Heliyon 9 (2023) e21924

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

The life of the cell membrane: A paradigmatic reading from Deleuze and Guattari

Rafael Maria Zamora-Prieto [a,*], Jorge Francisco Maldonado-Serrano [b], William González-Calderón [c]

[a] Facultad de Ciencias de la Salud, Universidad Autónoma de Bucaramanga - UNAB, Bucaramanga, 681003, Colombia
[b] Facultad de Ciencias Humanas, Universidad Industrial de Santander – UIS, Bucaramanga, 681002, Colombia
[c] Departamento de Ciencias Básicas, Universidad Autónoma de Bucaramanga - UNAB, Bucaramanga, 681003, Colombia

ARTICLE INFO

Keywords:
Fluid mosaic model
Membrane nanodomain
Territory
Machinic assemblage
Life

ABSTRACT

While the Fluid Mosaic model (FMM) is widely accepted as an account of the cell membrane's structure-function, its inability to explain certain phenomena has led to the lipid rafts hypothesis (nanodomains) that spontaneous spatiotemporal enriched zones of sphingolipids-cholesterol-protein exist within the membrane. In this text, we propose a novel approach that conceives the cell membrane as a living entity. The questions regarding the FMM revolve around the fact that, although these molecular components are present in many cell types, the membrane does not react in the same way to every external agent; for example, a virus evokes a particular response: why is there some marked specificity of virus (or toxin) attack on one (or some) of these cell types and not to other cell types that nevertheless have a similar membrane protein constitution? The crucial question, to explain this selectivity, would be what determines the specificity of attack on some cells and not others? While FMN assumes a dynamism between macrostates at the intramolecular, intermolecular, and/or collective levels in the membrane, the approach of the lipid raft model presupposes a much greater and more complex dynamics of microstates (even nano-states) of these molecular components. In other words, it implies higher and instantaneous mobility as assemblages ("intentional") and thus, of the membrane itself (as a collective), in response to changes in the internal and external physicochemical environment over a broad spatiotemporal scale. This suggests a mechanism of membrane adaptation in the face of evolutionary constraints. In this text, we propose a paradigmatic approach, from Deleuze-Guattari's philosophy: to conceive the cell membrane as living and not as a mere molecular conglomerate with particular functions and mechanical processes between molecules. For this, we employ the functional concepts of territory and machinic assemblage, whence the vitality of the membrane would allow us to postulate instantaneous updates, within wider spatiotemporal scales in its composition in contrast with the model that dominates as a more plausible explanation nowadays, that does not include smaller spatiotemporal events. If we resort to the concept of territory and its different media components, we could offer a more plausible explanation of the vigorous dynamism in the composition of the cell membrane since it would allow more subtle and complex differentiations between media and thus make visible the constant and instant changes. We propose that the model of nanodomains, understood as a process of dynamic territorialization, offers a more complex and subtle explanation of the instantaneous changes in the cell

* Corresponding author. Adress: 681003 Av. 42 #48 - 11, Bucaramanga, Santander Colombia.
E-mail address: rzamora@unab.edu.co (R.M. Zamora-Prieto).

https://doi.org/10.1016/j.heliyon.2023.e21924
Received 21 April 2023; Received in revised form 12 September 2023; Accepted 31 October 2023
Available online 10 November 2023

membrane's composition. This approach expands the explanatory framework for cellular phenomena and reveals their spatiotemporal complexity in accordance with other research.

We have understood that Matter-Energy and Information (MEI), when combined, mixed, and grouped in different and diverse ways, generate new physicochemical properties, emergent properties that go beyond the mere sum of the individual characteristics of the pieces that make them up. The cell, being a macro conglomerate of molecules, is no stranger to this phenomenon; therefore, cell membranes play a determinant role in the separation and delimitation between the non-living realm and the realm of the 'living'. What is the minimum physicochemical and/or biological limit where life begins within a space-time frame of reference? Are current theories about the cell membrane sufficient to account for this limit? What would its extension depend on? Could we turn to philosophy to broaden the conceptualization of the frame of reference? This is a problem that we would like to call the minimal molecular demarcation of/for life. In this article we present, working out of the philosophy of Deleuze and Guattari, an analysis of the ontological presuppositions underlying current biological representations of the cell membrane, and present some lines of possible development.

First, we consider some Deleuzian concepts that arise from his reading of Bergson. These are necessary for understanding the cell membrane, particularly the ontological and methodological assumptions. Using these as a background, we present the Fluid Mosaic Model (FMM) and its current complement called Membrane Nanodomains (MND formerly Lipid Microdomains or Lipid Rafts). With this purpose, in a second moment, from the concepts of *machinic* and *territorial assemblage*, we put forth a Deleuzo-Guattarian reading of the membrane mechanism.

1.

As Badiou points out, even over and above figures such as Spinoza or Nietzsche, Deleuze's master par excellence is Henri Bergson [1]. From Bergson's vitalist thought Deleuze constructs his idea of *life*, which he approaches only indirectly, deploying a bundle of interwoven concepts, among which multiplicity and difference emerge as of particular significance. Referring to 'The Conception of Difference in Bergson', Deleuze in *The Deserted Island and Other Texts* [2] observes that differences of nature imply the necessity of an internal difference since the difference between two individuals of the same genus cannot be external. Yet this way of differentiating is no longer sufficient for Deleuze. He explains that differences of nature have been replaced either by differences of degree or by differences of intensity; Deleuze indicates that science is responsible for the first substitution, while the second concerns the realm of metaphysics. Only at the end of his life, in his last publication and philosophical testament *Immanence: A Life?* [3] Deleuze explicitly expounds his idea of life, which we will return to at the end of this text.

Scientifically and according to the first substitution, the difference between individuals is expressed in degrees to the extent that the space in which these differences are expressed is homogeneous and that requires, in turn, that all the degrees be encompassed within the same utility, according to the scientific specification; that is, they are grouped in a utilitarian way so that they can be quantified, in spite of the fact that within this gradation many other forms in which reality is articulated overlap (uncontrolled factors) or overlapping forms that configure the reality to be studied are lost (excluded factors). It could very well be that the degrees are 'liberated' and, with each degree itself coming to represent a difference in nature. Deleuze illustrates this with an example that Bergson gives: 'The human brain, for example, according to whether we grasp it in its product or its tendency, will present in comparison to the animal brain a simple difference of degree or a whole difference of nature' [2]. As a product, a difference is the effect of a cause; as a tendency, it is a character that virtually encompasses its past and progressively develops toward the future.

According to the second (metaphysical) substitution, differences of intensity are differences in themselves, which means that they are neither the result of a comparison, nor the effects of causes. Differences of intensity best characterize life because they account for its relative autonomy and for the fact that once a life is initiated, it can neither be defined by a cause nor by comparison with other surrounding entities. Differences of intensity, however, arise in what Deleuze calls a zone of variable intensity,[1] a plane on which differences emerge, because these differences make life possible, since it does not emerge from absolute nothingness, but amid something. It may be that the living, life itself, is not materiality, but there is an event within materiality which, therefore, while not reducible to matter, does emerge specifically as life. Life, in this context, is best understood as a difference of intensity and not as a difference of degree. Nothing that is alive is more alive than another entity that is also alive; in other words, what is alive is just as alive

[1] In science, as well as in Deleuze's philosophy, the concept of singularity refers to the event (*l'événement*) which cannot be explained in comparison to other events. A zone of variable intensity refers to a singularity in the sense that any variation changes its essence, therefore a being, as such zone, is not comparable.

as any other living entity. What we will see is that, if a theory of the cell membrane does not appeal to this idea of difference of intensity, but to differences of degree, the membrane must be assumed to be non-living. Whereas if the membrane is understood as a zone of varying intensity in which differences of intensity arise at spatiotemporal instants, then it is more plausible to understand the membrane as a living entity in itself.[2]

Certainly, as Darwin's heir, Bergson is still theorizing on a level that we could call ethological, for he thinks in terms of individuals in an environment. Elizabeth Grosz describes the Darwin-Bergson-Deleuze relationship as follows: 'Bergson is the most Darwinian of the philosophers, as Deleuze himself is the most Bergsonian' [4]. As we will explain below, Deleuze seeks to go beyond this level, that of the sphere of the individual in an environment, to suggest a vitalist ontology that embraces the organic and the inorganic as integrated, while exposing the way in which life flows between the one and the other through the concept of territory.[3] A territory is a case of zone of variable intensity, therefore the concept of territory is a more biological way of thinking life as such zone. The following fragment illustrates well Bergon's proposal and at the same time raises a more fundamental problem: that of the membrane.

> If the vegetable renounced consciousness in wrapping itself in a cellulose membrane, the animal that shut itself up in a citadel or in armor condemned itself to a partial slumber. […] In two directions, in fact, we see the impulse of life to movement getting the upper hand again. The fishes exchanged their ganoid breast-plate for scales. Long before that, the insects had appeared, also disencumbered of the breast-plate that had protected their ancestors. Both supplemented the insufficiency of their protective covering by an agility that enabled them to escape their enemies, and also to assume the offensive, to choose the place and the moment of encounter. We see a progress of the same kind in the evolution of human armaments. The first impulse is to seek shelter; the second, which is the better, is to become as supple as possible for flight and above all for attack - attack being the most effective means of defense. So the heavy hoplite was supplanted by the legionary; the knight, clad in armor, had to give place to the light free-moving infantryman; and in a general way, in the evolution of life, just as in the evolution of human societies and of individual destinies, the greatest successes have been for those who have accepted the heaviest risks [5].

