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Adaptive behavior and learning in slime moulds: the role of oscillations

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Summary

The slime mould *Physarum polycephalum,* an aneural organism, uses information from previous experiences to adjust its behavior but the mechanisms by which this is accomplished remain unknown. This article examines the possible role of oscillations in learning and memory in slime moulds. Slime moulds share surprising similarities with the network of synaptic connections in animal brains. First, their topology derives from a network of interconnected, vein-like tubes in which signalling molecules are transported. Second, network motility, which generates slime mould behaviour, is driven by distinct oscillations that organize into spatiotemporal wave patterns. Likewise, neural activity in the brain is organized in a variety of oscillations characterized by different frequencies. Interestingly, the oscillating networks of slime moulds are not precursors of nervous systems but, rather, an alternative architecture. Here we argue that comparable information processing operations can be realized on different architectures sharing similar oscillatory properties. After describing learning abilities and oscillatory activities of *P. polycephalum*, we explore the relation between network oscillations and learning, and evaluate the organisms global architecture with respect to information

processing potential. We hypothesize that, as in the brain, modulation of spontaneous oscillations may sustain learning in slime mould.

1. Introduction

Every living organism uses sensory and information-processing mechanisms to evaluate and interact with both its internal milieu and its surroundings . Most processes underlying environmental monitoring, signal propagation or integration of motor and sensory functions are evolutionary conserved between single-celled organisms and animals. In this special issue, we emphasize that cognitive abilities such as perception, problem solving and learning are not restricted to the animal kingdom, but have evolved in all organisms to satisfy the existential needs for survival [1–6]. As Bourgine & Stewart [7] stated, "A system is cognitive if and only if sensory inputs serve to trigger actions in a specific way, so as to satisfy a viability constraint". Cognitive abilities rely on recursive chemical communication of intracellular signalling networks which are highly organized in space and time and which depend on historical and environmental context [8]. The functional link between dynamic processes in cells and their cognitive abilities remains to be elucidated. One of the recurrent patterns observed in cells are self-sustained oscillations which can encode various information [9–12]. The aim of this review is to discuss how learning in a unicellular organism might rely on self-sustained oscillations. Our model system is the acellular slime mould *Physarum polycephalum* which shows various oscillatory phenomena whose cognitive significance has yet to be demonstrated.

Learning, defined as the modification of behavior by experience, is one of the major innovations in the evolution of life. Using past experiences is often critical for optimal decision-making in a fluctuating environment and is involved in every aspect of an organism's life, including foraging and interacting with other individuals. We usually think of learning as a trait that is limited to Neurozoans (i.e., organisms with a central nervous system). Indeed, learning is often equated with neuronal changes like synaptic plasticity, implicitly precluding its existence in aneural organisms such as plants and unicellulars [13]. While the evolutionary benefits of learning are clear, very little is known about its origins. Even the simplest organisms must adapt to changing environments, raising the possibility that mechanisms for learning might pre-date the evolution of nervous systems, possibly existing in a breadth of as-yet unstudied organisms [3,5,6,14–19]. Evidence for learning in single-celled organisms remains scant and, to date, only few unequivocal reports of such processes have been described. Learning in single-celled organisms has been investigated mainly in ciliates and acellular slime moulds, and there are several reliable reports documenting learning in *Stentor sp*. [20], *Paramecium sp*. [21], *Tetrahymena sp*. [22] and *P. polycephalum* [23].

One of the most fundamental questions in cognitive science is: how can information inferred from interaction with the physical world be encoded in physical/chemical changes in an organism, and how is it decoded as future recall? Although many fundamental processes in the brain have been understood, the current state of the art in neuroscience is still far from providing a complete picture. In particular, there exists no coherent explanation for how higher cognitive function arises from the interplay of elementary biological mechanisms. To truly understand the most fundamental mechanisms underlying learning and memory, it is essential to study the origins of cognition in unicellular organisms that implement learning in a non-neural substrate.

Due to its comparably simple structure in relation to its behavioural complexity and due to the ease with which it can be cultivated and manipulated, *P. polycephalum* presents itself as an ideal model system for relating basal cognitive functions to biological mechanisms [24–26]. In principle, all processes are accessible, in many cases even without disrupting the system and with spatiotemporal resolution constrained only by the experimental setup. In this review, we explore how a simple physical process integrating oscillators could mechanistically explain complex abilities such as learning in *P. polycephalum*.

