# Space, Geometry, Motion and Interactions in Modeling Biological Systems: the BIOSHAPE Approach

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# Outline



# Motivation

- In **Algorithmic** (Computational) Systems Biology we want to use the computer science approach of modeling (originally) software systems on biological systems
- Space, in particular 3D space, plays a fundamental role in the real systems (the ones to model)
- The geometrical shape of a biological object often determines its functionality

# Motivation

## Within Computational Systems Biology

- Designing "in-silico" experiments (sets of simulations)
- Exploring known and unknown biological interactions
- Modeling different **scales**: molecules, cells, tissue, organ

## Virtual Physiological Human

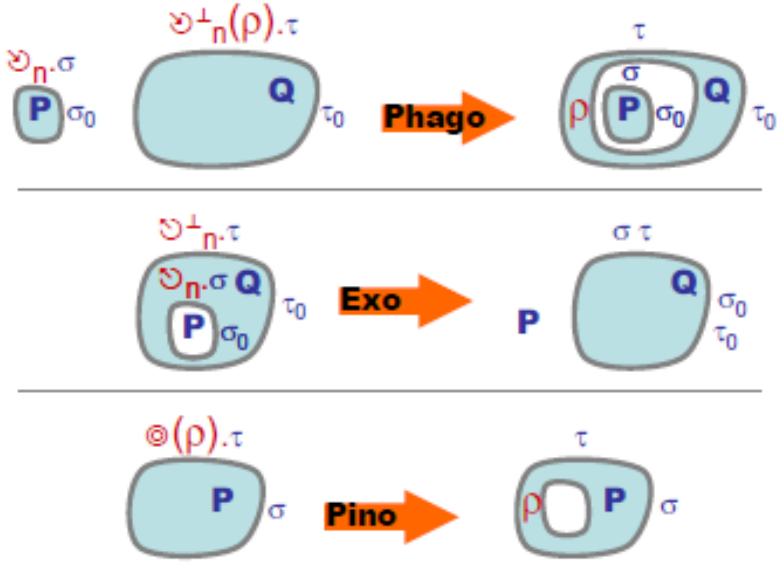
- Having a digital self, with personalized parameters
- Pre-test of drugs or therapies on the virtual self

## Nanotechnology

- Molecular self-assembly
- Molecular recognition

# Topological approaches

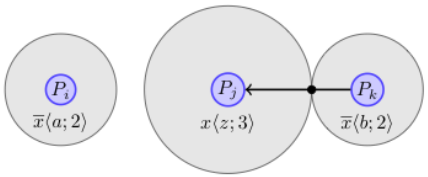
Describe space as a set of hierarchical and communicating well-stirred compartments: BioAmbients (Regev et al. 2004), Brane Calculi (Cardelli 2005), Membrane Computing (Paun 2000), etc . . .




http://lucacardelli.name/

# Sphere based approach

Entities are modeled as spheres in space: Spatial CLS (Barbuti et al. 2009), SpacePI (John et al. 2008), etc . . .




SpacePI: Spatial extension of $\pi$ calculus

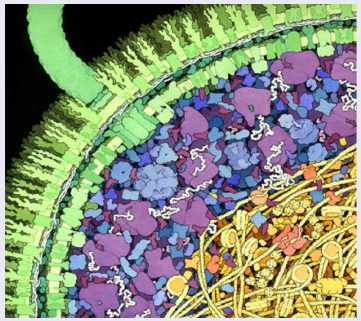
**Shape is not considered**

The shape of a biological entity plays a very important role in his interaction

# Our Approach: Space, Motion and Shape

## Space/Motion

- The exact positions and velocities of all biological entities are known



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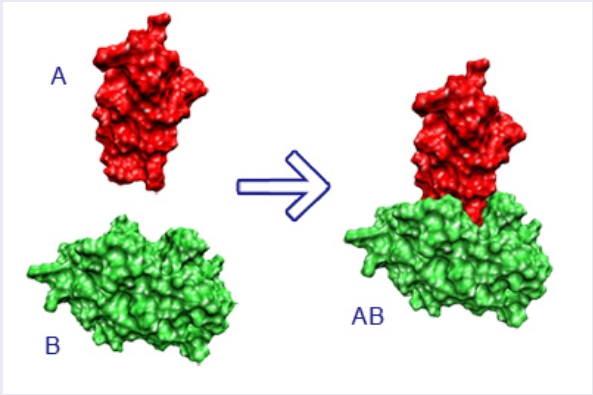
## Shape and communication

- Contacts (collisions) and shapes transformation determines biomolecular interactions



# Our Approach: twofold

## Shape Calculus

- Formal calculus for describing processes that are the shaped biological entities
- Language of specification: CCS-like
- Semantics of the evolution of a network of processes given by SOS-rules

## BIOSHAPE simulation environment

- Distributed environment for simulation of a given biological scenario
- Language of specification: (Java/C++) coding
- Stub of all entities and simulation features of shapes, motion and collision detection embedded

# Synergy between Simulation and Verification

Using the same system model (possibly at different levels of abstraction)

## By simulation

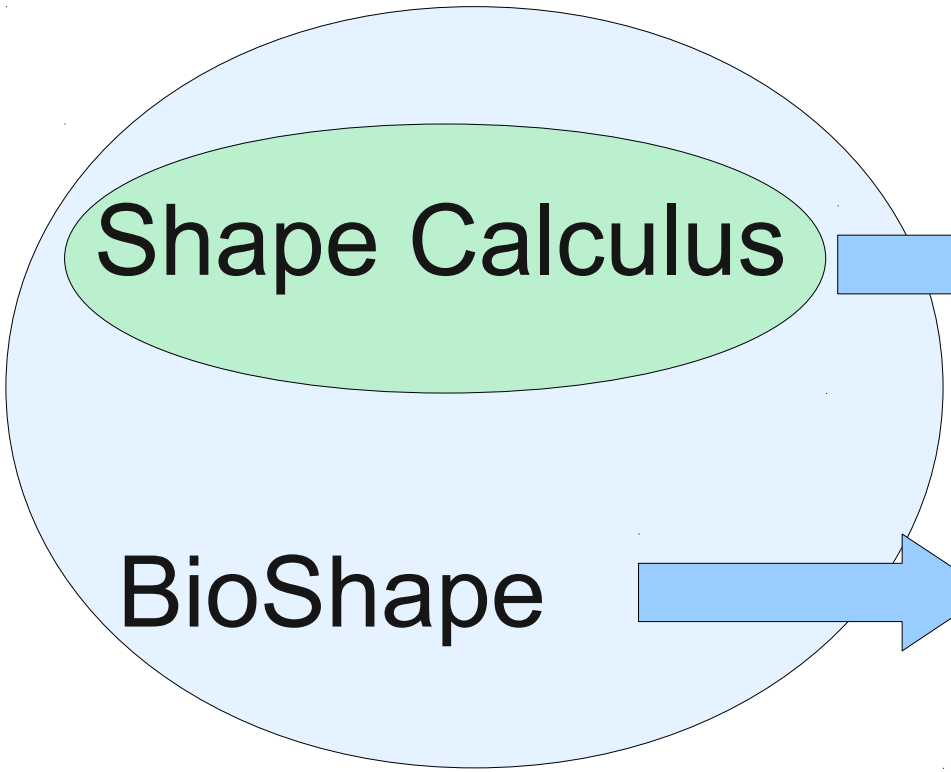
- Model validation and refinement by aggregation of simulation results
- Hypothesis testing rejecting unlikely scenarios
- Estimation of one or more parameters by fitting known aggregated data, e.g. concentrations, trends, rates, etc . . .
- Gain new biological information by perturbing a validated model, e.g. useful in drug design
- **Quantitative** information can be obtained natively, by tracking an counting

# Synergy between Simulation and Verification

## By Verification

- Sanity checks of the model using known biological properties, by model-checking or equivalence checking
- Computation of **quantitative** information if the model is quantitative, e.g. by diagnostic information of model-checking
- Gain information derivable form the model, e.g. by numerically computing the probability of a scenario if the model is probabilistic

# Shape Calculus vs BioShape




Model checking / Numerical Computation

Simulation Environment / In-silico experiment Desk

# Synergy between Biomedical Research and Our Approach

- Spatial/Shaped simulation/verification **is not** intended to replace other consolidated simulation methods and tool
- It gives powerful observation lenses, not always necessary
- At the moment: models at tissue/cellular levels often requires this resolution (e.g. bone remodelling)
- At the molecular level: specific cases

# Synergy between Biomedical Research and Our Approach

Molecular Level $>$ Biochemical Pathways

- Dynamic simulation: monitor, stop, add/delete molecules, continue, monitor, ...
- Well-stirredness hypothesis dropped: localization, aggregation
- Wet lab experiments design and optimization: hypothesis testing, simulate and aggregate cycle
- Gaining new information from literature/wet lab results: simulate and aggregate cycle

# Synergy between Biomedical Research and Our Approach

Molecular level $>$ Biochemical pathways $>$ Simulate and aggregate cycle, glycolysys example:
What is the number of Hexokinase molecule in a certain volume of the yeast cytoplasm?

