Formal aspects in spatial and hierarchical modelling: a survey

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joint work with
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Outline

1. Introduction
2. Bone Remodelling
3. Formal models for Bone Remodelling
   - Complex Automata
     - Bone remodelling in CxA
   - Spatial P Systems
     - Bone remodelling in SP
   - Hierarchical Timed Automata
     - Bone Remodelling in HTA
   - Shape Calculus
     - Bone remodelling in Shape Calculus
4. Conclusions

Hierarchical models

Hierarchical system

In **hierarchical systems**, *a component can be specified in terms of a subordinate system*

Some common examples are: *Statecharts and Hierarchical FSM; Ambient Calculi; Membrane systems*

Hierarchical models allows:

- Compositional and modular modelling of large systems
- Modelling of **multi-level systems**

Multiscale systems

Multiscale system

Multiscale systems *are a class of multi-level systems where each level has associated a* **spatial** *and a* **temporal** *scale.*

Natural phenomena are inherently multiscale, *"from atoms to galaxies, from amino-acids to living organisms . . . "* [Sun07]

Interactions occur between different scales $\rightarrow$ **scale integration** plays a key role

V. Krzhizhanovskaya and S. Sun.
Simulation of Multiphysics Multiscale Systems: Introduction to the ICCS2007 Workshop.
Computational Science–ICCS 2007, pages 755–761, 2007.

Goal

Classical single-scale models (ODE, PDE, Stochastic Processes, Petri Nets, ...) not suitable for complex biological systems

Our goal:
Formal multiscale modelling, by exploring:
Hierarchical formalisms → Multi-level
Spatial formalisms → Space and time

We compare **Complex Automata**, **Spatial P Systems**, **Hierarchical Timed Automata** and the **Shape Calculus** through a multiscale biological case-study: **Bone Remodelling**

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The bone remodelling process

Bone Remodelling (BR) is a multiscale phenomenon. We consider two different scales: **cellular** (micro) and **tissue** (macro).

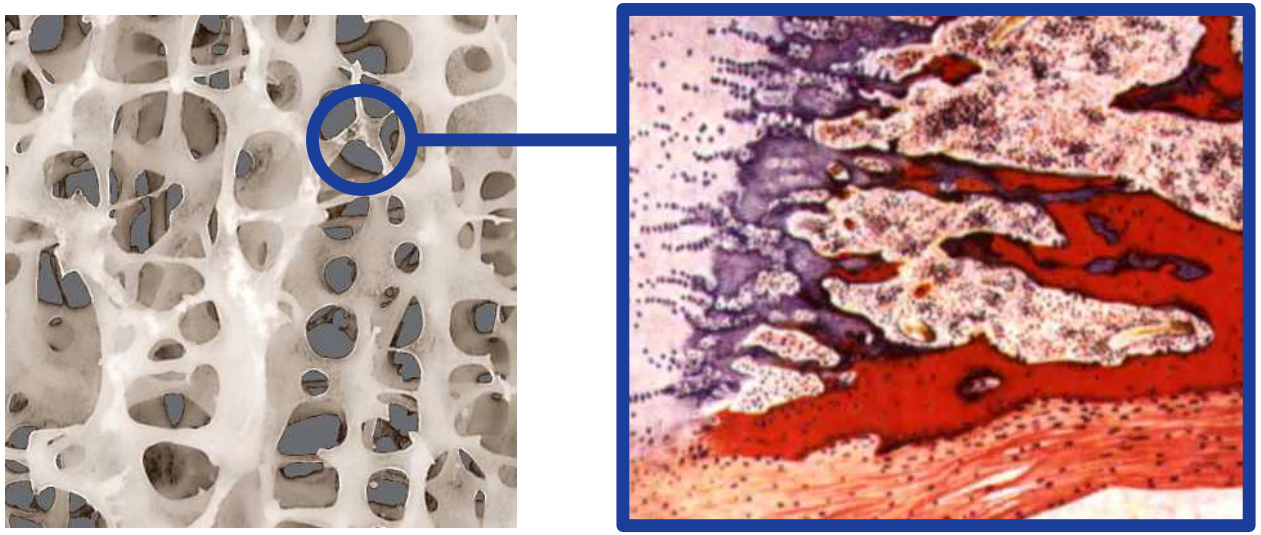
Biological facts:

- Old bone is continuously replaced by new tissue.
- Mechanical integrity of the bone is maintained.
- In healthy conditions: no global changes in morphology/mass.
- Pathological conditions alter the equilibrium between bone resorption and bone formation (e.g. Osteoporosis)

Bone Remodelling scales

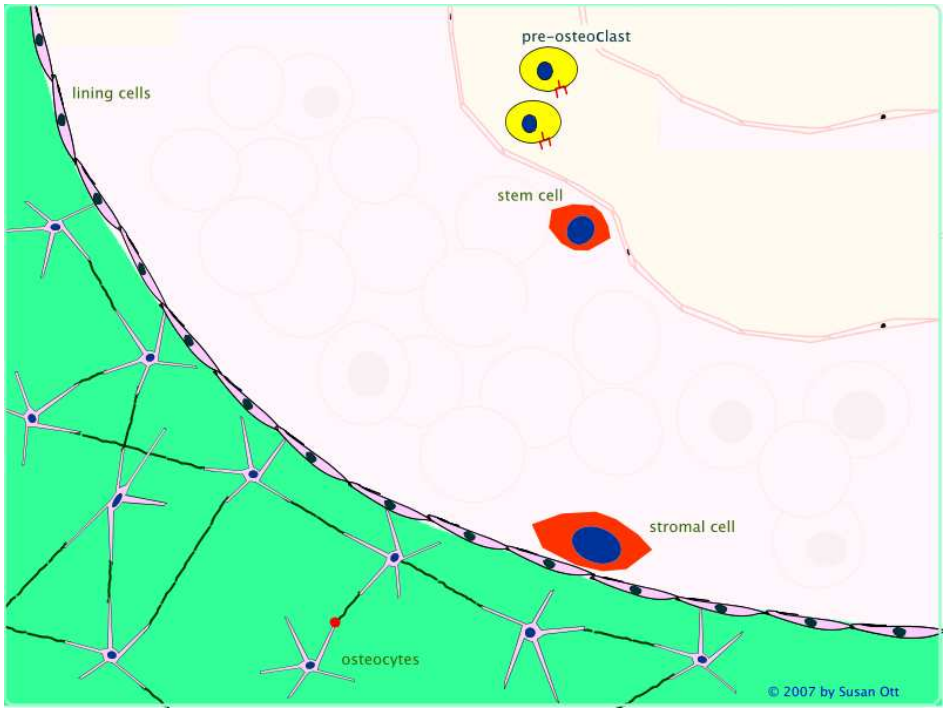
BR scales

- **Tissue level:** mechanical loading mainly affects the structure of the bone.
- **Cellular level:** the phenomenon is observed in the *Basic Multicellular Unit (BMU)*.



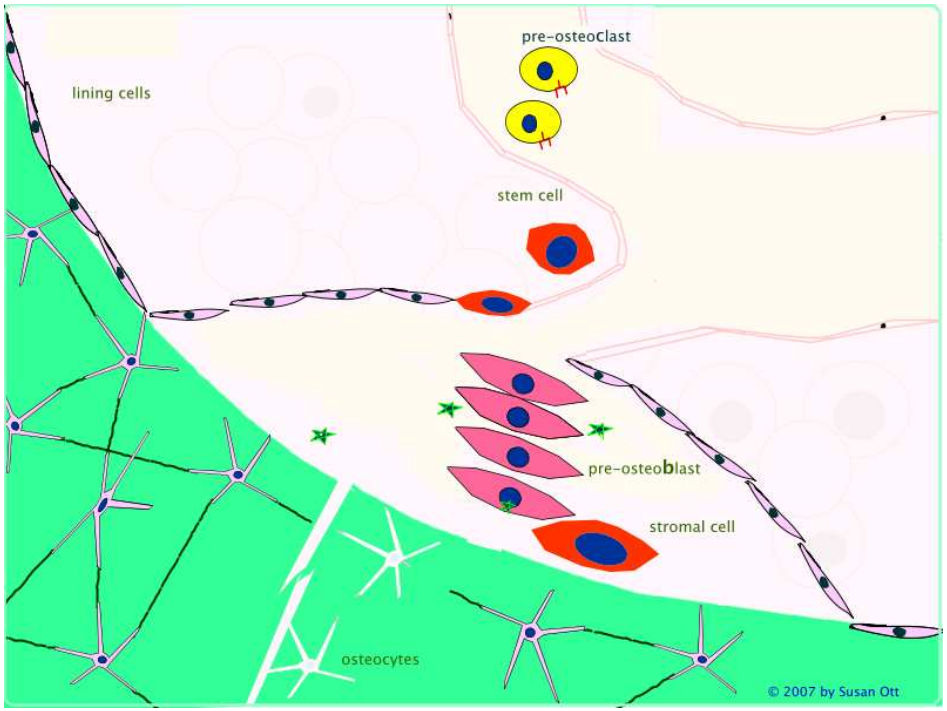
Tissue scale **Cellular scale**

BR at cellular level - BMU



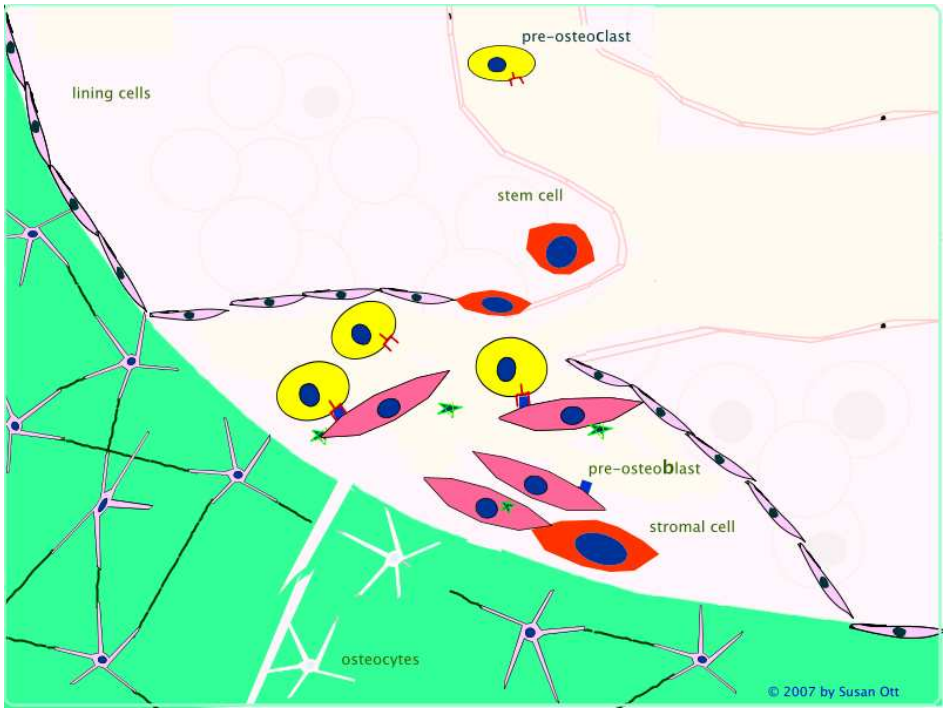
Osteocytes (O_y) are connected by a network of *canaliculi* in the mineralized part; *stem cells*, *stromal cells* and *pre-osteoclasts* (P_c) circulate in the fluid part.

BR at cellular level - BMU



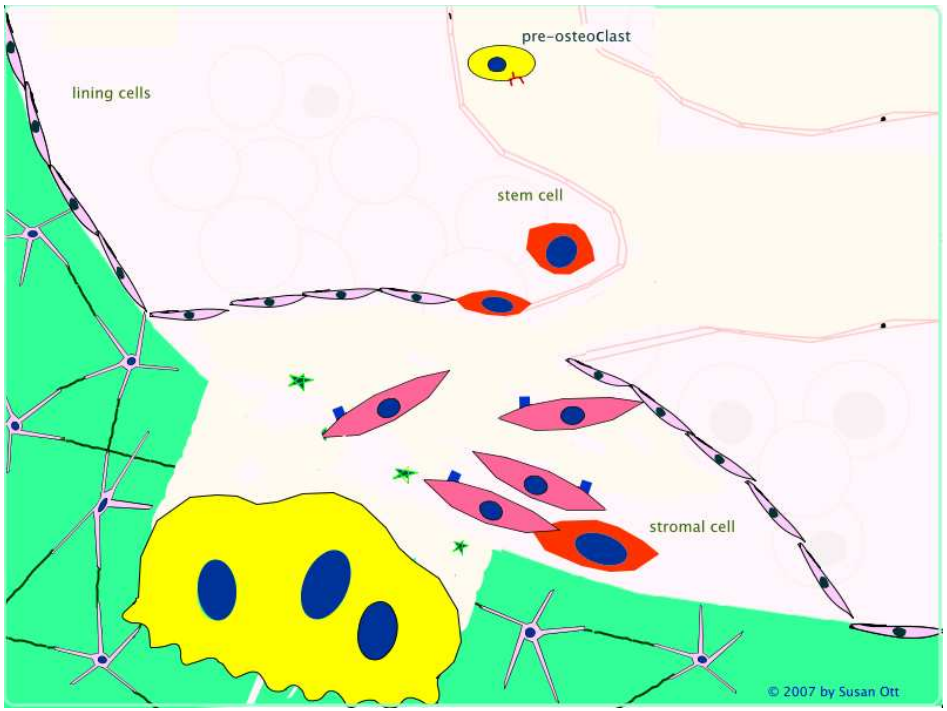
A sudden stress causes a micro-fracture to appear; O_ys near the crack undergo apoptosis; the other O_ys detect the strain and produce biochemical signals which activate the production of *pre-osteoblasts* (P_b).