2. Cognitive abilities of *Physarum polycephalum*

a) *P. polycephalum*: a unique model

The slime mould *P. polycephalum* is a remarkable organism belonging to the Amoebozoa. It is often used as a model system to study problem-solving in aneural biological systems (Figure 1)[24–27]. Its vegetative state, the plasmodium, is a giant mobile cell, whose basic structure consists of a syncytium of nuclei and an intracellular cytoskeleton that forms a complex cytoplasmic network of veins (Figure 1). The plasmodium can extend to up to hundreds of square centimetres and can be severed into viable and structurally similar yet smaller subunits. Upon contact, plasmodia can fuse with each other, giving rise to the (re-)formation of a giant plasmodium [28]. *P. polycephalum* can be reared and maintained in a liquid-shaking culture as micrometre-sized fragments (microplasmodia) or as macroplasmodia on a solid substrate. Lastly, a starving plasmodium can encapsulate and enter a dormant stage called sclerotium (Figure 1). *P polycephalum* can turn back from this resting stage to a plasmodium within 24 hours after transfer to fresh food medium.

Both *P. polycephalum*'s motion and its behaviour rely on its internal architecture. Its cytoplasm consists of a visco-elastic (gel, also named ectoplasm) and a liquid (sol, also named endoplasm) phase [28]. This compartmentation is due to a sharp concentration change of the fibrous proteins forming the cytoskeleton [29]. Ecto- and endoplasm are convertible into each other. The cell body of *P. polycephalum* is a transport network consisting of interconnected tubes (Figure 1). Ectoplasm, which contains actin and myosin, forms the contractile walls of the tubes (Figure 1). Within these veins flows the endoplasm, which contains organelles such as nuclei and mitochondria (movies S1 & S2). The veins contract and relax periodically, causing the endoplasm to flow back and forth, a phenomenon termed "shuttle streaming" [30]. The vein network of *P. polycephalum* bears two analogies with the vertebrates' circulatory systems. First, like the vasculature, the veins transport and distribute the endoplasm throughout the cell body. Second, the veins are pore-like capillaries, allowing respiratory gases, molecules and organelles to be exchanged with the surrounding cytoplasm [31]. This open network allows to maintain homeostasis in cells ranging from 10 square micrometres to 10 square meters. The spatial structuration of *P. polycephalum*'s vein network and its dynamics allows an efficient regulation of the cytoplasmic flow within the entire cell [32, 33]. This vein network and the interactions between ectoplasm and the endoplasm have been studied extensively by numerous biophysicists [34, 35].

The vein network is also responsible for cellular motility. *P. polycephalum* can migrate at a speed of up to 4 cm per hour [32] through the interplay of intracellular flow, adhesion and rhythmic contractions of the intracellular actomyosin cytoskeleton [30,32]. These contractions produce a pressure gradient that pushes the endoplasm towards the cell periphery where the veins vanish and the endoplasm can flow freely. Local cytoskeletal reorganization and local alteration of the actin-myosin cortex lead to the formation of pseudopods or fan shaped leading fronts which extend and retract in synchrony with the shuttle streaming of the endoplasm [30,36,37]. Based on internal and external cues, *P. polycephalum* can adapt and alter its shape, size and motion. The frequency and the amplitude of the cytoskeleton contractions depend on the quality of the environment [38–40]. For instance, higher frequencies are observed in response to attractive, high-quality resources [41], whereas lower frequencies are recorded when *P. polycephalum* encounters repulsive stimuli such as chemical repellents [40]. As a result, slime moulds migrate toward or away from a variety of external stimuli such as chemicals [38], light [42], temperature [43], humidity [44], gravity [45] or substrate distortion [46].

b) *P. polycephalum*'s learning abilities

Although slime moulds lack the complex dedicated neural hardware of Neurozoans, the environment they evolved in is no less complex and they face the same challenges: they must search for and choose between resources, adapt to changing conditions, avoid dangers and find suitable microclimates to inhabit. *P. polycephalum* demonstrates key aspects of complex decision making [24–27,47,48] (Figure 1). It can find its way in a maze [49], construct efficient transport networks [50], distinguish how different masses distort the substrate [46], avoid obstacles [51] and risky environments [52], optimize its nutrient intake [53,54], and use conspecifics' cues to choose what substrate to exploit [55,56]. All these feats rely on the abilities of *P. polycephalum* to sense and respond simultaneously to a wide range of biotic and abiotic stimuli [38–45].