1. Make several hypothesis on the aspect you want to analyse
2. Instrument and run simulations
3. Aggregate results and compare with **known** literature parameters
4. Fit: modify your hypothesis to better fit the known curves
5. Goto 3

# Shape calculus

## Main features:

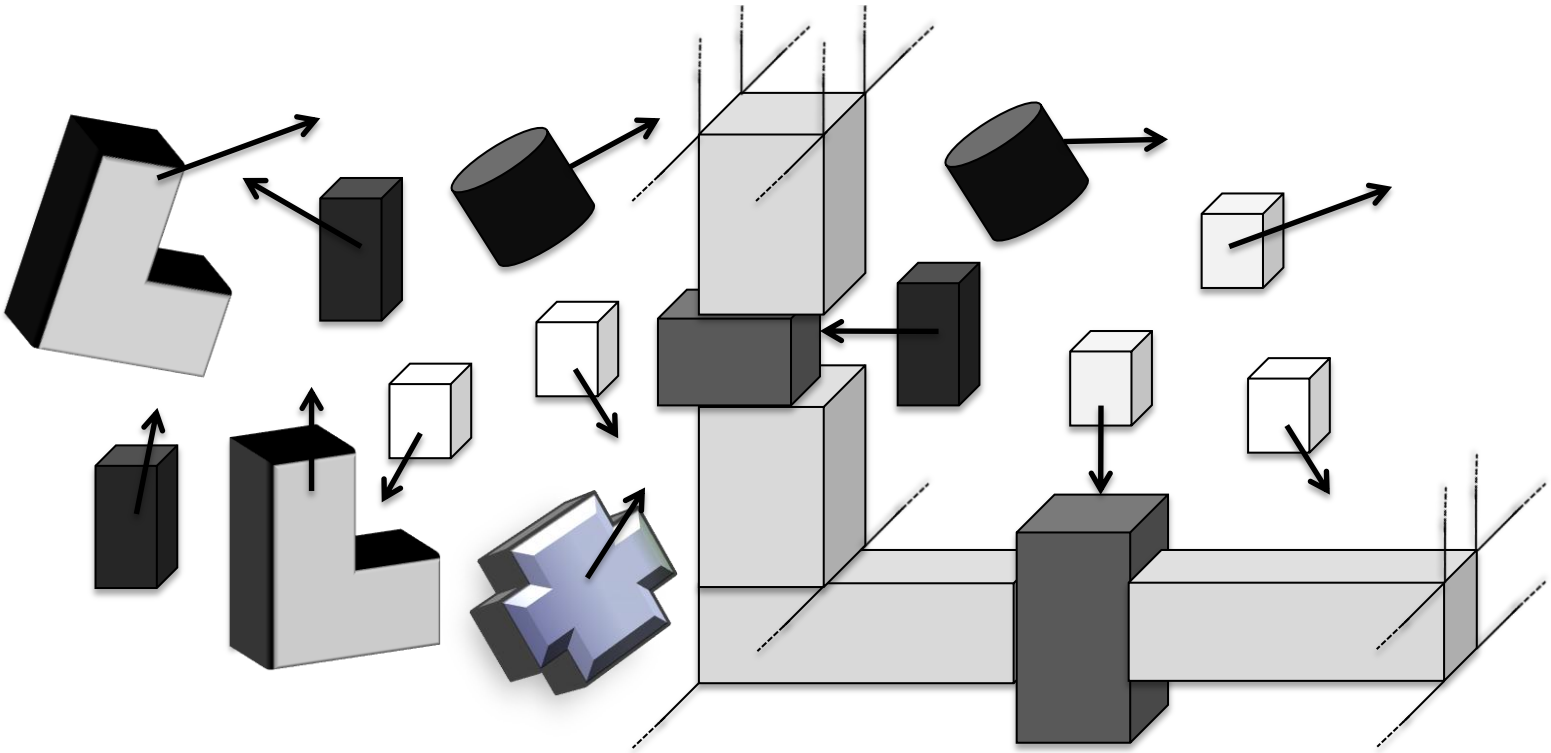
- Individual-based approach: we consider individual autonomous entities called 3D processes
- 3D processes: a 3D shape with a behavior
- A 3D process is situated in space and move accordingly to its specific motion law
- Processes can collide and possibly bind
- The binding depends on channels $\langle a, X \rangle$, $X$ is a portion of the surface of the process's shape in which the channel is "active"

# Shape calculus

## Main features:

- Compound processes can split weakly, by non-deterministically releasing a previously established bond, or “react”, by splitting strongly in as many pieces as the products of the reaction are
- If communication (i.e. binding) does not occur, the collision of two 3D processes is considered elastic, i.e. the shapes bounce and proceed independently

# A network of processes at a glance



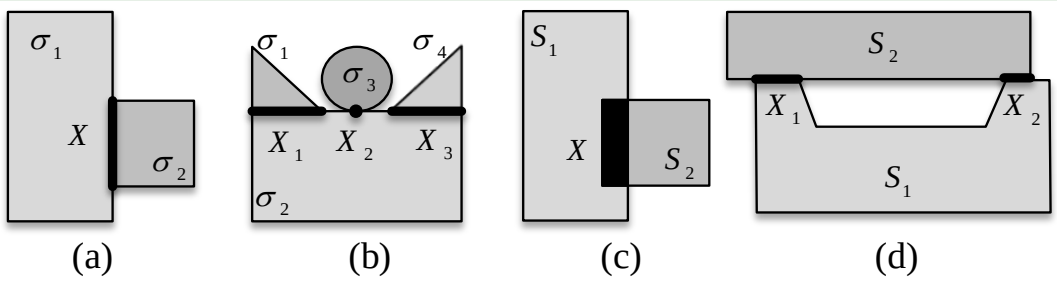
# Shapes in Shape Calculus

## Shape Syntax

Shapes can be:

- Simple: Spheres, Cylinders, Cones, Polyhedra
- Compound: Simple or Compound shapes “glued” together

