A tour of my soft matter garden – from shining globules, soap bubbles to cell aggregates

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Like *The Magic Flute*, my career has been paved by wonderful and unexpected stories played by enthusiastic and talented students, in close contact with experiments and industry. I participated to the birth of soft matter physics under the impulse of Pierre-Gilles de Gennes: polymer, liquid crystals, colloids and wetting, which I have later applied to the study of living matter. By teaching in the early days at the Institute Universitaire de Technologies d'Orsay, I got into contact with industry, which give me the chance to establish collaboration with several companies: Rhône Poulenc, Dior, St-Gobain, Rhodia and Michelin. These partners have not only largely financed my research activity in physical chemistry, but they also offered us a wealth of innovative research topics. In 1996, when Professor Jacques Prost became of the director of the PCC Curie laboratory, in the Pavillon Curie built for Marie Curie, I turned to biophysics.

Figure 1) FBW and PGG à Sanary en 1991.

Throughout this scientific adventure, I had a great guide, Pierre-Gilles de Gennes.

I)   Childhood in Annecy

I need to begin this autobiography by describing my childhood and my parents, who have been a model of life teaching to their five children to be strong and simple and to get to the bottom of things without fanfare. In March 2016, I was made "Officier de la Légion d'Honneur" by the Professor Yves Quéré, from Ecole Polytechnique. He summarized beautifully my origins:

Figure 2) Liliane and Pierre Wyart at the EDF dam in La Girotte
View of Mont Blanc from the early childhood of FBW.

« What parents you had!   Pierre Wyart, your father, whose own father was driving locomotives to the North Railroad Company, and whose brother, Jean Wyart, was the famous mineralogist and crystallographer, some of us were able to attend his classes at the Sorbonne. Your father started the Ecole Polytechnique at 17 years old in 1928, magnificently illustrating how one could climb the French social ladder of the time – not so blocked! His undergraduate studies were soon after interrupted by tuberculosis, which penetrated the vertebrae. He therefore entered in a sanatorium in Briançon where he stayed for 5 years. Dura calamitas for this young man full of ardor, vitality and desire to undertake, but also Felix calamitas since it is there, in the sanatorium of Briançon, that he met his future wife, Liliane Weber, your mother. Finally, he recovered and entered a School of Application in Saint Etienne where he learns hydraulics before being named in Annecy. This is during that time that you are born, on Sept 11th, 1944. The family now lives in the small town of Verrier du Lac, where you were a pupil in a single-class school. During these years, you have a lot of fun with the children of the neighboring farms. So much fun that when the family has to leave to go to Annecy where you were already enrolled in primary school, you burst into tears and repeat a class: bad luck for Francoise that worries her parents until she passes the 6th grade exam, her first intellectual high. Back to her father: in 1946, Pierre Wyart participated in the creation of nothing less than the company Electricity of France (EDF), which he quickly climbed the ladder, a company that he will even be proposed to become the general director. To the highest functions this man of intelligence, action and dialogue, a sort of Julien Sorel of modern times, will never forget that he is the son of a worker. Always active and full of energy, when he retires, he creates and leads an agency dedicated to the resolution of international conflicts on energy. Your mother was an amazing woman, full of energy and vision, who wished to be a doctor but she was born a little too early: studies are for men, so she became a nurse. Your mother, who became a nurse traveling to Northern African countries such as Algeria, from where, anticonformist as she was, she brought back a monkey and an antelope and moved to Briancon's hospital, where she met a charming young man suffering from Tuberculosis... Raising her 6 children, your mother practiced throughout her life the taste for culture (she managed libraries in old people home) and openness to others,

receiving at home young refugees and isolated elderly. She died in the summer of year 2000, with your father following her less than two months after, crushed with grief.
The young Françoise was a brilliant student who was born at the end of the Second World War and had the opportunity, that her mother did not have, to complete her education. After high school, Françoise went to the Ecole Normale Supérieure (ENS) Cachan in 1964 and pass her aggregation of physics in 1968, an unusual year to prepare such a hard exam! In the same year, she started her Ph.D. *in the Solid State Physics laboratory in Orsay.”*

II) Orsay   1968 - 1977

Two years after my admission in ENS Cachan, I enrolled in 1966 the master of Solid Physics where classes were instructed by notorious professors such as J. Friedel, A. Guinier, P. Nozières and P.G. de Gennes. Together, these great minds conveyed a novel, personal and exciting vision of physics. After passing the Aggregation of Physics, I joined the Laboratory of Solid Physics (Orsay) to prepare a Ph.D. under the supervision of P.G. de Gennes, referred to as “PGG”. After the events of May 1968, one could not enroll in a Ph.D. without a permanent position. Consequently, we were very few Ph.D. students! On my side, I got in the fall of 1968 a permanent assistant professor position at University Paris 11 so I started to teach and to do research while soon taking care of my first child, Pascale, born in October 68 and soon to be followed by my first son, Virgile.

From the roofs of Building 210 to Building 510

After a brief work on superconductivity under the supervision of Fyl Pincus, I joined as a theorist the Liquid Crystal Group to work in close collaboration with several experimental teams: Etienne Guyon, my former professor at ENS Cachan, who was key to build my confidence, Georges Durand, Madeleine Veyssié, Robert B. Meyer, Francis Rondelez and Pawel Pieranski. My colleague Liliane Leger initiated me to her beautiful experiments as we performed twin Ph.D., hers in experimental physics and mine in theory.
Nematic liquid crystals are very sensitive to external fields. At the time of my Ph.D., it was interesting and important for applications in display to understand their transient responses to magnetic or electrical fields suddenly applied. I therefore studied the dynamics of the Frederick's transition of a nematic liquid crystal. The nematic is aligned by the surfaces of the sample and distorted by a magnetic field perpendicular to the nematic orientation. A distortion is observed above a threshold field H_c [1,2]. I studied the hydrodynamic “back flows” [3] induced by the rotation of the molecules. For a given field $H > H_c$, the system may choose between two different distortions patterns and the nematic slab breaks into domains. I analyzed the structure of the walls separating two domains and showed that the thickness of the wall diverges at H_c. I modeled the motion of the domain and the slowing down of the dynamics near the critical magnetic field [4]. This project was a first step to study the dynamics of liquid crystals phase transitions. The different types of liquid crystals are indeed connected by remarkable transitions: at these transitions appear critical fluctuations much subtler than those of the usual systems (liquid - gas, magnetic...). My background in superconductivity became very useful in this area, as certain transitions, like smectic A / nematic or smectic C / A, resemble from the point of view of their symmetry superfluid transitions. Therefore, I built dynamic scaling laws in analogy with the models of Halperin and Hohenberg [5,6,7]. This work, which made up most of my Ph.D. thesis, was done in collaboration with several groups in Orsay.
At the end of my Ph.D., we extended these works to lipid-water mixtures, referred to as lyotropic liquid crystal. We calculated the collective modes of lamellar phases and found six classical modes of thermotropic smectics, and an additional mode, *the slippage mode*, due to

the addition of one variable, the lipid concentration [8]. This 7th mode was later observed at Harvard University by forced Rayleigh diffusion (Pershan, 1978). I defended my thesis in 1974 with the title "Dynamic properties of mesomorphs".