Despite their increasing recognition as a model for the study of complex behaviours in unicellular organisms, surprisingly little attention has been paid to the ability of slime moulds to learn and to modify their behaviour accordingly. Four studies have shown that *P. polycephalum* displays the capacity to learn [23,57–59]. In the first study, Saigusa et al. [57] showed primitive anticipatory and recall behaviours. Individuals exposed to periodically occurring negative stimuli were found to reduce their locomotive speed in response to each stimulus. When the negative stimuli were withdrawn, the slime moulds spontaneously reduced their locomotive speed at the point in time when the next negative stimulus would have occurred, *i.e,* they learned the periodicity. Once the spontaneous slowdowns stopped, they could be induced again by a single negative stimulus, which implies recall of the memorized periodicity. This study has sparked several models considering the involvement of oscillations in aneural learning, as will be further discussed in section 4. In the second study, Boisseau et al. [23] demonstrated habituation, the simplest form of learning, in *P. polycephalum*. Habituation is a progressive decrease in the magnitude of a behavioural response to an iterative stimulus. Using locomotion as the behavioural output and diverse chemicals as repellent stimuli, the authors showed that *P. polycephalum* learned to ignore a chemical when it was encountered repeatedly for 5 days (habituation), but responded again when the chemical was withheld for a certain time (spontaneous recovery). They also demonstrated stimulus specificity and ruled out sensory and motor fatigue, often mistaken for habituation. In the third study, Vogel & Dussutour [58] showed that non-habituated slime moulds were able to directly acquire a learned behaviour from a habituated slime mould via cell fusion. They revealed that the transfer of learned behaviour was effective only when the vein networks merged and the cytoplasm streamed back and forth between the fused individuals. In the last study, Boussard et al. [59] showed that the memory of habituation can be stored for a month during the dormant stage and retrieved once the slime mould is revived. Chemical analyses indicated an uptake of repellent during the process of habituation and its retention throughout the dormant stage. The authors showed a strong correlation between the level of intracellular repellent and the habituation performance, and revealed that constrained absorption of the repellent induced habituation in 2 hours. This study proposed that *P. polycephalum* absorbs the repellent and uses it as a "circulating memory".

c) Inferring learning from motion analysis

Motion is straightforward to capture in almost any living system. In this regard, time scale is the only difference between the wing flapping of hummingbirds and the pulsatile movement of *P. polycephalum*. While it is easy to detect motion, given the right sampling frequency, it is much harder to infer intent from movement [60]. This highlights the difficulty of designing experiments addressing cognitive abilities in aneural organisms. In other words, when do we interpret a moving system as cognitive, as opposed to a purely biochemical or biomechanical process? Regardless of

the organism, at the microscopic scale, motion results from simple biological processes. In most cells, diverse organization of the actin cytoskeleton can produce pushing, pulling, and resistance forces responsible for the whole cell shape and migration [61]. Studies investigating learning or decision making in *P. polycephalum* interpret motion as behaviours. For instance, Boisseau et al. [23] measured the migration speed *of P. polycephalum* when facing a repellent and concluded that habituation occurs when the speed ceased to be affected by the repellent. Thus, they implied that motion can reflect cellular "memory" to previous stimuli. One can question the relevance of interpreting motion as a cognitive output as opposed to simple biochemical processes.

Contrary to motion, demonstrating a cognitive ability in any living organism requires testable criteria. Cognition can be defined as the individual capacity to perceive, process and use information. Despite numerous evidence showing that cognitive abilities such as sensing, communication, memory, learning, decision making, etc. are found in prokaryotes, single-celled eukaryotes, plants and fungi [17], some authors restrict the existence of cognition to neural organisms. For instance, Dukas [62] defines cognition as "the neuronal processes concerned with the acquisition, retention, and use of information". Yet, a cognitive ability observed in several organisms could either rely on similar mechanisms and share a common evolutionary origin or result from an evolutionary convergence [63]. For instance, in Neurozoans, habituation results from the decreased release of chemical neurotransmitters at synaptic terminals which modulate the weights of certain neural connections. However, in *P. polycephalum* and other single-celled organisms, habituation cannot be encoded in a neural network. Yet, a detailed analysis of *P. polycephalum's* behaviour [23] suggests that this organism is capable of habituation as it fulfils all the criteria that define a habituation phenomenon [64]. Thus, should we restrict a cognitive ability to its underlying mechanisms, and by doing so, preclude its existence in many systems or should we consider together its biological function and its implementation [4]? As suggested by Marr [65], to study a cognitive system we need to answer three questions: what problem is the system trying to solve? How does the system solve the problem at the behavioural level? and what are the mechanisms underlying the behavioural response? The accumulating evidence supporting the existence of cognitive abilities in slime moulds challenge us to understand what kind of physical systems underlie such abilities. One of the hypotheses we make is that learning in slime moulds might result from intracellular oscillators, as oscillations can encode information in their frequency, amplitude or duration. We especially focus on how the coordination of relatively simple oscillatory processes at the cell and molecular levels results in the emergence of learning in *P. polycephalum*.