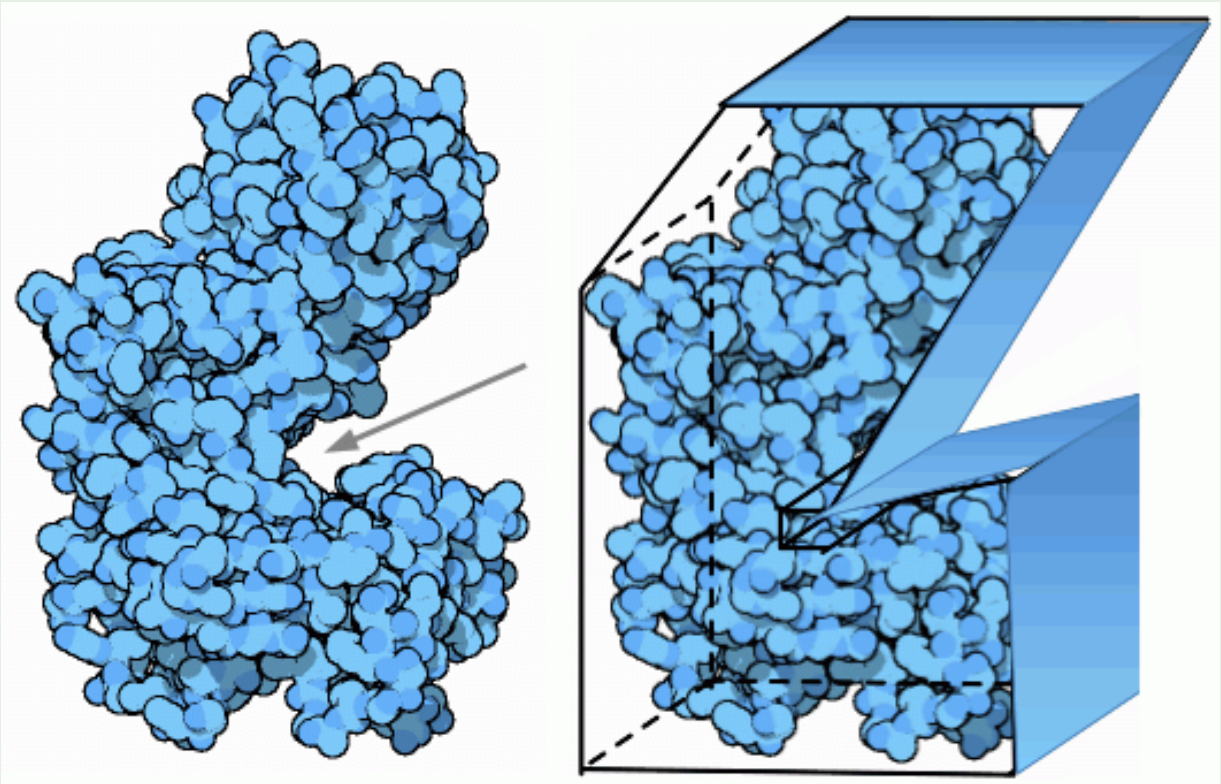
## Examples of compound shapes in 2D



# Examples

## Representation of enzymatic reaction in Shape Calculus

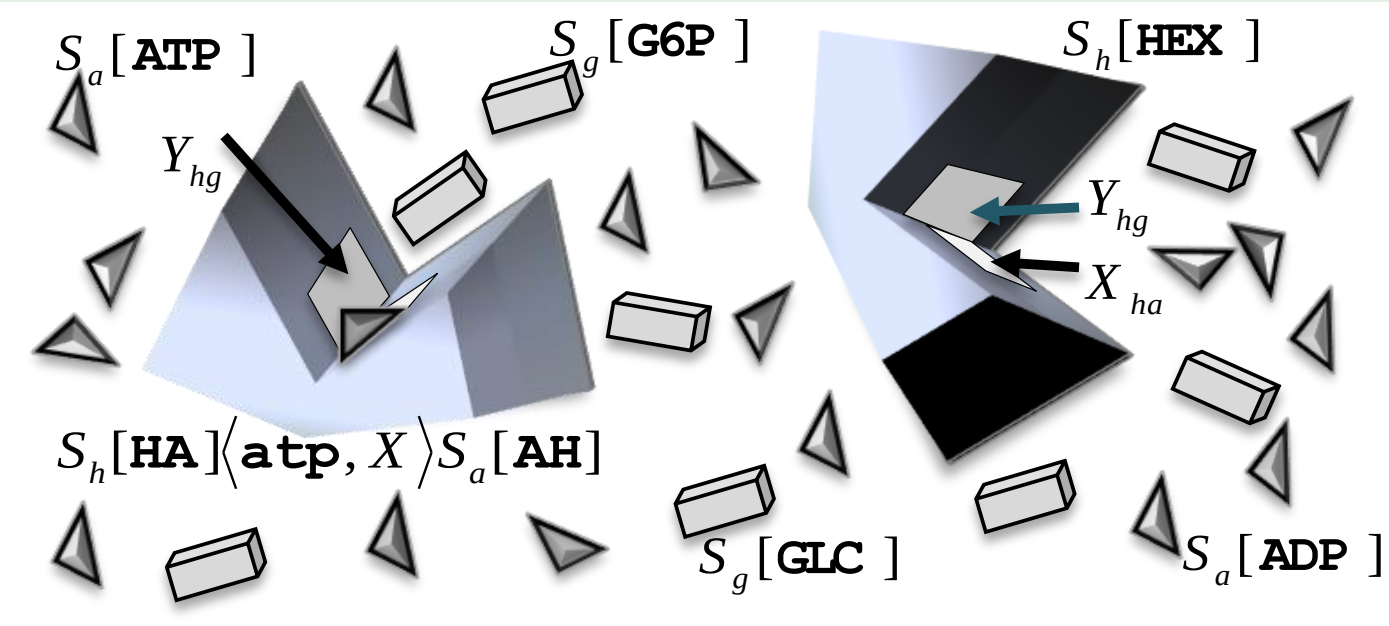
### Shape approximation



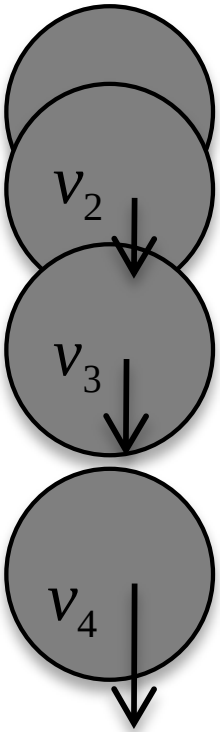
# Examples

## Representation of enzymatic reaction in Shape Calculus

### Network and binding sites



# Trajectories of Shapes




$$steer\ t_i S = [0, -\frac{1}{2} g(i+1)\Delta, 0] m/s$$

$$v_1 = steer\ t_0 S = [0, -0.245, 0] m/s$$

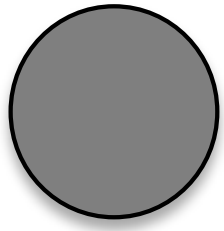
$$v_2 = steer\ t_1 S = [0, -0.49, 0] m/s$$

$$v_3 = steer\ t_2 S = [0, -0.735, 0] m/s$$

$$v_4 = steer\ t_3 S = [0, -0.98, 0] m/s$$

$$t_i = t_{i-1} + \Delta$$

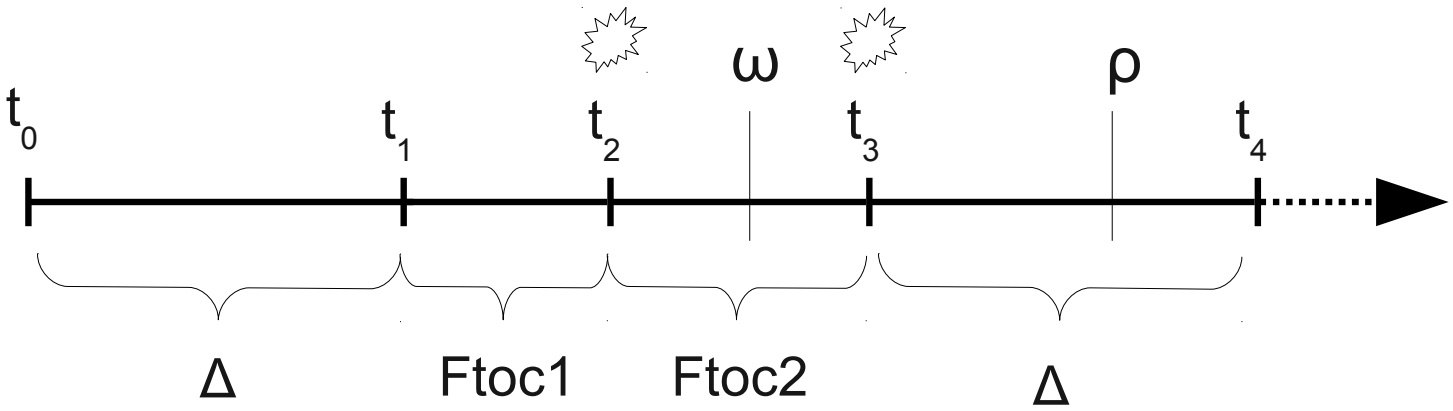
$$\Delta = 0.05s$$

$S =$ 

$$v = [v_x, v_y, v_z]$$

# Time evolution and velocity update

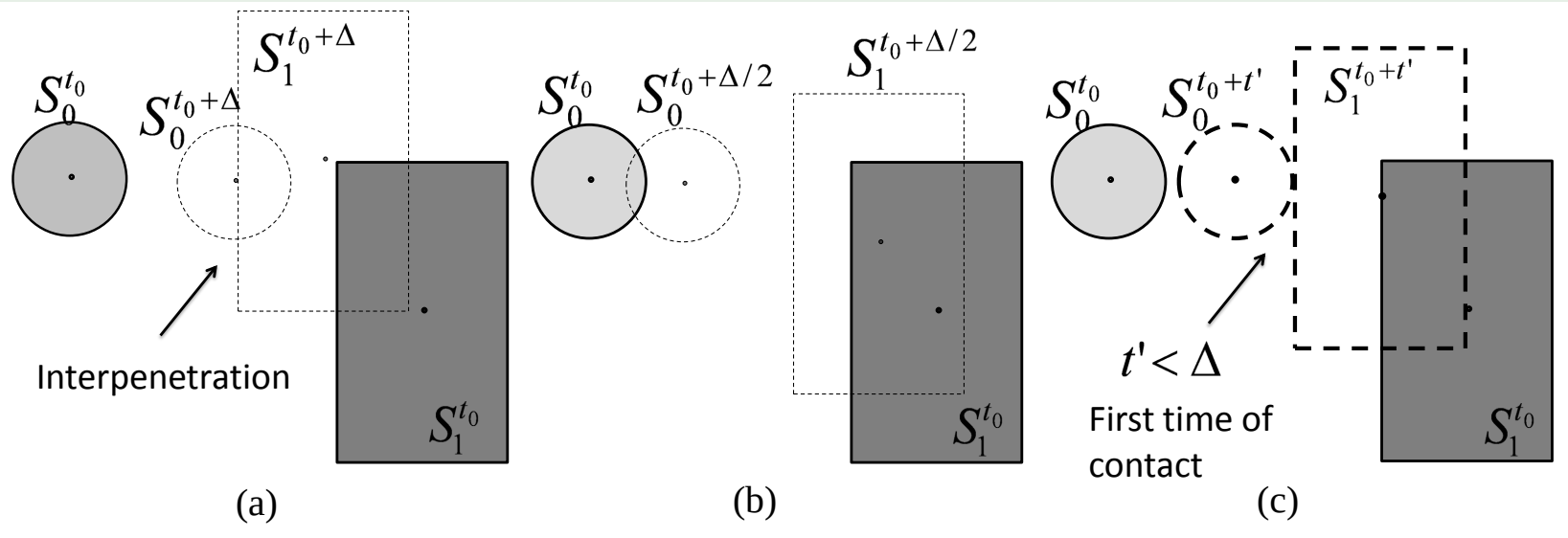
- Time domain $\mathbb{T} = \mathbb{R}_0^+$ is then divided into an infinite sequence of movement time steps $t_i$ such that $t_0 = 0$ and $t_i = t_{i-1} + \min(\Delta, \text{Ftoc})$.
- The updating of the velocities is represented by a function steer: $\mathbb{T} \to \text{Shapes} \hookrightarrow \mathbb{V}$ gives the velocity vector steer $t$ $S$ to assign to shape $S$ at time $t$