BR at cellular level - BMU



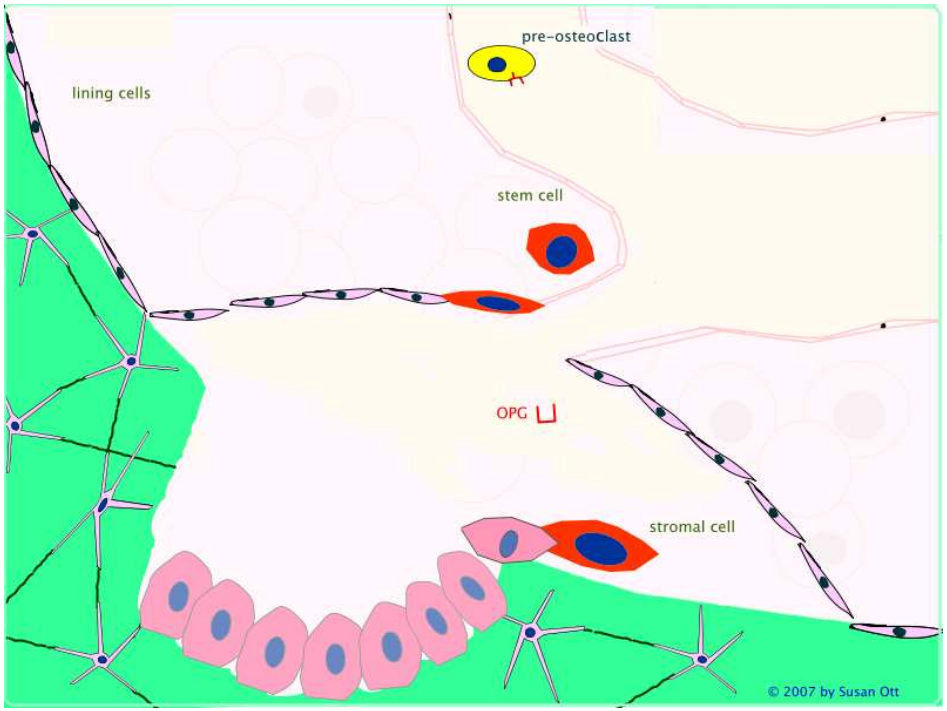
P_bs express the signal *RANK-L* attracting P_cs which have a *RANK* receptor on their surface.

BR at cellular level - BMU



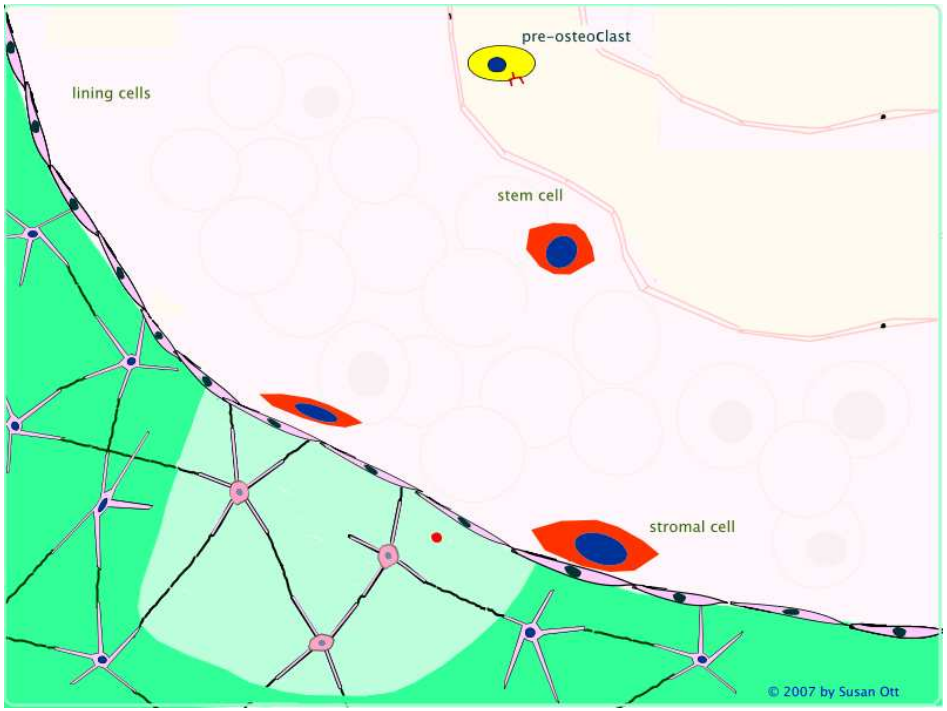
P_cs enlarge and fuse into mature *osteoclasts* (O_c). O_cs attach to bone surface, and create an acid environment to resorb the bone.

BR at cellular level - BMU



P_bs mature into *osteoblasts* (O_b); then, they line the resorbed cavity and mineralize it.

BR at cellular level - BMU



The network of canaliculi connecting the O_ys is re-established; the microdamage has been repaired.

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Cellular Automata

Definition (Cellular Automaton)

A Cellular Automaton (CA) is a tuple
$C = \langle A(\Delta x, \Delta t, L, T), S, s^0, R, G, F \rangle$ where

- A is the **spatial domain** of size L and made of cells of size Δx. Δt is the time step and T is the number of iterations.
- S is the set of **states**; $s^0 \in S$ is the **initial state**.
- R is the **evolution rule**.
- G is the **topology** describing the neighbourhood relation.
- F is the **flux of information** exchanged at each iteration between the system and its surroundings.

B. Chopard and M. Droz.
Cellular automata modeling of physical systems.
Cambridge University Press Cambridge, 1998.

Complex Automata

Complex Automata (CxA) are a formalism for **multiscale** complex systems.

Definition (Complex Automaton)

A CxA is a graph (V, E), where:

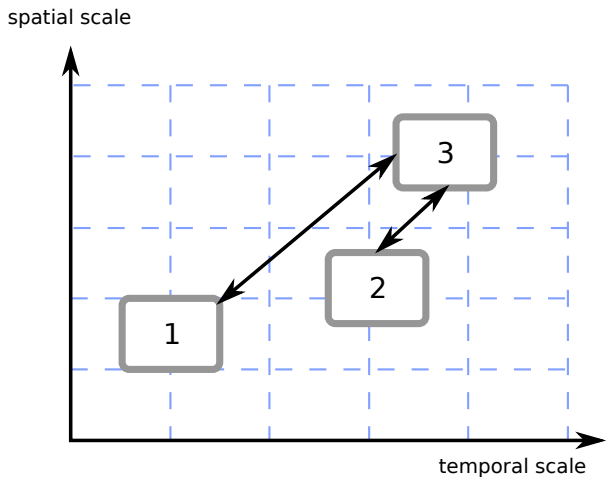
- each $C_i \in V$ is a single-scale CA, and
- each $E_{ij} \in E$ is a coupling procedure between C_i and C_j; coupling procedures regulate communication and interaction between vertex.

A. Hoekstra, J. Falcone, A. Caiazzo, and B. Chopard.
Multi-scale modeling with cellular automata: The complex automata approach.
Cellular Automata, pages 192–199, 2010.

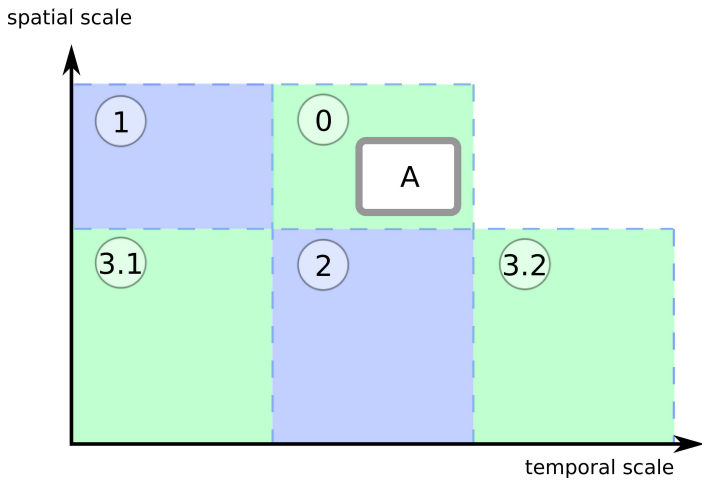
Scale separation map

A CxA can be represented through a **Scale Separation Map** (SSM).

- Each single-scale CA occupies an area wrt its spatial (x-axis) and temporal (y-axis) scales.
- Given two subsystems A and B, five different **interaction regions** are identified, according to the position of B on the map relative to A.



(a) Scale separation map



(b) Interaction regions

BR model in CxA

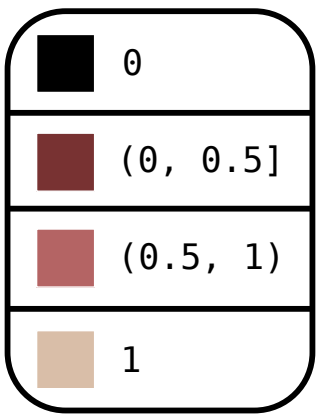
CxA multiscale model

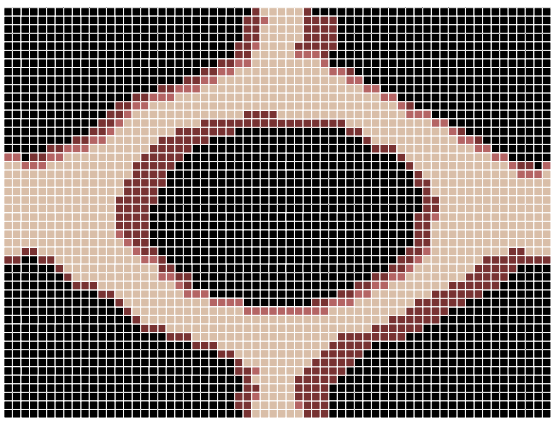
- **Tissue level:** modelled as a lattice of BMU with a **macro** CA, C_1
- **Cellular level:** for each cell i of C_1, a **micro** CA $C_{(i,2)}$ models a BMU as a lattice of O_ys.

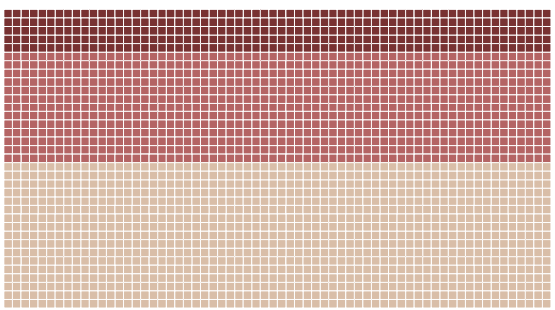
- Only mechanical stimuli; no cellular dynamics.
- Size of C_1 is linearly determined by the size of $C_{(i,2)}$, which depends on the density of O_ys.

D. Cacciagrano, F. Corradini, and E. Merelli.
Bone remodelling: a complex automata-based model running in BioShape.
In *ACRI 2010: The Ninth International Conference on Cellular Automata for Research and Industry*, 2010.

BR model in CxA - Execution flow







Macro execution flow: the state of a cell i of C_1 at time t_1 is determined by the density $m_1^i(t_1)$, varying from 0 (void) to 1 (fully-mineralized). Each iteration of C_1 corresponds to a complete simulation of $C_{(i,2)}$, whose outputs modify m_1^i.

Micro execution flow: the state of a cell j of $C_{(i,2)}$ at time $t_{(i,2)}$ is given by $m^j_{(i,2)}(t_{(i,2)})$, varying from 0 (fluid cell) to 1 (mineralized cell) and depends on the state of the cell i in C_1.

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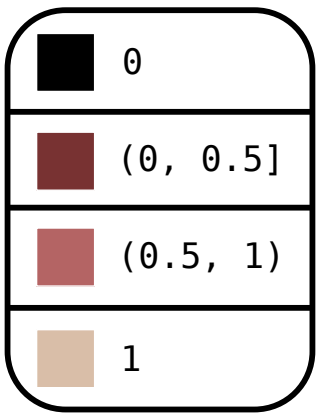

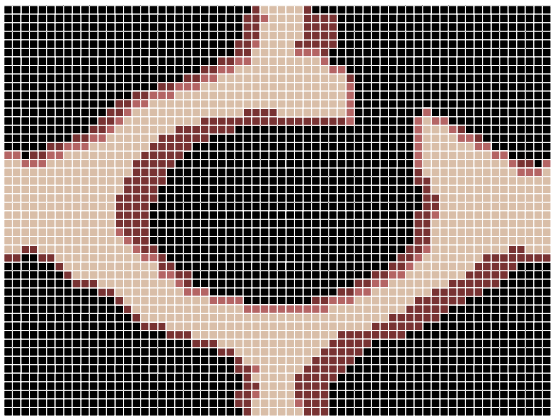

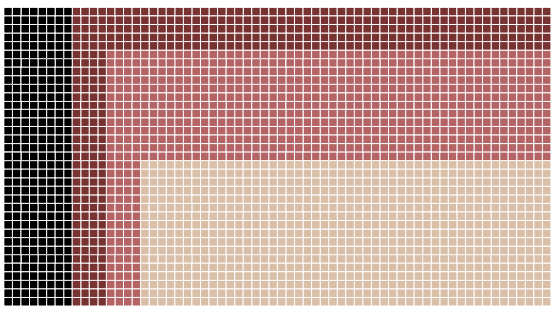

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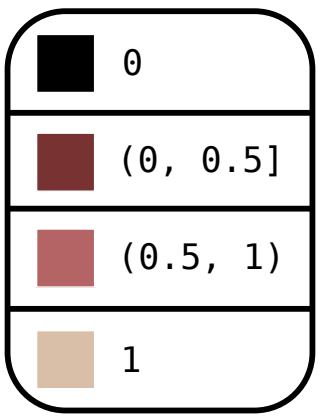