3. Oscillations in *Physarum polycephalum*

Oscillation occurs when "the values of variables characterizing the behaviour of a system repeatedly rise and fall" [66]. The minimal requirements for regular biological oscillations are the existence of a negative feedback loop, a time delay in the occurrence of this feedback and the nonlinear interactions involved in this feedback [67]. Longer time delays in the feedback cause longer periods of oscillation. Oscillations are ubiquitous in biology from the intracellular chemical level to the ecological level. They vary in time scale from seconds (ion transport or calcium release), to minutes (changes in protein levels during the cell cycle), to hours or days (changes in cell morphology), and up to years (generation time). The most universal oscillator is the circadian clock which is found in a variety of living organisms, including mammals, insects, plants, fungi, and cyanobacteria [68]. The pervasiveness of oscillations stresses the importance of thinking dynamically about the mechanisms underlying the behaviour of a biological system. Hence, a good appreciation of the timescale of this system is crucial for understanding its behaviour.

The human brain self-generates numerous oscillations, i.e., regular fluctuations in electrical potential occurring simultaneously in many neurons, whose frequencies range from infraslow <0.01Hz to ultrafast 600 Hz [69]. Neuroscientists categorize these oscillations according to their frequency (from the slowest to the fastest: slow-wave sleep, delta, theta, alpha, beta, gamma, and ripples oscillations). At a global scale, slow oscillations generate large and synchronous membrane potential fluctuations in large populations of neurons whereas, at a local scale, fast oscillations produce such fluctuations in smaller populations of neurons [70]. Indeed, contrary to what occurs in a computer, where communication is equally fast between close and distant units, in the brain, fast oscillations are limited to local assemblies of neurons, due to biological constraints (i.e. axonal conduction delays) [70]. Hence, brains use a complex system of multiple oscillators for its operations when a computer only uses one. These different oscillators in the brain coexist and interact with each other hierarchically: the slower oscillators often modulate the faster ones, a phenomenon referred to as cross-frequency coupling [71]. Using this coupling, brains can integrate distributed local processes into globally ordered states.

In the human brain, specific oscillation signatures are related to learning and memory processes. For instance, theta and gamma oscillations are mainly observed during learning processes. Slow-wave sleep and sharp-wave ripples are instrumental in consolidation of memories [72]. Neuronal oscillators are complex but rely nonetheless on principles that are comparable to those of oscillators in other biological systems. Similarly to the brain, *P. polycephalum* is organized at multiple temporal and spatial levels and it is tempting to relate this spatiotemporal architecture to its cognitive abilities. Our goal in this review is to understand the potential link between the oscillations observed in *P. polycephalum* and its learning capacities. In the next section, we will describe the variety of oscillations reported in *P. polycephalum.* We will highlight how oscillators play an important role in diverse organismal functions on a continuum of time scales. We will first focus on the relaxation-contraction cycle which relies on short-period oscillations (90 sec). Then, we will present the nuclear division and gene expression cycle which are characterized by long-period oscillations (few hours). Short-period oscillations could support short-term memory whereas longer-scale oscillations could be involved in long-lasting memories.

a) Short-period oscillations in *P. polycephalum*: the contraction cycle

When facing a repellent in its environment, *P. polycephalum* reduces its migration speed. However, as mentioned earlier, constrained absorption of the repellent quickly attenuates this behaviour, and the slime mould behaves almost as if the repellent was absent (habituation) [23]. Thus, the entry of repellents into the cell might interact with the shuttle streaming responsible for the migration of the organism [59]. In *P. polycephalum*, several well-defined chemical oscillators control regular relaxation-contraction patterns which locally drive the intracellular flow and are at the root of further large-scale patterns such as migration and cell shape. In turn, the shape and motion of the cell influence these local oscillations [73-75]. Relaxation-contraction patterns are generated through intrinsic nonlinear oscillatory phenomena in the plasmodium supported by complicated mechanochemical reactions among intracellular chemicals such as ATP, free intracellular calcium ([Ca2+]) and actin, but also among organelles. These oscillators are interconnected, often coupled, and partially dependent on each other [76]. Most of the observed chemical oscillators are associated with energy metabolism and respiration, with mitochondria being most prominently involved at the organelle level. In the following, we will present the chemical oscillators that have been described in *P. polycephalum*.

Calcium, as the universal signaling ion in cells, is involved at almost every level of intracellular signaling and bridges the gap between locomotion and energy metabolism. Oscillations in cytosolic [Ca2+] represent one of the

