

Computing with the Cytoskeleton : A Problem of Scale

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February 23, 2007

Abstract

Microtubules and actin filaments are dynamic fibres constituting the skeleton of living cells. They show seemingly computational behaviours. Indeed, depending on conditions of reaction, they self-organise into temporal and/or spatial morphologies *in vitro* and act as micro-machine processors and actuators in living cells. Other systems – such as the bacterium-actin system – exist that 'know' how to re-use the cytoskeleton for their own use (e.g. propulsion inside the cell).

We discuss here about the possible reuse of the cytoskeleton for constructing fibrillar-based computational systems. I analyze particularly the possible existence of computational events based on 'chemical collisions' between microtubules. A molecular model of microtubule disassembly has been developed to verify that heterogeneities of composition and/or concentration of the chemical medium can form from shrinking microtubules and persist. They could serve as an efficient communication channel between fibrillar agents. Numerical simulations show that only very weak heterogeneities of composition form around the microtubule ends. However, the model predicts that they are notable when produced by arrays of numerous fibres such as microtubule arrays or comets of actin.

1 Introduction

Computing by using the dynamic fibres of the cytoskeleton (microtubules, actin filaments and microfilaments) is a dream shared by many physicists since a long time. The benefits would be indeed the possibility to develop massive parallel computing devices or micromachines at the micrometer scale.

Those fibres are supramolecular assemblies always reacting, aggregating their subunits or restituting them to the medium, and consuming the chemical energy provided by triphosphated nucleotides. The cytoskeleton has its own reactive properties and behaviour but, in the cells, it is also combined with numerous associated proteins that give a cohesion to the cytoskeletal structure, organise it and add new properties to individual fibres. The cytoskeleton is controlled and used by the living cells to maintain or change their shape and to perform numerous functions – and form the associated organites – such as cell division, internal transport of vesicles, and the structuration and actuation of cytoplasmic extensions such as cilia, flagella and pseudopods. Examples where the cytoskeleton is particularly implied in a cellular process are numerous. Striking examples are the mitosis – during which a cell divides into two identical cells –, the exploration ability of lymphocytes or macrophages of the immune system driven by the cytoskeleton, and morphogenetic processes, for instance the symmetry breaking of the cell shape in early tissues – e.g. the formation of 'bottle' cells from cubic cells that constitute the mesoderm of the ventral furrow (future digestive tube) [1,2] – due to local metabolic or energetic changes in the cells. Further, parasitic bacteria such as *Listeria* or *Shigella* re-use the actin network to propel within cells [3,4].

Finally, the fibrillar proteins of the cytoskeleton, in particular microtubules, are well known for their ability to show self-organising behaviours. Solutions *in vitro*, starting from homogeneous 'soups of molecules', develop

oscillatory temporal series [5,6], spatio-temporal behaviours (wave propagation as in excitable media) [7,8] or well structured morphologies made of ordered populations of fibres [9–11]. Temporal oscillations of the concentration of microtubules in the solution are now well described by models of microtubular population dynamics. Spatio-temporal behaviours are also well described at the macroscopic scale by reaction-diffusion kinetics [8] but little is known about their spatial self-organisation. Theoretical models based on collective systems and reaction-diffusion dynamics at the level of individual microtubules were advanced in order to explain this phenomenon [11–13]. In this scheme, the microtubules, due to their dynamics, modify locally the chemical medium – that way generating a trail of chemicals when disassembling and a depleted area when assembling – and information is then shared between neighbouring individuals. Unfortunately, at least three counter arguments contradict strongly the idea that the microtubular cytoskeleton self-organises spatially from microscopic to macroscopic levels due to a chemical communication between individuals. (i) *in vitro* spatially self-organising solutions have a composition that favours microtubule stability [15–17] ; (ii) in such concentrated solutions, mechanical effects or electrostatic interactions should have intense effects compared to the relative effect of the action of chemical communications [18,19,33] ; (iii) the existence of the hypothetical chemical trails, possible vectors of a short range communication between microtubules, is being called into question because the diffusion of the released subunits that form the trail is such that the trail becomes inconsequential [14,17].

Viewed by a computational scientist, these living systems look like micromachines that integrate external signals and transform them into deterministic behaviours. This keeps out of sight the fact that those macroscopic observable deterministic-like behaviours emerge from a multitude of stochastic processes occurring at the lower scales between individual molecules. But the cells 'know' how to control this stochasticity: their structures self-organise from the lower scales to the higher scales, constituting imbricated meta-structures, until the level of the cell, the units of life. Stimulated by external signals or by signals intrinsic to the cell (genomic signals induced by internal metabolic cycles for instance), the cytoskeletal structures reorganise, producing an adapted response of the cell. Within this theoretical context, the cytoskeleton appears to be a central system in those biological 'micromachines'.

