Mathematical Descriptions of Bone Remodeling Dynamics in Myeloma Bone Disease

Bruce P. Ayati

Department of Mathematics and Program in Applied and Computational Mathematics

University of Iowa

Presented at the 13th International Myeloma Workshop

Carrousel du Louvre, Paris, France

May 3, 2011

The University of Iowa

Conflicts of Interest

I have no conflicts of interest.

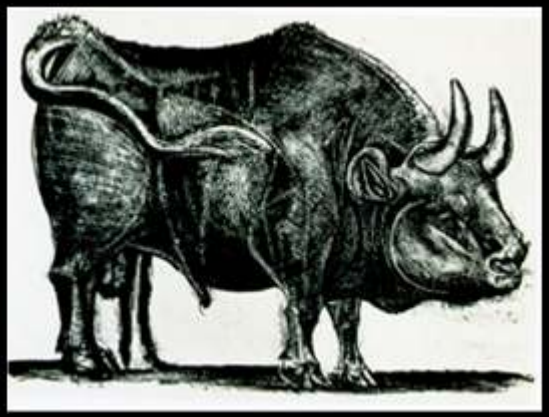
The University of Iowa

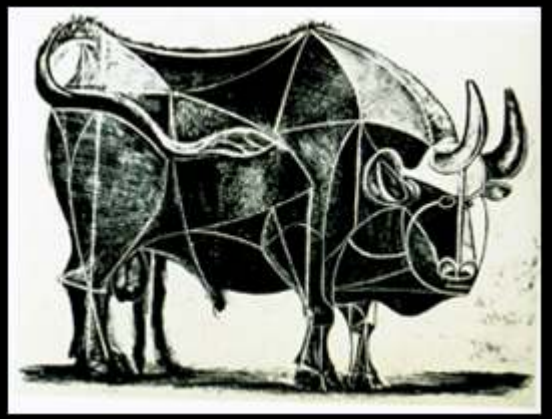
Value of a Mathematical Model

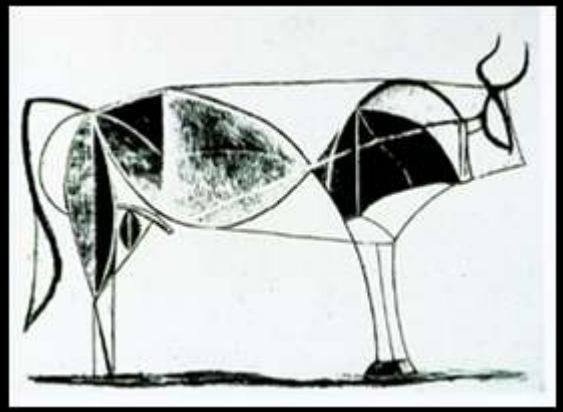
- Basic science:
  - ✧Link mechanisms to phenomena
  - ✧Generate hypotheses
- Rapid initial screening of drugs and therapies
- Predictive models facilitate patient specific medicine

