During this module, discuss bone fracture healing. What is the muddiest point? What surprises you the most? What else can you add to what we've learned on this topic in this module (provide references to resources)?

**What is the muddiest point?**

1. Both models are approximations of true biological cell behaviors, and several assumptions were made:

>> Limitation of the Diffusion model:

* The diffusion coefficients for different cell types were a weighted average of the diffusion coefficients of the surrounding tissue

>> Limitations of the random walk models:

* The algorithm seems rather simplistic regarding the stochastic walk; it could have integrated more sophisticated mechanisms, such as incorporating randomness in the number of jumps, considering feedback from the environment, cell-cell interactions, mechanical forces, or addressing low or high density regions with a dynamic step function.
* The anisotropic cell direction probabilities would need to be measured experimentally
* Other important factors such as biochemical gradients, preferred oxygen/nutrient pathways, and vascularization (critical for bone regeneration), for example, were not considered

1. Uncertainty in model validation: The diffusion model predicts a smoother and more uniform cell distribution pattern than the random walk model; however, histological analysis has not yet been performed to determine which model is more accurate.
2. The **150 and 500 µm micromotion values** were selected to represent **different levels of implant stability, but these values were arbitrarily set rather than derived from experimental studies.**

**What surprises you the most?**

At first, it is not immediately clear that as the tissue differentiates, a higher force (shear strain) is needed to produce a micromotion of 150 **µm between the bone compared to a displacement of 500 µm. The analysis made in the paper explained that excessive micromotion, such as 500 µm, prevents bone formation and leads to fibrous tissue and cartilage formation. As bone formation occurs, the tissue stiffens and requires extra force to maintain 150 µm micromotion.**

**What else can you add to what we've learned on this topic in this module (provide references to resources)?**

I was interested to learn more about bone fracture healing models addressing the shortcomings of the model from the lecture.

The model developed by Geris et al. 1, contrary to the model from the paper, does not consider mechanical regulation; it incorporates angiogenesis and describes various processes related to the migration of MSCs, chondrocytes, osteoblasts, fibroblasts, and endothelial cells. It includes chemotaxis, differentiation into osteoblasts and chondrocytes, endochondral replacement by chondrocytes, haptotaxis, random migration, and the growth and degradation of the fracture callus. The model demonstrated that cell motility, angiogenesis, vascularization, and chemical gradients are critical factors for successful healing.

Dicati et al. 2 recently developed a subject-specific finite element (FE) model to predict bone density distribution by integrating CT-derived femoral solid models with numerical simulations. and refined their methods by minimizing the difference between numerical simulations and clinical data collected from various patients. They built the FE model based on a femoral solid model derived from a CT scan. In comparison to the study by Perez 3 , the validation of the model was rigorous, and incorporating body mass and daily physical activity it reduced discrepancies between clinical and simulated bone density by optimizing model parameters.

Reference

1. Geris, L., Gerisch, A., Sloten, J. V., Weiner, R. & Oosterwyck, H. V. Angiogenesis in bone fracture healing: A bioregulatory model. *J. Theor. Biol.* **251**, 137–158 (2008).

2. Dicati, G. W. O., Gubaua, J. E. & Pereira, J. T. Optimum parameters for each subject in bone remodeling models: A new methodology using surrogate and clinical data. *Eur. J. Mech. - ASolids* **91**, 104409 (2022).

3. Pérez, M. A. & Prendergast, P. J. Random-walk models of cell dispersal included in mechanobiological simulations of tissue differentiation. *J. Biomech.* **40**, 2244–2253 (2007).