# Collision Detection

## Technology Imported from Computer Games

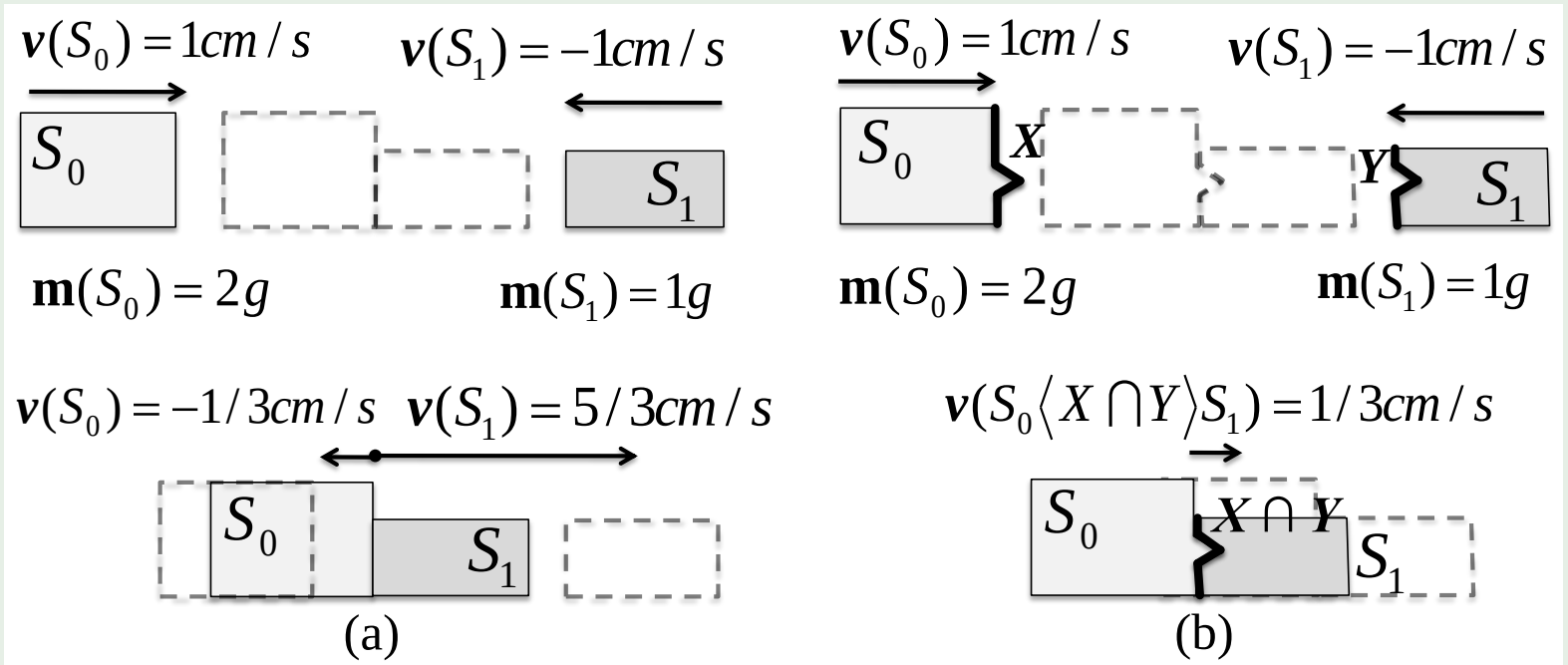
### First time of contact



# Collision Response

## Technology Imported from Computer Games

### Elastic and inelastic collision (one dimensional case)



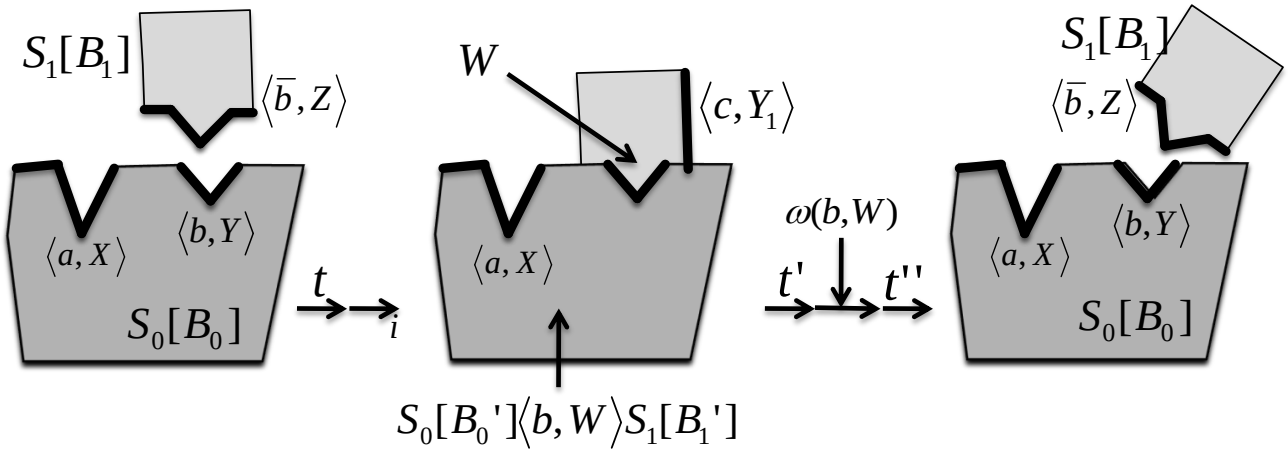
# Modeling behaviors in Shape Calculus

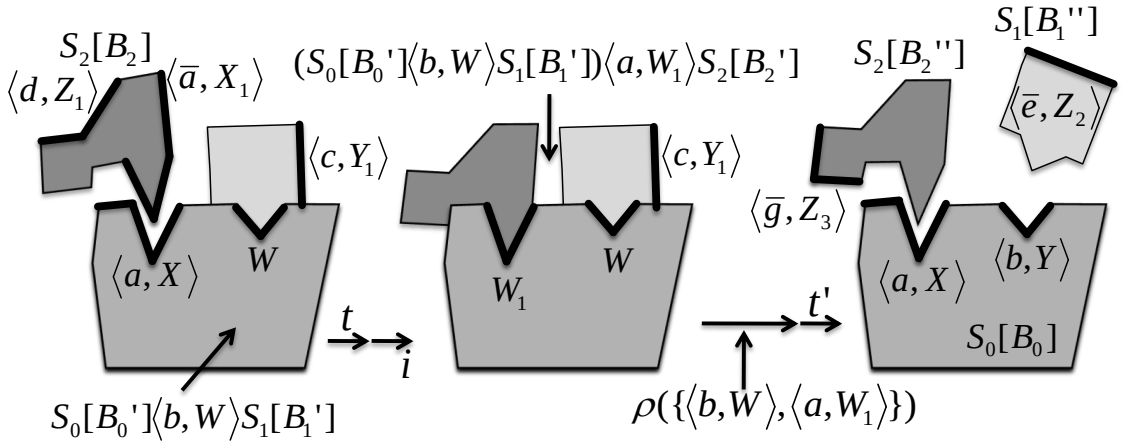
## The set $\mathbb{B}$ of *shapes' behaviors* is generated by the grammar

$$B ::= \text{nil} \mid \langle \alpha, X \rangle.B \mid \omega(\alpha, X).B \mid \rho(L).B \mid \epsilon(t).B \mid B + B \mid K$$

where $\langle \alpha, X \rangle \in \mathcal{C}$, $L$ is a non-empty subset of $\mathcal{C}$ whose channels are pairwise incompatible, $t \in \mathbb{T}$ and $K$ is a process name in $\mathcal{K}$.

# Binding and Splitting



# Modeling HEX, ATP and Glucose behaviors

$$\mathrm{HEX} = \langle \mathrm{atp}, X_{ha} \rangle.\mathrm{HA} + \langle \mathrm{glc}, X_{hg} \rangle.\mathrm{HG},$$

$$\mathrm{HA} = \omega(\mathrm{atp}, X_{ha}).\mathrm{HEX} + \epsilon(t_h).\langle \mathrm{glc}, X_{hg} \rangle.\rho(\{\langle \mathrm{atp}, X_{ha} \rangle, \langle \mathrm{glc}, Y_{hg} \rangle\}).\mathrm{HEX},$$

$$\mathrm{HG} = \omega(\mathrm{glc}, X_{hg}).\mathrm{HEX} + \epsilon(t_h).\langle \mathrm{atp}, X_{ha} \rangle.\rho(\{\langle \mathrm{atp}, X_{ha} \rangle, \langle \mathrm{glc}, Y_{hg} \rangle\}).\mathrm{HEX},$$

where $X_{ha}$, $Y_{hg}$ are the surfaces of contact.

