Bone Remodelling is a biological process that occurs in every living being that is skeleton-enabled. Such a process consists of the continuous substitution of old bone with new bone which guarantees that mechanical properties of the bone are maintained. The process follows a strictly sequence of phases in which different cellular actors, coming from the mellow bone, interact with the mineralized bone.

These phases are:

- **Resorption**: mineralized bone is dig out by particular cells called Osteoclast. Digging the bone, Osteoclast dissolve bone creating a cavity (called a resorption pit).
- **Reversal**: precursors of Osteoblasts, responsible for bone formation, starts to appear on the resorption pit.
- **Resting**: mature Osteoblasts starts to form new soft non-mineralized bone until the bone is completely reconstructed. This new bone will slowly mineralize.

In an healthy individual remodelling does not alter the global morphology/mass of the bone; on the contrary, in presence of Osteoporosis, Diabetes or other diseases, bone equilibrium lacks with high impact on the organism. A better understanding of this biological process and of how healthy (and non-healthy) conditions affects it, has social and clinical relevance. Unfortunately such phenomenon is difficult to study (test animals must be killed to execute ex vivo analysis) thus a simulated approach can turn out to be a key choice to understand its relevant aspects.

### Multiscale modelling approach

Most biological phenomena are inherently multiscale, i.e. they are characterised by interactions involving different scales at the same time. This is the case of bone remodelling, where macroscopic behaviours, such as mechanical stimuli, and microstructure (cell scale) such as hormones, strongly influence each other. Several approaches have been defined to model such a process, at different spatial and temporal levels and mostly in terms of continuum properties, abstracting in such a away from a realistic - and more complex - cellular scenario.

The organ level has been widely investigated in the past. The knowledge of the following two levels, on which we focus, is more scarce and need to be expanded with both qualitative and quantitative information.

- **Tissue level** that can be seen as a fixed 3D lattice where each vertex of each cube has a mineralization value (which, given a certain threshold, indicates if the cell is interested in the remodelling process).
- **Cellular level** that can be distinguished into two sides: the mineralized side and the fluid (mellow) side, where the main cellular actors of bone remodelling act (mainly, Osteoclast and Osteoblasts already presented above).

### BIO SHAPE - a uniform model

**BIO SHAPE**[1] is a powerful modelling and simulation tool based on a 3D approach to modelling of biological phenomena. **BIO SHAPE** is formally based on the Shape Calculus[4] a bio-inspired language that has been defined with the aim of fully describing crucial spatial aspects that characterize many (but not limited to) biological systems. In **BIO SHAPE** every actor of the simulation is defined by the means of 3D shapes moving/colliding and reacting in the simulated environment. Such an approach proven to be *scale-independent* as every resolution level can be modelled in terms of 3D (colliding) shapes; it also demonstrated to be *information lose-less* since passages from a scale level to another is reduced to a mapping between different granularity instances of the same (shape based) model. We exploited the **BIO SHAPE** model to simulate the bone remodelling process.

Bone tissue[2] level is represented as cube shapes (in concordance with the 3D lattice described above) holding a mineralization level. The surface cubes can be deformed in a finite number of pieces to represent any linear cut of the surface (picture represents them in 2D).

Bone cellular level[2] is represented in terms of the so called BMU (Bone Multicellular Unit). In a BMU the mineralized bone surface meet the bone fluid section. The BMU contains all the cellular actors of the bone remodelling process, mainly Osteoclast and Osteoblasts (and their precursors), RANK-L, OPG, and Osteocyte (mineralized or not, possibly containing an Osteocyte) and so on.

The two models are easily coupled. At every simulation cycle activated shapes for remodelling (randomly chosen or determined by models of forces) are simulated at the cellular level with the systemic factors personalised for that shape; the new value for the density is passed to the tissue model that updates the border surfaces of the remodelled shape (shape updating); the tissue model is re-applied to the new data to determine how the changes of density modified the effect of mechanical stimuli.

### Meshless Cells Method - not uniform models

**MCM** is a mathematical model based on the 3D lattice defined on the tissue level; it takes as *input* an external field of forces applied to the bone and the degree of mineralisation of the lattice and gives as *output* the deformation of the bone and possible damages that might occur (micro-fractures and fractures).

It is coupled with a cell-level *ODE-based model* that, given the mechanical forces applied to the bone (derived from the tissue model) and considering internal systemic factors (number of Osteoblasts/Osteoclast and other biological parameters), calculates the average density of mineralization of a given 3D cell of the lattice at the tissue level.

Currently, our group is developing a scalable approach to the coupling of the two model. In particular, we are exploiting *CUDA* (CUDA Graphics Processing Units (GPUs)) to resolve all the ODE computations.

The current code works as reported in the picture. MCM runs on a client machine where a piece of code, called Generation Manager, individuates the eligible cells for remodelling. Once selected, it sends (2) them to a CUDA-enabled machine via a TCP-IP connection. The CUDA machine (3-4) executes the complex ODE calculations and sends back the processed cells (5). At the end the Generation Manager reads the new data that are, then, made available to MCM (6).

### Conclusions

The bone remodelling phenomenon has a relevant clinical importance. Knowledge about the details of this process can help in improving clinical treatments of diseases related to bone physiology. With our work we aim to highlight its quantitative (and qualitative) aspects exploiting different simulation approaches.

Currently we are exploiting other approaches for the study of the phenomenon such as Cellular Automata[3] and membrane computing. In the near future, we aim to improve both simulators, refining the **BIO SHAPE** model and then *integrating* it into MCM cell level to improve its simulation faithfulness.

We thank Marco Vicente and his group at Rizzoli Orthopaedic Institute - Bologna, whose suggestions and discussions have had a lot of influence on this work. This work was partially supported by the Italian FIRB-MIUR LITBIO: Laboratory for Interdisciplinary Technologies in Bioinformatics. F. Buti, D. R. Cacciglione, F. Corradini, E. Merelli, L. Tesei BoneRemodelling: a spatial shape-based scale-independent simulation environment for biological systems. Simulation of Multiphysics Multiscale Systems, ICCS 2010. Procedia Comp. Sci. To appear., 2010.