At that time, PGG put me in contact with J.F. Lennon, a researcher from the Laboratory of Hematology from Pasteur Institute, who has carried out the first quantitative studies on the scintillation of red blood cells, a strange phenomenon observed for a long time in phase contrast microscopy, but totally unexplained at the time. The flicker of the red blood cell was seen as an active movement of the cell, at a physiological frequency related to the life of the cell, as the heartbeats. There a nice collaboration started to understand this phenomenon. Suddenly, the walls of my office in Orsay became decorated by the experimental data of Jean-François Lennon. He measured experimentally the correlations functions for the flicker intensities at two different points on the cell surface, at various filtering frequencies. We interpreted theoretically these results in term of the thermal fluctuations of the thickness of the biconcave cell shown in figure1, which modulate the transmitted light. In physiological conditions, the membrane surface tension vanishes and the resistance to deformation is mainly due to curvature energy. In this approximation, the fluctuations are of very large amplitude (a fraction of a micron) as required by the observations. The detailed shape of the correlation functions is in rather good agreement with the theory [9]. We conclude that a purely physical model is sufficient to interpret the flicker effect, but that rather stringent physiological conditions are required to maintain the zero-surface tension, which is critical to the effect. This early work will be crucial for my transition to biophysics many years later!
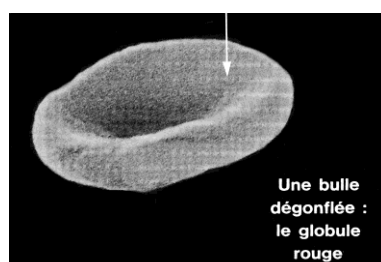

Figure3) Une bulle dégonflée : le globule rouge (La Recherche 1977)
A deflated bubble: the red blood cell

The end of the Ph.D. after *Mai 68* was a period of doubt for scientists of my generation in search for meaning. Some became physicians or moved to farms raising sheep in remote areas such as the plateau of Larzac in the south of France. On my side, in order to experience the life of a scientific editor, I wrote an article for the public journal La Recherche (Figure 3)[10], but I do not like the experience, so I decided to stay in academic research.

III) College de France 1977-1985

Pierre Gilles de Gennes had been nominated in 1971 as Professor for the Chair of Physics of Condensed Matter in College de France.

In 1977, I joined his laboratory where I found some of my "old friends" from Orsay, Madeleine Veyssié, Liliane Léger, Françis Rondelez. The same year my daughter Claire was born, and in 1978, my son Matthieu. I took part in the fast evolution of polymer physics, initiated by de Gennes with Jannink and des Cloiseaux. The famous theorem "n = 0" of PGG in 1972[1] was a revolution in polymer physics, where suddenly all the theoretical technics

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[1] This theorem is presented by PGG in his activity report "On the theoretical level, it has been possible to establish a rigorous relation between the statistics of the chains and the transitions of phase. This relation is quite abstract: it is to study a magnetic system whose magnetization possesses independent elements and to pass to the

developed for critical phenomena replaced mean field approaches. The scaling laws were visualized by PGG, who introduced the picture of "blobs", a statistical object to characterize the monomer-monomer correlations. My previous training in hydrodynamics and phase transitions became extremely useful.

Dynamics of polymers
Polymers confined in a pore

An interesting problem, important for enhanced oil recovery, is the dynamic behavior of polymeric chains trapped in very fine pores. My first calculation in polymers was to transpose the physics of polymer solutions in 3d to 1d, where polymers are confined to capillaries. I constructed dynamic scaling laws for these problems[11], which disproved a previous Debye analysis as PGG was proud to claim.

Subsequently, I worked closely with S. Daoudi on the forced passage of one single polymer chain through the entry of a pore and on the behavior of polymer solutions in convergent / divergent pores[12]. The two mechanisms shown in the Figure 4 are an affine deformation under convergent flows at the entry of the pore, and a suction of the polymer by the flow of solvent inside the pore. They both give the same threshold flow for the passage of the polymer. The experiments were carried out in the following years by a collaborative effort of researchers from the French Institute of Petroleum (G. Chauveteau) and the College of France (F. Rondelez and Léger).
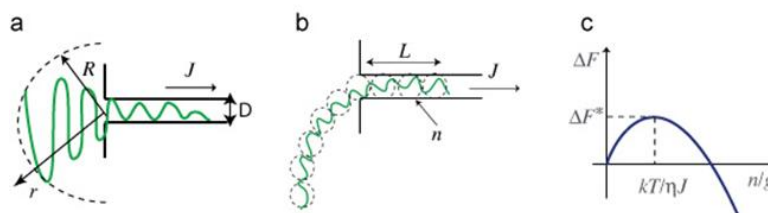

Figure 4) Forced passage of a flexible polymer chain under strong flows: a) affine deformation b) suction c) Free Energy of the chain versus the number of monomers sucked in the capillary

Later on, I studied the properties of melted polymer mixtures in confined geometry that was part of E. Raphael's thesis[13]. More recently, with C. Gay and T. Sakaue, we studied the passage of branched polymers, and showed that the forced penetration into a pore does not select the chains according to their length or their topology[14,15].

Polymers in solution
Polymers in bad solvents

With PGG, I studied the movements of a chain in bad solvent where it is strongly folded on itself, and where it forms many self-nodes[16]. This aspect, ignored in classical literature, leads to curious effects observed by neutron and light scattering (G. Jannink-M.Adam CEA), which do not follow simple dynamical scaling laws because there are two characteristic lengths, the monomer-monomer correlation length and the distance between the nodes[17].

We then studied the dynamics of swelling of a polymer droplet immersed in a good solvent, where we have introduced the *"Magic length"*. Polymer dissolution is a significant problem for many industrial processes, with a lot of empirical data available, but without an overall view. We have been able to analyze different steps in the process, and have shown on a

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(non-physical) case where n = 0. However, we know, many examples in theoretical physics, that the extension of some results to non-physical values of the parameters can be fruitful (as well as complex angular moments in collision physics). The "n = 0 theorem", established by us in 1972, has made it possible to transpose the enormous theoretical arsenal accumulated with regard to phase transitions to polymer problems Thanks to the n = 0 theorem, the problems related to self avoiding random walks have been fundamentally related to the physics of phase transitions, all of them having a very great universality, that is, laws independent of the local structure.

practical level that there is an optimum size for the concentrated polymer drops that must be prepared (by mechanical stirring) before starting the true dissolution: the time of dissolution decreases with the size of the droplets, but reaches a plateau value, because the chains have to disentangle.