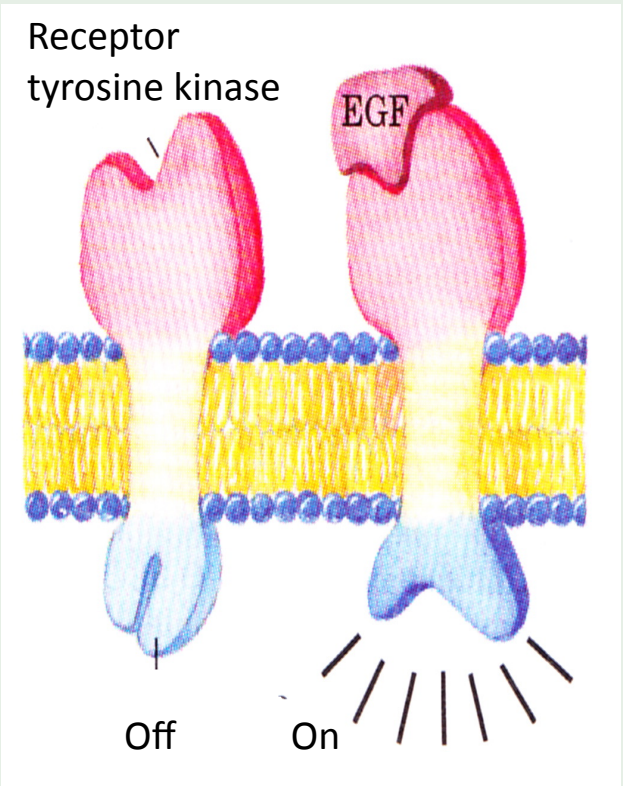
$$\mathrm{ATP} = \langle \overline{\mathrm{atp}}, X_{ah} \rangle.(\epsilon(t_a).\rho(\{\langle \overline{\mathrm{atp}}, X_{ah} \rangle\}).\mathrm{ADP} + \omega(\overline{\mathrm{atp}}, X_{ah}).\mathrm{ATP})$$

# Ongoing work on the Shape Calculus

## Work in progress

- Manage the Shape generation/transfomation
- Tayloring the Shape Calculus towards **verification** tools

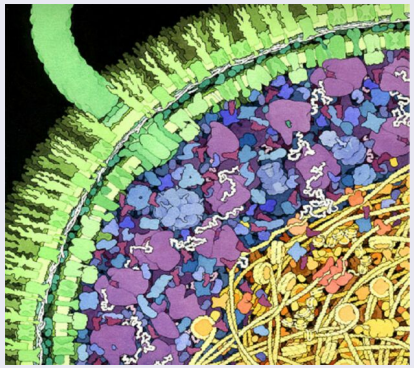
## Biosignalling by shape transformation



# BIOSHAPE: Geometrical 3D Space, Time and Shape

## Space/Time

- 3D **geometrical** space, not only logical compartments
- Exact positions and velocities of all entities are tracked



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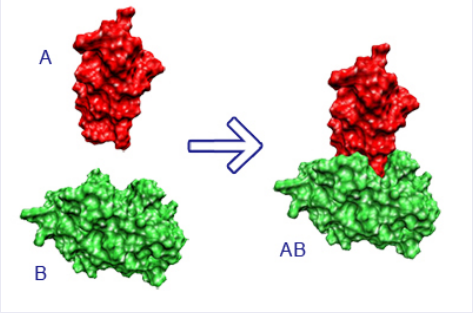
## Shape and communication

- Interactions can be collision-driven **or perception-driven**



# BIOSHAPE key concepts

- 3D space
- Geometry
- Particle-based models with shapes
- (Personalized) Movement
- Interactions, both collision-driven and perception-driven
- Multiscale feature: a level for each considered scale
- Multiscale feature: levels are related by simple spatial/shape mapping functions

# Motion of entities

- At the level of the **Shape Calculus** there is an all-knowing function that specifies movements for each shape at each time (too abstract concept)
- At the BIOSHAPE level, every entity has a strategic personalised class that implement its own motion law with its own needed parameters
- Thus, at the moment the behaviour is expressed in UML and then **coded** into the mentioned class
- Future Work: intermediate language (with spatial/values capabilities)

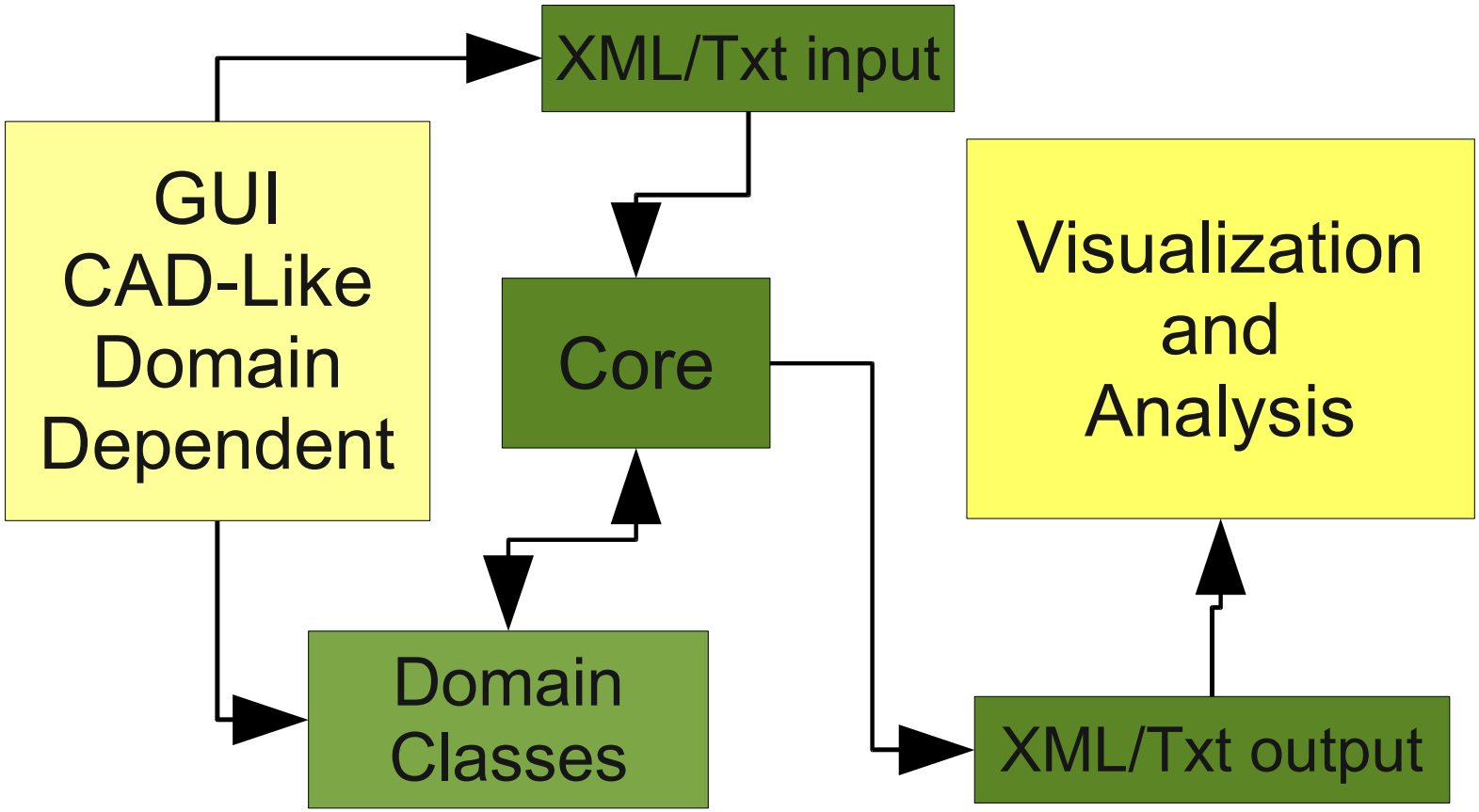
# Behaviours of entities

- A high level behaviour (only interactions) can be expressed with the **Shape Calculus**
- However, it is not sufficient for specifying all complex aspects of the entities in a real in-silico experiment
- Again, at the moment the behaviour is expressed in UML and then **coded** into the class of the entity
- Future Work: intermediate language (with probabilistic/quantitative aspects)

# Non-shaped actors of the simulator

- Concentration Grouped Entity: represents a concentration of something (of an enzyme, or an hormone, etc)
- Matrix Grouped Entity: represents a quantity of something (a molecule, a certain kind of cell) that is available in a certain position at a certain moment
- Gradient Grouped Entity: represents a field of something (electric charge, chemical attractors, ecc) at a certain moment
- Tuple Grouped Entity: represents a tuple space in which information defined in a policy is stored and read by the involved Actors
- Conservation Controller: controls that a global equilibrium is satisfied (with a given tolerance) by receiving by every involved Actor messages of changes

# BIOSHAPE general architecture: Open for Collaboration



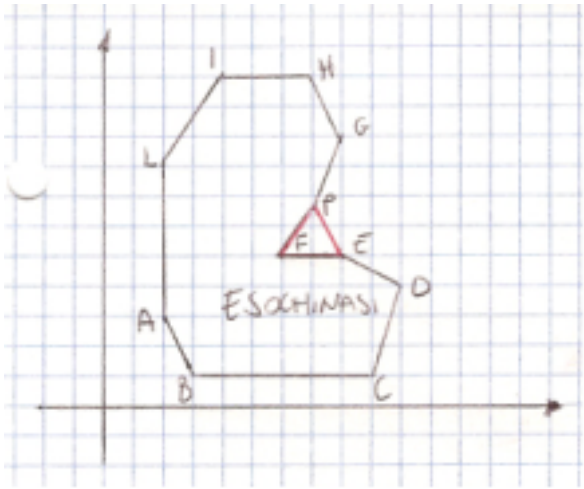
# BioShape: current status of implementation

- Core - Prototype implementation in Java (sufficient for testing non-crowded situations), version 0.95
- Prototype distribution of the computation using Agent-based Middleware - Hermes Platform developed at University of Camerino, tested on toy examples
- Currently started a porting on C++/MPI over a multiprocessor platform - Multiple Instruction Multiple Data (MIMD), version 0.3
- Input and Output managed semi-automatically

# Domain Classes

- Must be derived from classes in the core
- The user has to fill methods for:
  - Personalized Motion
  - Collision-driven Interactions
  - Non-collision-driven Interactions
  - Other operations
- Shape definition: text file or imported by specialized databases