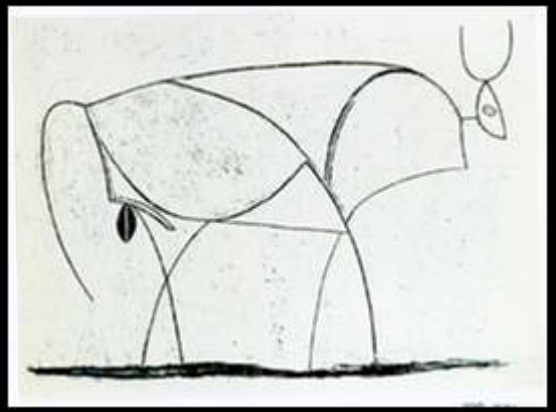
Level of Abstraction

Picasso's Bulls









THE UNIVERSITY OF IOWA

Nature of Abstraction

Georges Braque, Woman with a Guitar, 1913. Musée National d'Art Moderne

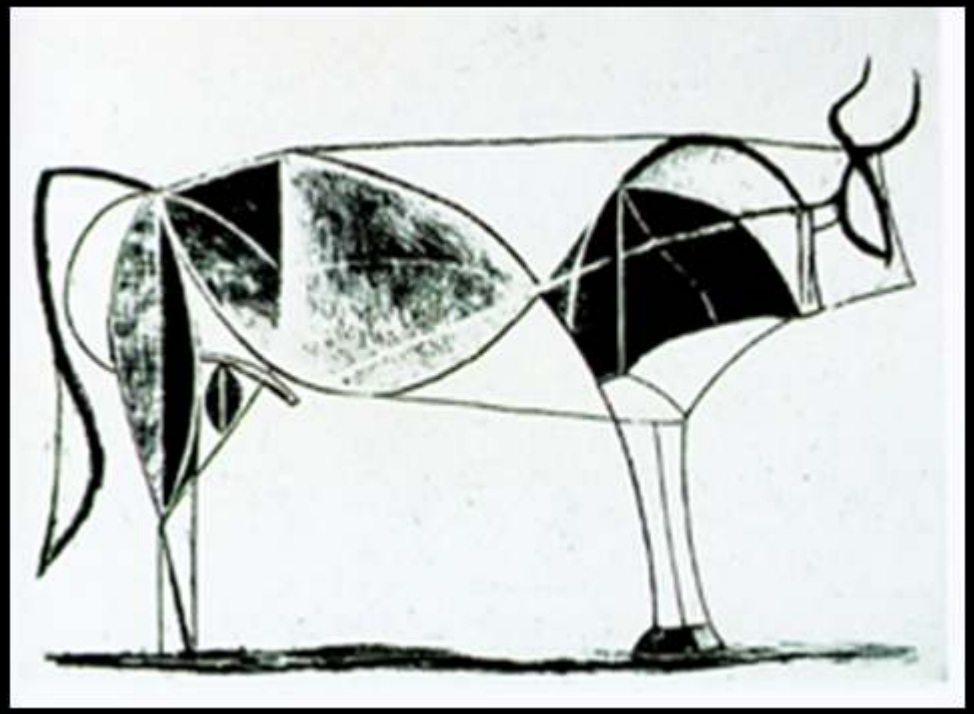
Abstraction in a mathematical model:

- Emphasize important relationships
- Represent things by what they do more than what they are

The University of Iowa

Non-Spatial Model

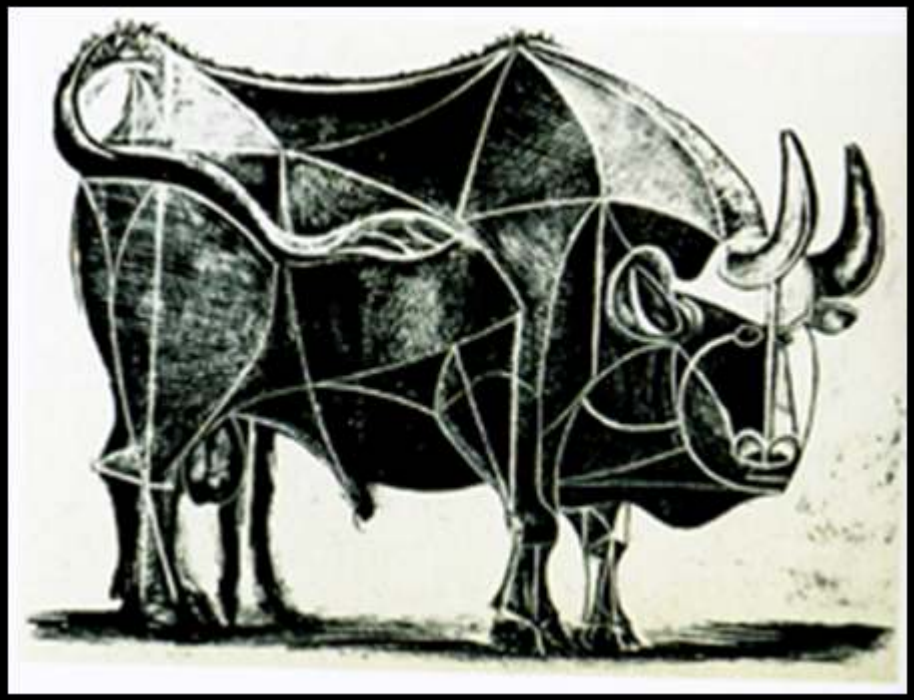
- Our representation of normal bone remodeling dynamics is taken from Komarova et al. 2003
- Power laws in the equations for cell types implicitly capture the cell signaling.