We also studied later with C. Williams the dynamics of collapse of one single chain [18] and the swelling of a gel with free polymer chains[19].

Polymers in liquid crystal solvents

I followed the experimental work of M. Veyssié, J. Dubault, on the usual polymer - liquid crystals mixtures. I modified my first description, which was limited to weak coupling situations. Quite often, the nematic order is completely destroyed inside the chain and one has a strong coupling situation: isotropic solvent droplet in the region of the cloud of monomers. For short chains (smaller than the coherence length ξ of the nematic), the unexpected result is an "ideal" chain behavior. For long chains (R> ξ), there is a "collapsed" regime. We also calculate the phase diagram of nematic polymer mixtures with P.Levinson[20].

Dynamics of polymer melt

Couplings of melt-compatible polymers are rare, but of great importance for industrial applications (polymer metallurgy, self-adhesion). For such couples, I had predicted unusual interdiffusion laws[21]. Following a collaboration with experimenters Prof. Lauwrence (Amherst), J. Klein (Cambridge) and E. Kramer (Cornell), it turned out that my results explained well the interdiffusion in the case of comparable lengths, but did not apply to the case of asymmetrical junctions.

My first theoretical interpretation, based on the model of reptation of polymer chains crawling in fixed "tubes", was incorrect for the case where one of the species is much shorter than the other. It took me five years to arrive at a satisfactory theoretical description, in which the tubes themselves move with a velocity unambiguously determined by a balance of forces on the tube[22] : the small chains swell the transient network of the long chains. I was very proud of this result, but I published it in French in the Comptes Rendus de l'Académie des sciences (Paris): Masao Doi who was first skeptical to the motion of tubes, recognized his importance, used it and asked me to put my name in his article!!! because my own article will be lost.

Polymers at interfaces: Role of Connectors

The graft polymers are used as *connectors* (example: metal / polymer adhesion), as *colloid stabilizers* (for example: Indian ink, "hairy" vesicles formed of partially water-soluble lipids and copolymers, which stand two days in blood, while simple vesicles are instantly destroyed), as *wetting control agents* (example: silanized silicon wafers).

These long graft chains also play an important role in the rheology of polymers at interfaces, which was studied at the College by Léger and H.Hervet. A polymer melt slides on a smooth surface. On a surface onto which a few chains have been grafted, the slip is destroyed at low shear rates because of the strong friction but restored at high shear rate because the chains undergo a coil-stretch transition and disentangle with the melt. With PGG, we introduced the concept of a *"marginal state"* for a wide range of sliding velocities (four decades), where friction becomes solid type[23]. We extended this study to the slip of a rubber on a grafted surface mainly with L. Leibler, A. Ajdari and C. Gay. It's amazing that a marginal state has been observed recently in the shearing of entangled fire ants glued to the wall of the rheometer with Velcro!

I also participated in the development of a theoretical model of brush-rubber adhesion, extended later to cellular adhesion induced by specific binders[24] and its measurement by enforced cell's detachment.

Wetting

The physics of wetting was initiated at the College de France thanks to the Petroleum French Institute IFP, concerned in the wettability of rocks and the role of polymers used in oil recovery.

The different regimes of wetting of a droplet deposited on a substrate (partial versus complete wetting) depend upon the sign of the spreading parameter S. For the case of complete wetting (S positive) the structure and the dynamics of the precursor film, named van der Waals pancake, was studied by J.F. Joanny, at this time a young student of PGG. I decided to extend their work to the wetting of fibers with two Ph.D. students D.Quéré and J.M.di Méglio [25,26].
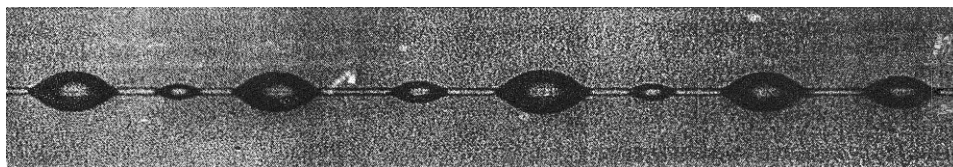

Figure 5) Instability of liquid films on fibers: An enlarged view of beaded thread (D.Quéré)

If the spreading on a solid plane was relatively well understood, the spreading on fibers (textiles, fiberglass, carbon, hair) remained mysterious. Why does a drop spreading on a plane no longer spread on a fiber? We have shown that in this situation, the excess L / G surface linked to the cylindrical geometry leads to a new situation, which we named "*pseudo-partial wetting*": the drop does not spread even if S is positive! The equilibrium state is a droplet in co-existence with a microscopic film. We predicted "Droplet-Manchon" transitions and studied the dynamical properties of the spreading: a drop placed on a fiber spreads by emitting two films of microscopic thickness. We also studied the stability of films deposited on a fiber, the threshold thickness beyond which the liquid sheath splits into droplets and the dynamics of this Rayleigh instability (Fig. 5). This work is crucial for the coating of textile fibers: during the extrusion of the polymer wire at gigantic speeds over the earth moon distance, the fiber must be covered with a lubricating liquid film. Any fault causes a break in the fiber and the coil becomes entangled. Visiting l'Oreal, I discovered that they used our work for the formulation of mascara: the drying must be faster than the rise time of the instability, to get a regular coating of the cilia.

We have also investigated the wetting phase diagram of solid substrates coated with a molecular film [27]. Comparing the polarizability of the film versus the polarizability of the solid, we predicted complete, partial and pseudo-partial wetting, for the case of a low polarizability solid (plastic) covered with a polarizable layer (gold). A sessile droplet spreads on gold but does not spread on golden plastic: at equilibrium a macroscopic droplet with a finite contact angle coexists with a nanoscopic precursor film.

At the end of my stay at the College de France, I attended a PGG's lecture on soap films. He described the growth of Newton black films observed by K. Mysels, which nucleate during the drainage of a vertical soap film. For fun, I transposed the theory that PGG described for suspended films to the case of films supported by a solid substrate. A black film becomes a dry patch, that opens up on a wet substrate. The dewetting was born! and it was going to keep me busy for almost 10 years! I can see dewetting every day in my shower when dry region open on my wet skin.

In 1984, my son Olivier was born.