Following this, Bergson explains the 'capital error' perpetuated since Aristotle of interpreting vegetative, instinctive, and intelligent life as a difference of degree and not of nature, that is, as graded products of the same movement of search for, for example, shelter and agility, and not as divergent directions of the same movement. Attention should be drawn to the fact that this question of armor is a consequence of the problem of the membrane or of the minimal molecular demarcation for life. Certainly, to speak of 'an animal that shuts itself up' is not a spatial or territorial metaphor, as the use of the term 'citadel' might be. Had it not been enclosed, the animal would be open or exposed, which is to say that the problem of survival is reduced to the question of the limit, of the space that is one organism and not another. Thus, if we make the opposite movement from the infantryman to the hoplite, and from the hoplite to his ancestors, the question would take the following form: are the differences in the membrane differences of degree (molecular structures that adjust and have dynamics) or of intensity (transformations in the molecular structures themselves)?

An approach to this problem requires an inquiry into the nature of the cell membrane. In what follows, some structural and functional characteristics of membranes will be presented according to the current scientific model of the cell membrane and its current complement or emerging model, in order to show the ontological assumptions underlying them. At the end, and when we take Deleuze's philosophical position on 'life' into account, it will be possible to consider why it is not enough to understand the membrane only as a non-living component of the cell, but rather why it is necessary to extend life to the membrane itself.

2.

Biological membranes are semi-permeable macromolecular systems, whose extension in two dimensions far exceeds their thickness, which is between 6 and 10 nm, and it is in the dynamics of their components (lipids and proteins) where their biological functionality lies. Currently there is a predominant or widely accepted biological model, called Fluid Mosaic, as well as an emerging model, called Membrane Nanodomain (MND). We will first present an overview of the FMM, with its strengths and weaknesses, and then turn our attention to the MND, to highlight how it is able to account for the gaps left by the FMM.

The most plausible biological explanation for the functionality and therefore the structure of the membrane was proposed in by

[2] If we were to quickly compare this to the string theory, which states in general that subatomic particles are the result of transitional states of vibration of a more fundamental object called string ("pure energy") that allows differentiating these particles from each other, the cell membrane and its different sectors or temporal territories could be understood as the result of vibrational molecular arrangements, but not as in a materialistic conception that understands the cell membrane as punctual molecular conglomerates.

[3] Kleinherenbrink [73] makes a thorough analysis of living beings with the concept of territory. Our bet is to change the level of analysis and concentrate on the membrane, a matter that this author does not detail, but, undoubtedly, opens the way for what we intend.

Bothorel [6,7] and Singer & Nicholson [8], known as fluid mosaic.[4] This model posits the existence of a semi-permeable barrier, both physical and chemical, between the interior of the cell and its environment. The membrane is considered to be a lamellar phase (L) in model membranes which is in the FMM is conceived as a disordered liquid barrier phase (L_{α}), despite its structure. This model begins by assuming that the cell membrane is distributed in a bilayer architectural pattern[5] constituted by homogeneously distributed lipids, varied in structure as well as in functions,[6] and by proteins that make the necessary and indispensable connections of MEI flow between the living and the non-living. One type of protein completely crosses the cell membrane; these are called integral (or transmembrane) proteins. Others are only immersed on one side of the layer, because they do not completely cross the cell bilayer, and are thus called semi-integral. A third type of protein is anchored in one of the layers (thanks, in turn, to other lipids and/or proteins), but protrudes either into the cell or towards the outside; these are called peripheral proteins. These various types of proteins make it possible to maintain the differences (electrochemical gradients) required for the cellular compartment to manifest the fundamental characteristics that we consider living beings to have: to be born, to grow, to reproduce, and to die. Here we note that it is the cell, rather than the membrane itself, that is assumed to be a living being. It's worth noting that a living structure maintains relative autonomy from its environment in an "intentional" way, more precisely and in a Deleuzian fashion free of any debt to consciousness, in an assemblage (*agencement*)[7]. For this purpose, a living structure temporarily evades the second law of thermodynamics, entropy, through syntropy (negentropy) which is the way in which it exports entropy out of the system in order to keep low entropy within. Dynamic events and their speed do not define whether something is alive per se, but this "intentionality" of negentropy can serve as a good indicator of life in some material entity.

Insofar as we are dealing with proteins and lipids, we must understand that they are built up of molecules. The general characterization made by this model of the molecules that are part of the membranes obeys the degree of affinity of each of the molecules with respect to water. Since a water molecule presents significant differences in electronegativity between the atoms that establish the bonds that constitute it, electrical polarities are produced.[8] All cell membrane molecules are classified as amphipathic (a mix of hydrophilic and hydrophobic) according to their polarity. In general terms, the polarity of a molecule allows it to interact with water (polar) or not (apolar). In the membrane, molecules have both polar and apolar fragments, which is why they are classified as amphipathic[9] with respect to water: they contain polar fragments that are similar to water, which allows them to have physicochemical affinity with it (hydrophilic: having a tendency to mix with water) and, at the same time, contain non-polar fragments that do not have a physicochemical affinity with water (hydrophobic: repellent of water).[10]

Thus, contemporary science defends the bilayer structure of the FMM on the basis of the dual polarity-apolarity characteristic of the

[4] At the end of the 18th century, the first investigations of lipids and their interaction with water were carried out. Benjamin Franklin in 1774 studied the behavior of oil in water. A century later, Lord Raleigh in 1890 measured the area and thickness of the layer studied by Franklin. Around the same time, Charles Ernest Overton found similarities between the behavior of biological membranes and lipids. Langmuir in 1917 raised the possibility that the cell membrane is a monolayer formed by carboxylic acids (a type of molecule) whose length of its aliphatic chains (made up of carbons and hydrogens) is relatively long, these in turn directed in the opposite direction to that of water (synonymous with apolar) and the deprotonated carboxylic groups (synonymous with polar) in contact with it. However, in experiments with red blood cells (blood cells), performed by Gorter and Grendel in 1925, the concept of lipid bilayer was introduced. The first model widely accepted in the scientific community was proposed by Danielli and Dawson in 1935, called paucimolecular: the membrane would be made up of apolar molecules in an apolar central region of lipid nature with variable thickness, limited on both sides by a monolayer of amphipathic lipids whose polar ends would be oriented towards the extracellular liquid (ECL) and towards the intracellular liquid (ICL), respectively, and an external monolayer of globular proteins. Robertson, in 1959, proposed the unitary theory, according to which all biological membranes would be constituted by a lipid bilayer whose protein component would be located on both the internal and external surfaces; the protein component, with a low percentage of the protein structure immersed in the apolar zone of the membrane [57,74–77].

[5] Initial theories considered the membrane as a monolayer. Subsequently, Fricke in 1923 determined that the electrical capacitance of the membrane varied between 1.0 and 6.0 $\mu F\text{-}cm^{-2}$, for which he attributed the difference to the thickness of the membranes studied, and Robertson in 1959, using electron microscopy on cell membranes, observed two zones of electronic density: the denser external zone (polar heads of lipids and/or proteins) and the less dense internal zone (apolar lipid chains), a characteristic that was observed in intracellular membranes. Thanks to these experiments, it is deduced that the membrane must be constituted as a bilayer. Once the cell membrane is understood as consisting of two layers, the explanations for the interaction of ICL and ECL are improved, although they become more complex. Thus, if it is understood that the ICL possesses water, then it can be explained why the membrane is not apolar but amphipathic.

[6] In a general sense membrane lipids can be classified into: Glycolipids (glycoglycerolipids and glycosphingolipids), phospholipids (phosphoglycerides and sphingomyelins) and sterols (cholesterol in animals and phytosterols in plants).

[7] The concept of territory implies the concept of machinic assemblage. As presented subsequently, a territory as the niche necessary for any living being, serves as the limit that permits and conditions relations, connections, or assemblages that in some ways are guided or selected. Since the attribute of consciousness is discarded at this level of the cell membrane, Deleuze's philosophy offers this concept of assemblage to be able to deal with the selectiveness of an event without having to recur to the idea of intelligent design or, more importantly, to conscious intentionality.

[8] Similar to a magnet. It has intra-molecular partial charges and is therefore classified as a polar molecule.

[9] The gradients of electronic distribution along the length and width of the molecule are the ones that confer polarity or not in certain specific sectors of the molecules, and in this way make possible the interaction of the molecules by forces of attraction or repulsion with water, allowing the organization and structure of the membranes.

[10] Indeed, we could also describe this idea in terms of polymerization: the cell membrane would be the result of a polymerization of polymers. Deleuze and Guattari, in '10,000 BCE The Geology of Morals', take up Francois Jakob to explain the double articulation in levels [69]. The second level of cellular chemistry corresponds to the processes of chemical polymerization of the cell. We decided not to follow this line of interpretation because the problem of the membrane is not directly addressed by DG nor by subsequent studies of DG's conception of life [78].

molecules that constitute it. That is, each transmembrane molecular segment is constituted by two inner apolar molecular fractions and two polar fractions or heads, which interact with the Extracellular Liquid (ECL) and Intracellular Liquid (ICL), respectively. Likewise, since membrane molecules (phospholipids, glycolipids, integral proteins, semi-integral proteins, and glycoproteins of these latter) are classified as amphipathic,[11] they have typically been assigned certain isolated architectures corresponding to forms of Euclidean geometry [9]. This type of geometry, which is static, does not properly represent the constant movement of charges (electrodynamic) due not only to intra-molecular dynamics, but also to interactions with the other molecular components and collectives within the membrane. In other words, the internal interaction of the membrane molecules depends on its electrodynamic surroundings, and a static architecture cannot account for this interaction. It is worth noting that here amphipathic molecules, which have a functional duality, possess an essential feature that enables them to be a molecular part of the cell boundary; they would be dead molecules outside of the cell, but in their interactions with the inside of the cell they are alive. As the cell boundary, they are like zombie molecules, half alive and half dead.