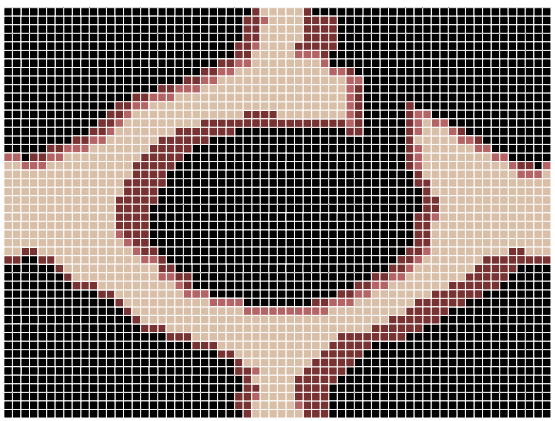

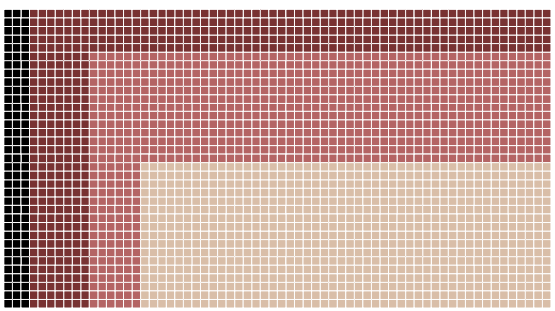

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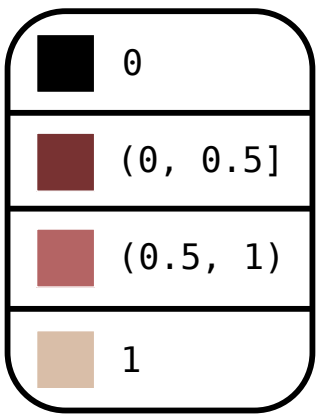

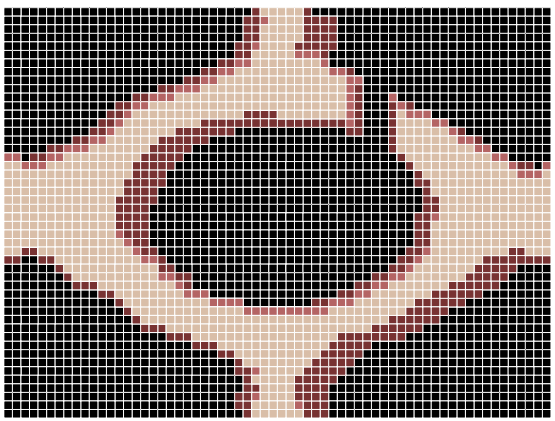

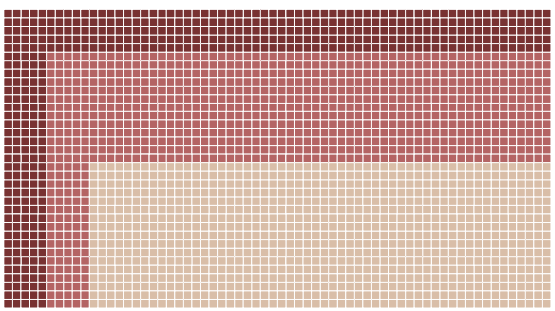

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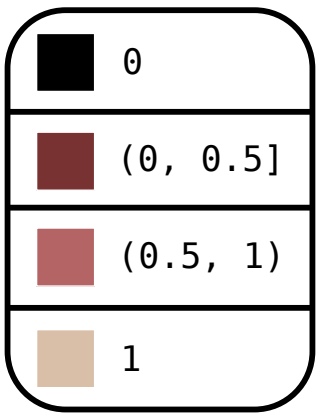

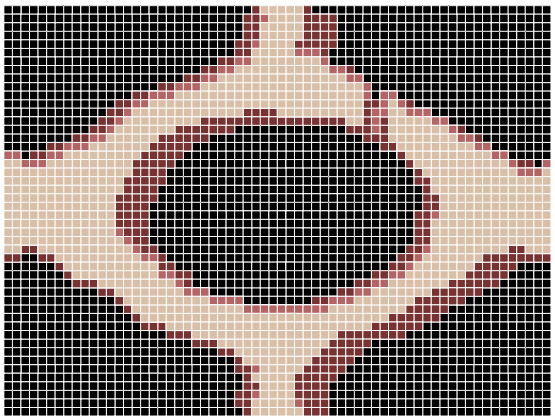

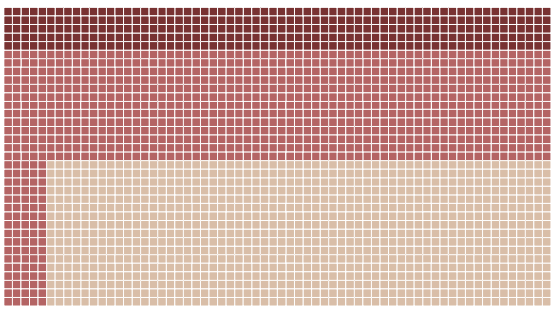

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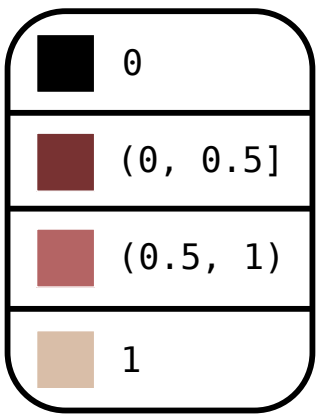

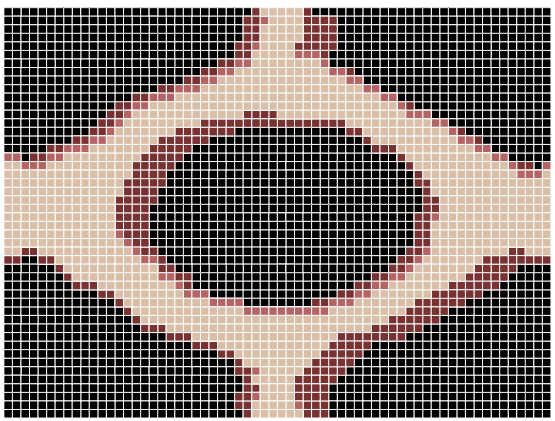

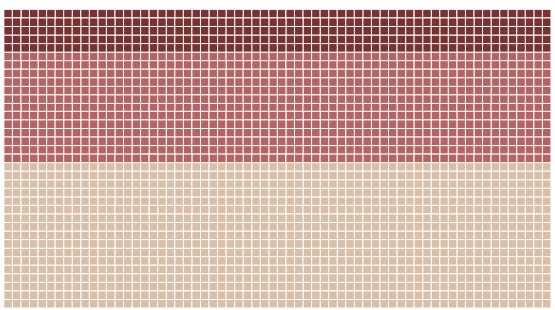

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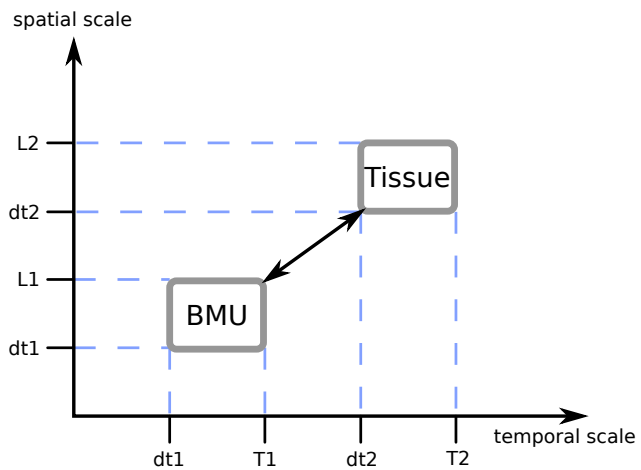
BR model in CxA - Coupling scheme

- The two models are linked with the "micro-macro" coupling mechanism: a fast process on a small spatial scale ($C_{(i,2)}$) is coupled to a slow process on a large spatial scale (C_1).
- The macro model takes input (mineralization values) from the micro model; this paradigm is called *Hierarchical Model Coupling (HMC)*.



CxA - Main features

Faithfulness

- CxA only considers mechanical stimuli; cellular level is approximated to a lattice of O_ys

Integration of different scales

- In CxA, integration schemes are native (edges of the graph); the *SSM* illustrates the single-scale processes wrt their spatial and temporal scales and of their mutual coupling

Spatial features

- Spatial information in a CA is limited to the cell size, the total size and the neighbourhood relation

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P Systems

P Systems

P Systems are bio-inspired computing devices, structured in a **membrane hierarchy**

- *Objects* in a membrane represent molecules
- *Evolution rules* of the form $u \rightarrow v$ model chemical reactions between reactant objects u and product objects v.
- *Target messages* specify whether the products of the reaction remain in the membrane or are moved out.
- The result of a successful (convergent) computation is the multiset of objects sent out the root membrane.

G. Pun.
Computing with membranes.
Journal of Computer and System Sciences, 61(1):108–143, 2000.

Spatial P Systems (1/2)

Spatial P Systems (SP) enrich P System with a **2D discrete space**

- Membranes are rectangular and objects occupy a single position.
- A single position can contain an arbitrary number of *ordinary* objects, but only one *mutually esclusive* object.

R. Barbuti, A. Maggiolo-Schettini, P. Milazzo, G. Pardini, and L. Tesei.
Spatial P systems.
Natural Computing, pages 1–14, 2010.

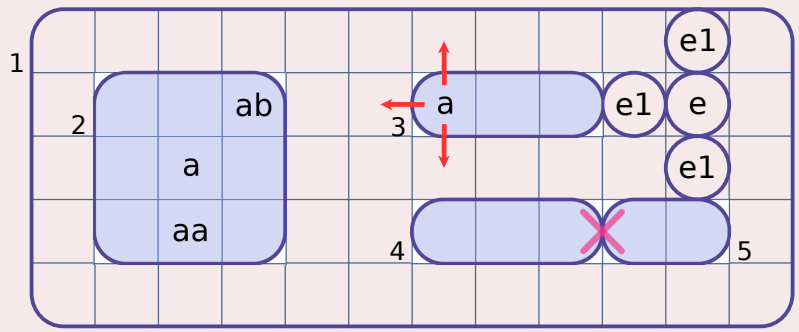
Spatial P Systems (2/2)

Target messages can be of the form:

- $v_{\delta p}$, $\delta p \in \mathbb{Z}^2$: objects v in position p are moved to $p + \delta p$ in the same membrane;
- v_{in_i}: send v in the nearest position of the child membrane i;
- v_{out}: sent v in one of the nearest positions outside the membrane.

Example

Membranes 4 and 5 are wrongly located, since adjacent edges are forbidden. Red arrows indicate the possible positions of the object **a** after an **out** rule.



SP - Definition

Definition (Spatial P System)

A **Spatial P system** Π is a tuple $\langle V, E, \mu, \sigma, W^{(1)}, ..., W^{(n)}, R_1, ..., R_n \rangle$ where

- V and E are disjoint alphabets of **ordinary** objects and **mutually esclusive** (ME) objects;
- $\mu \subset \mathbb{N} \times \mathbb{N}$ describes the membrane hierarchy; $(i, j) \in \mu$ implies that membrane j is child of i;
- $\sigma : \{1, ..., n\} \rightarrow N^2 \times (N^+)^2$ describes position and dimension of membranes;
- $W^{(i)} = \{w_{x,y}^{(i)} \in (V \cup E)^* \quad | \quad 0 \leq x < w_i, 0 \leq y < h_i\}$, with $i = 1, ..., n$ indicates the objects at each position of i;
- R_i is the set of **evolution rules** associated to i.

BR model in SP

SP multiscale model

- **Tissue level:** modelled with a **macro** SP, S_1
- **Cellular level:** for each cell i of S_1, a **micro** SP $S_{(i,2)}$ models a single BMU

D. Cacciagrano, F. Corradini, E. Merelli, and L. Tesei.
Multiscale Bone Remodelling with Spatial P Systems.
Membrane Computing and Biologically Inspired Process Calculi 2010, page 65, 2010.

BR in SP - Tissue model (1/2)

Each position p contains:

- A number j of objects c proportional to the mineralization density; in a superficial cell, $j \in [m, m+n)$
- An activator object a, if p is a surface cell
- At most one g object which models a micro damage; the corresponding cell will be selected for remodelling.
- At most one h object indicating that the cell is randomly selected for remodelling.