IV) Sorbonne University 1986-1991

In 1986, I was appointed Professor at Paris VI. With J.P. Badiali, M.P. Pileni and F. Rondelez, we create a team centered on the problems of structure and reactivity at interfaces in the laboratory of Physical Chemistry, in the Jean Perrin building. In this new environment,

I tried to keep the same style of work, dealing with various areas of physical chemistry (surfactants, polymers, hydrodynamics), and following fairly closely the industrial needs (textile, petroleum, cosmetic industries, chemical engineering). We started to work on wetting and dewetting, Ph.D. C.Redon, financed by Dior: we want to produce a shampoo to keep our hair dry when going to the pool! We did not succeed in achieving what nature has been able to do for the feathers of ducks, that remain dry thanks to nanoparticles which make them super hydrophobic, but we started the first fundamental studies of dewetting by nucleation and growth of a dry patch[28] (Fig.10A) and spinodal decomposition[29]. We monitored and modeled the dynamics in both viscous and inertial regimes, where capillary waves are induced by the motion of the rim collecting the liquid of the dry region[30]. Wetting is a science that seduced me because it intervenes in our daily life. On the aesthetic level, the experiences are very beautiful but not as simple as it seems! It also leads to many industrial processes, as illustrated in our book *Capillary and wetting phenomena* with PGG and D. Quéré (fig 16). This action gave me the opportunity to work with Dior, Atochem, Rhône-Poulenc, Michelin, Valéo and Airbus.

Thanks to Francis Rondelez, I became interested in phase transition in Langmuir monolayers. With D.Andelman and J.F.Joanny, we have shown that the interactions between permanent dipoles modify the phase diagram[31]: at the *liquid / gas* or *liquid-liquid / condensed liquid* transitions, long-range repulsions between dipoles give rise to periodic "super crystal" arrangements visualized directly by epifluorescence .

When the laboratory SRI moved to Jussieu in 1991, we decided with Francis Rondelez to join the Curie Institute, in the same building! in the section of Physics directed by Monique Pagès, which was changing orientation towards soft matter.

The same year, my son Marc was born.

V) Institut Curie 1991- present

In 1992, I entered the Physics and Chemistry section of the Institute Curie where we founded, with F. Rondelez and D. Chatenay, the team "Physics of Surfaces and Interfaces". In 1994, J. Prost brought our team and a team of chemists together to create the PCC, *Physico Chimie Curie* Unit. It lies at the interface between physical chemistry and cell biology. I started the team **Surface Douces** "Soft Surfaces" focused on hydrodynamics and polymers at interfaces with an outstanding experimentalist **Axel Buguin** and a great time started for me!

In 2000s, I began a gradual transition from soft matter to biology by studying biomimetic systems. Then we validated our approaches on cells, which raised new questions that I developed with my team, and in collaboration with groups in France and abroad. My experience with polymers was useful because the cells, from a mechanical point of view, can be considered as viscoelastic jelly beads, surrounded by a liquid membrane which gives them a surface tension, such as droplets.

In 2003, I was nominated member of the Institute of France IUF.

Soft matter 1992-2008
During these years, I was able to pursue an activity in soft matter and develop new projects in biology.
Dewetting at soft interfaces: aquaplaning and cellular adhesion
On the problem of adhesion, we started with Michelin a long-term program to investigate rubber / wet surface contacts. We first studied theoretically[32] the dynamics of dewetting of a liquid film intercalated between a soft rubber and a rigid substrate. Using Reflection Interference Contrast Microscopy (RICM) P. Martin was able to follow the dynamics of growth of dry adhesive contacts . With a macro AFM built by Axel Buguin where the tip is

replaced by a millimetric elastic ball, we studied the adhesion and the friction of rubber beads pressed on a rigid plate in air or immersed in a liquid. When the plate slides at a velocity U larger a threshold velocity, the contact is lubricated, corresponding to the aquaplaning that happens when a car looses control on a wet road (Fig. 6 A). However, if the sliding surface carries an asperity, a "dry wake" can be induced (Fig.6 B) in analogy with Čerenkov radiation, with a Mach angle derived from a competition between dewetting velocity v and invasion velocity U[33], which restores adhesion. We used the same set up to study cellular adhesion[34,35] which is also done by the elimination of a liquid film of comparable thickness. After having worked on model systems (elastomer ball immersed in a viscous liquid and sliding on smooth glass), adhesion was studied on systems closer to reality: I) microstructured surfaces (pillars) (Fig. 6 C) to simulate the asperities of the soil; ii) high speed friction. This project required microfabrications of surfaces and the realization of a rotating disk force machine to explore very high speed ranges.
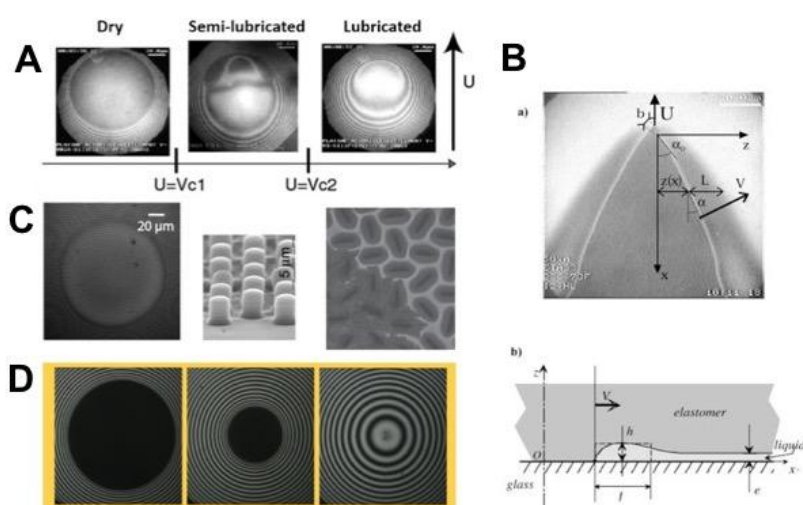

Figure 6) **A**: Aquaplaning: sliding of an adhesive rubber-glass contact immersed in a liquid versus the sliding velocity U: dry, semi lubricated and lubricated regimes (Pascal and Arnaud Martin). **B**: *Cerenkov* dewetting a) Mach angle and b) profile of the rim collecting the liquid. **C**: from left to right: « suspended» contact of a soft bead on a microstructured substrate (E. Echalier), pillars; Instability of an antifrost polymer film exposed to a moist atmosphere (H. Gerardin). **D**: Detachment of a soft bead adhering on smooth glass (J. Clain).

In addition, we built biomimetic models of cells at all scales, ranging from mm to micron: viscoelastic beads decorated with proteins to simulate the properties of the cytoskeleton and specific adhesion, soft shells to represent the cortex, suction cups for simulating the adhesion of amoebae in the intestine. These giant systems allowed us to more easily study the dynamics of adhesion and detachment on smooth (Fig.6 D) and rough surfaces[36].