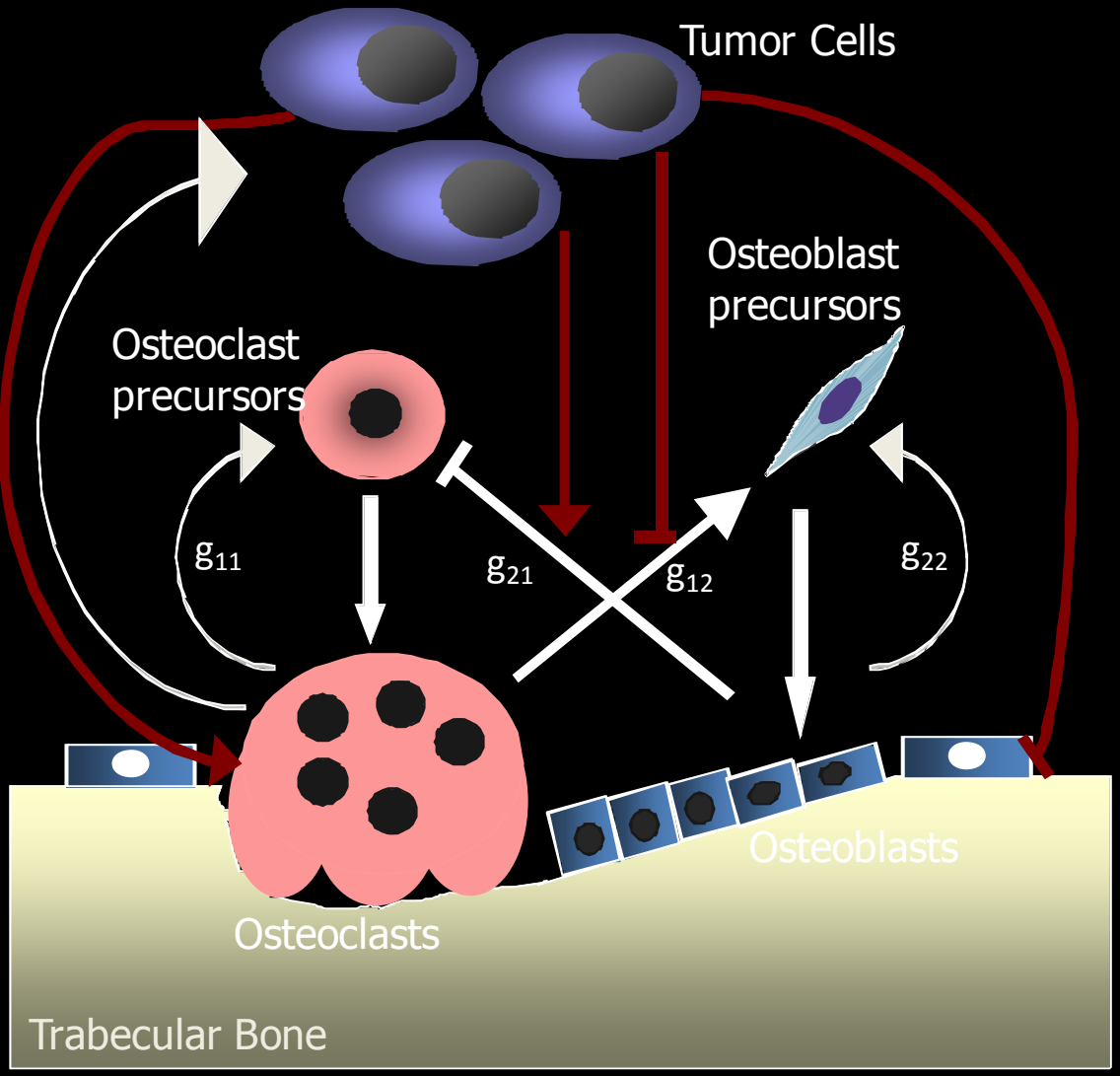
The University of Iowa

Non-Spatial Model

- A model with explicit compartments for the signaling molecules is given by Pivonka et al. 2008
- An approach of this type could form the basis of a more mechanistic model



Non-Spatial Model



THE UNIVERSITY OF IOWA

Model Equations

- We modify the Komarova power laws to incorporate the impact of myeloma cells on bone remodeling

- We add an equation for growth of myeloma cells which can include the effects of a proteasome inhibitor:

  - direct anti-myeloma effects and direct stimulation of osteoblast differentiation

Model Equations

$$\frac{d}{dt}C(t) = \alpha_1 C(t)^{g11(1+r_{11}\frac{T(t)}{L_T})} B(t)^{g21(1+r_{21}\frac{T(t)}{L_T})}$$
$$- \beta_1 C(t),$$
$$\frac{d}{dt}B(t) = \alpha_2 C(t)^{g12/(1+r_{12}\frac{T(t)}{L_T})} B(t)^{g22-r_{22}\frac{T(t)}{L_T}}$$
$$- (\beta_2 - V_1(t))B(t),$$
$$\frac{d}{dt}T(t) = (\gamma_T - V_2(t))T(t)\ \log\left(\frac{L_T}{T(t)}\right).$$

