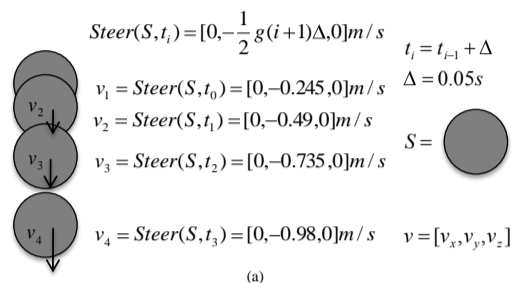


Shape Calculus

Shape Calculus is a non-deterministic timed calculus in which processes represent physical entities moving in a 3D space. Processes are composed of a 3D shape and a dynamic behaviour, represented by the terms $P ::= S[B] \mid P \langle a, X \rangle P$. Behaviours B are specified with a timed CCS-like process algebra where channels $\langle a, X \rangle$ are used to model binding sites on the surface of shapes S . In particular, a channel is a "type of binder" where the set of 3D points X represents the surface of S in which the channel a is active, i.e. it can bind with a corresponding type \bar{a} . Communication can only occur when two processes P_1 and P_2 collide on a compatible channels, i.e. $P_1 \xrightarrow{\langle a, X_1 \rangle} P'_1$ and $P_2 \xrightarrow{\langle \bar{a}, X_2 \rangle} P'_2$ and $X_1 \cap X_2 \neq \emptyset$. The resulting process $P_1 \langle X \rangle P_2$ has behaviour equal to the interleaving of the continuation behaviours of P_1 and P_2 and shape, $S_1 \langle X \rangle S_2$, composition of the shapes of P_1 and P_2 .



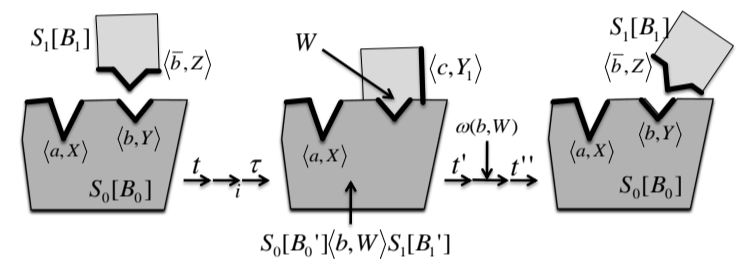
Collisions between processes occur due to their movement. Continuous trajectories of processes are simulated by discretely updating a velocity vector associated with their shape. The time domain $\mathbb{T} = \mathbb{R}^{\geq 0}$ is divided into an infinite sequence of movement timesteps t_i such that $t_0 = 0$ and $t_i = t_{i-1} + \min(\Delta, Ftc(t_{i-1}), Ftr(t_{i-1}))$. The small interval Δ is the timestep at which the velocity vector is updated for every process, unless before its expiration a collision occurs, in particular the first collision at the *First time of contact* (Ftc). In this case the time step is interrupted before Δ , all collisions are resolved and the next time step is started. The same early interrupt is performed if a reaction occurs before Δ and before the Ftc , in particular the *First time of reaction* (Ftr) is considered in this case. Let \mathbb{S} be the set of all shapes and \mathbb{V} the set of velocities, at every timestep t_i a function $steer: \mathbb{T} \mapsto \mathbb{S} \mapsto \mathbb{V}$ is called to update the trajectory of all the shapes that are in the network of processes at that moment. If a collision on a compatible channel

occurs, binding is managed according to the process behaviour defined as follows: $B ::= nil \mid \langle a, X \rangle . B \mid \omega(a, X) . B \mid \rho(L) . B \mid \epsilon(d) . B \mid B + B \mid K$

L is a finite set of channels, K is a process variable and $d \in \mathbb{T}$ is a time delay. A behaviour of type $\epsilon(d) . B$ let d time units elapse and then behaves as B . Note that inside a compound process interactions of type ω and ρ are possible. A communication between $\omega(a, X)$ and $\omega(\bar{a}, Y)$ produces an ω (non-urgent action) and causes a compound process to physically split from a previously established bond $\langle a, Z \rangle$, $Z = X \cap Y$ and continue as two new independent 3D processes. This kind of communication is needed to represent a non-deterministic non-urgent split of processes that is typical, for instance, in biochemical reactions. Finally, a communication of type $\rho(L)$ is used to model a reaction, i.e. an urgent (produces a visible action ρ) split of all the existing bonds of L where the pieces represent the products of the reaction and are new 3D independent processes.