BR in SP - Tissue model (2/2)

1

c	c	c	c	c	c	c^2	c^2	c^3	c^4	$ah\ c^5$	$a\ c^7$	c^8
c^2	c^2	c	c	c^2	c^2	c^3	c^3	c^3	c^4	c^4	$ah\ c^6$	c^8
c^3	c^3	c^2	c^2	c^3	c^3	c^3	c^4	c^4	$ah\ c^5$	$ah\ c^5$	$ah\ c^6$	c^8
c^4	c^4	c^3	c^3	c^4	c^4	c^4	$ah\ c^5$	$ah\ c^5$	$ah\ c^7$	c^8	c^8	c^9
$ah\ c^5$	c^4	c^4	c^4	c^4	c^4	$ag\ c^5$	$ag\ c^6$	$a\ c^7$	c^8	c^8	c^9	c^9
$ah\ c^6$	$ah\ c^5$	$ah\ c^5$	$ag\ c^5$	c^4	c^4	$ag\ c^6$	$a\ c^7$	c^8	c^8	c^9	c^9	c^9
$ah\ c^7$	$a\ c^6$	$a\ c^6$	$ag\ c^6$	c^4	c^3	c^4	$ag\ c^6$	$a\ c^7$	c^8	c^9	c^9	c^{10}
c^8	c^8	$a\ c^7$	$ag\ c^6$	c^4	c^3	c^4	$ag\ c^5$	$a\ c^7$	c^8	c^9	c^{10}	c^{10}

Rules

$r_1 : c^m a \to b_1 d_1$; $r_2 : c^n b_1 \to c^{n+m} b$; $r_3 : d_1 \to d$; $r_4 : db \to \lambda$;
$r_5 : db_1 \to c^m f$; $r_6 : fg \to r$; $r_7 : fh \to r$

BR in SP - Tissue model (2/2)

1

Rules

$r_1 : c^m a \to b_1 d_1$; $r_2 : c^n b_1 \to c^{n+m} b$; $r_3 : d_1 \to d$; $r_4 : db \to \lambda$;
$r_5 : db_1 \to c^m f$; $r_6 : fg \to r$; $r_7 : fh \to r$

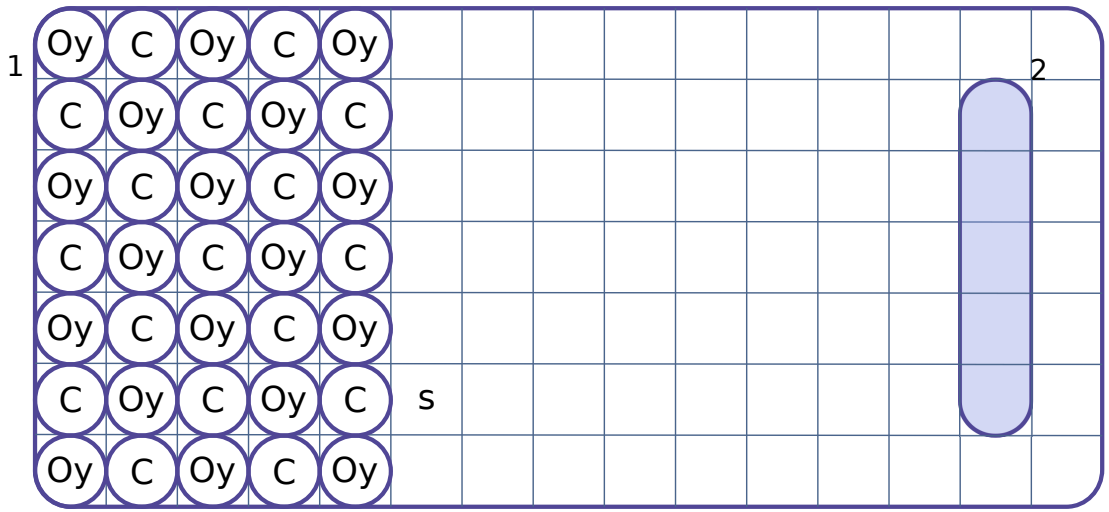
BR in SP - Cellular model (1/2)

The root membrane is divided in two zones:

- A *mineralized* part with two types ME objects: O_y (bone cell with an osteocyte) and C (bone cell with no osteocytes).
- A *non-mineralized* part; membrane 2 models the connection with blood and marrow, and produces P_bs and P_cs once the starter object s has entered it.

The initial configuration depends on the mineralization degree computed at the higher level.

BR in SP - Cellular model (2/2)

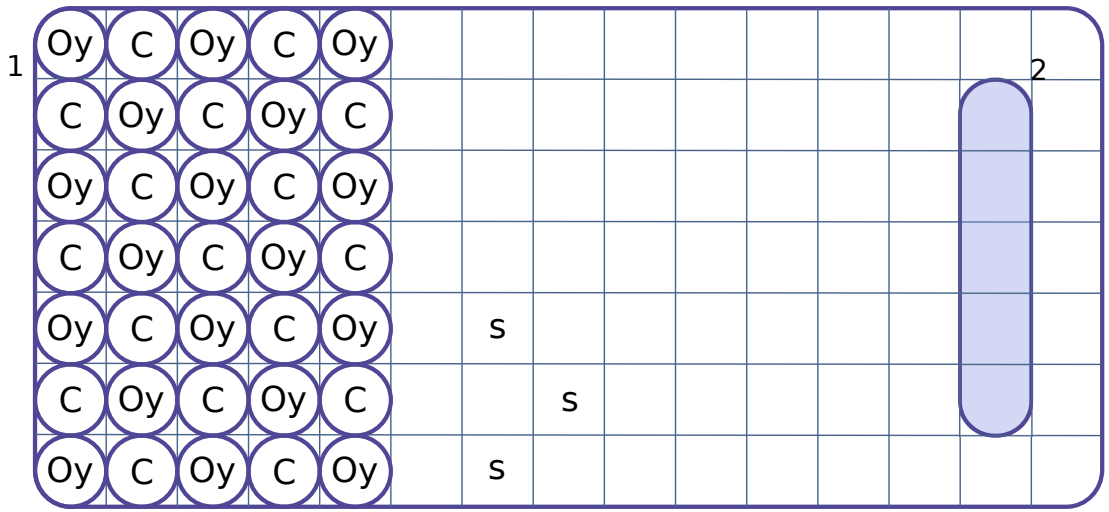


The biochemical signal s spread over the fluid part and moves towards East until it enters membrane 2.

Rule(s)

$$s \longrightarrow s_N s_E s_S \qquad s \longrightarrow s_E \qquad s \longrightarrow s_{in_2} \qquad s \longrightarrow s_{out}$$

BR in SP - Cellular model (2/2)



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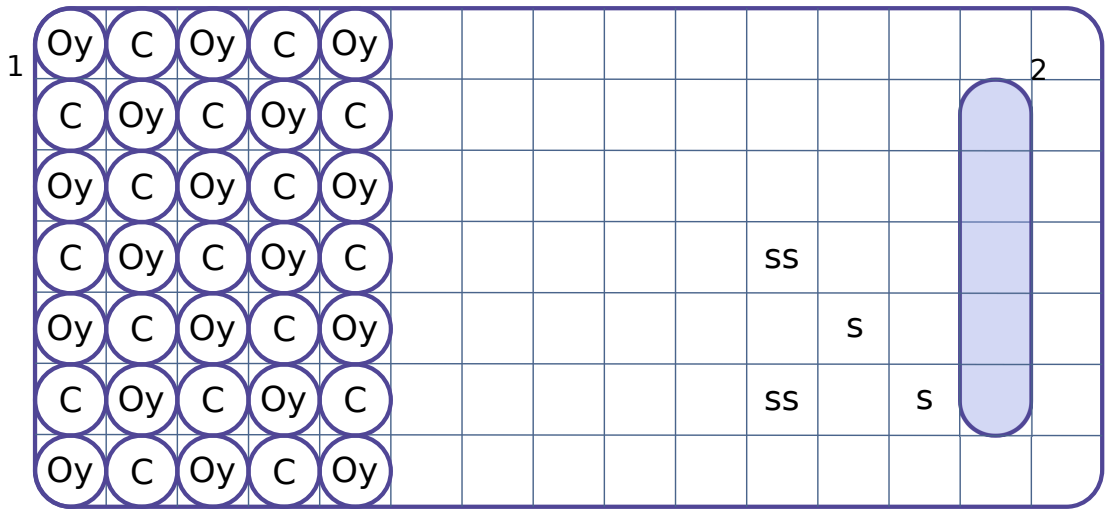

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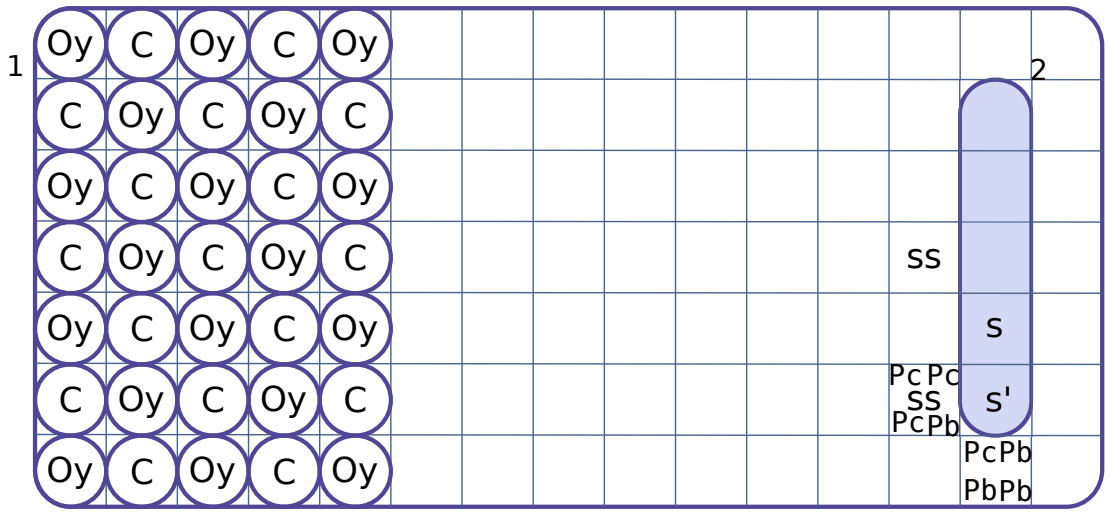
BR in SP - Cellular model (2/2)

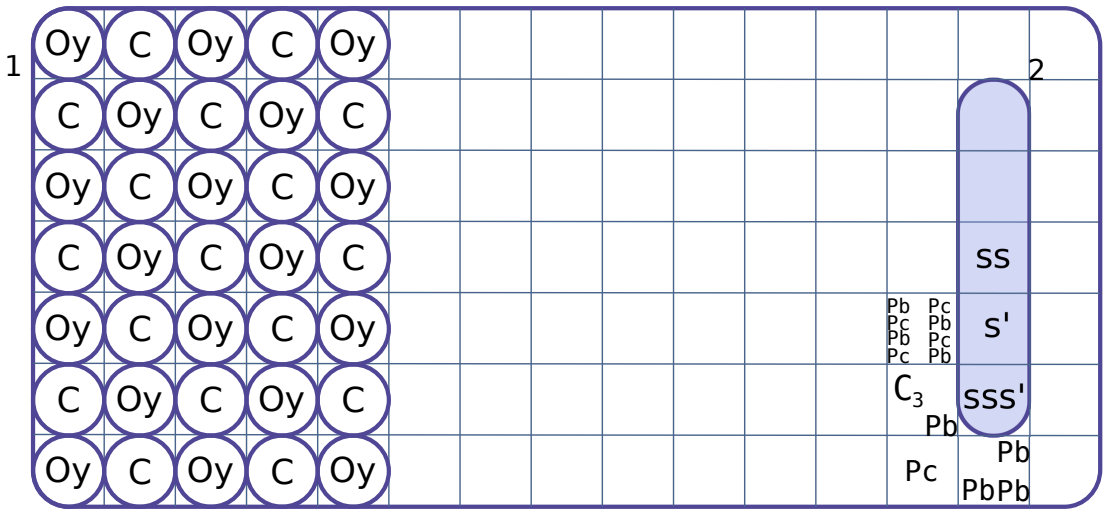


A single s produces k P_cs and l P_bs from membrane 2; here $k = l = 4$; any other object s entering the membrane is inactivated by s'.

Rule(s) - Membrane 2

$$s \to s'(P_c)^k_{out}(P_b)^\ell_{out} \quad s's \to s' \quad s' \to s's'_N \quad s' \to s's'_S$$

BR in SP - Cellular model (2/2)

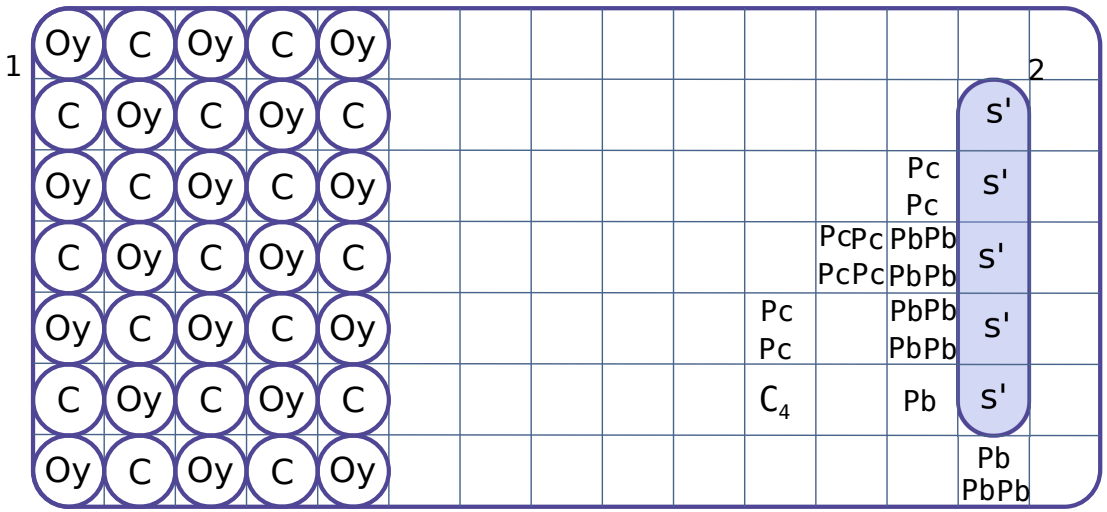


P_cs move randomly and aggregate to form a mature O_c. Object C_n, with $n < N\_OC$ denotes a conglomerate of n P_cs. N_OC is the number of P_cs needed to form a grown O_c. Here, $N\_OC = 4$.