most important examples of cellular rhythm in most organisms. In *P. polycephalum*, free intracellular [Ca2+] is directly linked to actomyosin contraction [77–79]. [Ca2+] and actomyosin contractions oscillate with a similar period but in approximate anti-phase [80,81], because the actin-myosin interaction is inhibited by [Ca2+] [82]. In the resting state, the cytoplasmic concentration of [Ca2+] is kept as low as possible. Excess [Ca2+] is either extruded via the cell membrane or sequestered in mitochondria and cytoplasmic vesicles. When the cell is stimulated, [Ca2+] increases due to its release from storage or the entry of extracellular [Ca2+]. This transient increase is used by the cell as a secondary messenger to regulate the interaction between actin and myosin. However, in contrast to animal cells, in *P. polycephalum* intracellular [Ca2+] is an inhibitor [83]. High [Ca2+] coincides with relaxation whereas low [Ca2+] induces contraction. The [Ca2+] oscillator was first modelled by Smith & Saldana [84], using a phosphorylation-dephosphorylation cycle of myosin light chain kinase. [Ca2+] waves travel at approximately 5 µm/s, suggesting that they are not propagated by shuttle streaming [85], which is much faster (up to several mm/s). Furthermore, in absence of external stimulations, [Ca2+] is not homogeneously distributed within the cell but forms a gradient throughout the plasmodium [86], the mean concentration at the front is higher than that at the rear, establishing cellular polarization during migration. Both repellents and attractants change the spatio temporal pattern of [Ca2+]. A stimulation with an attractant at the rear, increases the frequency of [Ca2+] oscillations, raising [Ca2+] at the stimulation site, whereas a repellent has the opposite effect.

Another oscillatory compound is ATP, which is distributed in patterns throughout the plasmodium [87] and exhibits oscillations in phase with the relaxation-contraction cycle [76,80]. ATP efflux increases during the contracting phase whereas it decreases during the relaxing phase. In a migrating plasmodium, ATP concentrations are approximately twice as high at the front [88] than at the rear. ATP provides energy for the contraction of the actomyosin cytoskeleton, which in turn generates cytoplasmic streaming. The ATP producing pathways, e.g., glycolysis in the cytoplasm and biological oxidation in mitochondria, influence directly the contractile activity of *P. polycephalum*. Hence, there is a strong link between energy metabolism and locomotion. When the plasmodium is starved, ATP synthesis is impacted and the slime mould is constrained to switch to different energy-generating mechanisms [89] or initiate more drastic measures (e.g. sclerotization or sporulation). Inhibition of both ATP synthesis and respiration in mitochondria stop locomotion but inhibition of ATP synthesis alone does not. Thus, it was suggested that another mitochondrial function, such as [Ca2+] regulation, controls the rhythmic contractions [76,90].

Oscillations of H+ and cAMP also accompany the oscillatory contractility of *P. polycephalum* [91]. Cytosolic H+ oscillations are a by-product of oxidative phosphorylation and are in phase with ATP oscillations; they are related to the energy metabolism [91]. cAMP oscillates ~ 60° ahead of the [Ca2+] oscillations [85,88], and is also involved in cell polarization. It forms a gradient from front to back, with the back showing several times higher concentrations than the front. Knowing that ATP and H+ trigger contraction and oscillate in phase whereas cAMP and [Ca2+] are responsible for the relaxation, Ueda et al. [88] proposed that a feedback loop consisting of ATP, H+, cAMP and [Ca2+] controls the contraction cycle. They postulated that a negative feedback occurs from [Ca2+] to ATP-H+ in the mitochondria where ATP is produced due to H+ influx and Ca2+ entrance in exchange of H+. Ueda et al. [88] suggested that these interactions between [Ca2+], ATP and H+ are involved in the time-keeping of the rhythmic oscillations.

Experimental and theoretical evidence indicates that mitochondrial energetic variables oscillate autonomously as part of a network of coupled oscillators [92]. The concentration of intracellular NAD(P)H in plasmodia of *P. polycephalum* was found to oscillate with the same period as the rhythmic contractions, but a third of the period ahead

[93]. When irradiated with UV light, the contractions can be stopped without affecting the rhythmic variation of NAD(P)H. Thus, the NAD(P)H oscillator works independently of the rhythmic contractile system, but seems to be entrained with it. A continuous energy production in the form of ATP appears to be necessary for oscillatory contractions. Both glycolysis, an oscillatory process in itself, and mitochondrial respiration influence the regulation of the contraction oscillations.

In addition to the chemical oscillators, it should be mentioned that spatiotemporal oscillations can also originate from mechano-chemical properties of an active material [94-96]. Spatial coordination can be achieved by mechanical interactions between different regions (e.g. [97]), and local positive feedback between deformation and contraction of the contractile apparatus induces the observed characteristic contractile behavior by hydrodynamic interaction alone via the streaming of endoplasm. However, more realistic models combine the interaction of mechanical and chemical oscillations. It was found that the temporal frequency is set by the chemical oscillator, whereas wavelength is determined by a mechanochemical instability [98]. In addition, only a combined model such as ([98], [94]) allows for migration of microplasmodia. Radszuweit and coworkers ([96]) proposed a model for the oscillations which is based on both chemical (i.e. exchange of calcium between the cytosol and storage vessels) and mechanical factors (i.e., flow and deformation).