The article reviews different manners to conceive a computation based on the cytoskeleton (see [14] for further details) ; they depend on the scale considered for the computation. Then, we will focus on a possible computation based on chemical collisions between agents assimilated to dynamic fibres. The potential of such an approach would be biochemical – or bio-inspired artificial – massive parallel computers based on real collective agents interacting at the micrometer scale.

2 Different scales, different manners to compute

Different – imbricated – levels of cytoskeletal-based computation can be considered :

- *The fibrillar scale.* A computation effectuated directly inside the fibre or at its surface has been proposed initially by R. Penrose, S. Hameroff and J. Tuszynsky [21–27] for microtubules or actin filaments. Charges or conformational states inside or captured by the monomers of these supramolecular assemblies could be used as biochemical bits of information. Such biochemical states were predicted by models to be able to propagate within a fibre or at its surface. Computational events could then occur such as collisions of propagating waves of biochemical states. Moreover, they predict that communication between fibres could be relayed by the associated proteins that connect individual fibres in the cytoskeletal network. This process is thought to play an important role in integration and 'pre-computation' of the bioelectrical signals in neurons. It's difficult to ignore such possible effects considering that microtubules represent 10% of the proteins in a brain. This suggests a new manner (subcellular) to understand the functioning of the brain, in addition to the concepts used habitually for describing neural networks.
- *The scale of a small number of fibrillar agents (small population).* At this scale can be described the chemical relationships between individual reacting agents and the chemical environment, connecting correspondingly and indirectly each agent to other neighbouring fibres (see Fig. 2A and B). This system is similar to ant colonies where a population self-organizes by way of the chemical trails – constituted by messenger molecules called pheromones – that the ants release behind them. The neighbourhood is delimited by the ratio between the diffusion rate of the molecules that constitute the released trails and

the reaction rate of the agents (here, the reacting ends of the fibres). When this ratio increases, the neighbourhood extends far away from the reacting tip from which the signal (the trail) originates, but in the same time the signal decreases in intensity. The intensity of the signal is related to the number of messenger molecules per unit of space. In those systems, an important parameter is also the amounts of matter implied in the chemical trails.

Moreover long fibres diffuse less rapidly than their monomers. They stay more or less in the same element of volume during their existence and are constituted by subunits taken from this element of volume. When they disassemble, they reconstitute the monomers to this small volume. The total amount of fibres in the considered element of volume depends on the conditions that have permitted their formation : in favourable conditions, numerous fibres can form (and reciprocal). In consequence, in this scheme, the supramolecular assemblies – or groups of fibres – can be viewed as ‘memories’ that store locally the information (the reactive conditions that prevailed before their assembly) into a condensed form.

- *A population at the millimeter scale (huge number of individuals).* Now, a description of macroscopic ordering is possible. This level can be viewed as the manifestation of a computation based on chemical communications between agents. When considering nanofibres (e.g. actin, microtubules), other mechanisms, however, such as mechanical effects (buckling of individual fibres, bundling into parallel arrays ...) that can not be controlled easily, can cause local self-ordering of fibres but also global self-ordering when influenced by global effects such as weak external fields (gravity, magnetic fields ...) [18,33]. Nevertheless, reactive conditions exist where mechanical effects are inconsequential and where the reaction-diffusion effects – as described before – are dominating. This explains how individual microtubules are synchronized within the propagating waves of microtubular concentration observed by Mandelkew et al [7,8], or how they synchronize within the entire solution for generating periodic temporal oscillations [5,6].
- *The same scale enhanced by the control of regulatory systems and organizing centers.* Finally, one can consider the same level of description, but in a different context, by adding cellular features such as organising centres (centrioles, linking or branching associated proteins (e.g. kinesin, dynein, Arp2/3), ...), associated enzymes (e.g. ADF cofilin for the Actin network), energetic molecules (ATP, GTP) or ionic species (Mg^{2+} , Ca^{2+} , ...) that regulate the reactivity of the fibres, and genetic regulatory systems that control the amounts of components in the system. Using this ‘arsenal’, living cells control accurately the cytoskeleton for realising various actions (moving, dividing, ...). This is close to the description of a micromachine.

