THERAPEUTIC EFFECT OF MECHANICAL LOADING ON BONE METASTASIS: AN HCA MODELLING FRAMEWORK

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Background and objectives

Bone metastases (BMs) are among the most debilitating complications for cancer patients. They are associated with poor prognosis and are often incurable. BMs develop through cancer-induced perturbation of the inherent bone remodelling process, which is responsible for healthy bone integrity through balanced resorption of old/damaged bone and formation of new tissue. Osteolytic BMs interfere with this balance in a vicious cycle whereby cancer cells favour bone resorption. Growth factors are released from the degraded matrix and enhance tumour growth, which in turn intensifies bone resorption. Mechanical loading naturally induces an opposite shift to the remodelling balance by stimulating bone apposition. Early in-vitro and in-vivo experiments suggest a therapeutic potential for mechanical stimulation against metastases in bone [1].
We developed a computational model of load-induced bone remodelling in the context of cancerous metastases, in order to screen for loading regimens with potential therapeutic benefits.

Methods

A hybrid cellular automaton (HCA) framework was implemented in FEniCSx. Cellular events (proliferation, differentiation, migration) were modelled using a cellular automaton on a regular 3D grid of 10 micrometer resolution. In parallel, a partial differential equation (PDE) problem was defined to solve for the local mechanical environment in response to external loading, based on a variational formulation of the equilibrium, constitutive, and stress-displacements equations. Another PDE problem was defined to represent the diffusion of osteoprotegerin (OPG), receptor activator of NF- kB ligand (RANKL), and parathyroid hormone-related protein (PTHrP) signals. The PDEs were solved using Finite Element solvers on linear elements with a mesh resolution of around 5 micrometers. Osteogenic cell secretion of OPG increased in response to increased strain, and decreased in response to PTHrP signals.
As a proof-of-concept, this model was tested for a sample of 20*20*20 cellular automaton grid, taken to represent an in-vitro experiment wherein cells would be seeded in a gel-type 3D carrier with no extra-cellular matrix (ECM) initially present. A 30% density of healthy cells was considered. Three scenarios were tested and compared: **Healthy bone** (only healthy cells were seeded), **Metastatic bone** (cancer cells were also seeded at a 20% density), and **Loaded metastatic bone** (cancer cells were seeded at 20% density and sideway loading was applied to the carrier).

Results

The concentration of osteogenic signal (relative concentration of OPG versus RANKL) dropped in the presence of cancer cells (Fig. 1). The signal was partially restored when loading was applied to the healthy + cancer cell co-culture. Mirroring these observations, the level of ECM deposition in the presence of cancer cells was lower than in a healthy culture. The level of ECM deposition in the metastatic culture was substantially increased when loading was applied. These qualitative predictions are consistent with the general observations reported in experimental BMs studies involving mechanical stimulation [1,2].

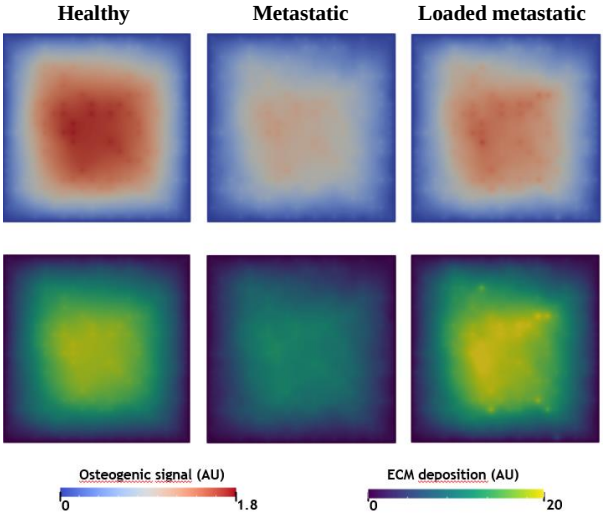

Figure 1: 2D slices of the model showing osteogenic signal shortly after loading (top) and ECM deposition after several cycles of loading (bottom).

Discussion & Conclusions

We have developed an HCA framework to facilitate investigations into the development of bone metastases and the influence of mechanical stimulation. In-vitro protocols are being developed to validate it. The validated model will be used to identify potential therapeutic regimens of loading.

References

1. Lynch et al., 2013. Journal of Bone and Mineral Research, 28(11), pp.2357-2367.
2. Yao et al., 2020. Bone research 8.1,1-11

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