Rule(s)

$$P_c \to P_c\ P_c \to P_{cN}\ P_c \to P_{cS}\ P_c \to P_{cO}\ P_c \to P_{cE}\ {P_c}^h \to C_h$$
$${P_c}^{h_1} - {P_c}^{h_2} \to \lambda - C_{h_1+h_2} \quad C_h - P_c \to C_{h+1} - \lambda \quad C_h P_c \to C_{h+1}$$
$$C_{N\_OC-1} - P_c \to O_{c0} - \lambda \quad C_{N\_OC-1} P_c \to O_{c0}$$

BR in SP - Cellular model (2/2)



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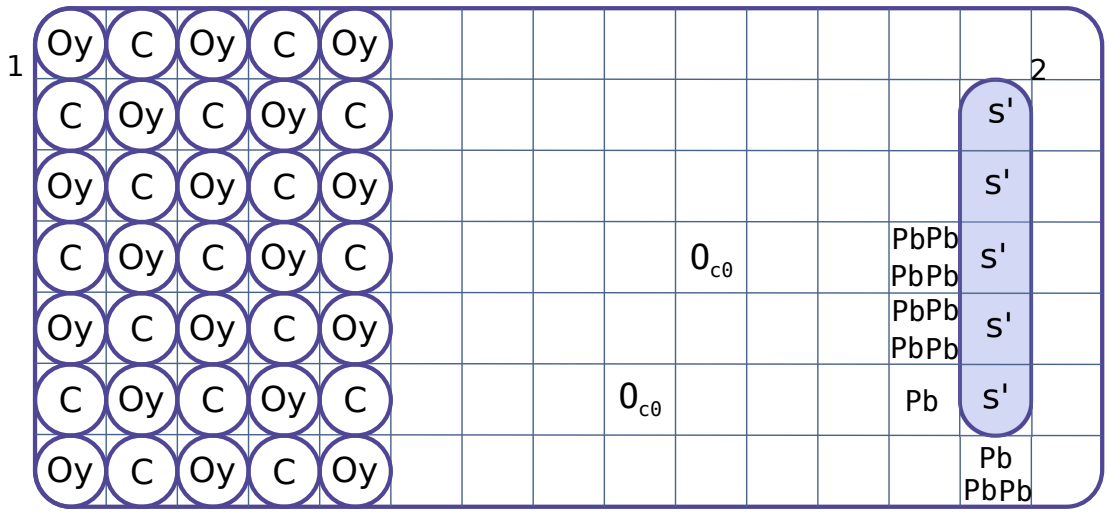
$${P_c}^{h_1} - {P_c}^{h_2} \to \lambda - C_{h_1+h_2} \quad C_h - P_c \to C_{h+1} - \lambda \quad C_h P_c \to C_{h+1}$$
$$C_{N\_OC-1} - P_c \to O_{c0} - \lambda \quad C_{N\_OC-1} P_c \to O_{c0}$$

BR in SP - Cellular model (2/2)

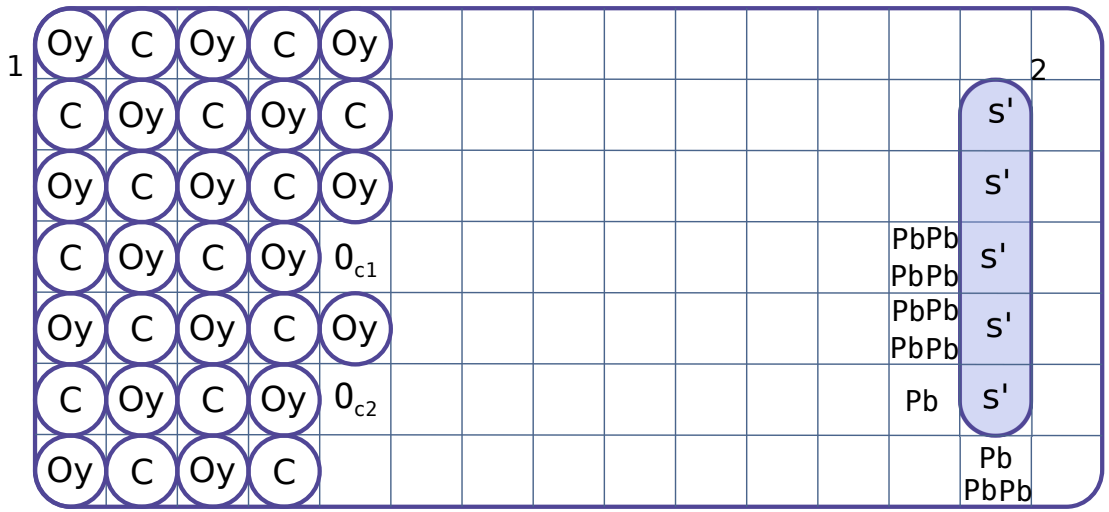


The O_cs move towards West to the mineralized part.

Rule(s)

$$O_c \rightarrow O_{cW}$$

BR in SP - Cellular model (2/2)

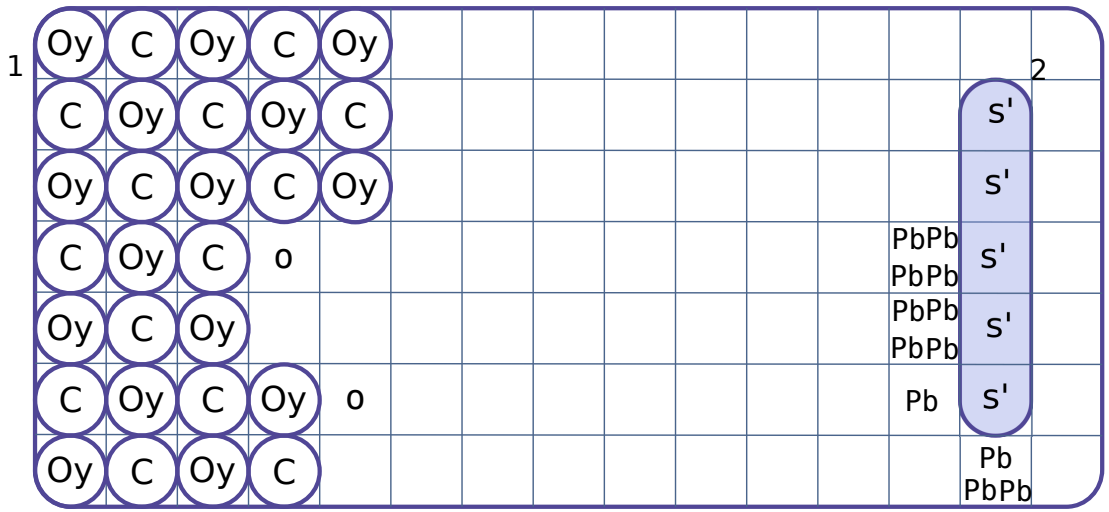


O_{ci} is an osteoclast which has consumed i mineralized cells, with $i \leq N\_DC$; here $N\_DC = 3$.

Rule(s)

$$O_y - O_{cz} \rightarrow O_{cz+1} - \lambda \quad C - O_{cz} \rightarrow O_{cz+1} - \lambda \quad O_y - O_{cN\_DC-1} \rightarrow \lambda - o$$

BR in SP - Cellular model (2/2)



Once absorbed N_DC cells, the O_c dies and release an object o, the biochemical signal that will trigger the production of O_bs for bone formation.

Rule(s)

$$C - O_{c\,N\_DC-1} \rightarrow \lambda - o$$

BR in SP - Coupling scheme

Scale Integration Functions

- **f $\downarrow$ (top-down):** if a cell i of S_1 is subject to remodelling, the function puts the starter object s in $S_{(i,2)}$. Moreover, $f\downarrow$ sets the initial configuration of $S_{(i,2)}$ according to the number of c objects in i.
- **f $\uparrow$ (bottom-up):** after the simulation of $S_{(i,2)}$, it determines the number of c objects to be placed on the cell i of S_1.

SP - Main features

Faithfulness

- CxA only considers mechanical stimuli; cellular level is approximated to a lattice of O_ys
- SP includes complex cellular dynamics (biochemical signals, P_bs and P_cs formation, ...)

Integration of different scales

- In CxA, integration schemes are native (edges of the graph); the *SSM* illustrates the single-scale processes wrt their spatial and temporal scales and of their mutual coupling
- SP systems don't include *a priori* integration mechanisms

Spatial features

- Spatial information in a CA is limited to the cell size, the total size and the neighbourhood relation
- SP systems implement *compartmentalization*, a *2D space*, and movement of objects by *evolution rules*

Outline

1. Introduction
2. Bone Remodelling
3. Formal models for Bone Remodelling
   - Complex Automata
     - Bone remodelling in CxA
   - Spatial P Systems
     - Bone remodelling in SP
   - Hierarchical Timed Automata
     - Bone Remodelling in HTA
   - Shape Calculus
     - Bone remodelling in Shape Calculus
4. Conclusions

Timed Automata (1/2)

A Timed Automaton (TA) is a non-deterministic Finite State Machine (FSM) with a finite set of real-valued *clocks* C and a set of *clock constraints* (guards) $\mathcal{B}(C)$.

Definition (Timed Automaton)

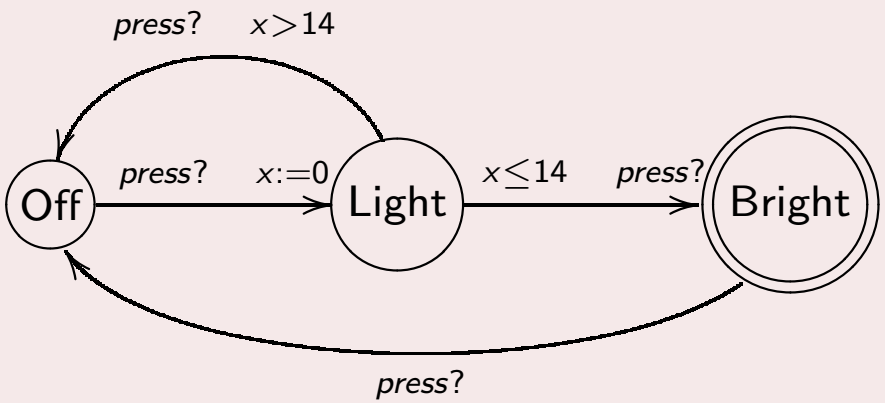
A **timed automaton** over a set of clocks C and a finite set of actions Act is a tuple (L, l_0, E, I), where

- $L = \{l_0, l_1, ...\}$ is a finite set of **locations**;
- $l_0 \in L$ is the **initial location**;
- $E \subseteq L \times \mathcal{B}(C) \times \text{Act} \times 2^C \times L$ is a finite set of **edges**;
- $I : L \to \mathcal{B}(C)$ assigns **invariants** to locations.

Given an edge $l \xrightarrow{g,a,r} l'$, g is the guard, a is the action and r is the set of clocks to be reset.

Timed Automata (2/2)

Example (Light switch)



From the initial location *Off*, the automaton can reach the location *Light* with a *press*? action and a clock reset ($x := 0$). Then, if a *press*? action is fired when $x > 14$, the active location will be *Off*, while if *press*? is performed before, we move to *Bright*.

R. Alur and D. Dill.
A theory of timed automata.
Theoretical computer science, 126(2):183–235, 1994.

Statecharts (1/2)

Statecharts

Statecharts are a visual formalism for Hierarchical Finite State Machines.
Locations can be of two types:

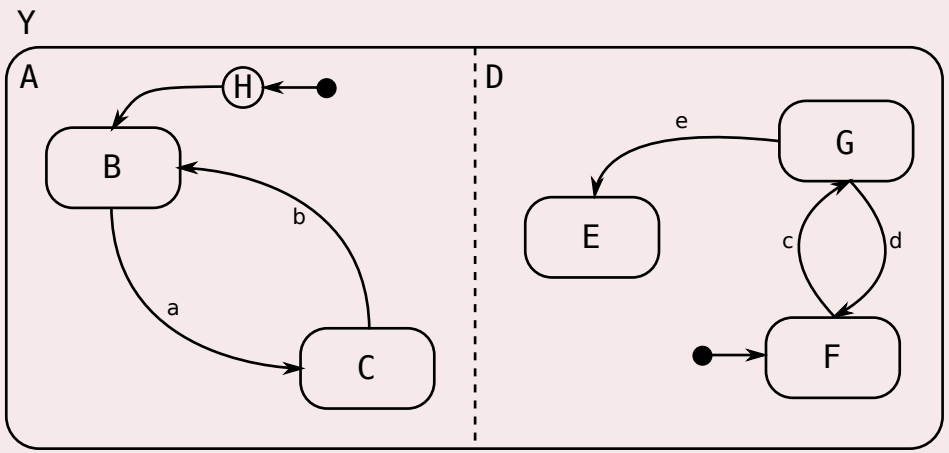
- *XOR-locations* $\rightarrow$ **alternative composition**. When a XOR-location is active, only one of its sublocation is active.
- *AND-locations* $\rightarrow$ **concurrency**. Given a state where an AND-location is active, then all its sublocations are active.

D. Harel.
Statecharts: A visual formalism for complex systems.
Science of computer programming, 8(3):231–274, 1987.

Statecharts (2/2)

Example

Y consists of two AND sublocations, A and D; B, C and E, F, G are XOR-locations contained in A and D, respectively. The first location to be entered in D is F; the presence of the history element in A means that the last visited location between B and C must be entered (B, if it is the first time in A).



