Bone metastasis is the spread of cancer cells from a primary tumor (e.g., prostate, breast) to the bone tissue. Clinically, it is considered incurable. Metastatic cells trigger a vicious cycle within the bone microenvironment by manipulating bone cells (osteoblasts, -clasts, -cytes) in order to sustain its invasion. Using ecological principles, we examine this complex interaction network with mathematical models. Applying optimal control theory we aim to study bone metastasis treatments. The optimal treatment is modeled to minimize side-effects and the cost.

**DENOSUMAB TREATMENT**

\[
\min J(u) = \int_0^T \left( g(x) + u^2 \right) \, dt,
\]

subject to

\[
x(t) = x_0 + \int_0^t u(s) \, ds,
\]

\[
x(0) = x_0,
\]

\[
\dot{x}(t) = f(x, u(t)),
\]

\[
0 \leq u(t) \leq B_0,
\]

\[
0 \leq \dot{u}(t) \leq B_1.
\]

**RADIATION TREATMENT**

\[
\min J(u) = \int_0^T \left( g(x) + u^2 \right) \, dt,
\]

subject to

\[
x(t) = x_0 + \int_0^t u(s) \, ds,
\]

\[
x(0) = x_0,
\]

\[
\dot{x}(t) = f(x, u(t)),
\]

\[
0 \leq u(t) \leq B_0,
\]

\[
0 \leq \dot{u}(t) \leq B_1.
\]

**POSTRYAGIN'S MAXIMUM PRINCIPLE**

Hamiltonian

\[
H(x, u, \lambda, t) = x_0 + \int_0^t u(s) \, ds + \lambda(t) \cdot \dot{x}(t),
\]

Control Characterization

\[
a^* + \frac{\partial H}{\partial u} = 0.
\]

**FORWARD-BACKWARD ALGORITHM**

1. Prepare an initial guess \( a^0 \).
2. Solve \( x^* = g(x, u), \dot{x}(x) = a \).
3. Obtain \( a^* \) in \( a^* \).
4. Solve \( x^* = f(x, u), \dot{x}(x) = a \).
5. Obtain \( a^* \) in \( a^* \).
6. Update control \( a^* \) using characterization and \( a^* = a^* \).
7. Converge?

**FUTURE WORK**

- Find a way to introduce specific, explicit cost terms (economical, side-effects).
- Analyze the case of linear controls or another types of cost functionals.
- Model other treatments used on bone metastasis disease.
- Parameter estimation/data fit and incorporate into optimal control problem.
- Combine multiple BMUs/regions and study their dynamics under treatments.
- Apply optimal control framework for Lemaire-type models.
- Propose a spatial model for BMU-metastasis interactions + treatments.

**REFERENCES**