Morvan and collaborators' [10] review about the usefulness of the solid-state Nuclear Magnetic Resonance (ssNMR) technique,[12] the great intramolecular, intermolecular, and collective mobility that occurs in the cell membrane on a wider spatiotemporal scale is revealed; at the spatial level these movements range from angstroms through nanometers and ending in microns respectively; at the temporal level these same events correspond from picoseconds through nanoseconds and ending in microseconds.

For the FMM, the structural function of the membrane (maintaining the uniqueness of the cell) and the separation function (separating the inside from the outside of the cell) are explained by the lipids and proteins that constitute it. However, the vital function of the membrane, that of maintaining life, was initially centered in proteins. Thus, this model held that membrane proteins served different functions. In general, the functions are as follows: (i) to be channels that allow the passage of ions and water (low molecular weight hydrophilic substances) more rapidly between the inert and the living; (ii) to function as translocases[13] of higher molecular weight hydrophilic substances between the P (Protoplasmic or inner) side and the E (Extracellular or outer) side or vice versa; iii) act as anchors of the cytoskeleton by momentarily connecting to a new conformation and/or configuration of the cell morphology, thus becoming part of the movement of matter at the intracellular level and/or serve as receptor-transmitters of the cell with its external inert world and/or with other cells; iv) allow the union and connections between cells (examples of this are gap junctions); v) act as catalysts that accelerate chemical reactions.[14] Typically, this type of mechanistic representation involves the modeling or generation of artificial systems that attempt to represent real visible or invisible worlds in a simplified way.[15]

The FMM became more complex; using fluorescence techniques and electron paramagnetic resonance at first, later with calculations to model membranes of only lipids and complete using computational tools, they shed light on the complex motor processes of the molecular components of the membrane (lipid-proteins) and of the membrane itself. Also, ideas such as rotational motions of polar and apolar heads, wobbling motions, C–C chain elongation or shortening, translational motions (lateral diffusion or restricted lateral diffusion), molecular ordering (phase states), confinement and free diffusion zones, changes of phase states therein, phase transition energies, flip-flop motions of lipids between opposing monolayers, membrane elasticity, dispersion and order (thickness) began to be conceptualized [10,11–25]. Furthermore, the membrane seems to adapt in its thickness (ductile and deformable) in response to the physicochemical environmental conditions surrounding it and therefore can modify its thickness over time differentially in sectors of it on its surface; this is possible through reducing unfavorable hydrophobic and hydrophilic interactions [10,26–29]. These ideas are the seed of the emerging model that we will discuss later called membrane nanodomains.[16]

Despite the complexity gained in the FMM, the observed functions in cell membranes are not all explained. This, in effect, constitutes a first approximation to the understanding and explanation of multivariable biological processes. Thus, by analogy, we might turn to Foucault's description of natural history. Unlike nineteenth-century biology, for which life was structured as a science and which therefore had an epistemic commitment to the concept of life, eighteenth-century natural history had an epistemic commitment only to the living being. Similarly, the FMM maintains mechanistic assumptions, precisely because according to this model the membrane is not alive in itself, and cannot be alive because the membrane has not been understood within the concept of life, but as a non-living part of life. This is why, for this model, the explanation of the membrane functions in the following way:

[11] The general pattern structure of cell membranes is constituted by amphipathic molecules that are both lipids and proteins. The one and/or the other can combine with carbohydrates, thus increasing their polarity, to give rise to glycolipids and glycoproteins, which constitute the glycocalyx on the outer face of the cell membrane, whose functions range from being biomarkers of intercellular signaling (molecular communication) with implications for transduction (intracellular communication in response to external and/or internal physicochemical messages) to connection to the extracellular matrix.

[12] This technique provides a global and quantitative description of the membrane dynamics over different spatiotemporal scales and provides parameters such as movement velocities (correlation time and associated activation energy), order (membrane thickness), activation energy, membrane elastic coefficients and phase transition enthalpies (amount of membrane defects) among others.

[13] Proteins that contain hydrophilic molecule binding domains present in ECL or ICL; these domains are oriented towards either of these aqueous solutions: translocases have the characteristic of undergoing conformational changes allowing 'engulfing' the transported molecule from one place to another and thus enabling faster transport of these hydrophilic molecules. An example of these are the GLUT carbohydrate transport proteins.

[14] These are only five predominant functions of membrane proteins, but there are several more specific functions [57,74,75,77,79,80].

[15] Simplifying, for example, by decreasing the number of variables and/or attempting to weight them in order to reduce the degree of uncertainty or unpredictability of life phenomena.

[16] Different thicknesses, stiffness, and transient lateral separation between Lα (Liquid-disordered) and Lβ (Gel: Solid -ordered) phases previously passing through Lo (Liquid -ordered) on the membrane surface, which could explain certain biological functions of the membrane.

> [The latter] is provided by surfaces and lines, not by functions or invisible tissues. The plant and the animal are seen not so much in their organic unity as by the visible patterning of their organs. They are paws and hoofs, flowers and fruits, before being respiratory systems or internal liquids. systems or internal liquids [30].

The problem of mechanistic representation implies a reduction through which we have tried to concatenate the molecular structures that make up cell membranes in analogy with the visible world. However, when thinking in evolutionary terms, this would mean that the cell membrane has not evolved, because the mechanistic model universalizes for all living beings a kind of universal membrane that is the same or standard for any cell. But evolutionarily, as well as for the visible world, we ask: Are all animal limbs the same? Do they descend from a single structural mold? We pose this question working from a neo-Darwinian presupposition, evolutionary gradualism, according to which living beings are the result of staggered processes of selection (links between links) in which chance plays little role, understanding that chance implies unknown processes. It could be that different types of legs have arisen randomly as *singularities*, e.g., as processes of convergent evolution, genetic drift, and/or historical contingencies. Similarly, do all the cell membranes of evolved animal and plant cells descend from a proto-membrane of procaryotic cells? Do we have cellular fossils that confirm such universality in the case of the cell membrane? Shouldn't we see that cellular evolution could be part of the process of organic evolution?

How can we understand the idea of non-living parts within the living, without wondering, at least in some sense, about the notion of life itself? In order to try to answer the question, we will consider Grosz's reading of the Bergsonian difference between the living and the non-living: '…If matter compresses and thus reduces the past to its present forms, to the actual contained in the present, the living are distinguished from the non-living through the ever-continuous growth and accumulation of the past, through their inherent immersion in virtuality' [4]. In this vision of things, the demarcation between life and non-life cannot rest on a membrane of discrete states, represented by topologic mobile structures of a mechanistic model and assumed to be non-living. The FMM establishes only a difference of degree drawn from the spatiality of the cell, while ignoring its temporality. It deals only with differences of degree that would correspond to degrees of 'exteriority,' lacking an understanding of the differences of intensity that must be accounted for in terms of past events virtually accumulated in the present state of the membrane.[17] In other words, it still cannot explain why in a state of molecular conglomeration of the membrane there would be a change. Does this possible change not imply a singularity that irrupts and transforms the state of things and actualizes something that was virtually present, as Bergson suggests?

From the FMM, in any case, the membrane can be understood as a zone of variable intensity, that is, as a real prior condition that makes it possible for there to be differences in intensity. Precisely because it is understood that the molecular structure self-assembles, self-repairs, and fuses with other membranes, for the FMM the membrane has autopoietic characteristics. However, this model does not include an explanation of the changes, intensities or singularities that burst into any particular present moment. It is these changes that the following model intends to explain.

3.

Over the past few decades we have learned that there is no uniformity in the membrane, and according to several research studies, we can identify asymmetric sectors.[18] This is because we now have a better understanding of membrane structure and dynamics that were previously unknown or poorly understood; *in vivo* molecular motricities observations are largely due to the advent of new spectroscopy techniques, especially Förster Resonance Energy Transfer (FRET) microscopy. These asymmetric structures emerge due to a differential in their molecular constitution, that accompanied by lateral movements of the molecular components (lateral diffusion) segregate their constituents. This ability is based on the dynamic liquid-liquid immiscibility and underlies the concept of membrane subcompartmentalization [31] and thus can explain membrane functional responses. We can, therefore, identify new functional responses (changes that burst in a particular present moment, a constant updating of molecular reality as a result of accumulated changes in the face of past contingencies).

According to these investigations, there are sectors within the membrane that are diverse in composition and function, a fact that could explain the variety of cellular forms. On the basis of this, the existence of external glycocalyx (carbohydrates from glycoproteins and glycolipids anchored to the membrane that interact with the extracellular matrix and its surrounding environment) has been demonstrated. It has also been shown that the two monolayers differ in their lipid constituents, despite the fact that there is a dynamic flow of MEI between them. Finally, we can recognize, then, that the proteins immersed or interacting in the membrane differ in their functionality in response to the surrounding lipids and/or carbohydrates. In other words, the cell membrane appears to exhibit a structural multifunctionality of simple molecular architectures that, when combined differentially, result in complex patterns of response or expression, namely, adaptations (flexibility) to both the external and internal environment if we conceive life as a continuous and non-discrete series of instantaneous updates of both structures and functions where we could observe (or not) movements according to our current technological and/or conceptual limitations. This is why the membrane would be part of the phenomenon of life.