Ayati, Edwards, Webb, Wikswo, Biology Direct 2010

Model Results

The model was found to reflect accurately the basics of myeloma bone disease

- tumor burden is decreased and bone volume or markers of bone formation are increased in response to proteasome inhibitor

Spatial model

Current work: embedding the models for local interactions into a spatial model that reflects what are seen in sections of bone marrow biopsy

- 2D level-set formulation with normal bone remodeling is complete (Graham, Ayati, Ramakrishnan, Martin, submitted)
- Need refinement and parameterization of the local dynamics and extension to 3D

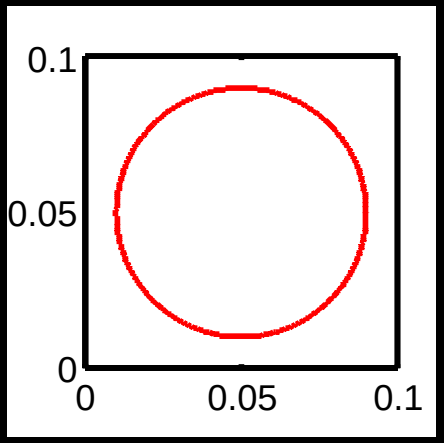
The University of Iowa

Spatial model
(proof of concept)

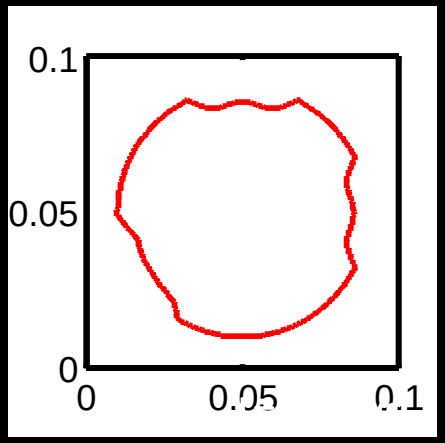
- We use a level set to define regions of bone and marrow.
- The interface moves according to the local dynamics of the interacting cell types (no-myeloma case), which are also simulated.
- A circular geometry is chosen for illustrative purposes and simplicity.