Bursting of viscous bubbles
We are in 1991, when PGG receives the Nobel Prize. Rhône Poulenc offers us a box in plastic containing a magic paste with the inscription "la matière molle: vous connaissez?" This paste has kept all its properties: rolled in small ball, it bounces at short times and it spreads like a liquid. Playing with this paste to make a thin film, I saw the formation of holes.
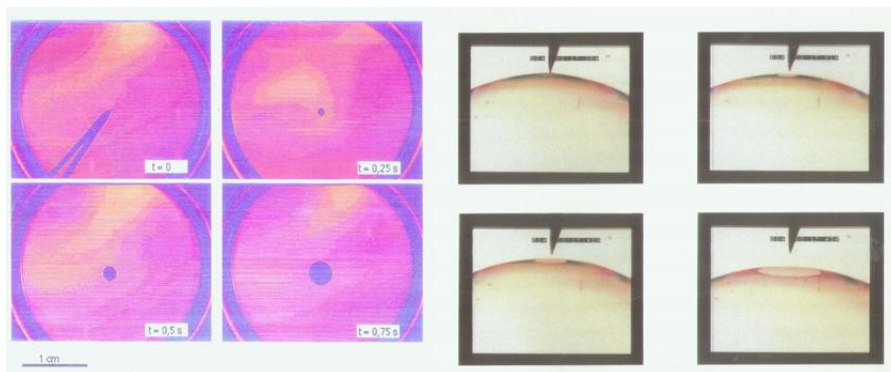
Figure 7) Bursting of suspended polymer films and viscous bubbles (G. Debrégeas)

If for a hundred years, physicists (Dupré, Rayleigh,...) have been passionate about understanding the bursting of soap films, G. Debrégeas is the first to have made films of viscous polymers without surfactants, and studied their bursting (Fig. 7) which gives new laws: the inertia is negligible and the viscoelastic properties of the film control its rupture which is as fast as the bursting of soap bubbles, because of the radial plug flows that gives rise to a very small viscous dissipation [37,38].

Hydrodynamic extrusion of membranes tubes   A hydrodynamic probe was developed by O. Rossier based on the extrusion of membrane tubes from giant vesicles[39].A vesicle is attached to a microstick and submitted to a flow (Fig. 8A). A tube is extruded above a threshold force f_0, at which we have coexistence between a spherical vesicle and a membrane tether. We modeled this transition in analogy to the unbinding of a polymer chain in a bad solvent. Nicolas Borghi applied the tube hydrodynamic extrusion to test the properties of cell membranes (Fig. 8B) and the adhesion of the plasma membrane to the cytoskeleton[40,41]. We modeled the non-linear relation between the force and the velocity of extrusion by a thinning of the tube when the viscous stress increases[42]. Manufacturing micro-structured substrates to attach dozens of cells, it will be possible to establish statistical laws characterizing the extrusion of nanotubes of different cell lines, and to determine the effect of drugs or genetic mutations. The membrane nanotubes are used in vitro and in vivo to transport active molecules between vesicles or cells. We have shown that the transport is achieved by a Marangoni flow from the tense vesicle towards the soft vesicle[43].
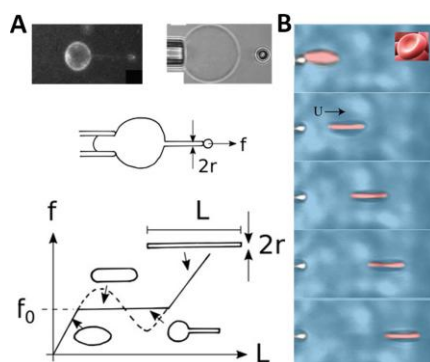

Figure 8) Extrusion of membrane tube from vesicles (A) and red blood cells (B).

Antagonist wetting: "fried eggs droplet"

Rhone Poulenc was interested in the wetting of mixtures where the components have antagonist wetting properties. They came to me with a bottle filled with sticky complex liquids. I simplified the system, using a polymer in solution in a good solvent: the monomer. With R. Fondecave[44,45,46], we explored the laws of wetting of polymer solutions on model

surfaces (salinized wafer) in antagonistic situation: the solvent totally wets the surface, but the molten polymer wets it only partially (finite contact angle). By diluting the polymer, it was thought naively to encounter a wetting transition. In fact, we observed a transition from a new type of "leak out" where the wetting solvent escapes from the drop and wets the substrate by forming an aureole around the drop, looking like a fried egg. Below this composition, the contact angle remains finite. A phase separation is coupled to the wetting.

Floating contact lines (X.Noblin) [47,48].

We have explored the dewetting of liquid films on a liquid substrate and observed a cascade of shocks waves(capillary waves in the front, gravity waves in the back) and the fluctuations of the contact lines, named *Triplons*, studied in parallel at ENS using superfluid helium[49].

DNA under strong flow: trumpet and stem-flower

In labelling DNA with chromophores, Steve Chu (Standford) was able to observe single macromolecule and manipulate it with optical or magnetic tweezers: he visualized the reptation of one chain in a polymer solution. In parallel, I described the deformation regimes of a DNA molecule attached at one end and subjected to a uniform flow (velocity V)[50]. I predicted for the configuration of the DNA a shape of a "trumpet" of size L (Fig. 9a) obeying to simple scaling laws and I send my article to Steve Chu. He told me "Thanks to you, we did the experiments but your result is wrong!". I realized that the regime of the trumpet is valid only for a narrow range of velocities, and above a threshold velocity, we predicted a "*stem and flowers*" regime (Figure 9b)[51]. The total length L do not obey simple scaling laws, but the length of the flowers does.
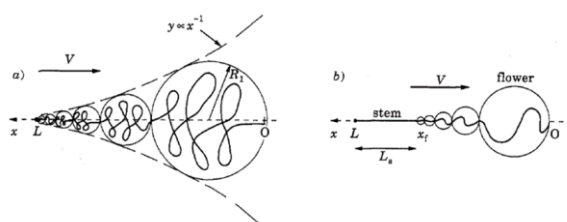

Figure 9) Deformation of a tethered chain under uniform flow: a) trumpet b) stem and flower.

With A. Buguin, we became interested in the unfolding and relaxation of the globular DNA in "bad" solvent. This work could have an impact on the denaturation of proteins. It also led to a new theoretical model of the collapse of a polymer chain suddenly placed in bad solvent. We then described the relaxation of a chain initially stretched, which reforms a coil from the free end, in collaboration with P. Cluzel and J.L. Viovy, who watched the relaxation of highly stretched DNA molecules. This model can also describe the helix-coil transition of synthetic polypeptides. With Fyl Pincus, we studied the transient regimes: the unfolding of the chain when, at time t = 0, a force or a flow is applied. I studied the eigen modes of flexible chains stretched by a flow, in the shape of trumpets (thesis Y. Marciano)[52].

Adhesion of vesicles

The non-specific adhesion of giant and fluctuating vesicles to substrates was first studied by fluorescence microscopy by Olivier Sandre, who saw that strong adhesion can lead to the bursting of the vesicle. To slow down the dynamics, I told to Olivier to use a viscous solvent and a great discovery occurred! He saw the opening and the closure of a succession of transient pores. It was in June. Before the summer vacation, it was published in PNAS [53].