# Shape design




HEXOKINASE SHAPE

```
atomic esochinasiPart1
a 2.0 3.0 4.0
b 3.0 1.0 4.0
c 9.0 1.0 4.0
d 10.0 4.0 4.0
e 8.0 5.0 4.0
f 6.0 5.0 4.0
aa 2.0 3.0 0.0
bb 3.0 1.0 0.0
cc 9.0 1.0 0.0
dd 10.0 4.0 0.0
ee 8.0 5.0 0.0
ff 6.0 5.0 0.0
```

```
*
f0 a aa bb b
f1 b bb cc c
f2 c cc dd d
f3 d dd ee e
f4 e ee ff f
f5 f ff aa a
f6 a b c d e f
f7 ff ee dd cc bb aa
*
```

# Input/Output

- Currently Input files are edited by hand
- Typical XML Schemas defined
- Output is textual, possibly in XML format
- Currently visualized off-line using Matlab

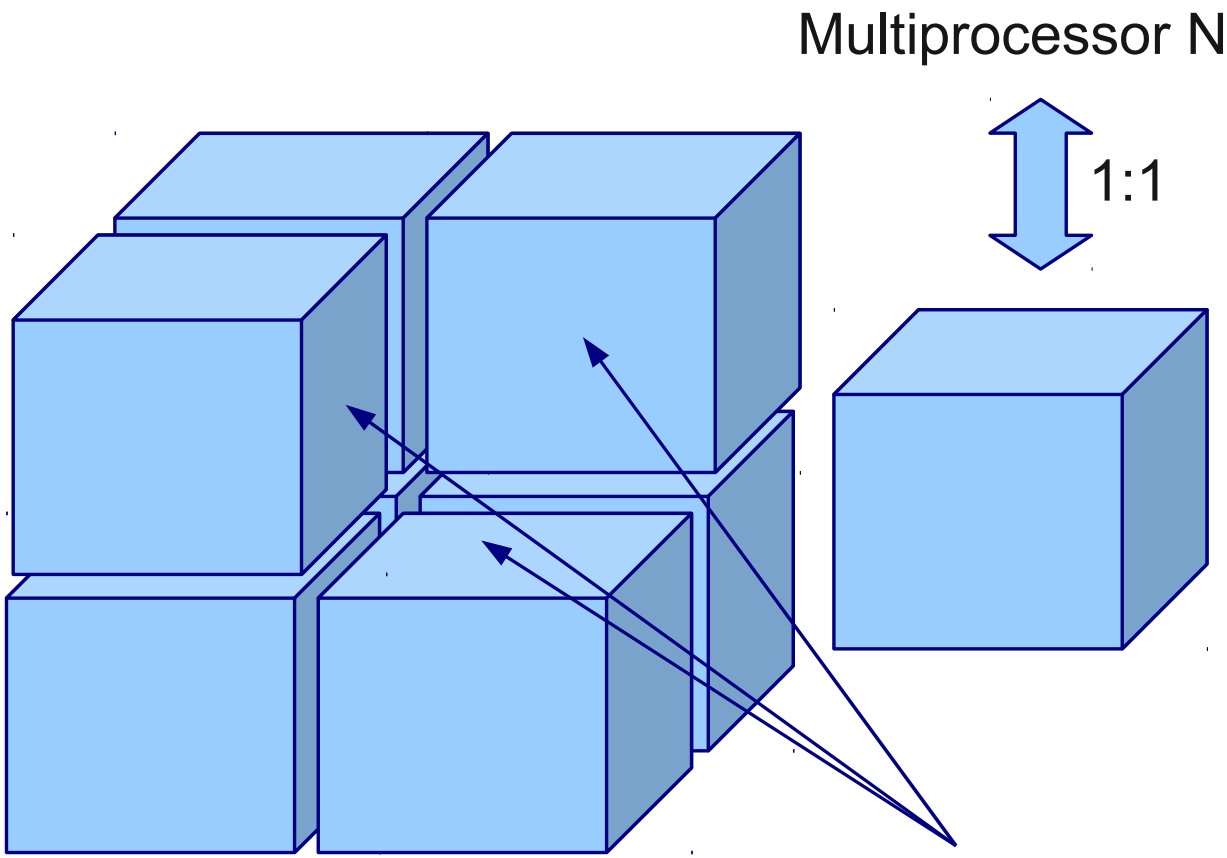
# Visualization

- Currently Output files are loaded in Matlab
- Using Matlab libraries, shapes are rendered at every time step
- A movie is then generated by the frames
- Different filters available to focus on certain entities or to zoom in/out

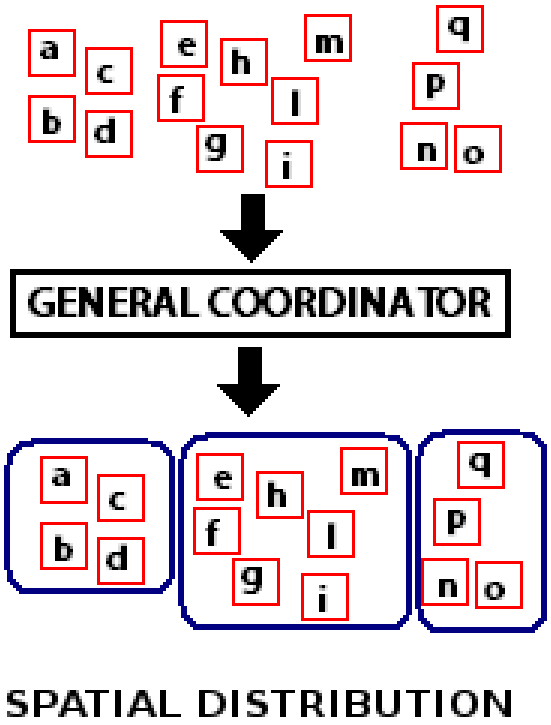
# Overcoming Computational Complexity: Splitting and Distribution

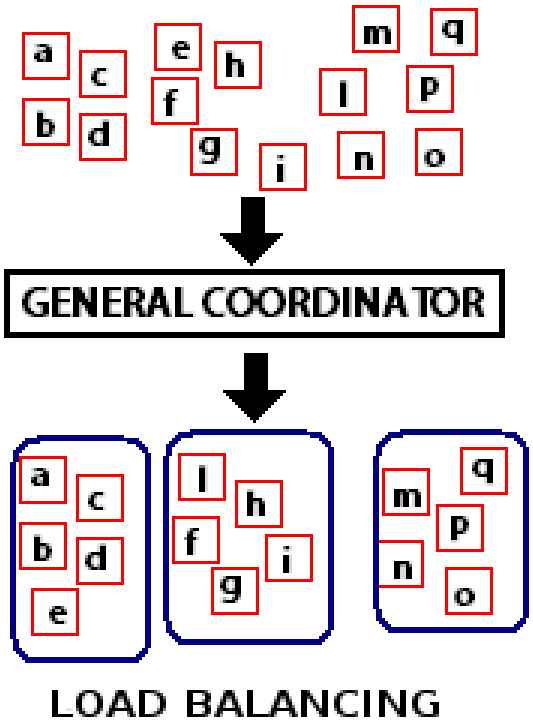
- The simulated volume is split in several parts, e.g. subcubes of the cube
- Each part has a coordinator that manages the entities at its slice virtual space
- The decomposition is completely transparent to components
- A global coordinator guarantees spatio-temporal consistency
- Each part runs on a different processor over a MIMD architecture

# Splitting


Multiprocessor Node
1:1
Interaction surfaces
Transparent to components

# Distribution of entities




# Current Case Studies

- Biochemical reactions: original "starting" case study
- Bone Remodelling: tissue scale and cellular scale, **Multiscale** capabilities of BIOSHAPE
- Bone Formation: growth of an osteon around a blood vessel (very initial phase)
- **We are Open to Collaborations in Challenges . . .**