THE UNIVERSITY OF IOWA

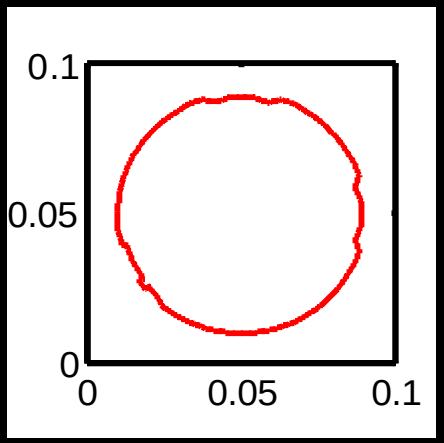
Spatial model
(proof of concept)



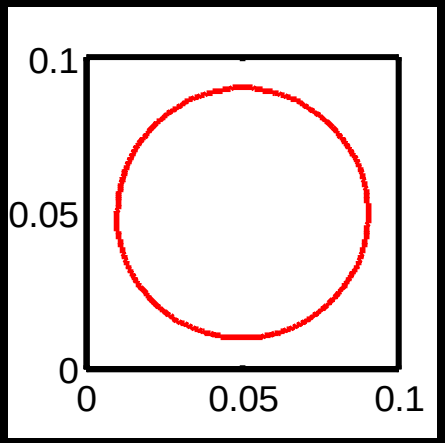
t=0 days



t=20 days



t=30 days



t=150 days

Snapshots during remodeling of a circular section of trabecular bone at three remodeling sites.

THE UNIVERSITY OF IOWA

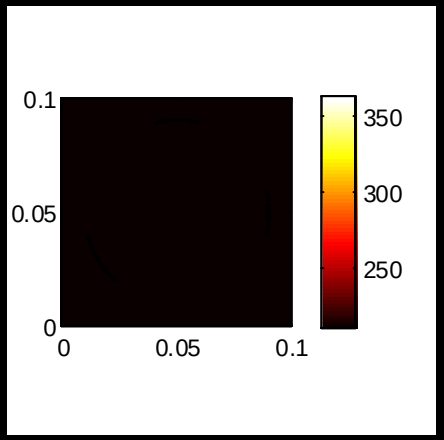
Spatial model
(proof of concept)

- In addition to the bone/marrow interface, we compute the densities of osteoclasts and osteoblasts (and in other simulations the explicit concentrations of RANKL and OPG concentrations).

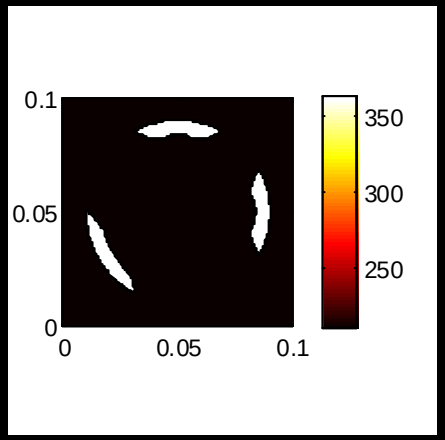
- The local Ob/Oc interactions are what actually drive the bone/marrow interface dynamics in our simulation.