We can assume that the contraction cycle in *P. polycephalum* relies on a feedback system between the contractile apparatus (i.e. the actomyosin system), the calcium regulatory system, and the energy metabolism [99,100]. It stands to reason that, since all of these oscillators are highly interconnected, they must be synchronised in some manner to produce coordinated behaviours as a function of environmental conditions (e.g. [101]). These oscillators might be involved in learning and memory as any encounter with a stimuli could be encoded and stored as changes in the contraction cycle and by extension as modifications of the vein network architecture.

b) Long-period oscillations in *P. polycephalum*: the cell cycle

In *P. polycephalum*, a lower level of intracellular repellent is sufficient to trigger the memory of habituation after the dormant stage [59]. This suggests that the interaction between the repellent and the relaxation-contraction cycle, which could support short-term habituation, is not the only mechanism supporting long-term habituation. In the brain, memory consolidation—the process by which a short-term memory is transformed into long-term memory—requires gene transcription and de novo protein synthesis to strengthen synaptic connections, e.g. facilitation and maintenance of synaptic plasticity, growth of new functional synapses, or physical insertion of new receptors [102]. Gene transcription and protein synthesis could be responsible for memory consolidation also in *P. polycephalum*. In all eukaryotic cells, gene transcription requires the chromatin to be "open", allowing easy access of transcription factors to target genes. In a non-dividing cell, such as a neuron, chromatin can be readily open and gene transcription can occur at any time. In contrast in a dividing cell, such as *P. polycephalum*, chromatin undergoes dramatic compaction during mitosis which precludes gene transcription [103]. Hence, in *P. polycephalum*, gene transcription is temporally restricted, setting up critical temporal windows during which this process must take place. In addition, as the cell division cycle globally disrupts and reorganizes the molecular content of the cell, it can profoundly influence learning and memory performances. In the following, we will briefly describe the mitotic cycles of *P. polycephalum*.

The plasmodium of *P. polycephalum* is a polynucleated cell that undergoes nuclear division every 8 to 12h [28]. In contrast to most cells, mitosis is not followed by cytokinesis and it occurs within the nuclear membrane (closed mitosis) which is common in protists and fungi. In *P. polycephalum*, the phase G1 is absent, the S-phase lasts for 2-3

hours, followed by a long G2 phase and 30 minutes mitosis (the nuclear division itself) [28]. In *P polycephalum*, gene transcription, and in particular mRNA transcription, goes from zero during mitosis to a maximum in early S-phase [103]. Remarkably, the plasmodium exhibits synchronous mitotic division of its entire population of nuclei and therefore, the number of nuclei doubles every cell cycle [28]. Pieces cut off from a plasmodium maintain this synchrony for a certain time and two asynchronous plasmodia can synchronise their mitotic rhythm after fusion [104, 105]. Experiments on the cell cycle, particularly those employing fusion techniques in *P. polycephalum* [104, 105] gave rise to pioneering theoretical models [106, 107] that presented the mitotic oscillator as a dynamical system and suggested that synchronous mitotic division emerges from dynamic interactions of regulatory molecules. *P. polycephalum* was considered as the ideal organism to study the cell cycle in the seventies. However, due to the lack of tools to disrupt gene function in *P. polycephalum*, in the eighties most researchers turned to other model systems in which they could test their hypothesis.

In the last decades, numerous independent genetic and biochemical studies using different organisms such as xenopus and yeast identified a major evolutionarily conserved regulatory network for cell-division cycle (*i.e* mitosis) regulation [108]. This network includes a cyclin that is periodically synthesized and degraded at specific cell cycle phases and a kinase (cyclin-dependent kinases CDK) that is regulated by phosphorylation and interaction with activators and inhibitors. The oscillations in CDK activity, in complex with regulatory cyclin subunits drive the cell-division cycle. In parallel to experimental measurements, mathematical modeling of the cell cycle has proved helpful in unravelling how interacting proteins such as Cyclin and their partner CDK control the dynamics of cell-division. These models contributed to the modern understanding of the cell as a complex dynamical system [109-111].

Cyclins and CDK are present in all eukaryotes, including *P. polycephalum* (Schaap). In *P. polycephalum,* the vigorous actomyosin-driven cytoplasmic streaming described earlier ensures that local accumulation of Cyclin/Cdk complexes diffuses and triggers the activation of Cyclin/Cdk complexes in neighboring nuclei [112], maintaining mitotic synchrony [113]. Until now, Yeasts have historically been a major model system to understand the control of the cell-division cycle in animals, taking advantage of their powerful genetics and rapid duplication times. However, many otherwise conserved cell cycle regulators have been lost in this organism. In contrast the complete set of Physarum cell cycle regulatory molecules has been identified [112]. Hence, with new options for experimental manipulation and in conjunction with mathematical modeling, *P. polycephalum* could become once more an attractive model organism to study cycle regulation at the regulatory complexity of a mammalian cell.