3 Multi-agents collision-based computation

3.1 Considering individual fibres as units of a collective system

In order to showcase the existence of a possible communication between individual fibres, a molecular model of microtubule has been conceived where all monomers (tubulin-GTP and tubulin-GDP) are represented and where an unique fibre or an array of fibres disassembles. During the simulation, we observe the distribution of the released particles (tubulin-GDP) all around the reacting tips of the microtubules [14,17]. In this model, all molecules (monomers and polymers) are assimilated to ellipsoids, and their diffusion rates along their 3 axes are calculated in function of their 3 respective radiuses. This allows observing the effect of anisotropic diffusion, particularly for the polymers that have a very long axis compared to their diameter and a limited diffusion perpendicular to this principal axis.

It results from this very simple model that the homogeneization by diffusion of the ‘hypothetic trail’ formed by the released subunits is largely faster than its formation. Small heterogeneities of composition of the medium (weakly concentrated isles of tubulin-GDP in very high concentrated regions of tubulin-GTP) can be measured when allowing several grouped microtubules to disassemble (see Fig. 1).

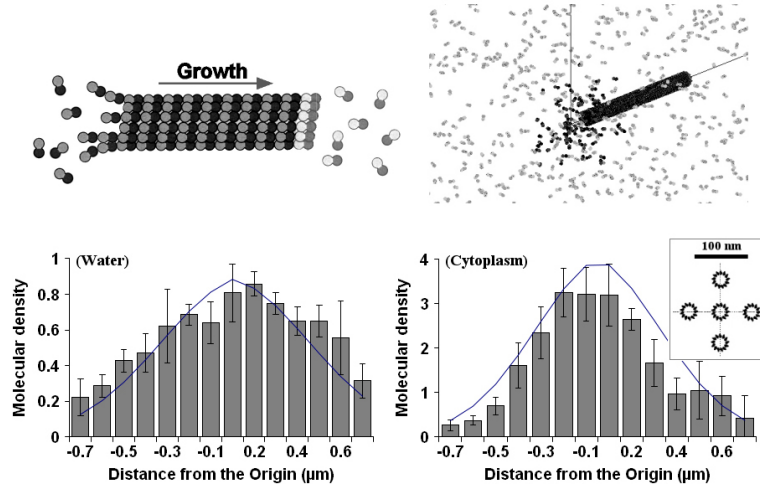


Figure 1: **(Up, Left)** Scheme of a microtubule while treadmilling: the microtubule grows at the right end and disassembles at its left end. **(Up, Right)** Concentrated area of tubulin-GDP (black) forming at the shrinking end of a microtubule. Tubulin-GTP heterodimers are displayed in grey. In this simulation, the microtubule disassembles about 1000 times faster ($2000 \mu\text{m}\cdot\text{min}^{-1}$) than a normal microtubule. **(Down, Right)** Density profile of tubulin-GDP around the tips of disassembling microtubules, measured during a similar simulation from the origin of an array of 5 diffusing microtubules (inset: transverse cross section of the x axis and of the 5 MTs at their initial position), each of them respectively separated by 30 nm (one microtubular diameter). All microtubules disassemble simultaneously at $20 \mu\text{m}\cdot\text{min}^{-1}$ ($1.85 \text{ms}\cdot\text{heterodimer}^{-1}$) which is a quite quick disassembling rate. The macroscopic diffusion rate of individual tubulin dimers corresponds to that measured in the cytoplasm ($5.9 \cdot 10^{-12} \text{m}^2\cdot\text{s}^{-1}$) [29]. The quantity of released tubulin-GDP molecules is very low and needs to be integrated in time for obtaining average profiles. The graphic has been reconstructed by integration of the density maps of 6 independent simulations, during 1.8 ms, between the simulation times 9.2 ms and 11 ms, along the 3 axis. **(Down, Left)** The same in water at 37°C . The average value of the global diffusion constant obtained ($4.9 \cdot 10^{-11} \text{m}^2\cdot\text{s}^{-1}$) is about 8x larger than in the cytoplasm, as measured in water by [29]. The resulting density profile of tubulin is weaker but detectable with 5 disassembling microtubules.