[17] Although a difference between plant and animal cell membranes can be noted, only a study of, for example, bacteria frozen for thousands of years in the polar caps, could confirm an evolution of the cell membrane. Bramkamp [32] explored the possibility of the existence of lipid rafts in prokaryotic cells and Bhat [81] presents the probable role of pathogen entry into plant cells through the formation of a probable microdomain, evidencing the possible importance of these structures in cell membranes in this kingdom.

[18] Several investigations or reviews address specific and/or general features of this approach to biological membranes, which are called lipid nanodomains [9,32,31,33–56,82].

Many recent research [9,32,31,33–56] has led to the emergence of an alternative or complementary model to the FMM. Initially, it does not seem to be a matter of *a* new model but, rather, a complementary view of the initial membrane prototype. This perspective is known as the Lipid Nanodomains or Lipid Rafts hypothesis [44,45]. In this complementary MND, it is suggested that, although the membrane should be considered as a disordered fluid liquid ($L_{\propto,}$ a fluid mosaic), an ordered solid phase (L_{β}: Gel; through a previous ordered liquid phase, L_o) arises in this at an instant of time with respect to the disordered liquid environment of the rest of the membrane [57,35]. This is a spatiotemporal territory enriched in cholesterol and sphingolipids with diameters ranging from 10 to 200 nm [58]. This is precisely the kind of event that is difficult to explain mechanically. Speculatively, it has been proposed that these anisotropic territories with respect to the rest of the membrane could originate from the predominance of counter-balanced van der Waals forces of "push and pull" between the apolar molecular fragments of lipids and proteins both immersed and not in the nanodomains [59–61]. This ordered liquid phase or lipid raft, which Schutz called Transit Confinement Zone [22], would cover, at any given time, an extension of about 15 % of the entire membrane; thanks to this "the entire [nanostructure] would present a greater stability that allows interactions with the cytoskeleton and the extracellular matrix, facilitating events of endocytosis, signal transduction and even fusion between membranes, entry of toxins, bacteria, parasites and viruses" [62]. The other explanations given by the FMM would remain valid.

What is the relevance of cholesterol in the formation of nanodomains? Cholesterol, at levels close to 40 %, has a defined effect on lipid thermotropism. It completely suppresses the gel-fluid transition phase, and this effect begins to manifest in concentrations above 25 %, through the formation of a new ordered liquid phase (L_o). This phase shares properties of both an ordered solid phase and a disordered liquid phase, leading to lipids limited in their movements, similar to the gel phase, but still diffusing laterally in the membrane plane, albeit in a restricted manner, generating a confinement zone with a high degree of packing of aliphatic chains. Shorter C–C structures in the aliphatic chains and/or branching in these chains result in fewer van der Waals interactions, reflecting a decrease in the transition phase. In such chain types, the presence of cholesterol elongates the chain, leading to higher transition energy and an increased transition phase. Phytosterols are more efficient in this regard, possibly explaining the adaptive resistance mechanisms of some plants to low temperatures [10,63].

Paraphrasing Morvan, sterols would serve as a 'mechanical buffer' by leveling the ordering in energy fluctuations and imposing molecular dynamics during temperature and hydration level changes, as they cross the L_{α} -L_o- L_{β} transition phase. This is evident in varying thicknesses within the membrane plane, attributed to longer C–C aliphatic chains and a higher concentration of cholesterol. This accounts for the greater thickness and, as a result, increased resistance to deformation.[19] Conversely, shorter C–C aliphatic chains and a lower cholesterol concentration lead to a reduction in membrane thickness and greater susceptibility to membrane rupture. In other words, average cholesterol levels of 30 % create a damping effect on the undulations in membrane fragments consisting of thousands of molecules (collectives). This effect may partly be attributable to the inherent intramolecular order of cholesterol (S_{CH} parameter), allowing efficient polarization transfer with hydrophobic portions of membrane molecules, thereby increasing the attractive forces between them and facilitating the persistence of the gel or L_o phase.

The questions regarding the FMM revolve around the fact that, although these molecular components are present in many cell types, the membrane does not react in the same way to every external agent; for example, a virus evokes a particular response. This anomaly in membrane response, which should be due to the molecular constitution, raises crucial questions. First, why is there some marked specificity of virus (or toxin) attack on one (or some) of these cell types and not to other cell types that nevertheless have a similar membrane protein constitution? The crucial question, to explain this selectivity, would be what determines the specificity of attack on some cells and not others?[20] Secondly, although cell membrane fusion is relatively 'easy' as indicated by *in vivo* studies in cell cultures (laboratory experiments)[21] [64,65] for some reason it does not seem to be so easy in nature, since these fusions do not occur frequently. Why, then, is their frequency in nature so low? Furthermore, fusion between the cell membrane and vesicles or certain pathogens occurs frequently. It is worth noting that membrane fusion is not yet well understood: How two bilayers manage to overcome the energy barriers, allowing fusion between them and their reorganization leading to the formation of a single continuous bilayer [66], remains a question that hasn't been fully comprehended.

Seemingly membrane fluidity plays a crucial role in understanding the process of fusion between them. The fluidity of nuclear membranes and some lipid-rich viruses with unsaturated phospholipids appear to be higher than in the plasma membrane, which contains cholesterol. In other words, these exhibit greater bending elasticity, allowing the fusion of viral and cellular membranes to occur more easily, enabling the entry of the virus into the cell or the formation of nuclear invaginations [10,67,68]. It seems that fluidity is required for these events to take place. In our opinion, if cholesterol is not present, membrane fusion between larger membranes appears to occur with greater difficulty. This phenomenon could be attributed to the order and stiffness effects that cholesterol imparts to certain regions of the membrane during certain spatiotemporal moments, a phenomenon known as membrane nanodomains. This maintains a state of fluidity that does not significantly change with temperature, which is more evident in plant

[19] The viscoelastic parameters are higher compared to a membrane without cholesterol, but this leads to a decrease in the bending elasticity of the membrane.

[20] For example, HIV only penetrates $CD4^+$ lymphocytes, which contain this protein ($CD4^+$) in their membrane. Yet although neurons and enterocytes also have the same protein in the molecular structure of their membrane, HIV does not enter them.

[21] While fusion of membranous structures such as vesicles or lipoproteins (both of which are significantly smaller than a single cell membrane) with the cell membrane frequently occurs, fusion between cell membranes is infrequent. In the case of the cell type called myoblast, such a fusion does occur and generates skeletal myocytes, which are functional polynucleated cells in living beings, this phenomenon occurs both *in vivo* and in cell culture, but this fusion is not common in other cell types of the body under natural conditions.

phytosterols compared to the disorder of unsaturated phospholipids.

The hypothesis of the existence of these lipid platforms in the cell membrane could account for these events, since not only would the presence of certain molecules be sufficient for both phenomena (the specified viral attacks and their relatively low incidence) to occur, but it would also be necessary to contemplate momentary configurations of the membrane molecules, which would be the lipoprotein intermolecular interactions or lipid rafts. On the other hand, we contend that understanding the rafts only as a complementary addition to the FMM undermines the full research potential of such a proposal. This is where Deleuze and Guattari's philosophy can conceptually expand the meaning of this theoretical advance and open the possibility of rethinking the nature of the cell membrane.

As we stated previously, Deleuze and Guattari deploy a series of concepts that allow us to describe life (and the function of the membrane) outside the sphere of the individual organism or cell. In what follows, we frame an answer to the question*:* Which physicochemical, biological, and/or other aspects are indispensable for a membrane to be able to create the minimal molecular demarcation of an animate being? The living being cannot be understood as an entity independent of its environment. In the field of ecology, this environment is defined as a *niche,* which is an n-dimensional hypervolume containing all the organic and inorganic resources necessary and indispensable for the existence of a living being. This is a concept that goes beyond that of the habitat.[22] We consider that this hypervolume constantly deforms topologically, thus adapting itself to the physicochemical and biological contingencies of both its external environment and the internal environment of a living being; in other words, a living being is an integral and vital part of that particular niche, establishing the minimum conditions of functional consistency of its own life through active disposition or assemblages.

This notion is accounted for by Deleuze and Guattari in their concept of *territory*. Their concept of territory allows us to understand that a living being must be understood with and in its niche, which in turn means that the territory is part, albeit externally so, of the living being. Now, it is necessary to understand that their concept of territory is a functional concept, which allows them to use its flexibility for addressing the various problems that interest them. A territory implies a relationship between what is inside of it and what is outside of it since a territory implies a limit. The cell could be thought of as a territory, whose limit would be the membrane, but the interest of this article is rather to consider the membrane as a territory in itself.

For Deleuze and Guattari a territory implies an autopoietic process, for there is no external subject that a priori creates it. On the contrary, the organism is a process of territorialization and in this sense an autopoietic process. Even if a flux of MEI is always involved in a territorialization, the process of territorialization is not given from outside the territory that it is being established; thus, the process is autopoietic. For them, a characteristic of this autopoietic process is found in its expressive nature, that is the individuality is gained not only because the territorialization process involves an interchange of MEI but because this MEI expresses the individuality as different from other individuals.