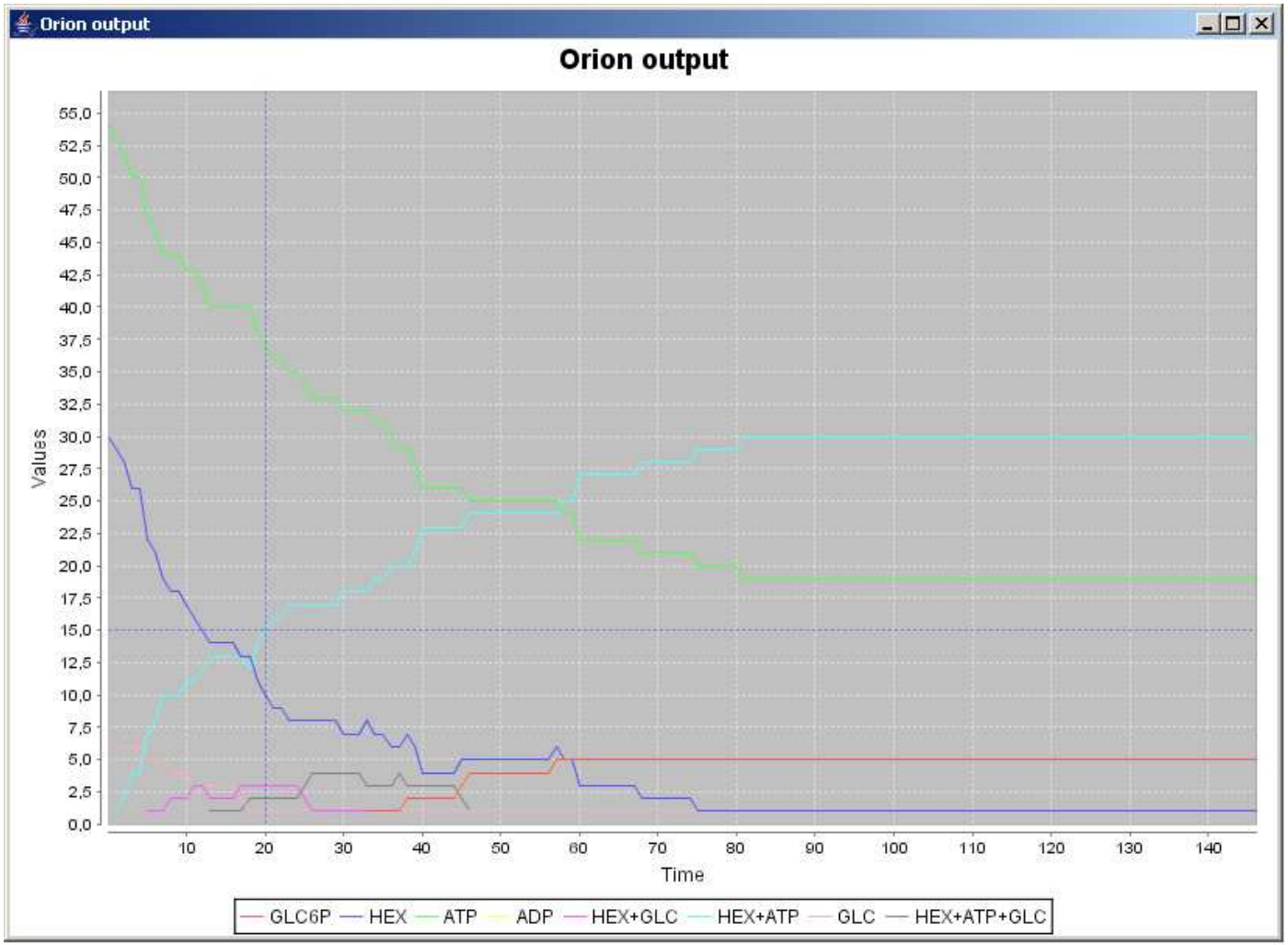
# Biochemical Reactions - Case Study

- Domain classes developed (version 0.9)
- Tested on first reactions of glycolysys
- Visualization via Matlab available
- **We are Open to Collaboration on Challenges at this Scale**

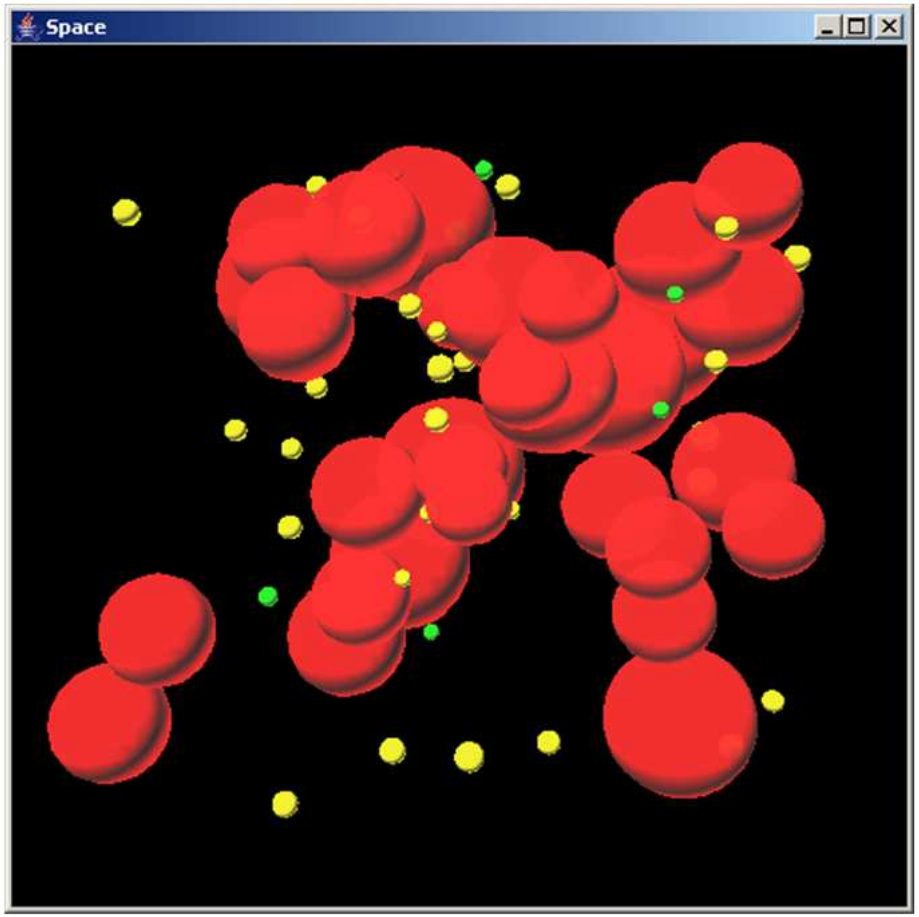
# Prototype example run

- Activate only the first reaction of the glycolysys (i.e. the one mediated by Hexokinase)
- Small volume of cytoplasm ($10^{-18}\ell$)
- Initial 0.0112817 $mMol/\ell$ concentration of glucose (GLC), corresponding to 6 molecules
- 54 molecules of ATP and 30 of Hexokinase (HEX)
- After 33$ms$ of simulation time the first molecule of glucose-6-phosphate (GLC6P) appears
- After nearly 60$ms$ we can find 5 molecules of GLC6P in our little portion of cytoplasm. After about 80$ms$ the system stabilizes.

# Run results


Orion output
Orion output
Values
Time
55,0
52,5
50,0
47,5
45,0
42,5
40,0
37,5
35,0
32,5
30,0
27,5
25,0
22,5
20,0
17,5
15,0
12,5
10,0
7,5
5,0
2,5
0,0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
GLC6P
HEX
ATP
ADP
HEX+GLC
HEX+ATP
GLC
HEX+ATP+GLC

# Visualization - Post-processed



# Bone Remodeling - Case Study

- In collaboration with Rizzoli Orthopaedic Institute of Bologna, Italy
- Multiscale challenge: tisse and cellular levels modeled simultaneously within BIOSHAPE
- Tissue classes not implemented yet, derived from PDE-based methods
- Cellular classes under development (version 0.5)

# Bone Remodelling

Biological facts:

- Old bone is continuously replaced by new tissue
- Mechanical integrity of the bone is maintained
- In healthy conditions: no global changes in morphology/mass
- A **multiscale** phenomenon: macroscopic behaviour and microstructure strongly influence each other

## Case study

Bone remodelling is a suitable case study to test the multiscale capabilities of models and simulators.

# Bone Remodelling

Pathological conditions can alter bone remodelling balance. In particular:

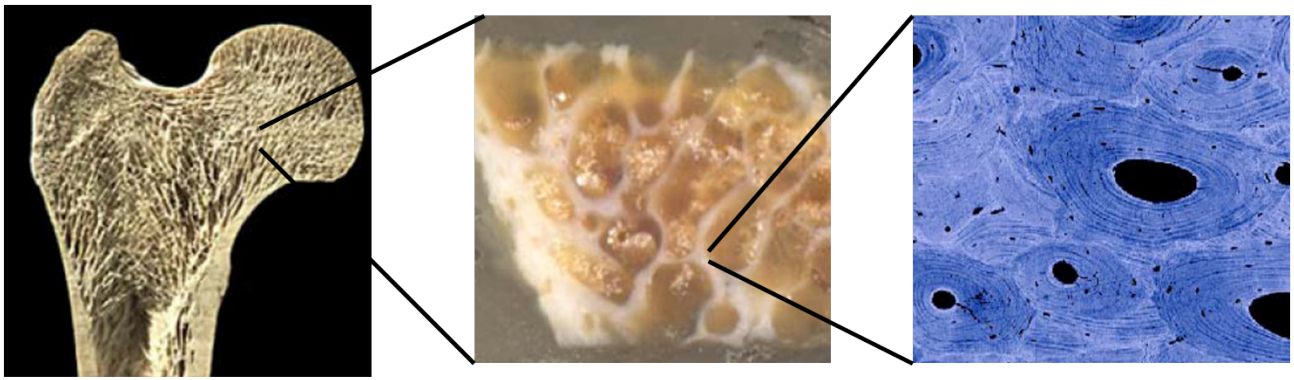
- Osteoporosis: the balance is negative, thus there is higher risk of spontaneous bone fractures
- Bone metastases: secondary tumours forming in the skeleton from malignant tumour cells in blood
- Renal osteodystrophy: defective mineralization resulting from renal disease

## Social and Clinical Relevance

A better understanding of the bone remodelling process and of how it is influenced in these and other diseases has social and clinical relevance.