The result given in figure 1 means that the probability that the reactivity of a growing microtubule in the neighbourhood (able to 'see' the present chemical medium) is modified is very low. In a solution at $10 \mu\text{M}$ ($5400 \text{monomers}\cdot\mu\text{m}^{-3}$) the maximum ratio of tubulin-GDP, produced by 5 disassembling microtubules, versus tubulin-GDP would be about 1/1500 in the cytoplasm and 1/6000 in water. This is also the probability that the growing microtubule encounter one molecule of tubulin-GDP ; this probability multiplied by the probability the microtubule reacts with this molecule gives an idea of the very low frequency of microtubular catastrophe (disassembly) induced by tubulin-GDP in these conditions. Chemical communication is consequently not very efficient when one consider only a few number of fibres. Nevertheless, the chemical species released by numerous fibres have a real effect, visible on the behaviour of some *in vitro* solutions of fibres. In the conditions found by Mandelkow et al [7, 8], the microtubules are synchronized over long distances (millimeters). Propagating waves of microtubular concentration can appear due to this synchronization. Moreover, in the other conditions found by Pirollet et al [5] and Carrier et al [6], the synchronization also appears over the whole sample (several millimeters to centimeters). Finally, during the spatial self-organising process as observed by Tabony [9–11, 13], an unique overshoot is observed at the beginning of the reaction (5 minutes after the beginning). The presence of an overshoot signifies that at the early stage of the reaction, microtubules react in a synchronized manner during a few minutes over the whole sample. The reactivity of microtubules increases with the concentration of magnesium. The more reactive microtubules are found in Mandelkow's solutions (20mM Mg^{2+}), then in Pirollet's or Carrier's solutions (10mM Mg^{2+}) and finally in Tabony's (1mM Mg^{2+}). For a synchronization at the scale of only one micrometer, one would necessitate reactivities 100 to 1000 times faster than those of Mandelkow's solutions (waves of 1 mm large) [7]. Microtubules *in vitro* have typical disassembling rates of about 1 to several tens of $\mu\text{m}\cdot\text{min}^{-1}$. Increasing the reactivity 1000 times would mean microtubules

disassembling at about 1000 to 10000 $\mu m.min^{-1}$. This is in agreement with the simulation that predicts the formation of consistent tubulin-GDP trails (Fig. 1 Left).

3.2 Zoom-out: the agents are synchronized arrangements of fibres

We just have seen that the greater is the reactivity and the weaker is the diffusion, the shorter is the range of synchronization of the fibrillar agents. Unfortunately, until then, there's no evidence that conditions exist - with very high reactivity - allowing to synchronize the activity of cytoskeletal fibres by chemical communications at a microscopic scale. Of course, Mandelkow's microtubular waves are consistent objects emerging from a chemical communication between individuals, but this doesn't correspond to our idea of developing a computing system based on molecular ants.

A system exists that looks similar to what we expect : the system composed by intracellular parasitic bacteria and the actin cytoskeleton [3, 4]. Some bacteria such as the *Listeria* family or the *Shigella* family infect cells and hijack their actin cytoskeleton to propel in the cytoplasm. As they express at their surface actin nucleators, a 'comet' develops, composed of actin filaments and associated proteins (e.g. Arp2/3). The propulsion process is not completely understood, but it seems that the addition of new actin monomers between the surface of the bacterium and the comet causes the movement.

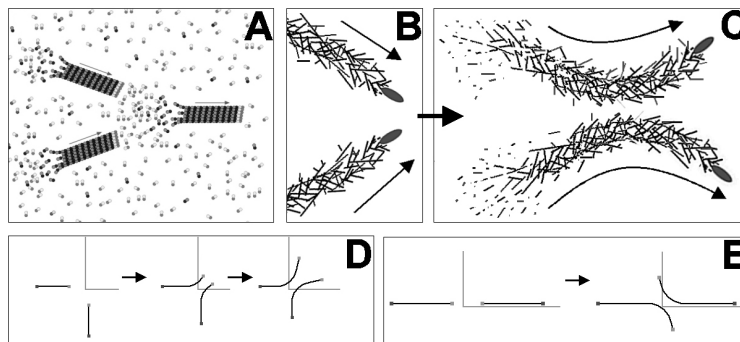


Figure 2: (A) Scheme of the idealized chemical collision between three individual microtubules. The two microtubules behind can sense the tubulin trail let by the microtubule moving upstream. (B to C) Scheme of the possible chemical collision between two 'actin - bacterium' systems. (D) Simulation with a 2D toy-model showing what could be a lateral chemical collision, (E) or a frontal one, in a similar system.