Hierarchical Timed Automata

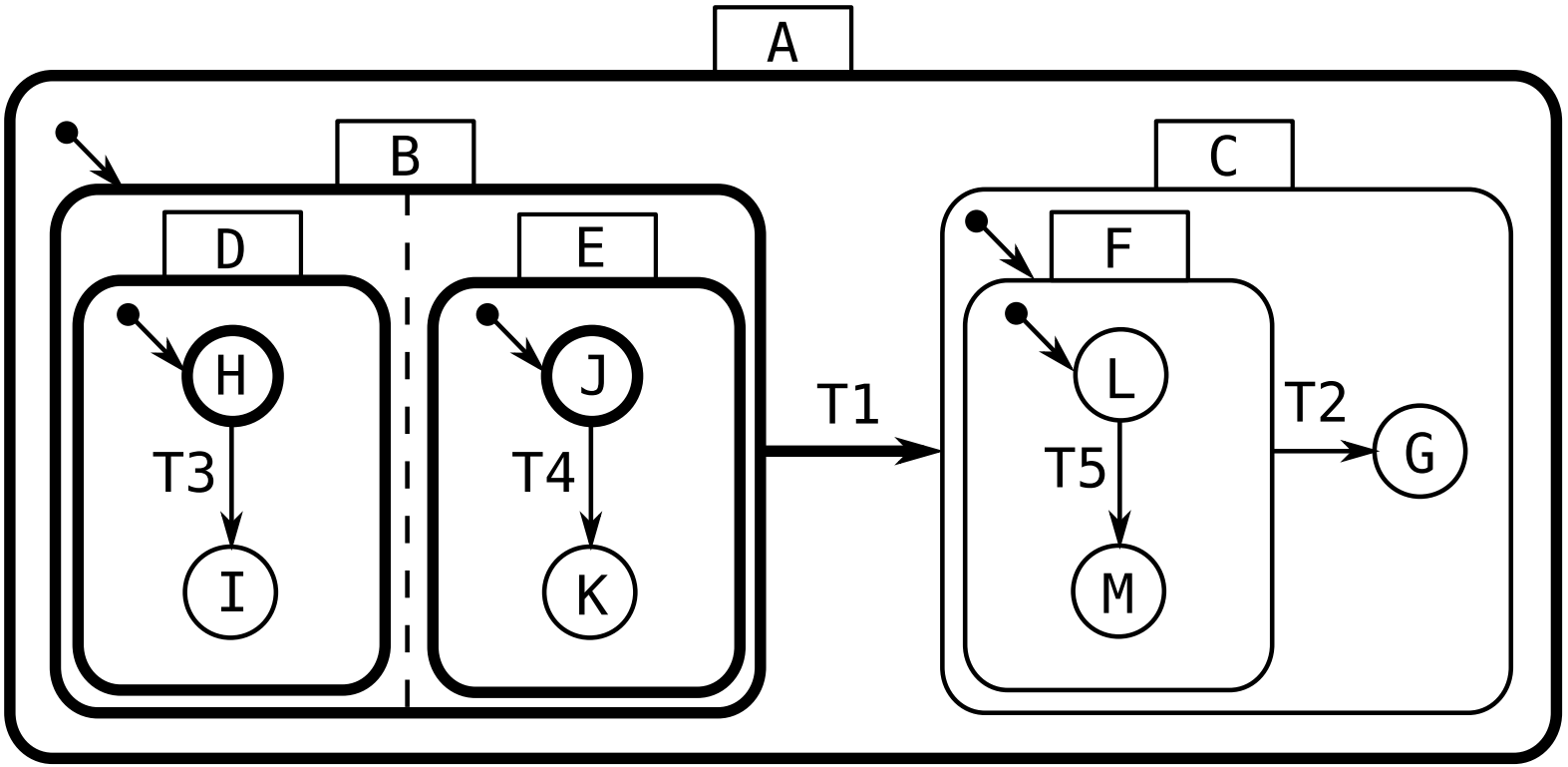
Hierarchical Timed Automata (HTA) extend UPPAAL's Timed Automata with a Statecharts-like **hierarchical structure**. It features:

- AND-locations and XOR-locations
- Real-valued clocks and integer variables (including arrays of variables)
- Synchronization channels
- Urgent edges
- A *Structural Operational Semantics (SOS)* for HTA states.

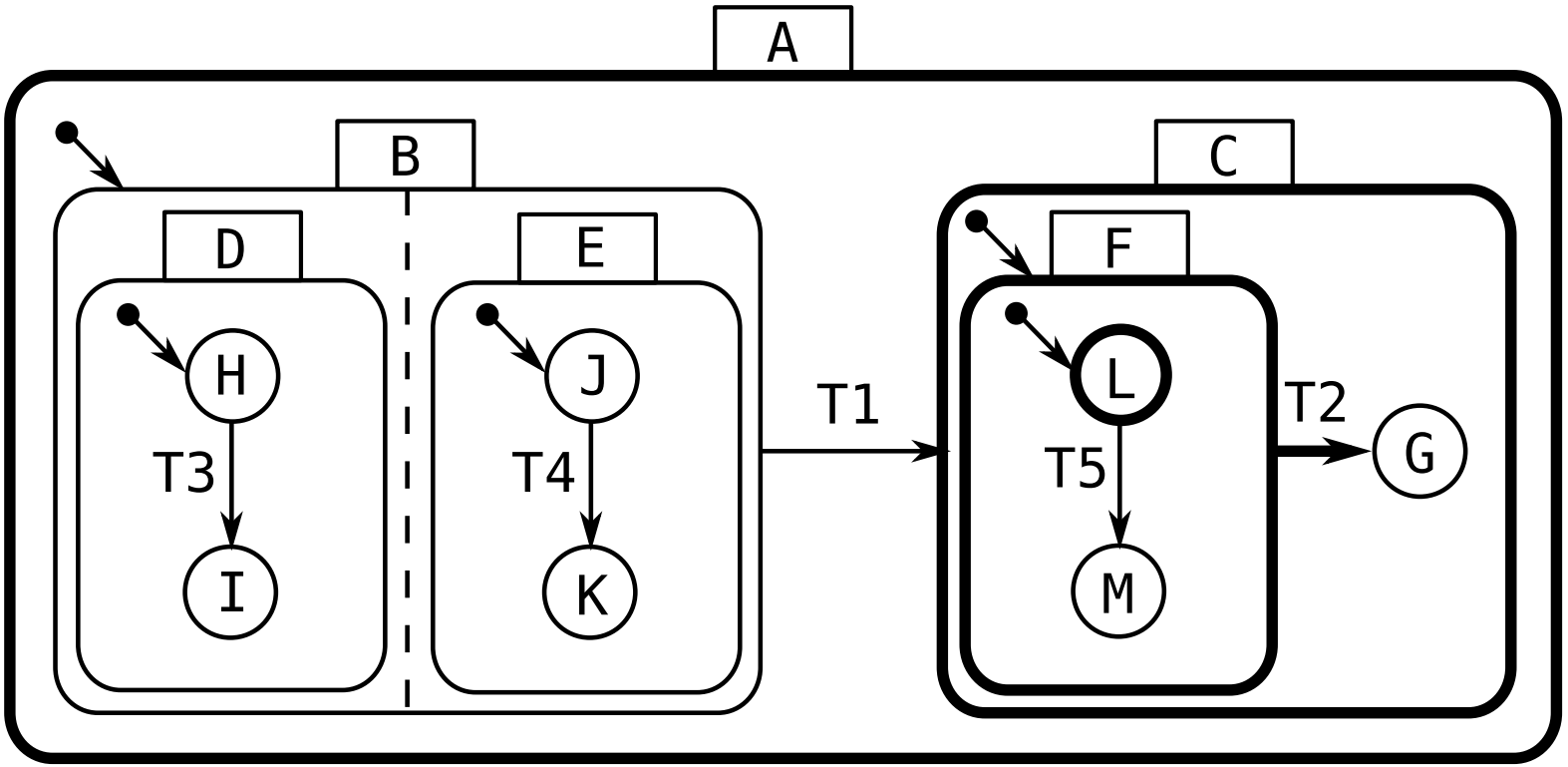
Simulation and verification with UPPAAL is possible by applying flattening algorithms.

A. David.
Hierarchical modeling and analysis of timed systems.
PhD thesis, 2003.

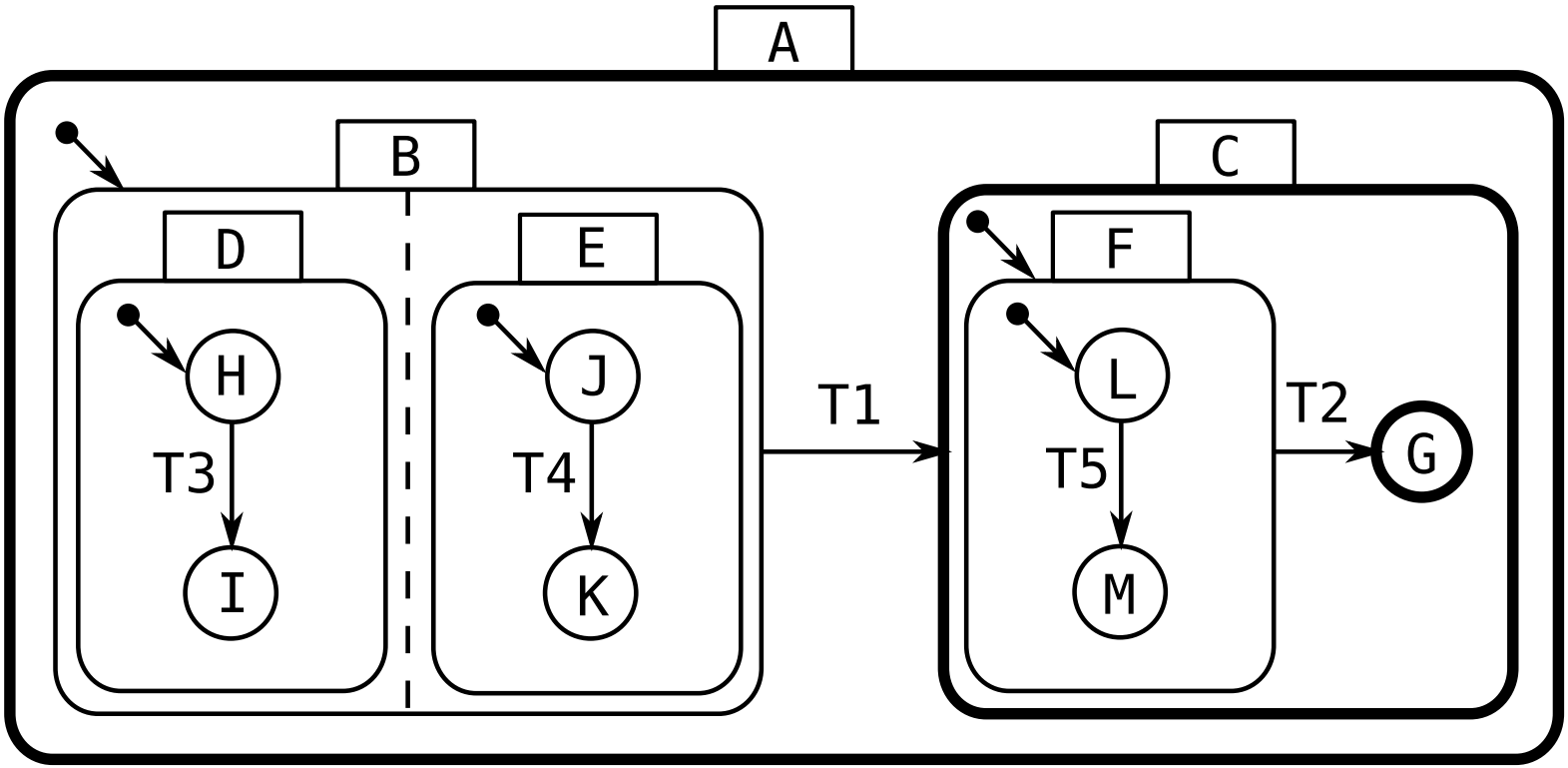
Evolution of a HTA



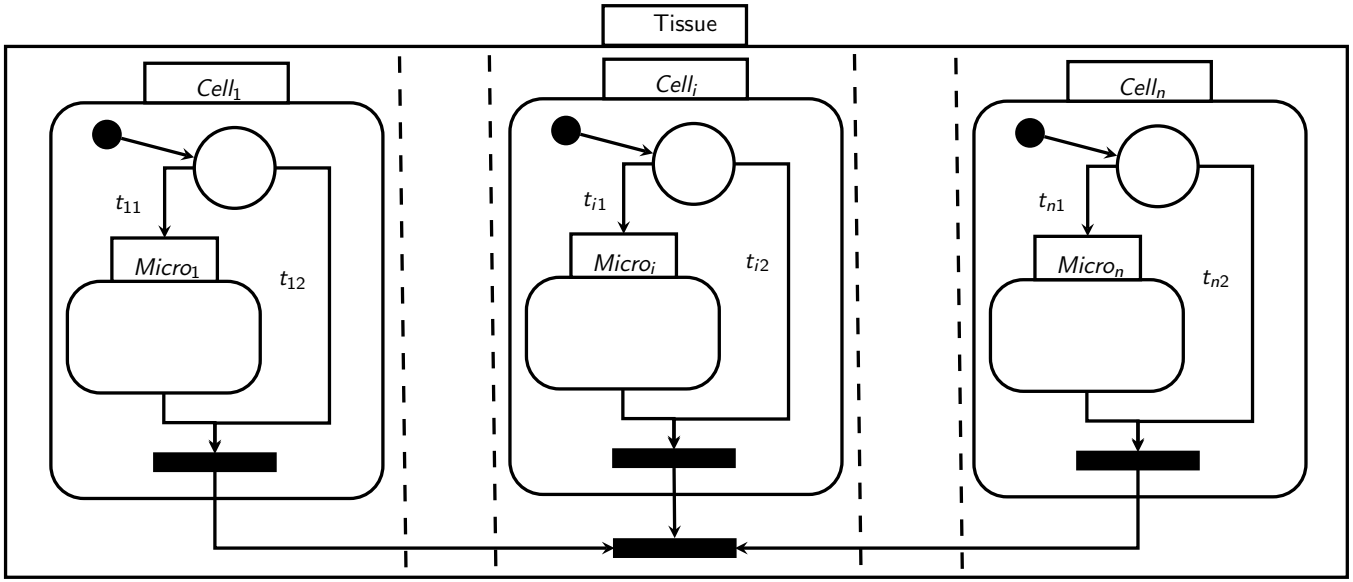
Evolution of a HTA



Evolution of a HTA



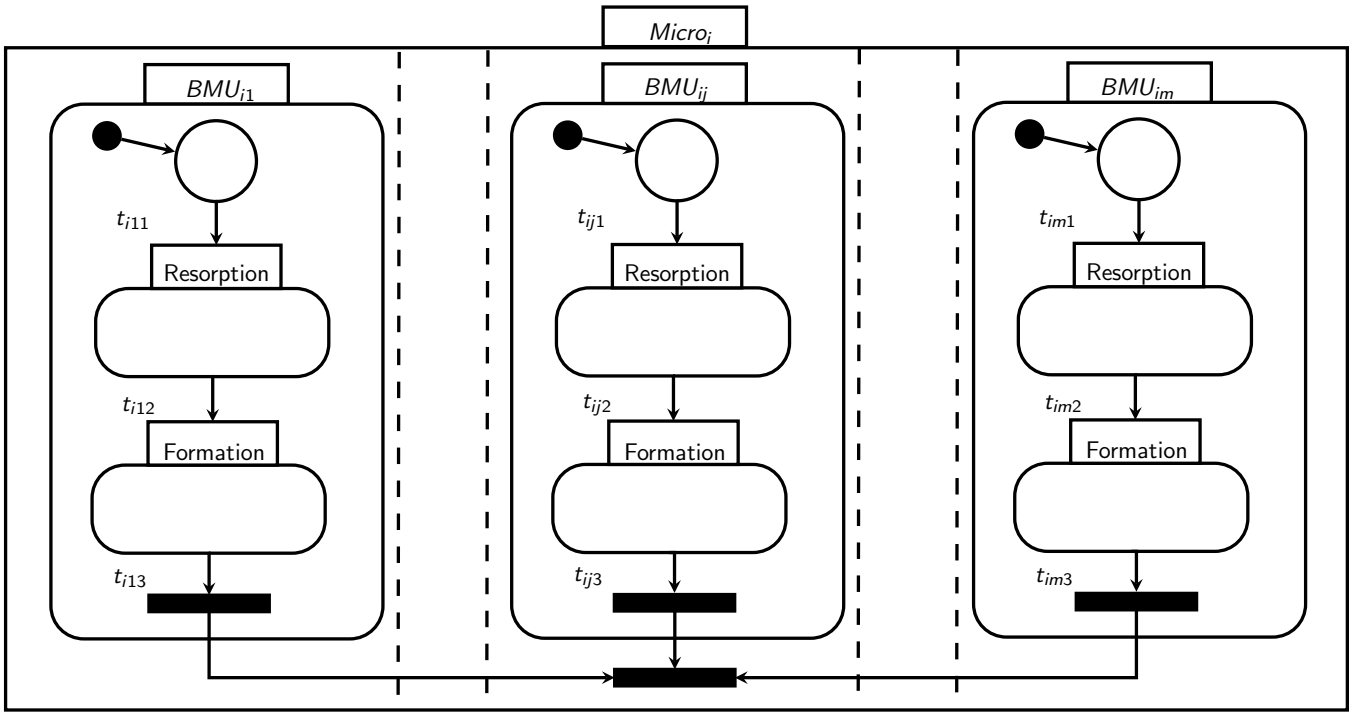
BR in HTA - *Tissue* location



$Var(Cell_i)$
density: an integer proportional to the mineralization density
stress: magnitude of mechanical stress