Opening of *transient pores (Fig.10)*: When a floppy vesicle (Fig.10A) is stretched by an external action (Fig.10B), pores open to relax the tension of the membrane. If the vesicle is immersed in a very viscous liquid, macroscopic pores open and close slowly because the leakage of the internal liquid is slowed down. In water, the leak is so fast that the pores close

again before reaching an observable size. We performed a complete theoretical description of the dynamics of these transient pores.

   Line tensiometer: N. Borghi and E. Karatekin[54] studied the role of surfactants on the mechanical properties of the membrane, and the line energy associated with holes in the membrane. Some surfactants are able to drop by a factor of 100! this line energy and make the membrane permeable. We tested several families of surfactants based on their hydrophilic / hydrophobic balance, and their affinity for insertion into the membrane.

   These large membrane permeabilities, induced by tension and favored by certain surfactants, may have applications in the transfer of drugs or to understand certain biological processes (endocytosis, exocytosis)[55]. They are now a model for the pores observed in the *nuclear membrane*, when cells migrate in small capillaries or through the extracellular matrix. They can also be harmful to the life of our cells.
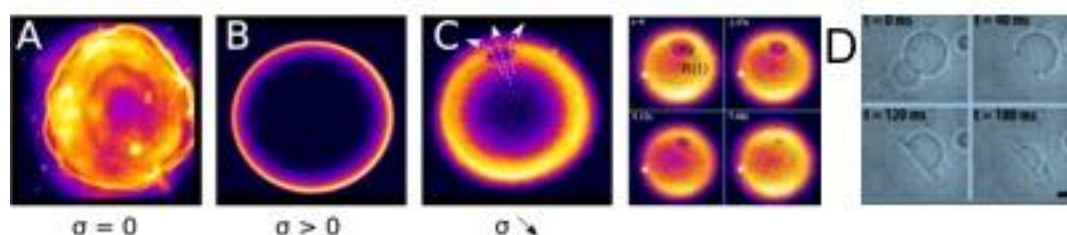

Figure 10) A: Floppy vesicle. B: Tense vesicle. C: Opening and closure of transient pore (O. Sandre). And D: Light sensitive polymersome bursting under UV illumination.

   Bursting induced by curling: Later, we extended these studies to the bursting of asymmetric light sensitive polymersomes[56] observed by E. Mabrouk and M.Li (Fig. 10D), which represents a new phenomenon because the light induces an increase of surface area of one of the two leaflets, which should lead to a decrease in membrane tension , and not an increase causing usually the bursting. I proposed a mechanism inspired by a very simple and beautiful experiment shown to me by E. Reyssat when visiting Mahadevan at Harvard : the curling of tracing paper gently deposited at the surface of water, caused by the swelling of one side of the paper. We suggested that the growth of a pore in polymersome membranes is driven by the same curling instability. The opening of the pore relaxes the curvature energy stored in the membrane as shown by the membrane curling of the rim (Fig. 10D).

Living matter 2008-2018
Over the past ten years, our Physico Chimie Curie laboratory has been moving towards cellular organization under the impetus of the new Department of Developmental Biology. Our culture in soft matter, critical phenomena, liquid crystals and self-organized liquids, wetting, brings new points of view to biologists. Thus, in the early stages of Drosophila development, a cellular organization close to a two dimensional foam, exhibits a symmetry breaking with an isotropic → anisotropic organization that is similar to that of crystals liquids. A bold idea of J. Prost was the analogy between cancer and 1st order phase transition, that is, discontinuous. A tumor would be indicative of growth instability, and could only grow beyond a critical radius of nucleation, an idea that we tried to test and which was the starting point for my work on cell aggregates these last ten years, and that has jostled the field anyway.
We have introduced and worked on the broad field of *entangled active matter,* a novel class of non-equilibrium materials composed of many interacting units that individually consume energy and collectively generate motions or mechanical stresses. Unlike swarms of fish and flocks of birds, both ants and cells can support static loads. This is because both cells and ants are also entangled, so that the individual units (cell, ant) are bound by transient links. With David Hu, we have explored and establish analogies between aggregates of both ants and

cells [57].

For experimental purposes, assemblies of cells are among the simplest examples of active matter made of live entities. Increasingly, biologists, pharmacologists, and toxicologists are using cell aggregates as substitutes to animal studies. They are reliable and cost-effective systems for drug screening, bridging the gap between 2D cell-based assays and animal studies.

Our team, in collaboration with S. Dufour, has been working on applying soft matter physics[58], to study the biophysics of model tissues (tissue rheology, aspiration, spreading, mechanosensitivity, wetting and dewetting, adhesion and fracture). Our practice of phase transitions in liquid crystals and instabilities of wetting films has been useful for understanding the spreading of cell aggregates and wetting transitions by playing on adhesion with substrate and intercellular adhesion. The results obtained from such analogies have suggested important implications to both tissue development and cancer. In September 2013, I was appointed Professor Emeritus, my group Surface Douce was dissolved and I joined the Theoretical group of Jean-François Joanny

Since 2014, I collaborate with Françoise Winnik's team in Japan on inert matter-living matter hybrid systems with two main questions: 1) Nanoparticles can stick the cells together and substitute for cell adhesion molecules and 2) Cellular noise can give movement to the inert macroparticles "Active Granular Matter"

I remain concrete theoretician, working closely with experiments, and in collaboration with biologists who present us with complex situations, where we have to unmask a simple idea and develop it.

Cellular dewetting

Macroapertures in epithelial cells (Collaboration E. Lemichez Nice)

Pathogenic bacteria migrate from blood and lymphatic vessels to host tissues by opening transient macro apertures, MAs, in endothelium cells. To accomplish this, staphylococcus aureus infect cells with EDIN, which produces a sudden disruption of the contractile cytoskeleton network. Cell membrane tension is no longer resisted by contractile acto-myosin fibers, leading to the opening of MAs (Fig. 11B). The opening is opposed by the line tension at the rim of the hole, which is induced by specific lipid sorting in the curved membrane. This induced line tension limits MA maximal size and eventually closes the hole, limiting endothelium permeability and preventing cell death. We modeled the opening and closure of MAs by analogy with the dewetting of a liquid film[28] (Fig.11A) and transient pores in vesicles [53,54]. We calculate the minimal radius for hole nucleation, as well as the maximal MA size as a function of the initial membrane tension, assuming a constant line tension T. We show that the radius of a transient MA obeys simple scaling laws if T is small, leading to large MAs.
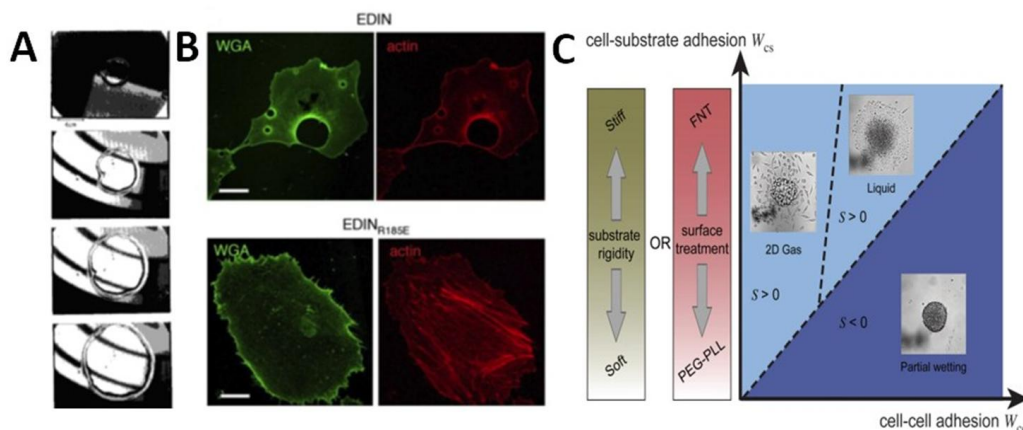
Figure 11) **A**) Snapshots of the opening of a dry patch in a liquid film (C. Redon), **B**) Opening of MA in endothelial cells, **C**) wetting phase diagram of cellular aggregates[58].