Mitotic and genetic oscillators are relevant to understanding learning and memory in *P. polycephalum* not only due to their oscillatory nature, but also because they provide a way to encode past experiences as epigenetic changes. The concept of epigenetic memory was defined by D'Urso & Brickner [114] as "a stable propagation of a change in gene expression induced by developmental or environmental stimuli". Epigenetic memory impacts gene expression and their associated feedback loops over both short and long timescales. Several evidence suggest that epigenetic mechanisms can regulate the ability to store long-term memories in Neurozoans, it might also be true for aneural organisms [115].

4. From oscillations to learning

Biological systems of very different architecture and complexity, representatively the (central) nervous system and the slime mould *P. polycephalum*, possess the ability to orchestrate complex behavioural patterns. This includes reacting to external stimuli in a well-controlled manner, and adapting their responses based on past experiences which indicates capabilities for information processing and learning. Despite their independent evolutionary histories [63],

close inspection of the dynamics of both systems reveals that they share a basal feature: they show rich oscillatory dynamics (section 3).

In biology, in artificial intelligence, and in physics, a system requires a certain level of complexity to process time-variant information presented by multiple inputs while recalling and adjusting past experiences. This complexity may be driven by the complexity of the system's microscopic units themselves, or/and by the nature and topology of their interactions in conjunction with the system size. Systems of interacting oscillators are known to self-organize their dynamics into diverse spatiotemporal patterns, possibly providing the required complexity. Once all differences in structure, function and complexity between nervous systems and the tubular network of *P. polycephalum* are put aside, what remains are biological systems that self-organize their structure as complex networks and their function as interacting and oscillatory units that give rise to emergent properties, resulting in well-controlled behaviours.

Physics procures universal frameworks to apprehend the complexity of such biological systems, and in particular unraveling the working principles of information processing in Neurozoans has seen significant progress in the recent past. In this section, as a perspective for future research, we raise the question whether similar microscopic interactions result in similar capacities among seemingly very different organisms. To lay the basis for developing this perspective further, we provide in section 4.a a brief overview of synchronization phenomena. In section 4.b we explore how integration of environmental information can be facilitated by oscillating systems via the modification of an attentive resting state, and candidate mechanisms that can generate and maintain such a state are discussed in section 4.c. Interestingly, the very same mechanisms support adaptation and learning in artificial and non-artificial systems. This is addressed in section 4.d.

a) Synchronisation, a prerequisite

Synchronization, a phenomenon arising from the interaction of two or more oscillators, can be observed in many biological systems. The position of an oscillator in its cycle can be described in terms of its phase, which advances at a pace set by the oscillator's natural frequency. Interacting oscillators influence each other's phase progression (Figure 2). A paradigm for synchronization is a population of globally coupled oscillators (*i.e* each oscillator in the population is affected by the dynamics of the rest) in which the natural frequencies are initially heterogeneously distributed. As time progresses, the oscillators minimize their pairwise phase differences, resulting in a pattern known as full synchronisation, where all oscillators operate at the same instantaneous frequency and phase. This is described mathematically by the canonical Kuramoto model [116], which predicts a phase transition between desynchronised and synchronised states, based on the global coupling strength (Figure 2.d and 2f, Supplementary movie 3). Synchronous mitosis in *P. polycephalum* illustrates such global coupling leading to a state of full synchronisation. Here, nuclear division is robustly controlled across the entire organism and occurs when the ratio of DNA to cytoplasm in the plasmodium drops below a certain value due to an increase of the cellular volume [117].

Modifications of the Kuramoto model give access to a much richer spectrum of synchronisation patterns as observed in many biological systems such as cardiac cells, populations of fireflies or assemblies of neurons. Strikingly, employing local instead of global coupling or combinations thereof can lead to the emergence of complex spatiotemporal patterns. These patterns range from full synchronisation or desynchronisation to spiral waves, traveling waves (Figure 2.e), and even to curious chimera states [118], where part of the population is synchronised and part is not. Notably, the Kuramoto model can be modified to account for local coupling and is also well suited for describing populations of oscillators coupled through a network topology [115], as shown in figure 2.d and 2.e and supplementary

movie 4 for a random planar network. Indeed, synchrony in a population of oscillators is crucially affected by the topology of their network (regular lattice, random network, small-world network, etc.). This lies as the foundation of diverse dynamics observed in biological networks, such as the central nervous system. Synchrony in the brain supports neural communication and neural plasticity and is relevant for many cognitive processes [119]. Similarly, synchronisation phenomena observed in the plasmodium's intrinsic cellular oscillations have been suggested to support complex behavior in *P. polycephalum* [120].