$t_{ij} : \xrightarrow{g_{ij}, s_{ij}, r_{ij}, u_{ij}}, j \in \{1, 2\}$
$g_{i1} = density \geq d_{min} \ \wedge \ density < d_{min} + \delta \ \wedge \ stress > f_{min}$
$u_{i1} = true; \ u_{i2} = false$

BR in HTA - $Micro_i$ location (1/2)



$Var(BMU_{ij})$
n_{Oy}: number of Osteocytes
n_{minC}: number of mineralized cells

$Clocks(BMU_{ij})$
x

BR in HTA - $Micro_i$ location (2/2)

Inv
$Inv(Resorption) = x \leq t_{resorption}$; $Inv(Formation) = x \leq t_{formation}$
$t_{ijk} : \xrightarrow{g_{ijk}, s_{ijk}, r_{ijk}, u_{ijk}}, k\{1,2,3\}$
$r_{ij1} = \{x := 0, n_{Oy} := f(density), n_{minC} := g(density)\}$
$g_{ij2} = x \geq t_{resorption}$
$r_{ij2} = \{x := 0, n_{Oy} := n_{Oy} - oy_{resorption}, n_{minC} := n_{minC} - c_{resorption}\}$
$g_{ij3} = x \geq t_{formation}$
$r_{ij3} = \{x := 0, n_{Oy} := n_{Oy} + oy_{formation}, n_{minC} := n_{minC} + c_{formation}\}$

- *Resorption* and *Formation* are **basic** locations
- This model can be further refined by specializing *Resorption* and *Formation* to the cellular level

HTA - Main features (1/2)

Faithfulness

- CxA only considers mechanical stimuli; cellular level is approximated to a lattice of O_ys
- SP includes complex cellular dynamics (biochemical signals, P_bs and P_cs formation, ...)
- HTA can potentially express complex cellular dynamics

Integration of different scales

- In CxA, integration schemes are native (edges of the graph); the *SSM* illustrates the single-scale processes wrt their spatial and temporal scales and of their mutual coupling
- SP systems don't include *a priori* integration mechanisms
- In HTA, a single level in the location hierarchy maps a single scale of the system

HTA - Main features (2/2)

Spatial features

- Spatial information in a CA is limited to the cell size, the total size and the neighbourhood relation
- SP systems implement *compartmentalization*, a *2D space*, and movement of objects by *evolution rules*
- HTA don't provide a notion of space (integer variables may model discrete coordinates)

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Shape Calculus (1/2)

Shape Calculus

The **Shape Calculus** is a bio-inspired **spatial** process algebra for describing 3D processes moving and interacting in the 3D space. A 3D process is characterized by

- a *behaviour* specified in Timed CCS
- a *shape* (basic or complex). Shapes have a position, a velocity and a mass, and can be composed by *binding* on compatible channels exposed in their surface.

E. Bartocci, F. Corradini, M. Di Berardini, E. Merelli, and L. Tesei.
Shape Calculus. A Spatial Mobile Calculus for 3D Shapes.
Scientific Annals of Computer Science, 20, 2010.

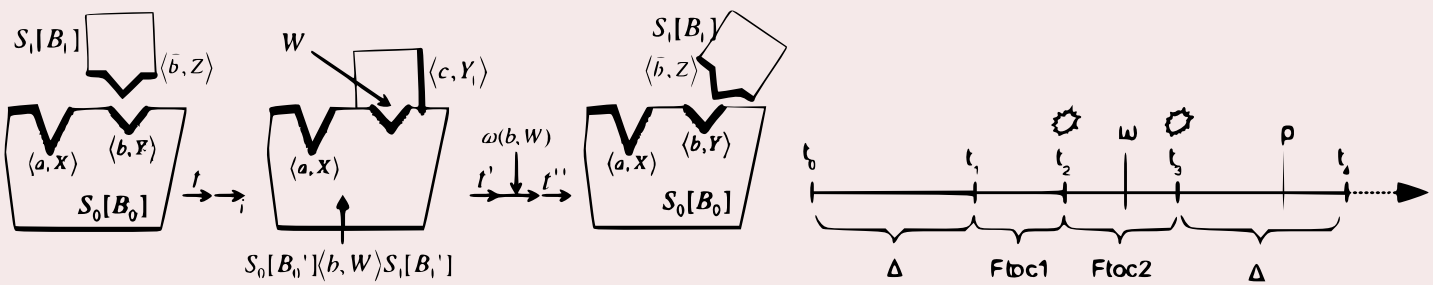
Shape Calculus (2/2)

- Two operators for breaking bonds: ρ, *strong-split* (urgent) and ω, *weak-split* (not urgent).
- The time domain is continuous, but divided into small time steps Δ. At each step, collisions are resolved and velocities are updated. The detection of a collision can break the timeline before Δ has elapsed.

Bind, split, collision detection

Example

In figure (a), the binding of the processes $S_0[B_0]$ and $S_1[B_1]$ on channel $\langle b, \cdot \rangle$; the resulting composed process is $S_0[B_0]\langle b, W\rangle S_1[B_1]$, where W is the common surface of contact $Y \cap Z$; eventually, a weak split occurs.
Figure (b) shows an example of timeline; collisions break the timeline, while splits are resolved at the end of the time step Δ.



(a) Binding and weak-split (b) Timeline and events

3D Shapes

Definition (3D Shape)

The set $\mathbb{S}$ of **3D shapes** is generated by the grammar $S ::= \sigma | S\langle X \rangle S$, where σ is a basic shape (*sphere*, *cone*, *cylinder* or *convex polyhedron*) and X is the common surface.

Definition (Shape behaviours)

The set $\mathbb{B}$ of **shape behaviours** is given 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 K is a process name, and $\epsilon(t)$ is the delay operator.

3D Processes

Definition (3D Process)

The set 3DP of **3D processes** is generated by the grammar $P ::= S[B] \mid P\langle\alpha, X\rangle P$, where $S \in \mathbb{S}$, $B \in \mathbb{B}$, and $\langle\alpha, X\rangle$ is a channel with $X \neq \emptyset$.

BR model in the Shape Calculus

Shape Calculus multiscale model

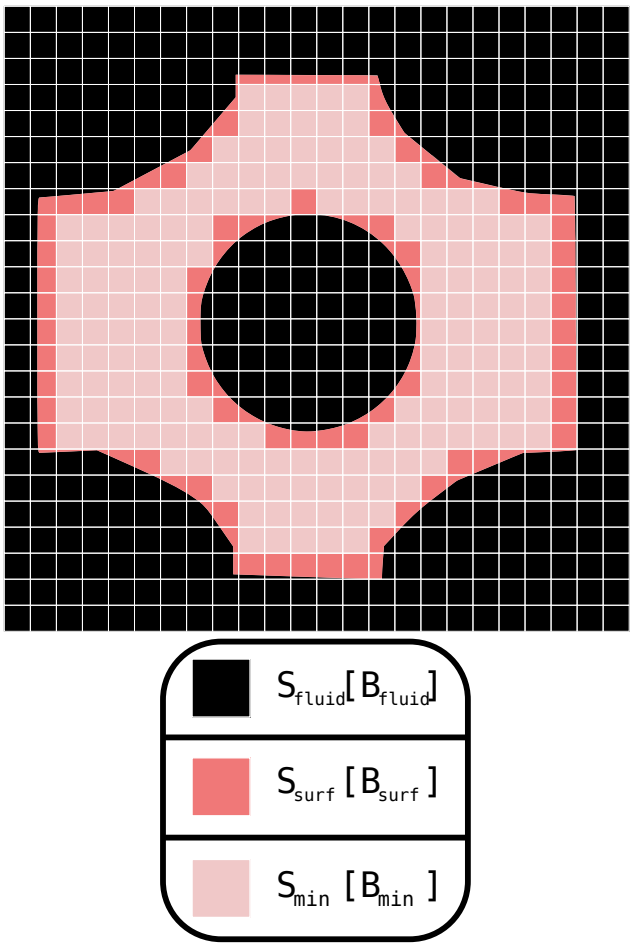
- **Tissue level:** is modelled with bone and fluid cubes; surface cubes are decomposed in more complex shapes.
- **Cellular level:** a BMU is represented as a network of 3D processes (O_ys, L_cs, P_bs, P_cs, O_bs, O_cs).

BR in the Shape Calculus - Tissue model

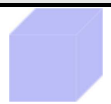
The process involved are:

- $\mathbf{S_{min}[B_{min}]}$, a mineralized component with mass $\mathbf{m + n}$
- $\mathbf{S_{fluid}[B_{fluid}]}$, a fluid component with mass $\mathbf{m}$
- $\mathbf{S_{surf}[B_{surf}]}$, a surface component with mass $\mathbf{m} + \delta\mathbf{n}$

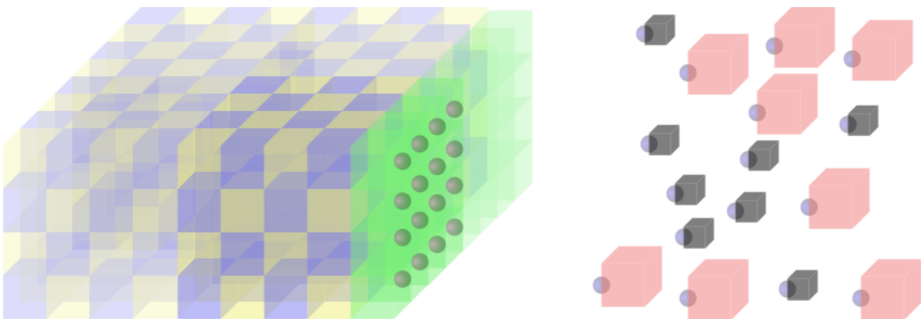
δ is the mineralization density of a cell; in S_{surf}, $0 < \delta < 1$, in S_{min}, $\delta = 1$, while in S_{fluid}, $\delta = 0$.



BR in the Shape Calculus - Cellular model (1/2)

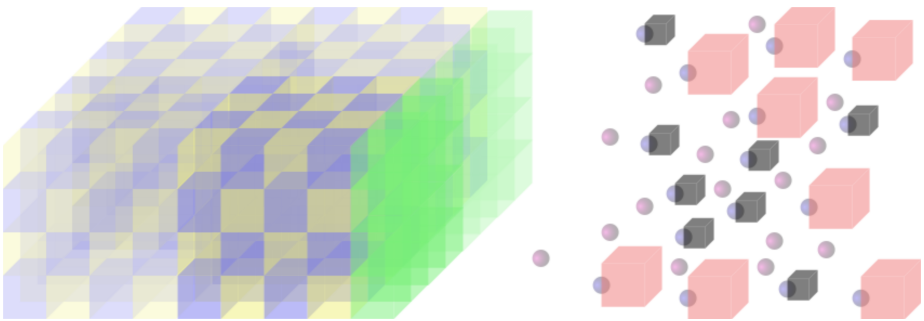
3D Process	Description	Shape
$\mathbf{S_{oy}[B_{oy}]}$	a cell with an O_y	
$\mathbf{S_{c}[B_{c}]}$	a cell without O_ys	
$\mathbf{S_{lc}[B_{lc}]}$	a L_c	
$\mathbf{S_{sig}[B_{sig}]}$	the signal produced by a O_y	
$\mathbf{S_{pb}[B_{pb}]}$	a pre-osteoblast	
$\mathbf{S_{pc}[B_{pc}]}$	a pre-osteoclast	
$\mathbf{S_{rec}[B_{rec}]}$	the receptor for $\mathbf{S_{sig}[B_{sig}]}$	

BR in the Shape Calculus - Cellular model (1/2)



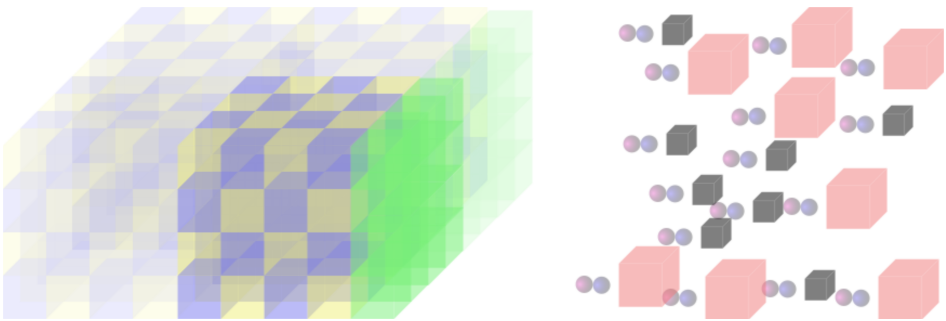
Mineralized cells are bound together, so implementing the network of canaliculi. O_ys activates remodelling by performing a $\overline{can}$ action which propagates towards the lining cells. A receptor is attached to each P_b and P_c.

