finished the model construction and in vitro experimental validation part for the dual cytokine treatment on bone stem cell. Our model well recapitulated the experimental observations and accurately predicted the outcomes held out from the training part.

2. We also conducted global sensitivity and uncertainty analysis on the constructed model, and identified those critical model parameters shaping the model output. We also showed that our model is reliable with negligible uncertainty.

3. Since last reporting, we have tidied up our simulation codes and tested them for reliability and reproducibility. Then we opened them via a public link for free download and use to the community.

* 1. Actions and activities classified within the CPMS TSR framework (item-by-item summary table). If any of the TSR items are not being implemented/considered or additional items are being implemented, this information should also be explicitly stated

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| **Ten Simple Rules (TSR)** | **Implementation** |
| 1. Define context clearly | The context of our multiscale model has been defined to simulate the bone regeneration within cytokine loaded prevascularized scaffold. This has been stated in our publications and open codes. |
| 2. Use appropriate data | We used in vitro and in vivo data at multiple scales to calibrate and validate our model. The data generation protocol were elaborately designed to account for sufficient spatial and temporal resolutions for model construction and evaluation. |
| 3. Evaluate within context | We evaluated our model at both molecular, cellular and tissue scales to ensure the reliability and generalizability of our model. |
| 4. List limitations explicitly | The limitations has been discussed in our publications and sated as pitfalls in our proposal. |
| 5. Use version control | Currently we are developing the initial version of our model, but will control the versions in an appropriate way. |
| 6. Document adequately | Codes for model simulations have been well documented. |
| 7. Disseminate broadly | The first version for modelling bone stem cell differentiation under temporal delivery of dual cytokines has been published for public access and use. |
| 8. Get independent reviews | The papers were peer-reviewed. |
| 9. Test competing implementations | Bone stem cell differentiation process was simulated and tested under various treatment schedules. Since currently there are no existing model of similar process, it has been compared to other models yet. |
| 10. Conform to standards | We strictly followed the institute approved protocols for our in vitro and in vivo experiments. Data collection, processing and interpretation also followed corresponding instructions. |

* 1. Description of how the planned activities will lead to a credible model

Through the terms and conditions of the cooperative agreement provided by this RFA, we will work with the IMAG project scientists to identify appropriate groups in the MSM Consortium to perform an independent evaluation of the multiscale model as it is being developed.

We will track the number of users, training of users, requests for services, successful use of our models, publications citing uses, numbers of students, use of training materials, and the ability to extend the utility of tools through collaborations with other investigators, among other metrics. The research community being served will be documented through mechanisms such as user feedback, and letters of support.

* 1. Progress to-date and plans for the next reporting cycle (6 months). What has been achieved since last reporting?

**Modeling part:**

1. We constructed a multiscale systems model to simulate the BMSC lineage commitment under cytokine treatments (BMP2, IGF1) at both molecular and cellular levels. The multiscale model integrated our experimental data of various scales to represent a coordinated system. We also evaluated the significance of involved parameters to model output through global sensitivity analysis. We validated our model with an independent set of experimental data, and consequently proposed a convincing mechanism to explain the outcomes of combined treatment with specific growth factors. We opened our multi-temporal scale model for GF combination treatment simulation on the following link for free public download and use. This site will be moved to our lab webpage and maintained continuously.

<https://sites.google.com/site/bonelineagesimulator/>

2. We established a 3D mechanistic hybrid multi-scale model (HMSM) for systematically understanding the immunity leading to castration-resistant prostate cancers (CRPC). In our HMSM model, we infer the cell-cell interaction and connected cytokines from our RNA-Seq data generated under various co-culture conditions. Based on the inferred cell-cell interaction networks, HMSM model simulated tumor growth, immune infiltration, and angiogenesis with in an integrated 3D space, which included tumor spaces and lymph node. After optimized with the dynamic cell population data quantified from our mice model, HMSMS is capable of predicting the optimal treatment strategies for CRPC.

3. We will calibrate the model with data from in vivo sequential cytokine treatment experiments.

**Data generation part:**

1. We have prepared cell samples for epigenetics study. Specifically, we are going to do ChIP-seq data for RUNX2 and Osterix to study their genome-wide DNA binding profile switch over cell differentiation, including both binding sites change and binding abundance dynamics.

2. We have systematically evaluated the effect of 3D printing parameters on 3D printed scaffolds. This work allows us to establish a toolbox and roadmap for the following experiments. This work is significant because it will significantly improve the reproducibility of samples and data by using automation, leading to improved model credibility.

3. We have established a new method for loading growth factor containing gels onto 3D macroporous scaffolds, and evaluated the BMP2 release profile within 5 weeks. The new development will allow us to study the dual delivery release profiles.