The dynamics of life, in this order of ideas, translates into the dynamics of the living being in its territory and of its territory, autopoietic and expressive. But territories continue to constantly selectively exchange MEI with their neighboring territories, i.e., a semiclosed thermodynamic system having a semi-permeable selective boundary). Even though this mobility occurs at very low rates, such as in the lysogenic state of a virus or the lethargic state of a seed.[23] Territories are not still or immobile units, but processes. For this reason, the concept of territory is composed of the concepts of territorialization, deterritorialization, and reterritorialization. This triad of concepts allows us to think the processes or flows of territorial exchange or, as Deleuze and Guattari also conceptualize it, the territorial assemblages.

There is, in this sense, a constitutive dynamic between what is outside the territory and what is inside of it. Paraphrasing Deleuze and Guattari, it is a matter of the deterritorializations or openings of the territory of the membrane to new entries of MEI, or of exits from the territory in search of MEI not found in the original membrane territory, and also of reterritorializations or returns to a membrane territory, new or old. As they write, 'on its own stratum, assuring its autonomy and bringing it into a set of aleatory relations with the exterior, the more deterritorialized it is.' [69].

The degree of deterritorialization is directly proportional to the possible interactions with the environment. But this means that the organism depends on the medium with which it must maintain an equilibrium that is apparently homeostatic from a macromolecular (cellular) perspective, or equilibrium between macrostates, but really homeodynamic from a molecular perspective, or equilibrium between microstates, even nanostates. Thus, even if we assume an equilibrium between inside and outside, which may well be explained in exclusively physical terms, we cannot explain the opening of the membrane in those terms alone. The FMM seems to explain the equilibrium between microstates of the membrane, but a more detailed explanation of the equilibrium between microstates (even on smaller spatiotemporal scales like nano or picoscales, where molecular and collective behaviors of the membrane are observed along with their resulting sectorial compartmentalizations), which actually accounts for its functioning is required. Always, the existence of an organism implies the relations of the interior of the organism with the exterior or its environment, and so does the existence of the membrane.

We could assume that the cell membrane is a niche of repeated molecules and that each one can be understood to be in equilibrium - to the point that they can be said to be machines within an even more complex machine called the membrane - with the outside of the cell and with its interior. The membrane itself, however, has to be understood as a system with two different exteriors. The first (ECL) is the very outside of the cell, but the second (ICL) is the inside of the cell. How does it achieve an equilibrium with two physically and chemically different exteriors to the membrane, while taking into account the thermal equilibrium that governs every system?

[22] Habitat refers more to the physical space required for the existence of an organism population, to an ecosystem.

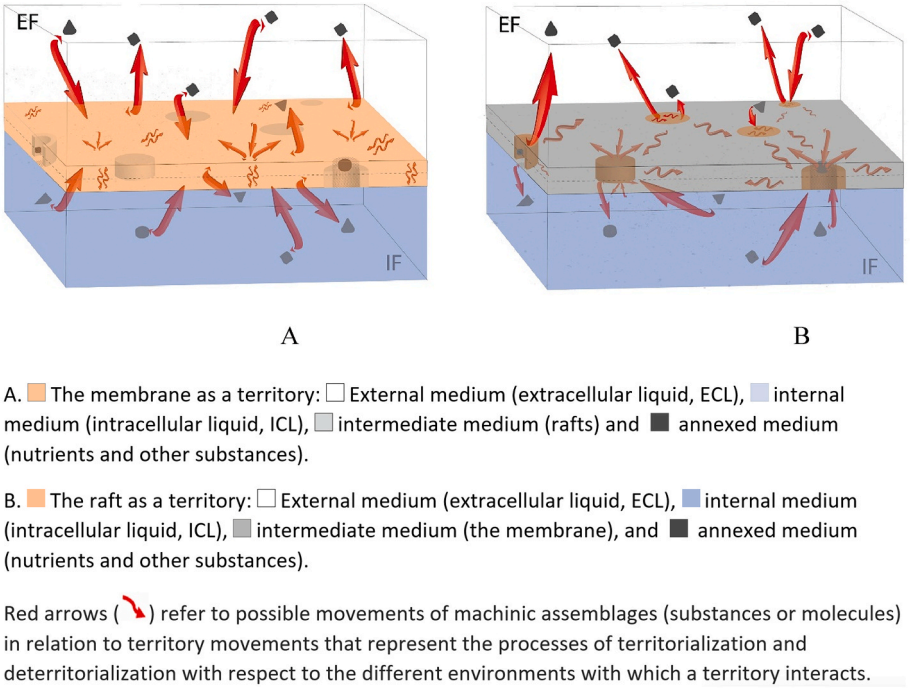
[23] The dormant state of a seed that is viable and mature, but in some cases does not germinate despite favorable external physicochemical factors such as temperature, humidity, and oxygen pressures. Wouldn't this indicate some degree of autopoiesis on the part of the seed?.

Now, as we have seen, the membrane is characterized by being autopoietic and by having a spatio-temporal consistency in its structure (dimensional) and functionality (expression). A third concept of great utility is that of machinic assemblage. Guattari in *Chaosmosis* [70], when speaking of Machinic heterogenesis, reflects on the ontological reaches of the concept of autopoiesis introduced by Francisco Varela [71] to refer to the quality of living organisms to maintain themselves, self-organize, and reproduce. Living organisms exhibit the properties of an autopoietic machine and not of an allopoietic one, which produces something different from itself. According to Guattari [70], the concept of autopoiesis, not only 'entities enclosed within themselves' (that is the metaphor of the citadel) can and should be understood to be autopoetic, but also relations of alterity: the human being, social systems, institutions and technical machines. This reading of Varela's concept influences Deleuze and Guattari's development of the notion of machinic assemblage as a way to conceptualize agency in human and non-human bodies, for example in geological bodies. In this order of ideas, and in relation to what was explained above with respect to Bergson, that the process of the living implies a kind of border or protection, the concept of machinic assemblage (which includes other uses of the concept of territory and territorialization) is relevant and pertinent for understanding how Deleuze simultaneously embraces and goes beyond the ethological plane when thinking about biological changes.

It is possible to think of the cell membrane, then, as a Deleuzo-Guattarian territory. As such, it is constantly deterritorializing in order to achieve adaptation to the uncertainty of its internal and external environment (ECL and ICL), an uncertainty produced by the constant flow of molecules coming in and going out of this territory. It is important to clarify, however, that for Deleuze and Guattari, the territory involves not only external and internal zones but also two other zones, an intermediate and an annexed one:

> The territory is in fact an act that affects milieus and rhythms, that 'territorializes' them. The territory is the product of a territorialization of milieus and rhythms. […] It is built from aspects or portions of milieus. It itself has an exterior milieu, an interior milieu, an intermediary milieu, and an annexed milieu. It has the interior zone of a residence or shelter, the exterior zone of its domain, more or less retractable limits or membranes, intermediary or even neutralized zones, and energy reserves or annexes [69].

We propose to use this more complexly spatialized concept of territory at two different levels, that of the membrane and that of the raft. In the first level (see Schema 1. A) we assume the membrane to be the territory, with the outer medium corresponding to the ECL



Schema 1. Scheme of the proposed territories.

A. The membrane as a territory: External medium (extracellular liquid, ECL), internal medium (intracellular liquid, ICL), intermediate medium (rafts) and annexed medium (nutrients and other substances).

B. The raft as a territory: External medium (extracellular liquid, ECL), internal medium (intracellular liquid, ICL), intermediate medium (the membrane), and annexed medium (nutrients and other substances).

Red arrows ( ) refer to possible movements of machinic assemblages (substances or molecules) in relation to territory movements that represent the processes of territorialization and deterritorialization with respect to the different environments with which a territory interacts.

and the inner medium corresponding to the ICL, the intermediate medium corresponding to the lipid raft, and the annexing medium corresponding to nutrients, hormones, viruses, toxins and metabolites (products and wastes). In the second level (see Schema 1. B), we assume the lipid nanodomain to be a territory, while the rest of the membrane that does not become a raft corresponds to the intermediate medium.

Further developments of the concept of territory to understand cell membrane rafts imply empirical research which could and should be done in the future if this proposal is to be considered. But still, a conceptual consideration about membrane rafts can be made as we understand it as territory: a cell, as a living unit, depends not only upon a unifying membrane, but also upon life running across all its molecular components. A membrane is not a non-living part but a living module or territory itself. As explained above, living organisms imply their territory. Let us understand non-reducible DNA life, as in hematocytes and in viruses, from the angle of the rhythms that constitute a territory.

In the membrane we find repeated molecules that are the reflection of repeated gene systems, but how is the differentiation of these components from those that make up the ECL and the ICL achieved? The explanation lies precisely in the variations of the vibrational rhythms of the molecules that are in one territory or in another, or that are transiting between them (deterritorializing), alterations centered in the movements of electrons and nuclear particles. Both structures are repeated and the differentiation between them generates the complexity that we see in the world, simplified by modern science as a hierarchy of coupled gear pieces whose paradigmatic example is DNA:

> For example, we know today that the difference between humans and chimpanzees consists not in their genetic difference, which is minimal anyhow, but in the spatial organization and folding of their cells. Such an insight counters the reductionism of those biologists who place the emphasis on the determination of genes and so erase the trace of genetic indetermination. It is precisely the endogenous powers of spatio-temporal rhythms and intensities that Deleuze is privileging in *Difference* and *Repetition* as a model of 'evolution' over the strictly exogenous mechanism of selection [72].