THE UNIVERSITY OF IOWA

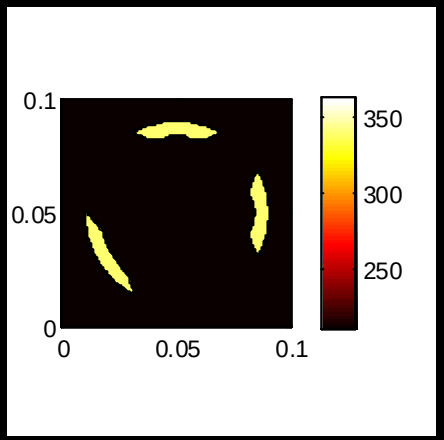
Spatial model
(proof of concept)



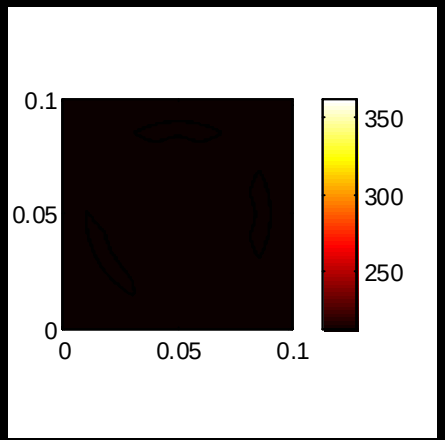
t=0 days



t=20 days



t=30 days



t=150 days

Snapshots during remodeling of osteoblast densities at three remodeling sites.

THE UNIVERSITY OF IOWA

Spatial Model

(Extension)

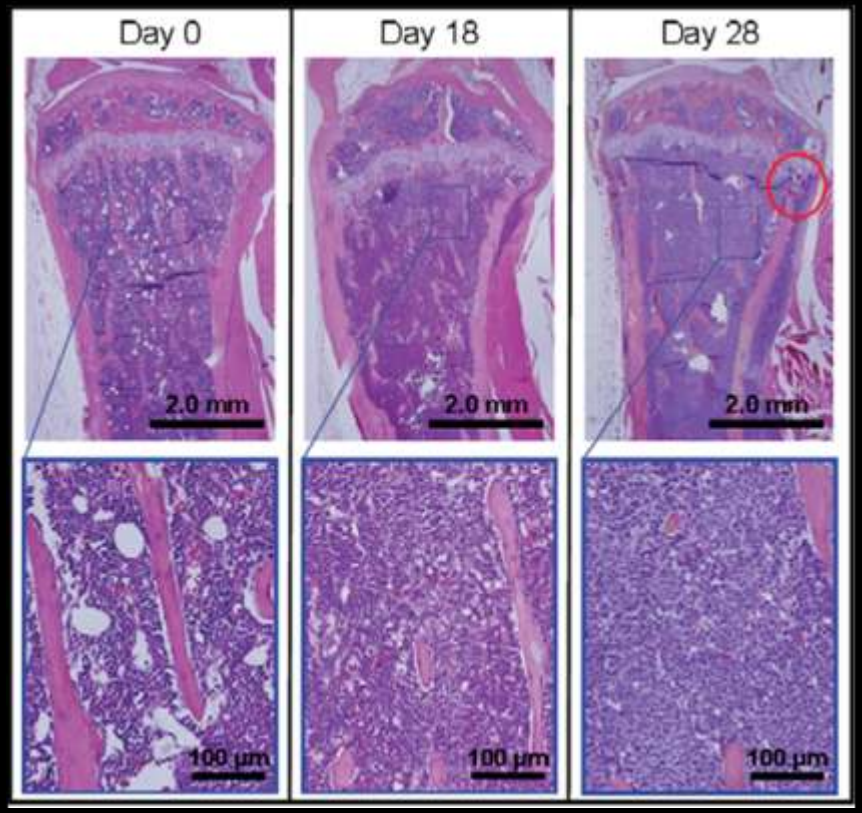


Figure courtesy of C. Edwards

The level set method is designed for much more complicated geometries.

Framework extends naturally to these geometries at a range of spatial scales

Thanks

- My graduate student Jason Graham
- Claire Edwards, Glenn Webb and John Wikswo at Vanderbilt University
- The Vanderbilt Integrative Cancer Biology Center (VICBC)
- Jim Martin and Prem Ramakrishnan at University of Iowa Orthopaedics and Rehabilitation
- Régis Bataille and the organizers of the 13th IMW for their kind invitation to speak

The University of Iowa