Project title:MULTISCALE MODELING OF BONE ENVIRONMENT RESPONSES TO METASTATIC PROSTATE CANCER
PIs: David Basanta and Conor Lynch

Drs. Basanta and Lynch have been members of the consortium for over 2 years. Our project aims to develop a multiscale model of prostate cancer to bone metastases. This application will generate two powerful multiscale computational models integrating data from the molecular and cellular scales to predict curative strategies for the eradication of bone metastatic prostate cancer. Our work also aims to understand how multiscale modeling can be applied to the understanding of macrophage-led bone injury repair.

Dr. Basanta is part of the leadership of the PDE outreach working group.

Model credibility plan and reusability updates:

A. Sharing methods: papers.
   We are currently finalising the first manuscript based on our multiscale work trying to elucidate the role of macrophages in bone health and injury repair. The model will allow us to capture the complexity of the bone ecosystem at the cellular and molecular levels and will help us investigate how metastatic prostate cancer cells can leverage interactions with this ecosystem to establish themselves. As usual we plan to make our manuscript available in a pre-print server while our paper is under consideration by a journal.
B. Reproducibility: sharing methods and code.
   As we have done previously, we will make our code available in github. In the meantime we have shared our research both internally (several seminars at Moffitt), Nationally and Internationally (last time in the context of the Society for Mathematical Biology in Sydney in July 2018). We have also used online tools like twitter and Basanta's own website (www.cancerevo.org) to share updates of our progress.

C. Outreach
   We understand the importance of showcasing our work through outreach which is why the contact PI, Basanta, is part of the PDE outreach working group and why so much of our work is presented to both scientists in lay people through tools like twitter and blog posts.

1. Defining the context.
   As defined in the specific aims of our project, we are currently developing multiscale mathematical and computational models of bone that integrate cellular and molecular scales. The aim is to elucidate the bone biology, the ecology of metastatic prostate cancer and design new treatment options for bone metastatic prostate cancer patients.

2. Using appropriate data

The close collaboration between the Lynch lab and the CancerEvo group means that in vivo experiments are designed to parameterize and validate the mathematical models and that mathematical models are used to guide experimental work. For example, we have been using flow cytometry to mathematically test a number of biological hypothesis in regards to the role of macrophages in bone homeostasis. The data allowed us to select the right mathematical model which in turn suggested how different drugs could impact the role of macrophages in bone injury and homeostasis which are now being validated in vivo. A similar approach is now being used to explore the role of MSCs in the context of the bone ecology and cancer.

3. Evaluating the context.
   As it is to be expected, we have tested our models and challenged them against in vivo data from a pre-clinical model. For the agent-based models, graphic files are generated each time step showing the spatial distribution of relevant cell types and the microenvironment, and checked for consistency. The ODE models generate plots that can be readily contrasted to the experimental data. We also carry sensitivity analyses of the models.

4. Limitations.
   As expected in a mathematical model, we have simplified the biology and made assumptions with regards to the cellular types and signals that drive prostate cancer to bone metastases. Our framework is flexible enough that would allow for some of those assumptions to be relaxed and extended if necessary. We have also used pre-clinical models for parameterization and validation. Those provide rich amounts of data but are removed from the patient data that would be ideal for a model like this.

5. Version control.
   We have started using github for the agent-based models implemented in Java but have not yet started with the ODE models in Matlab.

6. Documentation.
   At the moment the documentation is limited to the methods and supplements of the manuscript we are working on.

7. Dissemination
   We have attended cancer biology, mathematical modeling and evolutionary meetings to disseminate the work our group has performed. We have also used our own websites and social media to spread our work beyond the usual academic circles.

8. Independent reviews.
   Basanta's department at Moffitt, the Integrated Mathematical Oncology department, is one of the first and the largest mathematical modeling department in a cancer center. We present our work regularly within the department and readily take the feedback we

get from physicists, mathematicians and ecologists. We also have presented our work to cancer biologists and physicians at Moffitt to get their feedback.

9. Testing.
   We have used both agent-based and ODE models to approach the same biological questions. We have also contraste on and off lattice versions of the same agent-based model to ensure that the results we get are not an artifact of the specific multiscale approach being used. Also we have challenged our models with experimental data to ensure that they capture the biological processes whose elucidation we aim to utilize for clinical use.

10. Standards.
    Both the biological data and the mathematical tools used (Java, Matlab, ImageJ, etc) are based on known standards. Whenever possible we use open source tools with the aim to ensure that our work can be used by as wide as possible an audience of researchers.