We find a first exemplary case of life without DNA with the analysis of a hematocyte (mature red blood cell). This cell has no nucleus or mitochondria and, therefore, no DNA; however, it remains alive for more than 120 days performing metabolic functions to maintain itself and fulfill its purpose of life: the gaseous exchange between body tissues and the outside of the body, which it achieves thanks to the red blood cells. Red blood cells carry oxygen, which comes from outside of the body, to all the cells of the body, and they also collect the carbon dioxide produced by them, and transport it to the outside of the body, through the lungs. Collecting oxygen, leaving it in the cells, and collecting and releasing the carbon dioxide are all made possible by the *existence* of a functional and *dynamic* membrane in a very short period of time (able, in a cycle of 2 min, to oxygenate the 37.4×10^{12} cells of the body). All this implicit dynamism indicates a certain degree of immanence without the presence of DNA.

A second important case of life not reducible to DNA are viruses. 'The case of viroid life is a little more strange, it has to be admitted, since this 'life' is a virtual, abstract machine that exists both within and without us in a state of suspension-insisting on existing between life and non-life, and between virtuality and actuality.' [72] A virus, thus, does not have the rest of the living machinery to transcribe and/or duplicate itself and continue to live. The virus is a protein capsule, sometimes combined with lipids, containing DNA or RNA information to copy the proteins. This double structure or entity is what we can consider to be a living form, for neither can exist without the other: if there is no DNA or RNA the proteins could not be replicated, and the information, which is the DNA or RNA of the virus, is only of those proteins. The problem is that such replication can only happen if the virus penetrates a cell, for all the process of replication needs other machines, which a cell does have, to be alive. If the virus is to survive, it must find a host, that is, it needs to territorialize in a cell.

But the cell membrane is a machine of machines (made up of repetitive molecules), which is why it is also a niche: a complex autopoietic system that delimits a territory (a space) that is dynamic in time, and which, within *momentums,* territorializes and deterritorializes components both intramembranous and between the ECL and ICL territories. The difference between the components, according to each territory, would lie, perhaps, in the variations of vibrational rhythms of the atoms that constitute the molecules. These variations allow them to maintain the consistency of each territory over time. The membrane would therefore be a subgeneris territory, a territory between territories, with characteristics of both the ICL and ECL territories and with its own particularities, but which in the end is also a particular niche that, to a large extent, integrates and delimits a larger niche that is a singularity, the ICL and all its contents, the structural unit of *a* life[24] that we call a cell (the membrane delimiting *a cell* from others and from its environment -ECL-). This delimitation prevents, or at least postpones, chaos or entropic disorder, since *a cell,* in its autopoiesis, presents a negantropy (negative entropy). The membrane is flexible; allowing the flow of MEI between the media and within itself, and thus functions as a *transducer*: 'It is a question of keeping at a distance the forces of chaos knocking at the door' [69].

The membrane can be thought of as a process of molecular symbiosis, where each molecule is a symbiont necessary for the structural integrity and functionality of the membrane, as a whole, to be able to reach vibrational and rhythmic fullness. Each symbiont is, in itself, a *singularity* of adaptation to the uncertainty of both the internal and external environment of the membrane, a machine that stabilizes or not the membrane itself: 'Machines are always singular keys that open or close an assemblage, a territory' [69]. If molecular symbionts are the keys to the *consistency* of the membrane, abrupt variations in the concentrations of each of its variants (with an increase or decrease of molecules, as in cholesterol ingestion that would change the presence of rafts in the membrane, and/or of

[24] Deleuze employs the concept of a life [3] and not that of life as it is commonly used in the field of natural and social sciences, emphasizing that there is no such reified 'universal matter' that we call life. Instead, what exists are vital phenomenological peculiarities or singularities that should be approached as what they are: a life.

intra-molecular vibrations or Brownian movements) will affect the spatio-temporal permanence of the membrane and of the territories it separates or differentiates (ECl and ICL), territorial coexistence or succession:

The problem of *consistency* concerns the manner in which the components of a territorial assemblage hold together. But it also concerns the manner in which different assemblages hold together, with components of passage and relay. It may even be the case that consistency finds the totality of its conditions only on a properly cosmic plane, where all the disparate and heterogeneous elements are and heterogeneous elements are convoked [69].

Intra- and inter-atomic particles act and relate to each other, giving rise to atoms, which in turn do the same among themselves, and in turn give rise to molecules, which repeat this game generating molecular conglomerates that give rise to cell membranes and to *a cell as such.* Each part of these repetitions maintains its uniqueness but, at the same time, produces collective differences or emergent properties through the scalar and intercalary effects of the components. This is a play consisting of an infinity of intra- and inter-actions as well as of relationships that increase the degree of self-consistency. This self-consistency is a way of seeing that the membrane is a living unit.

4. Conclusion

1. Although a theory of the membrane is a formal cut, such a theory must understand the continuum that the membrane implies at its four levels: continuum in the clusters of molecules that make up each of the two membrane layers; continuum between the two layers; continuum between the intermediate medium (the membrane) and the nanodomain (the territory); continuum between the external medium and the annexing continuum between the internal medium and the territory. In other words, the membrane is not properly understood without its connections with the other media.
2. The consistency of the membrane must be explained dynamically, because the membrane and all phenomena involving it are in motion. In this sense a membrane theory like that of lipid nanodomains is preferable because it works directly with the dynamism of the membrane, while the FMM, on the other hand, can only give a partial explanation.
3. There is a need for more complex experimentation that can account for this dynamism.

   In biological terms, the FMM and the MND are not necessarily either separate or opposed, rather, they are complementary because the latter can be understood as a development or extension of the former. But our analysis of these models using Deleuze and Guattari's concept of territory makes clear the difference in the epistemic frameworks of each. The former conceives of the membrane in a mechanistic way and accounts for the molecular components and its movements or mechanisms in such terms. The latter assumes a greater dynamism that responds to the variations of the physical-chemical environment, both internal and external, over time as assemblages of constant real-time responses to serial events. The result of these differences in assumptions about the nature and functioning of the membrane results in an understanding of the membrane as itself alive and not just a non-living material wall. Because of its vitality, its dynamic composition can be postulated to involve instantaneous changes with higher frequencies than could be thought if its mechanisms were explained exclusively from a materialistic point of view; this dynamic composition also requires more subtle and complex differentiations that begin to become visible when we turn to the Deleuzo-Guattarian concept of territory and its components of internal, external, intermediary and annexed media. Although empirical observation may be refined, either by extending or simplifying, this theory, empirical research currently available already shows that the FMM cannot account for certain facts (virus entry, nutrient entry, exit of products or debris, membrane fusion, signal transduction, and so on). We believe that the NDM, understood as instantaneous territorialization processes, does allow us to encompass these phenomena because it broadens the explanatory framework for interpreting them. The examination of the assumptions of both models that we have undertaken in this article, allows us to use the theory of territory to broaden the horizon for reading the relevant observed facts in their temporality.
4. What has been mentioned throughout raises the intriguing possibility of the constant renewal of the membrane. This continuous, non-discrete process would imply adaptations to variations in the physicochemical environment of the territory (nanodomain and/or membrane, depending on the perspective) in response to changes occurring in the four environments it interacts with, as the Deleuzean notions of territorialization-deterritorialization propose. This diversity, whether structural, functional, or in the intrinsic intramolecular, intermolecular, and collective dynamics of the membrane, could be highly relevant in explaining phenomena such as membrane fusion, substance transport across it, and cellular extravasation between intercellular spaces. Interpreting Morvan*: this high molecular dynamics observed in the membrane is an evolutionary adaptation mechanism that occurs instantaneously in response to external physicochemical changes (LIC and LEC) and even internal ones within the same membrane that* "will trigger the synthesis of membrane components that allow a rapid response by the cell to maintain adequate fluidity to function." [10].

Many other questions remain open, such as those posed by Levental [37] and Sezgin [42]: What are the best tools for analyzing raft behavior? What is the role of the complex lipidome of mammalian cells with respect to membrane organization? What are the mechanisms that drive raft formation and determine their properties? How can rafts be modulated? How is membrane compartmentalization (raft formation) integrated into signaling? We maintain that the positive use of philosophical concepts, such as the ones that we have proposed here, will enable researchers to create new forms of scientific inquiry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This article is the result of the Project "Approach to a basic mathematical model on the stability of a lipid raft prototype that may be involved in the cellular pathophysiology of a complex disease," under grant number 031.I00065, funded by the Autonomous University of Bucaramanga (UNAB), Colombia. We appreciate the ongoing support that the University provides to professors for conducting research in these interdisciplinary areas.