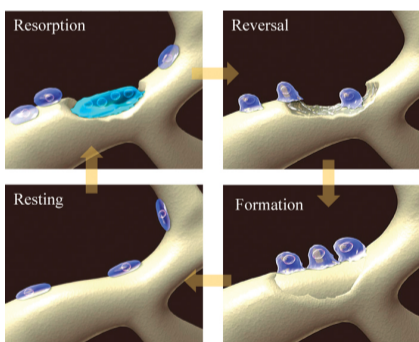
A set of networks of 3D processes is generated by the following grammar: $N ::= nil \mid P \mid N \parallel N$

A network N is a collection of 3D processes moving in space, colliding, binding and splitting. A proper operational semantics can be defined to precisely describe the evolution of a network of 3D processes taking into account collision detection, weak splitting (ω) and reactions (ρ). The resulting observable object is a timed labelled transition system containing all possible network configurations.



BIO SHAPE

BIO SHAPE is a simulating tool in which an **individual-based geometric 3D environment** is composed of a network of Shape Calculus processes - the *entities* - enriched by specific information about motion and behaviour. An autonomous entity, having a (possibly complex) 3D shape, moves independently and communicates by (non-)collision-driven interactions with other entities. As soon as a specified model is validated with available qualitative and quantitative data from literature, BIO SHAPE can be used to perform in silico experiments (simulations) that are useful to biologists and bioengineers for hypothesis testing, in vitro and in vivo experiment design, and ultimately for gaining of new qualitative and quantitative biological information.



BIO SHAPE has been applied on a particular biological case study, the **bone remodelling**. This process is the continuous substitution of old bone with new bone and occurs in every live being that is skeleton-enabled. It 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), reversal (precursors of Osteoblasts, responsible for bone formation, starts to appear on the resorption pit), formation (mature Osteoblasts starts to form new soft nonmineralized bone until the bone is completely reconstructed) and resting (bone site remains dormant continuing to mineralize until the next cycle).

In an healthy individual such a process does not alter the global morphology/mass of the bone; on the contrary, in presence of Osteoporosis, Diabetes or other diseases such an equilibrium lacks. BIO SHAPE has been used to show in a finer manner, w.r.t. coupled continuous-based models, the blurry synergy between the macroscopical aspects (such as mechanism stimuli) and the microscopical ones (hormones/cellular concentration and other systemic factors) that influence the process.

Toward quantitative aspects

Shape Calculus has been proposed to represent a great variety of scenarios especially to describe complex biological phenomena like the bone remodelling process. Together with BIO SHAPE, we have a powerful framework to analyse such phenomena starting from qualitative and quantitative data available from literature. However, to naturally complete the framework we need to provide formal verification techniques for the Shape Calculus. The objective is to find the right abstractions and boundaries that permit the application of existing quantitative model checking or quantitative equivalence checking techniques to the evolution of a given network of Shape Calculus processes. For instance, probabilistic timed automata could be useful to describe in more detail the behaviour of the processes and their interactions while hybrid automata could be used to specify schemes of motion to be associated to certain classes of processes. Suitable logic languages for specifying the properties must also be identified. Referring to bone remodelling process, we would answer questions like the following ones, in the context of gaining quantitative information from the model:

- ▶ How much mineralized bone is destroyed by an Osteoclast (i.e. the cell responsible for bone resorption) and in how much time?
- ▶ How many cells are created by an Osteoblast (i.e. the cell responsible for bone regeneration) and in how much time?
- ▶ Which is the maximal size an Osteoclast can reach before starting to erode the mineralized bone?
- ▶ How orientation of involved actors (Osteoblasts & Osteoclast) affect resorption/regeneration activities in term of time and energy loss?
- ▶ ...

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