# Bone Remodelling scales

- The phenomenon has been studied at different scales
- Typically **from** organ-level, where fractures take place
- **Towards** cells/molecules, where mechanisms are present that influence the whole bone structure and resistance



a. Femur cortical and trabecular bone.

b. Cut surface of bone: cortical and trabecular bone surrounded by marrow tissue

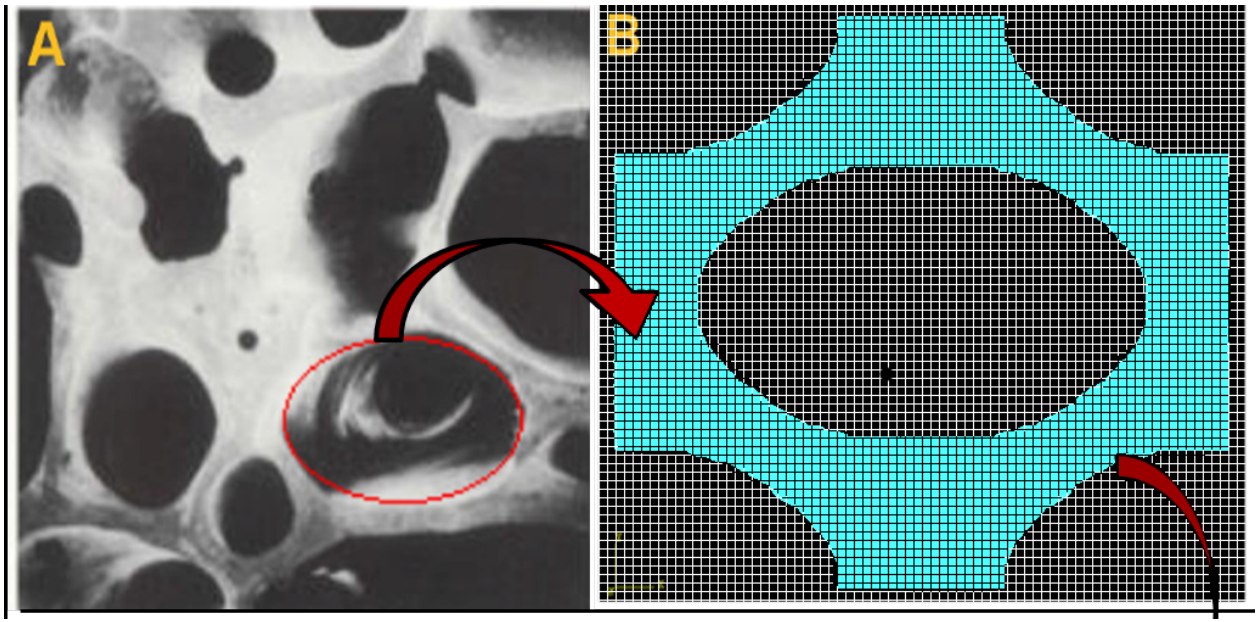
c. Haversian systems in cortical bone. The central canal supplies blood, while the small black dots are spaces containing osteocytes.

# In this case study:

- We focus on two levels: tissue and cellular
- Organ-level has been intensively studied in the past
- Existing models of different scales can be integrated, but their coupling is a difficult and tricky task
- We show how to model phenomena of different scales into a unique integrated/homogenized framework
- The simulator BIOSHAPE is intended to support this uniform approach

# Tissue Scale

- A fixed 3D lattice can be defined
- Each vertex of each cube has a **mineralization** value
- Depending on a given threshold, some cubes are at the **surface**, where remodelling happens



# Cellular Scale: Bone Multicellular Unit Animation

A qualitative visual description of the bone remodelling at the cellular level can be found at

`http://courses.washington.edu/bonephys/physremod.html`

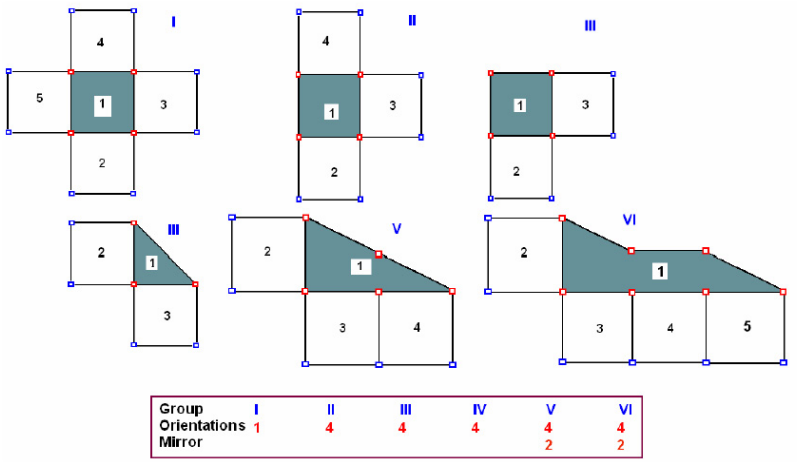
© Susan Ott, Associate Professor, Department of Medicine, University of Washington

# Tissue scale: Meshless Cell Method

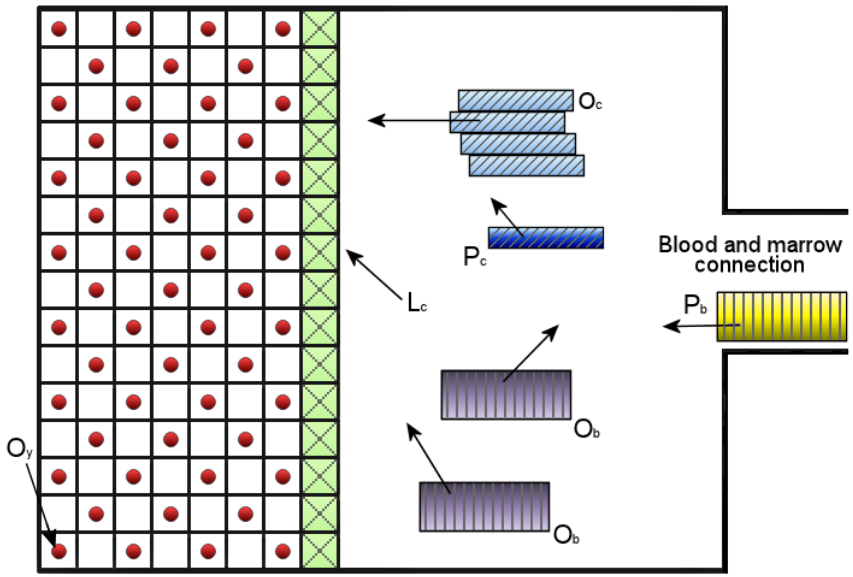
- The Meshless Cells Method (MCM) is a mathematical model based on the 3D lattice defined on the tissue
- INPUT: an external field of forces applied to the bone (considered invariant in an in-silico experiment)
- INPUT: degree of mineralisation of each point of the 3D lattice
- OUTPUT: deformation of the bone and possible damages that might occur: both micro-fractures and fractures

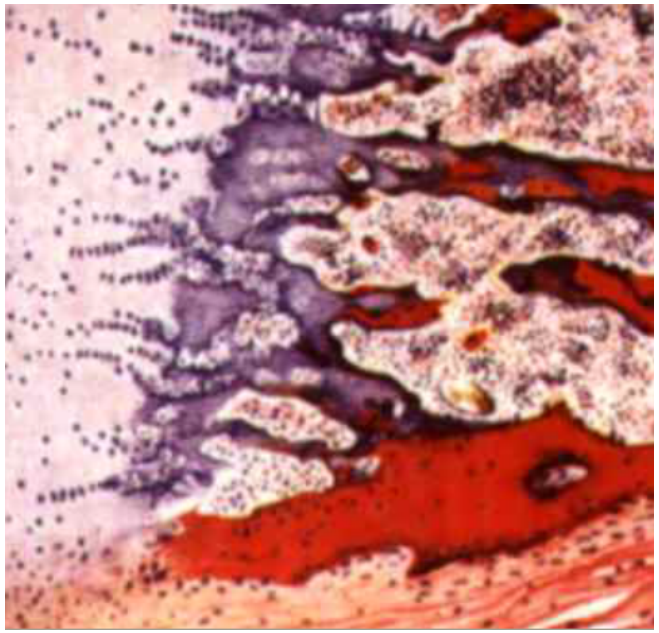
# Tissue modelling in BIOSHAPE

- We can use the 3D lattice of the MCM method to define cube shapes that do not move
- Each cube is an entity holding the information about the mineralization
- The surface cubes can be decomposed in a finite number of pieces to represent any linear cut of the surface:



# BMU modelling in BIOSHAPE



# BMU modelling in BIOSHAPE

Current set of entities:

- Cell (mineralized or not, possibly containing an Osteocyte)
- PreOsteoclast
- AggregatedPreOsteoclast
- Osteoclast
- OsteoclastPathCollector
- RANK-L
- OPG
- PreOsteoblast
- Osteoblast

# Coupling the two representation within BIOSHAPE

Cycle:

- for each shape at the tissue scale there is a mineralization density value
- each activated shape for remodelling (randomly chosen or determined by the model of forces) is 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 (by shape updating)
- re-apply the tissue model to the new data to determine how the changes of density modified the effect of mechanical stimuli

# Coupling the two representation within BIOSHAPE

The time scale is different at the two levels:

- cell events occurs at a pace of days
- tissue timing is in the order of months
- the simulator basic time step is in the order of a (simulated) day
- when a (simulated) month elapsed, one step of the tissue level is performed

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LitBio: Laboratory of Interdisciplinary Technologies in Bioinformatics `http://www.litbio.org/`


CoSy Research group: `http://cosy.cs.unicam.it`

# Credits

## Shape Calculus Design

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## BIOSHAPE Design and Development

Flavio Corradini, Emanuela Merelli, Luca Tesei, Diletta Cacciagrano, Federico Buti, Carmine Oliva

# Credits

## BMU Design and Development in BIOSHAPE

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## Matlab Visualization

Matteo Rucco

## BIOSHAPE website

`http://cosy.cs.unicam.it/bioshape/`

# Thank you!


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Thanks!