References

[1] A. Badiou, Deleuze: the Clamor of Being, University of Minnesota Press, 2000.
[2] G. Deleuze, Desert Islands and Other Texts 1953-1974, Semiotext(e), New York, 2004.
[3] G. Deleuze, Two regimes of madness, in: Texts and Interviews 1975-1995, revised edition, MIT Press, 2007.
[4] E. Grosz, Deleuze, Bergson and the concept of life, Rev. Int. Philos. 3 (2007) 287–300, https://doi.org/10.1215/9780822394433-003.
[5] H. Bergson, Creative Evolution, Random House, 1944.
[6] P. Bothorel, C. Lussan, On a biological membrane model based on lipid-protein interactions, C R Acad. Hebd. Seances. Acad. Sci. D 266 (1968) 2492–2494.
[7] C. Lussan, P. Bothorel, Some new aspects of a biological membrane model, C R Acad. Hebd. Seances. Acad. Sci. D 268 (1969) 1118–1120.
[8] S.J. Singer, G.L. Nicolson, The fluid mosaic model of the structure of cell membranes, Science 175 (1972) 720–731, https://doi.org/10.1126/science.175.4023.720.
[9] J. Fantini, N. Garmy, R. Mahfoud, N. Yahi, Lipid rafts: structure, function and role in HIV, Alzheimer's and prion diseases, Expet Rev. Mol. Med. 4 (2002) 1–22, https://doi.org/10.1017/S1462399402005392.
[10] E. Morvan, N. Taib-Maamar, A. Grélard, A. Loquet, E.J. Dufourc, Bio-membranes: picosecond to second dynamics and plasticity as deciphered by solid state NMR, Biochim. Biophys. Acta Biomembr. 1865 (2023), 184097, https://doi.org/10.1016/j.bbamem.2022.184097.
[11] P. Devaux, C.J. Scandella, H.M. McConnell, Spin-spin interactions between spin-labeled phospholipids incorporated into membranes, J. Magn. Reson. 9 (1973) 474–485, https://doi.org/10.1016/0022-2364(73)90190-X.
[12] J.R. Lakowicz, Fluorescence spectroscopic investigations of the dynamic properties of proteins, membranes and nucleic acids, J. Biochem. Biophys. Methods 2 (1980) 91–119, https://doi.org/10.1016/0165-022X(80)90077-9.
[13] R.A. Badley, W.G. Martin, H. Schneider, Dynamic behavior of fluorescent probes in lipid bilayer model membranes, Biochemistry 12 (1973) 268–275, https://doi.org/10.1021/bi00726a015.
[14] J.L.R. Arrondo, F.M. Goñi, Structure and dynamics of membrane proteins as studied by infrared spectroscopy, Prog. Biophys. Mol. Biol. 72 (1999) 367–405, https://doi.org/10.1016/S0079-6107(99)00007-3.
[15] A. Watts, D. Marsh, P.F. Knowles, Characterization of dimyristoylphosphatidylcholine vesicles and their dimensional changes through the phase transition: molecular control of membrane morphology, Biochemistry 17 (1978) 1792–1801, https://doi.org/10.1021/bi00602a034.
[16] J.H. Davis, The description of membrane lipid conformation, order and dynamics by 2H-NMR, Biochim. Biophys. Acta Rev. Biomembr. 737 (1983) 117–171, https://doi.org/10.1016/0304-4157(83)90015-1.
[17] H.L. Casal, D.G. Cameron, I.C.P. Smith, H.H. Mantsch, Acholeplasma laidlawii membranes: a Fourier transform infrared study of the influence of protein on lipid organization and dynamics, Biochemistry 19 (1980) 444–451, https://doi.org/10.1021/bi00544a007.
[18] E.C. Kelusky, E.J. Dufourc, I.C.P. Smith, Direct observation of molecular ordering of cholesterol in human erythrocyte membranes, Biochimica et Biophysica Acta (BBA) - Biomembranes. 735 (1983) 302–304, https://doi.org/10.1016/0005-2736(83)90306-1.
[19] H. Schindler, J. Seelig, Deuterium Order Parameters in Relation to Thermodynamic Properties of a Phospholipid Bilayer. A Statistical Mechanical Interpretation?, (n.d.)..
[20] J. Seelig, Deuterium magnetic resonance: theory and application to lipid membranes, Q. Rev. Biophys. 10 (1977) 353–418, https://doi.org/10.1017/S0033583500002948.
[21] H. Schindler, J. Seelig, Deuterium order parameters in relation to thermodynamic properties of a phospholipid bilayer. Statistical mechanical interpretation, Biochemistry 14 (1975) 2283–2287, https://doi.org/10.1021/bi00682a001.
[22] G.J. Schütz, G. Kada, V.Ph Pastushenko, H. Schindler, Properties of lipid microdomains in a muscle cell membrane visualized by single molecule microscopy, EMBO J. 19 (2000) 892–901, https://doi.org/10.1093/emboj/19.5.892.
[23] P.J. Bond, J. Holyoake, A. Ivetac, S. Khalid, M.S.P. Sansom, Coarse-grained molecular dynamics simulations of membrane proteins and peptides, J. Struct. Biol. 157 (2007) 593–605, https://doi.org/10.1016/j.jsb.2006.10.004.
[24] S. Bernèche, B. Roux, Molecular dynamics of the KcsA K+ channel in a bilayer membrane, Biophys. J. 78 (2000) 2900–2917, https://doi.org/10.1016/S0006-3495(00)76831-7.
[25] P. Van Der Ploeg, H.J.C. Berendsen, Molecular dynamics simulation of a bilayer membrane, J. Chem. Phys. 76 (1982) 3271–3276, https://doi.org/10.1063/1.443321.
[26] J.H. Ipsen, O.G. Mouritsen, M. Bloom, Relationships between lipid membrane area, hydrophobic thickness, and acyl-chain orientational order. The effects of cholesterol, Biophys. J. 57 (1990) 405–412, https://doi.org/10.1016/S0006-3495(90)82557-1.
[27] M. Bloom, E. Evans, O.G. Mouritsen, Physical properties of the fluid lipid-bilayer component of cell membranes: a perspective, Q. Rev. Biophys. 24 (1991) 293–397, https://doi.org/10.1017/S0033583500003735.
[28] M. Bloom, O.G. Mouritsen, The evolution of membranes, Can. J. Chem. 66 (1988) 706–712, https://doi.org/10.1139/v88-123.
[29] O.G. Mouritsen, M. Bloom, Models of lipid-protein interactions in membranes, Annu. Rev. Biophys. Biomol. Struct. 22 (1993) 145–171, https://doi.org/10.1146/annurev.bb.22.060193.001045.
[30] M. Foucault, The Order of Things: an Archaeology of the Human Sciences, Psychology Press, 2002.
[31] D. Lingwood, K. Simons, Lipid rafts as a membrane-organizing principle, Science 327 (2010) 46–50, https://doi.org/10.1126/science.1174621.
[32] M. Bramkamp, D. Lopez, Exploring the existence of lipid rafts in bacteria, Microbiol. Mol. Biol. Rev. 79 (2015) 81–100, https://doi.org/10.1128/MMBR.00036-14.
[33] J.A.G. Briggs, T. Wilk, S.D. Fuller, Do lipid rafts mediate virus assembly and pseudotyping? J. Gen. Virol. 84 (2003) 757–768, https://doi.org/10.1099/vir.0.18779-0.
[34] D.A. Brown, E. London, Functions of lipid rafts in biological membranes, Annu. Rev. Cell Dev. Biol. 14 (1998) 111–136, https://doi.org/10.1146/annurev.cellbio.14.1.111.
[35] F.G. van der Goot, T. Harder, Raft membrane domains: from a liquid-ordered membrane phase to a site of pathogen attack, Semin. Immunol. 13 (2001) 89–97, https://doi.org/10.1006/smim.2000.0300.
[36] S. Kundu, Stochastic modelling suggests that an elevated superoxide anion - hydrogen peroxide ratio can drive extravascular phagocyte transmigration by lamellipodium formation, Theoretical Biology 407 (2016) 143–154, https://doi.org/10.1016/j.jtbi.2016.07.002.
[37] I. Levental, S.L. Veatch, The continuing mystery of lipid rafts, J. Mol. Biol. 428 (2016) 4749–4764, https://doi.org/10.1016/j.jmb.2016.08.022.
[38] S.-L. Niu, B.J. Litman, Determination of membrane cholesterol partition coefficient using a lipid vesicle-cyclodextrin binary system: effect of phospholipid acyl chain unsaturation and headgroup composition, Biophys. J. 83 (2002) 3408–3415, https://doi.org/10.1016/S0006-3495(02)75340-X.
[39] P. Oh, J.E. Schnitzer, Segregation of heterotrimeric G proteins in cell surface microdomains, MBoC 12 (2001) 685–698, https://doi.org/10.1091/mbc.12.3.685.
[40] A. Ono, E.O. Freed, Plasma membrane rafts play a critical role in HIV-1 assembly and release, Proc Natl Acad Sci U S A 98 (2001) 13925–13930, https://doi.org/10.1073/pnas.241320298.

[41] A.G. Ostermeyer, B.T. Beckrich, K.A. Ivarson, K.E. Grove, D.A. Brown, Glycosphingolipids are not essential for formation of detergent-resistant membrane rafts in melanoma cells. methyl-beta-cyclodextrin does not affect cell surface transport of a GPI-anchored protein, J. Biol. Chem. 274 (1999) 34459–34466, https://doi.org/10.1074/jbc.274.48.34459.

[42] E. Sezgin, I. Levental, S. Mayor, C. Eggeling, The mystery of membrane organization: composition, regulation and physiological relevance of lipid rafts, Nat. Rev. Mol. Cell Biol. 18 (2017) 361–374, https://doi.org/10.1038/nrm.2017.16.

[43] G. van Meer, The different hues of lipid rafts, Science 296 (2002) 855–857, https://doi.org/10.1126/science.1071491.