Cellular monolayer dewetting

We have shown that cohesive cellular monolayers deposited on non-adhesive substrates are metastable and "dewet" by nucleation and growth of dry patches[59]. The dewetting can be induced either chemically by a non-adhesive surface treatment or physically by a decrease in the substrate rigidity. We interpret the dynamics of growth of holes in the monolayer by an analogy with the dewetting of viscous films. This analogy can be used to estimate parameters characterizing the mechanical properties of cellular sheets.

Spreading and aspiration of living drops

Since 2010, we have started a new research project on the characterization of the mechanical properties of biological tissues, the role of cell-cell adhesion on the tissue mechanics and eventually on the conditions for the growth of cancer tumors and formation of metastasis. Our studies are performed on spherical cellular aggregates, which are useful systems to study the mechanical properties of tissues since the adhesion energy between the cells can be controlled. We have used murine sarcoma (S180) cell lines transfected to express various levels of E-Cadherin molecules at the surface of the cells (coll. S. Dufour UMR 144), thereby controlling the intercellular adhesion energy and CT26 murine carcinoma cells in collaboration with D. Vignevic interested in the role of fibroblast in cancer extravasation.

Wetting transitions of cellular aggregates

We have studied the spreading of spheroidal aggregates of cells (S180), expressing a tunable level of cadherins (adhesion energy W_{cc}), on glass substrates decorated with fibronectin PEG mixtures (adhesion energy W_{cs})[60]. As shown on the phase diagram (Fig. 11C), we observed both partial and complete wetting depending upon the sign of the spreading parameter $S = W_{cs} - W_{cc}$. We monitored the contact area by optical interferometry and the profile by side-view microscopy. At short times, the aggregate flattens and the contact area increases as $t^{2/3}$. We interpret these results by modeling the aggregate as a viscoelastic droplet. At long times, we observe a precursor film with two possible states: in strongly cohesive aggregates this film is in liquid state, while in weakly cohesive aggregates the constitutive cells escape from the aggregate forming a 2D gas. The progression of a non-invasive tumor into a metastatic malignant carcinoma, known as the epithelial-mesenchymal transition, can be interpreted as a wetting (liquid-gas) transition. On soft gels decorated with fibronectin and strongly cohesive aggregates, we have observed a wetting transition induced by the substrate rigidity[61]. We model the spreading dynamics of the monolayer expanding from the aggregate by balancing driving forces at the film periphery and viscous forces associated to the penetration of the cells from the (3D) aggregate into the (2D) film. By confocal microscopy, we observe this new mechanism named *permeation* by tracking single cell[62]. Using Particle Imaging Velocimetry, we characterize the flow field versus substrate rigidity. If cells spread like a viscous liquid on stiff substrate, the flows become irregular, with formation of holes as the rigidity decreases. This work will shed light on the dynamics of tissue spreading occurring during cancer progression and embryonic development.
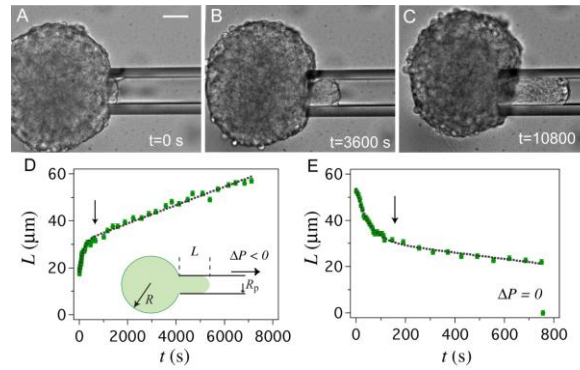
Aspiration of cellular aggregates

Figure 12) Aspiration of a cellular aggregate. (A)-(C) snapshots of aspiration of an aggregate inside a pipette, scale bar 50 μm, ΔP = 1200 Pa. From the length of the tongue L(t), one can measure the surface tension, the elastic modulus and the viscosity of the tissue[63].

We have developed a new method based on micropipette aspiration technique to measure the viscoelasticity and the surface tension [63,64,65] of cellular aggregates. As shown in figure 12, the aspiration curve has two distinct regimes; a rapid deformation followed by a slow flow. This creep behavior is a signature of viscoelastic materials. At short time scales the material deforms like an elastic rubber, whereas at long time scales it flows like a liquid. Surface tension, viscosity, and elastic modulus of these aggregates have been deduced by analogy between cellular aggregates and viscoelastic liquids. We found that the surface tension of the aggregate is stress dependent, suggesting that upon the application of an external stress, tissue cohesion is reinforced.

We have observed that the aggregates behave like "living" viscoelastic liquids (Guevorkian K, 2010). However, unlike an inert fluid, we observe aggregate reinforcement with pressure, which for a narrow range of pressures results in pulsed contractions or "shivering" (Guevorkian K, Gonzales-Rodriguez D, 2011). We interpret this reinforcement as a mechanosensitive active response of the acto-myosin cortex.

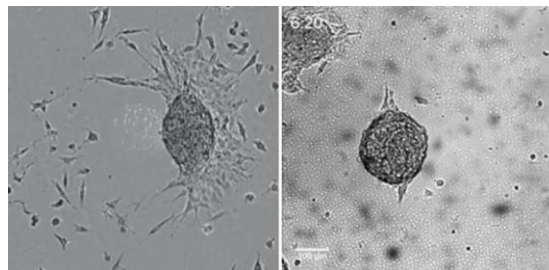## Spontaneous Migration: "Giant Keratocytes"

Figure 13) Spontaneous migration: Cell aggregates on soft gels move spontaneously. They crawl with a stick-slip motion and adopt the fan shape of giant keratocytes or a bipedal motion: penguins.