BR in the Shape Calculus - Cellular model (1/2)



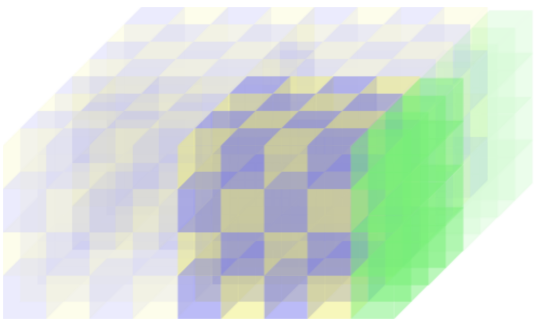
A remodelling signal is attached to each L_c; when a L_c binds with a mineralized cell on an exposed channel $\langle can, \cdot \rangle$, a weak split causes $S_{sig}[B_{sig}]$ to detach and move towards the fluid part.

BR in the Shape Calculus - Cellular model (1/2)



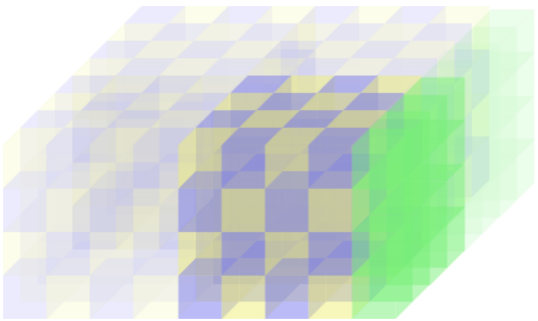
Signals collide and bind with receptors on channel $\langle a_{sig}, \cdot \rangle$, provoking another weak split which involves pre-osteoblasts and pre-osteoclasts.

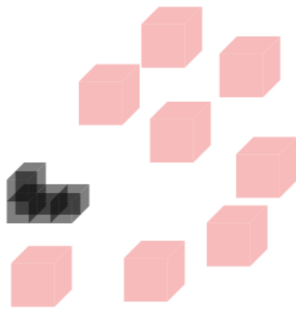
BR in the Shape Calculus - Cellular model (1/2)



P_cs move randomly and aggregate by binding in order to form a full O_c

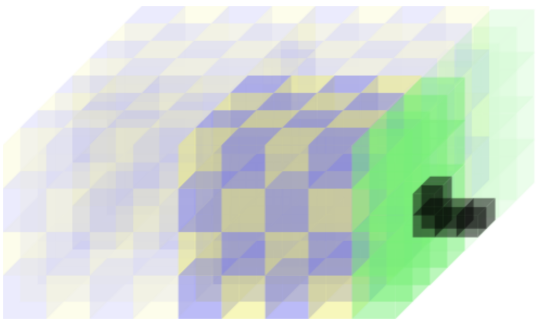
BR in the Shape Calculus - Cellular model (1/2)





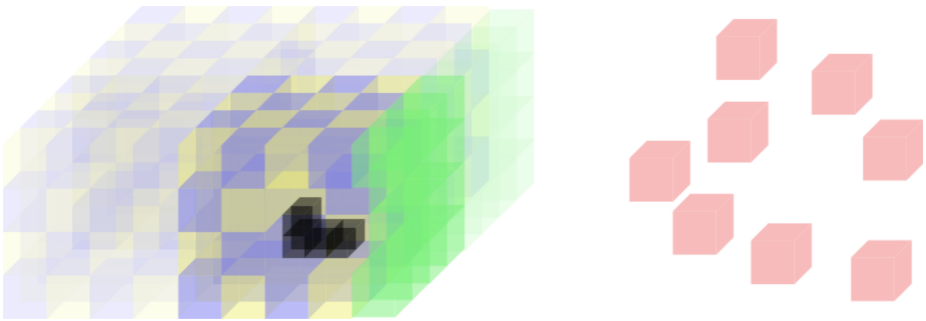
A grown O_c corresponds to the composition of n_OC P_cs. Here, $n\_OC = 8$

BR in the Shape Calculus - Cellular model (1/2)



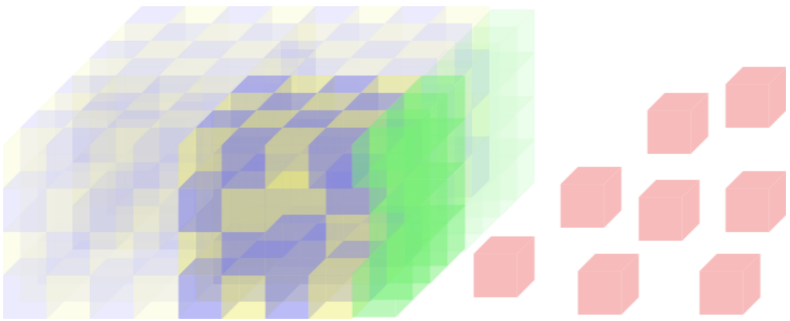
Once the osteoclast is formed, its velocity is updated so that it can reach the mineralized part in a time t_{OC}.

BR in the Shape Calculus - Cellular model (1/2)



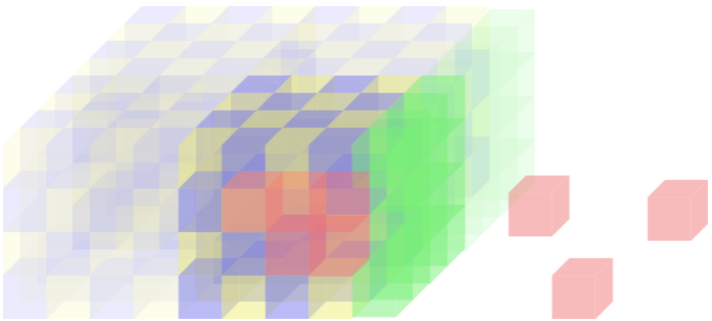
A O_c can erode a single mineralized cell (or L_c) for each of its free surfaces. A mineralized cell is absorbed when it binds to an O_c on a channel $\langle del, \cdot \rangle$; then, a strong split breaks all the bonds of the cell which is send out of the BMU.

BR in the Shape Calculus - Cellular model (1/2)



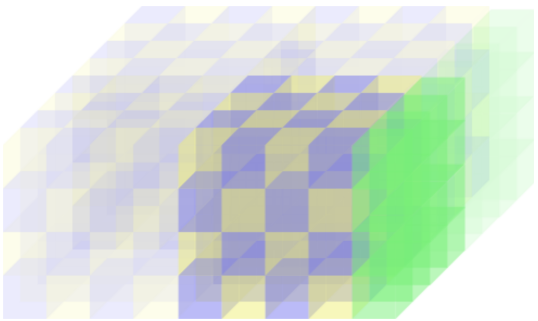
After a time t'_{OC}, the O_c undergoes apoptosis; at the same time, P_bs turn into mature osteoblasts and reach the bone surface in a time t_{OB}.

BR in the Shape Calculus - Cellular model (1/2)



Each O_b attach to a bone cell and behaves as B_{oy} or B_c, so replacing the consumed cells. The bone formation process lasts a time t'_{OB}, after which the remaining O_bs replace the absorbed lining cells.

BR in the Shape Calculus - Cellular model (1/2)



The original structure is re-established.

BR in the Shape Calculus - Coupling scheme

Scale Integration Functions

- **f $\downarrow$ (top-down):** computes the number of mineralized cells in the BMU model, which is proportional to the mass of the corresponding tissue cell $\mathbf{m}(S_{surf})$, which in turn depends on the density δ.
- **f $\uparrow$ (bottom-up):** after the execution of the BMU model, $f\uparrow$ modifies $\mathbf{m}(S_{surf})$ according to the new mineralization values of the lower level.

Shape Calculus - Main features (1/2)

Faithfulness

- CxA only considers mechanical stimuli; cellular level is approximated to a lattice of O_ys
- SP and Shape Calculus include complex cellular dynamics (biochemical signals, P_bs and P_cs formation, ...)
- HTA can potentially express complex cellular dynamics

Integration of different scales

- In CxA, integration schemes are native (edges of the graph); the *SSM* illustrates the single-scale processes wrt their spatial and temporal scales and of their mutual coupling
- SP systems and Shape Calculus don't include *a priori* integration mechanisms
- In HTA, a single level in the location hierarchy maps a single scale of the system

Shape Calculus - Main features (2/2)

Spatial features

- Spatial information in a CA is limited to the cell size, the total size and the neighbourhood relation
- SP systems implement *compartmentalization*, a *2D space*, and movement of objects by *evolution rules*
- HTA don't provide a notion of space (integer variables may model discrete coordinates)
- In the Shape Calculus, processes are located in the *3D space*, and have a *shape*, a *mass*, and a *velocity*; it supports *elastic collisions*, *inelastic collisions* (binding) and *splitting*

Outline

1. Introduction
2. Bone Remodelling
3. Formal models for Bone Remodelling
   - Complex Automata
     - Bone remodelling in CxA
   - Spatial P Systems
     - Bone remodelling in SP
   - Hierarchical Timed Automata
     - Bone Remodelling in HTA
   - Shape Calculus
     - Bone remodelling in Shape Calculus
4. Conclusions

Comparison table

Formalism	Time	Space	Hierarchy
Complex Automata	Discrete step	Discrete lattice Neighbourhood	∅
Spatial P Systems	Discrete step	Discrete lattice Compartmental	Membrane Hierarchy
Hierarchical Timed Automata	Continuous ($\mathbb{R}$) Discrete event	Not explicit	Location Hierarchy
BioAmbients	Discrete event	Compartmental Particle-based	Compartment nesting
Bio-PEPA	Discrete event ODE semantics	Compartmental	Compartment nesting
$L\pi$	Discrete event ODE semantics	Lattice (subvolumes) Compartmental	Compartment nesting
Shape Calculus	**Continuous** ($\mathbb{R}$) **Δ approximation** **Discrete event**	**Continuous** ($\mathbb{R}^3$) **Particle-based** **Physical laws**	∅

Other spatial and hierarchical formalisms

- **Dynamic Cellular Automata (DCA)**
- **Hierarchical Petri Nets**
- **Hierarchical Markov Processes**
- **Algebra of Hierarchical Graphs**
- **Spatial and geometrical PAs:** 3π, Spatial CLS, Space π, Shape Calculus, $L\pi$, Attributed π ($\pi(L)$)
- **PAs with localities/compartments/membranes:** Bio-PEPA, BioAmbients, Join-calculus, Klaim, Beta-binders, Brane Calculus, Calculus of Wrapped Compartments (CWC), ...
- ...

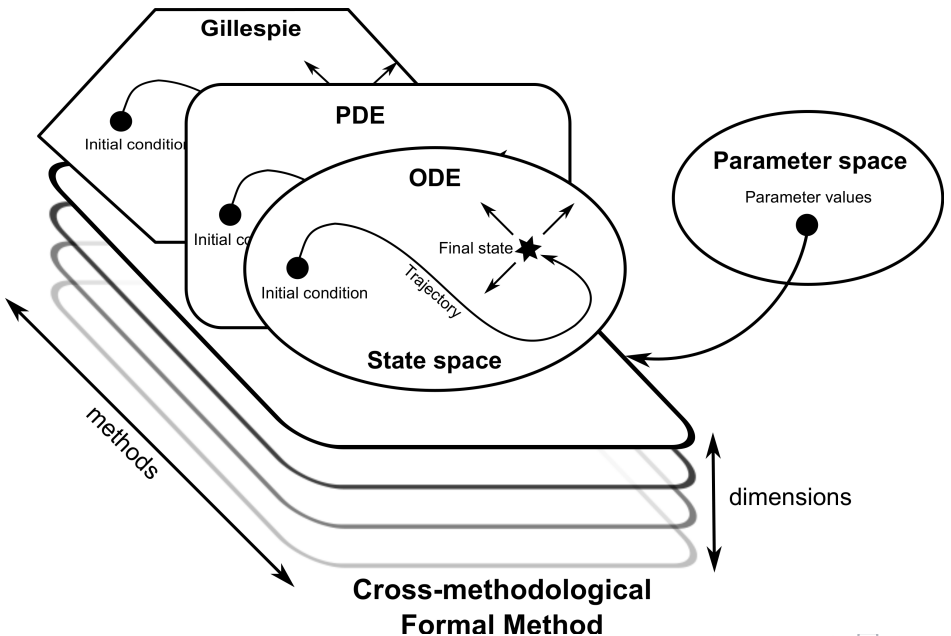
Current work

- Simulation of a BMU model described in a Shape Calculus-like syntax, in **Repast Symphony** [1], an agent-based modelling and simulation platform.
- Collaboration in the development of BioShape [2], a particle-based spatial 3D simulator and a multiscale modelling environment for biological systems.
- Implementation of an ODE model at BMU level in **CUDA (Compute Unified Device Architecture)** [3], a parallel computing architecture for GPU-computing.

[1] http://repast.sourceforge.net/
[2] http://cosy.cs.unicam.it/bioshape/
[3] http://www.nvidia.com/object/cuda_home_new.html

Future work

- Investigation of new **uniform** computational approaches for multiscale modelling
- A study on the relative expressiveness of the Shape Calculus wrt other Spatial and Mobile PAs.
- **Formal verification** of qualitative and quantitative properties in the Shape Calculus



Acknowledgements

Marco Viceconti from the *Istituto Ortopedico Rizzoli* [4] for his scientific support and his collaboration with our research group

UNICAM **CO**mplex**SY**stems Research Group [5]

[4] http://www.ior.it
[5] http://cosy.cs.unicam.it/

Thank you!