[44] K. Simons, E. Ikonen, Functional rafts in cell membranes, Nature 387 (1997) 569–572, https://doi.org/10.1038/42408.

[45] K. Simons, D. Toomre, Lipid rafts and signal transduction, Nat. Rev. Mol. Cell Biol. 1 (2000) 31–39, https://doi.org/10.1038/35036052.

[46] B.H. Meyer, J.-M. Segura, K.L. Martinez, R. Hovius, N. George, K. Johnsson, H. Vogel, FRET imaging reveals that functional neurokinin-1 receptors are monomeric and reside in membrane microdomains of live cells, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 2138–2143, https://doi.org/10.1073/pnas.0507686103.

[47] S. Thomas, A. Predapais, S. Casares, T. Brumeanu, Analysis of lipid rafts in T cells, Mol. Immunol. 41 (2004) 399–409, https://doi.org/10.1016/j.molimm.2004.03.022.

[48] E. Nagy, Z. Balogi, I. Gombos, M. Åkerfelt, A. Björkbom, G. Balogh, Z. Török, A. Maslyanko, A. Fiszer-Kierzkowska, K. Lisowska, P.J. Slotte, L. Sistonen, I. Horváth, L. Vígh, Hyperfluidization-coupled membrane microdomain reorganization is linked to activation of the heat shock response in a murine melanoma cell line, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 7945–7950, https://doi.org/10.1073/pnas.0702557104.

[49] Y. Yamazaki, Y. Horibata, Y. Nagatsuka, Y. Hirabayashi, T. Hashikawa, Fucoganglioside α-fucosyl(α-galactosyl)-GM1: a novel member of lipid membrane microdomain components involved in PC12 cell neuritogenesis, Biochem. J. 407 (2007) 31–40, https://doi.org/10.1042/BJ20070090.

[50] E.C. Jury, D.A. Isenberg, C. Mauri, M.R. Ehrenstein, Atorvastatin restores lck expression and lipid raft-associated signaling in T cells from patients with systemic lupus erythematosus, J. Immunol. 177 (2006) 7416–7422, https://doi.org/10.4049/jimmunol.177.10.7416.

[51] L. Rajendran, K. Simons, Lipid rafts and membrane dynamics, J. Cell Sci. 118 (2005) 1099–1102, https://doi.org/10.1242/jcs.01681.

[52] M.D. Collins, S.L. Keller, Tuning lipid mixtures to induce or suppress domain formation across leaflets of unsupported asymmetric bilayers, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 124–128, https://doi.org/10.1073/pnas.0702970105.

[53] J.-S. Bae, L. Yang, A.R. Rezaie, Receptors of the protein C activation and activated protein C signaling pathways are colocalized in lipid rafts of endothelial cells, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 2867–2872, https://doi.org/10.1073/pnas.0611493104.

[54] C. Wang, Y. Yu, S.L. Regen, Lipid raft formation: key role of polyunsaturated phospholipids, Angew. Chem. Int. Ed. 56 (2017) 1639–1642, https://doi.org/10.1002/anie.201611367.

[55] P. Yaqoob, The nutritional significance of lipid rafts, Annu. Rev. Nutr. 29 (2009) 257–282, https://doi.org/10.1146/annurev-nutr-080508-141205.

[56] P.S. Niemelä, S. Ollila, M.T. Hyvönen, M. Karttunen, I. Vattulainen, Assessing the nature of lipid raft membranes, PLoS Comput. Biol. 3 (2007) e34, https://doi.org/10.1371/journal.pcbi.0030034.

[57] A. Cambi, D.S. Lidke (Eds.), Cell Membrane Nanodomains: from Biochemistry to Nanoscopy, CRC Press, 2015.

[58] L.J. Pike, Rafts defined: a report on the Keystone symposium on lipid rafts and cell function, JLR (J. Lipid Res.) 47 (2006) 1597–1598, https://doi.org/10.1194/jlr.E600002-JLR200.

[59] C. Dietrich, L.A. Bagatolli, Z.N. Volovyk, N.L. Thompson, M. Levi, K. Jacobson, E. Gratton, Lipid rafts reconstituted in model membranes, Biophys. J. 80 (2001) 1417–1428, https://doi.org/10.1016/S0006-3495(01)76114-0.

[60] A. Iglič, H. Hägerstrand, P. Veranič, A. Plemenitaš, V. Kralj-Iglič, Curvature-induced accumulation of anisotropic membrane components and raft formation in cylindrical membrane protrusions, J. Theor. Biol. 240 (2006) 368–373, https://doi.org/10.1016/j.jtbi.2005.09.020.

[61] S.L. Regen, The origin of lipid rafts, Biochemistry 59 (2020) 4617–4621, https://doi.org/10.1021/acs.biochem.0c00851.

[62] R.M. Zamora, La membrana celular (frontera biológica): ¿Un límite de discontinuidad entre la materia viva y la materia "inerte"? Univ. Industrial de Santander, 2016.

[63] J.G. Beck, D. Mathieu, C. Loudet, S. Buchoux, E.J. Dufourc, Plant sterols in "rafts": a better way to regulate membrane thermal shocks, Faseb. J. 21 (2007) 1714–1723, https://doi.org/10.1096/fj.06-7809com.

[64] L. Martínez-Balbuena, A. Maldonado-Arce, E. Hernández-Zapata, Elasticidad de las membranas biológicas, Rev. Mexic. Fisica E. 56 (2010) 107–122.

[65] Á.R. Proaño, A. Medrano, G. Garrido, O. Mazza, Células madre derivadas de músculo para la incontinencia urinaria de esfuerzo, Actas Urol. Esp. 34 (2010) 15–23.

[66] M. Letrou, S. Cribier, N. Rodriguez, J. Heuvingh, Studying membrane fusion using supported lipid bilayers on superparamagnetic beads, Biochimica et Biophysica Acta (BBA) - Biomembranes. 1865 (2023), 184070, https://doi.org/10.1016/j.bbamem.2022.184070.

[67] R. Dazzoni, C. Buré, E. Morvan, A. Grélard, C. Gounou, J.-M. Schmitter, A. Loquet, B. Larijani, E.J. Dufourc, Tandem NMR and mass spectrometry analysis of human nuclear membrane lipids, Anal. Chem. 92 (2020) 6858–6868, https://doi.org/10.1021/acs.analchem.9b05052.

[68] R. Dazzoni, A. Grélard, E. Morvan, A. Bouter, C.J. Applebee, A. Loquet, B. Larijani, E.J. Dufourc, The unprecedented membrane deformation of the human nuclear envelope, in a magnetic field, indicates formation of nuclear membrane invaginations, Sci. Rep. 10 (2020) 5147, https://doi.org/10.1038/s41598-020-61746-0.

[69] G. Deleuze, F. Guattari, A Thousand Plateaus: Capitalism and Schizophrenia II, University of Minnesota Press, Minneapolis, 1987.

[70] F. Guattari, Chaosmosis: an Ethico-Aesthetic Paradigm, Indiana University Press, 1995.

[71] F.J. Varela, Principles of Biological Autonomy, Prentice Hall, 1979.

[72] K. Ansell Pearson, Deleuze and Philosophy: the Difference Engineer, Routledge, Londres, 1997.

[73] A. Kleinherenbrink, Territory and ritornello: Deleuze and Guattari on thinking living beings, Deleuze Stud. 9 (2015) 208–230, https://doi.org/10.3366/dls.2015.0183.

[74] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, Molecular Biology of the Cell, Garland Publishing, Incorporated, 2002.

[75] C.V. Córdoba, Biofísica, Síntesis Editorial, 1992.

[76] U. Meza, A.C. Romero-Méndez, Y. Licón, S. Sánchez-Armáss, La membrana plasmática: modelos, balsas y señalización, Rev. Educ. Bioquímica 29 (2010) 125–134.

[77] G. Vereb, J. Szöllosi, J. Matkó, P. Nagy, T. Farkas, L. Vigh, L. Mátyus, T.A. Waldmann, S. Damjanovich, Dynamic, yet structured: the cell membrane three decades after the Singer-Nicolson model, Proc. Natl. Acad. Sci. U S A 100 (2003) 8053–8058, https://doi.org/10.1073/pnas.1332550100.

[78] C. Colebrook, Deleuze and the Meaning of Life, Bloomsbury Publishing, London, 2011.

[79] D. Axelrod, D.E. Koppel, J. Schlessinger, E. Elson, W.W. Webb, Mobility measurement by analysis of fluorescence photobleaching recovery kinetics, Biophys. J. 16 (1976) 1055–1069.

[80] A. Nusrat, C.A. Parkos, P. Verkade, C.S. Foley, T.W. Liang, W. Innis-Whitehouse, K.K. Eastburn, J.L. Madara, Tight junctions are membrane microdomains, J. Cell Sci. 113 (Pt 10) (2000) 1771–1781, https://doi.org/10.1242/jcs.113.10.1771.

[81] R.A. Bhat, M. Miklis, E. Schmelzer, P. Schulze-Lefert, R. Panstruga, Recruitment and interaction dynamics of plant penetration resistance components in a plasma membrane microdomain, Proc. Natl. Acad. Sci. U.S.A. 102 (2005) 3135–3140, https://doi.org/10.1073/pnas.0500012102.

[82] K. Simons, M.J. Gerl, Revitalizing membrane rafts: new tools and insights, Nat. Rev. Mol. Cell Biol. 11 (2010) 688–699, https://doi.org/10.1038/nrm2977.