Single cell migration is studied extensively, but processes such as embryonic development or tumor metastasis often require the collective motion of a group of cells. We have observed a spontaneous collective migration of cellular aggregates on soft gels coated with fibronectin. During the spreading, the cell monolayer expanding outwards becomes unstable and dewets[61]. It leads to a symmetry breaking of cell polarities causing the entire aggregate to move. Decreasing the substrate rigidity, we observe stick-slip motions and different shapes (Fig:13): "Giant Keratocytes", where the lamellipodium is a multicellular monolayer expending in the front and retracting in the back and "Penguins" characterized by bipedal locomotion and

"Running Spheroids". We characterize the flow field and the stresses that drive the migration. Our study provides a powerful in vitro model of the mechanisms of multicellular cell migration. These results underscore the biological predisposition for living material to migrate, independent of length-scale.

Cellular aggregate – nanoparticles hybrid systems.
In January 2015, I got with Françoise Winnik a fellowship from WPI International Center for Material Nanoarchitectonics (MANA-NIMS) for "Developing new theories based on soft matter physics to describe and understand the mechanical properties of cell as they interact with nanoparticules". Grégory Beaune, my postdoc in Curie accepted to move to Japan.
We have studied how cells and particles play together. We name this project *"eating-dancing":* nanoparticles and microparticles are eaten by the cells or adsorbed on the cell's membrane. On the other hand, macroparticles, which are too big to be digested, are put into motion by the cells, they *dance*: this is our project for the following year.
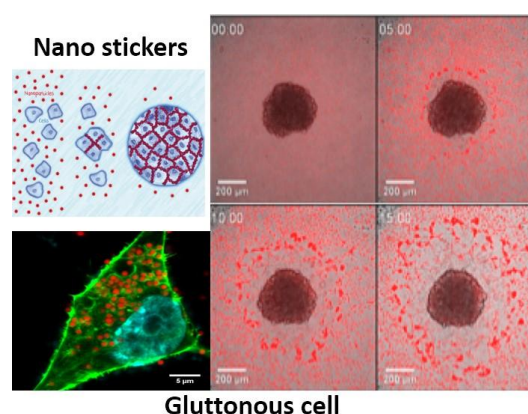

Figure 14) nanoparticles sticking cells together and multicellular uptake of microparticles.

I) Nano stickers (size 20 nm): We show that nanoparticles can be used as a glue "*Nano stickers*" to enable the formation of self-assembled aggregates by promoting cell–cell interactions[66] (Fig.14). We find that carboxylated polystyrene NPs are more efficient than the silica NPs of the same size, which were reported to induce fast wound healing and to glue soft tissue by L. Leibler. *Nano stickers* by increasing the cohesion of tissues and tumors may have important applications for cellular therapy and cancer treatment.

II) Microparticles (size 1micron): gluttonous cells: We study the spreading of cell aggregates deposited on adhesive substrates decorated with microparticles. A cell monolayer expands around the aggregate. The cells on the periphery uptake the microparticles by phagocytosis, clearing the substrate and forming an aureole of cells full of particles (Fig.14). We study the dynamics of spreading, the width of the aureole, and the level cell internalization. It leads to an easy, fast, and inexpensive cell – particle internalization measurement[67]. We want to study the role of the rigidity on phagocytosis by using microfluidic fabrication of soft jelly beads.

Project: Hybrid dead-living matter
After Japan, I continue to collaborate with G. Beaune who joined the Active Matter Group of J. Timonen in Finland. Our aim is to study granular active matter by using hybrid aggregates of microparticles and cells. The hybrid aggregates will be prepared by a flocculation of a solution of micrometric passive beads (soft or rigid) and active cells. For micrometric particles, we do not expect Brownian motion: aggregates of beads are frozen. On the other hand, the aggregates of cells are liquids because of the activity of the cells produces a large

non-thermal noise: they form spheroids to minimize their surface energy. Our project is to investigate the conformation and the physical state of cell-particles hybrid aggregates versus the particle volume fraction for which we predict a jamming transition and a phase separation. It's a fundamental question, with applications for all types of mixtures of active matter, as for example cell's nucleus or cell mixtures

1) The hybrid aggregate is a solid or a liquid?

By the pipette aspiration technique, we shall measure the elastic modulus and the viscosity of the aggregate. We expect a liquid-solid transition as the volume fraction of the cells decreases. We will compare our data to simulations performed by David Gonzalez Rodriguez. Moreover, we expect to observe active Brownian motion of the particles in the dilute regime, which will allow to measure an effective temperature of the cells.

2) Do cells and beads form an aggregate of uniform composition?

As in the case of the genome of eukaryotes that is partitioned into domains of functionally distinct chromatin states, euchromatin containing active genes and heterochromatin containing silent genes, we anticipate that hybrid aggregates will contain domains enriched/depleted in particles. Phase separation is predicted also by simulations and analytically in a mixture of particles with different level of activity, where one phase is enriched in active particles (cells) and the other in passive particles. This hypothesis will be tested by imaging with phase contrast microscopy or confocal fluorescence microscopy (for fluorescently labeled particles or/and cells) the distribution of passive particles within hybrid aggregates versus the composition of the suspension used to prepare the aggregates.

Figure 15) Books coauthored by FBW

Finally, I will quote the conclusion of Yves Quéré's speech, which expresses my style of work and the meaning of my life.

The 'hallmark' of your scientific output is very strong: most of your articles are those of a theoretician (you) who are joined by excellent experimenters, in small groups that you form, inspire and animate. You're not the only one working in this way but you do it in an exemplary way. You, dear Françoise, gave birth to a lot of new knowledge, but also to many beings, the hundreds of your university students, the dozens of researchers with whom you worked who all love you, and also of course to six wonderful children whom I am glad they are all present today at your side.
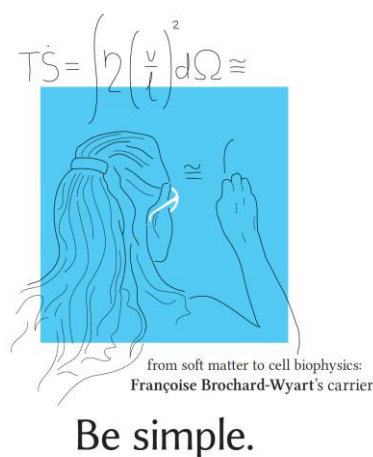
$$T\dot{S} = \int \eta \left(\frac{v}{l}\right)^2 d\Omega \cong$$

from soft matter to cell biophysics:
Françoise Brochard-Wyart's carrier

Be simple.

Figure 16) Poster for a meeting on Oct. 1-3, 2018 to celebrate the scientific career of FBW and her contribution to soft and biological matter.

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