Such systems are very interesting for the design of a computing system because they solve numerous problems:

- *Communication between agents can exist.* The comets form by addition of free diffusing actin monomers to the existing filaments connected to the bacterium. The growing rate is about several micrometers per minute and the diffusion rate of actin monomers is about $10^{-11} m^2.s^{-1}$. The typical size of the bacterium-actin comets is about 5 to 10 μm long and hundreds nanometers large. That means that the size of the elongated objects (bacterium + comet) is comparable to the extend of the molecular diffusion. Moreover, the comets are constituted by thousands of actin filaments. That means that the intensities of the chemical signals emitted by the reacting ends of the system (a depletion of actin monomers at the growing end (bacterium) and a concentrated trail of actin monomers at the shrinking end) are notable. As we already said, a communication and a synchronisation of the activity of neighbouring individual agents is possible if the heterogeneities caused by the reactivity of the 'fibres' do not extend too much and have a sufficient intensity. That's the case in this system. The comets are sharing their components in the chemical medium. A comet travelling in the neighbourhood of another one will capture components of the other, and reciprocal. This will induce a change of direction of both objects ; in other terms, a chemical collision occur.

- *Flexibility.* Contrary to individual filaments of actin or microtubules, due to their big size, the comets of actin are pliable. This allows the system exploring the chemical medium by following the most concentrated regions of reactants (gradient searching). This is very similar to the behaviour of individual ants that follow the concentrated trails of pheromones instead of walking randomly. This is also similar to the original idea proposed several years ago that microtubules could self-organise as molecular ants [11–13], a hypothesis not verified and now contradicted by recent studies [14, 17].
- *Spatial stationary states and symmetry breaking.* When nucleators of actin are distributed over all the surface of the object (it’s the case in some bacterium mutants or on artificial systems composed of latex bead with nucleators), the actin network grows in every direction. As long as it is the case, the object stays in a stationary position until a accident occurs or another comet chemically collides, that way breaking the symmetry (its stationarity) [30, 31].

4 Conclusion

We proposed to imagine a system where fibrillar shaped objects reacting at their ends could be used for a new kind of computation based on chemical collisions. For the reason it is composed by such fibres, the dynamic skeleton of living cells appeared to be a good candidate. We have shown however that, due to an unadapted reactivity compared to molecular diffusion and to the dimensions of the fibrillar agents, the use of such systems at the level of individual fibres is call into question.

Fortunately, another system appears to be a better candidate for the role of ‘molecular ant’ : the bacterium-actin comet system. Due to its size, it is less sensitive to thermal agitation and is theoretically able to realise chemical communications based on concentrated trails or depletions of free diffusing components.

People know now how to realise artificial systems of actin comets. They use latex beads covered by actin associated proteins. These systems behave exactly as bacteria systems. Moreover, other physicists are currently trying to develop artificial dynamic nanotubes. Some succeed with self-assembling tiles of DNA [32,33] although their reactivity is not yet well controlled. Nevertheless, one can expect two realise one day an artificial system that behaves as actin-bacteria systems for realising unconventional chemical computers based on the principle of elastic chemical collision between molecular ant-like molecules.

In this context, a new algorithmic framework has to be developed as proposed by Adamatzky [34]. The problem is similar to collision-based computing systems in cellular automata [35,36] but now new features have to be taken into account such as variable angles, speeds and distances between colliding objects, and most of all randomness.

Seeing natural processes as computing processes gives to biologists and physicists a different point of view and sometimes helps to break accepted paradigms. Microtubules, actin and intermediate filaments serve as simple mechanical elements in the cell structure (tensegrity models of the cytoskeleton). In addition, the cytoskeleton is acting as an autonomous system sensible to external stimuli, conferring very complex behaviours to the cell. Comparing behavioural phenomena at the cellular scale and those that exist at the level of whole organisms is revealing. The motion of a migratory cell looks similar to that of an octopus, an organism more complicated. Flagella organelles are primitive caudal fins of swimming cells (e.g. spermatozoids). The bacteria *Listeria* and *Shigella* reuse the actin cytoskeleton as a propelling motor in infected cells. Those simple organisms developed many techniques to reuse the cytoskeleton, creating that way micro-machines.

In addition to the aspects of micro-machinery, it’s tempting to imagine the role of primitive brain the cytoskeleton could have had in simple organisms (e.g. ciliate organisms) during millions years of evolution. About the ‘seemingly intelligent’ behaviours of single cell protozoa, C. S. Sherrington said “*of nerve there is no trace, but the cytoskeleton might serve*” (yet mentioned by Hameroff and Tuszynski in [25]).

Acknowledgements

I’m very indebted to J. Demongeot (TIMC-IMAG, CNRS) for offering me the access to his Lab, allowing me to continue this unconventional work. I also thank J. Berro (TIMC-IMAG, CNRS) for all stimulating discussions about the actin system and its helpful suggestions and A. Adamatzky for his interest in that work.

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