As described previously (section 3.a), transport of cytoplasm in *P. polycephalum* is actively driven by rhythmic contractions associated with biochemical oscillations. The rhythmic contractions typically organize as traveling waves [32, 121], but other patterns such as rotating spirals are observed [122]. Although a variety of active materials is capable of generating such patterns, they can also be indicative of locally coupled oscillator systems. Unlike neural networks or cardiac cells, the plasmodium of *P. polycephalum* is not composed of discrete, interacting units but instead forms a continuous yet inhomogeneous material (section 2.a). It has been shown that *P. polycephalum* reproduces the dynamics of coupled oscillators at large spatial scales when introducing an artificial discretization by shaping the plasmodium into extended patches connected by thin veins [73, 123]. In this setting, due to the imposed asymmetry, the connections were largely passive. In contrast, in naturally-grown plasmodia the connecting veins contribute actively to the oscillatory dynamics. Here, it appears necessary to move to smaller spatial scales by regarding the plasmodium as a continuum of oscillators coupled locally via diffusion, advection of chemicals through active transport, and through mechanical interaction. This approach has been pioneered by Kobayashi et al. [124].

b) Integration of environmental information

Both in nerves and in *P. polycephalum*'s veins, chemical oscillations are responsible for conveying macro-oscillations as well as transport or motion at the organism scale. What we call macro-oscillations might be the rhythmic movement of the human legs, the wings of a bird, as well as the centre of gravity of a *P. polycephalum* plasmodium [30]. Why are these motions rhythmic? An enticing argument arises from a neuroscience perspective, stating that rhythmicity provides a powerful tool for organisms to infer easily from their environment. Buzsáki [70] sees leg movements as an oscillating system in which perturbations indicate an environmental change. Considering leg movement, a change of the floor topology will disturb the movement rhythmicity and therefore will become a piece of integrated information allowing motion continuation.

Hence, an environmentally-driven behavioural change can be seen as integration of environmental information through change in the oscillatory pattern. A prominent example is found in rats, in which active movement of the whiskers generates the sense of touch. The perturbation of the whisker movements following a contact with an object elicits a sensory signal that carries information about the object. In rats, whisker motion over a texture produces a specific temporal profile of velocity, which is encoded in the temporal pattern of neural activity, for instance rougher surfaces evoke higher firing rates [125]. Hence, the information given by mechanoreceptors is directly encoded into a new oscillatory pattern in the brain. This kind of functioning pervades the neural sensing of external stimuli, and changes in oscillatory patterns are likely to be a common mechanism by which Neurozoans integrate and store information.

P. polycephalum's biochemical and cytoplasmic oscillations may have a similar purpose and might offer a possible explanation for the organism's ability to process, integrate and store information. *P. polycephalum* exhibits sustained oscillations even when not faced with any stimuli (*i.e.* resting state). Upon encountering an external stimulus,

P. polycephalum responds first by adjusting its oscillation frequency and amplitude locally. This change then spreads over the entire network [126] and finally the morphology of the slime mould adapts to the environment [127]. Positive stimuli such as chemoattractants lead to increased frequencies whereas negative stimuli such as chemical repellents lead to a decrease (section 3.a.). Consequently, it appears reasonable to assume that the stimulated regions in- or decrease their importance for the global oscillation pattern: positively stimulated fronts act as pacemakers, whereas negatively stimulated regions concede. Indeed, it is observed in small fragments [121] and in macroplasmodia (personal observation), that travelling waves responsible for mass displacement are directed towards those fronts where the slime mould extends, underlining the plausibility of this concept. Hence, an encounter with an external stimulus could be memorized as a change in the spatiotemporal dynamics of the system. Returning to the results of Boisseau et al [23], we might wonder: how does the global oscillation pattern change in response to repetitive stimulations to allow habituation? We do not have the answer yet, but we believe that the process of habituation in *P. Polycephalum* relies on both an attentive resting state and mechanisms to adapt the oscillation patterns to changing environments.

c) Maintaining excitability: resting state activity & self-organized criticality

As outlined in the previous section, disturbance of an oscillatory resting state via an input is an efficient mechanism for integrating environmental information. This mechanism is extensively used in Neurozoans' central nervous systems. Here, we describe how the resting state affects neural functioning and introduce a number of advanced mechanisms that can maintain or modify the resting state of an oscillatory system. These mechanisms have proven to be relevant in the context of self-organization or adaptive control, in particular in neural systems. Their involvement in *P. polycephalum* is unclear yet appears to be entirely possible in the light of the analogy proposed in this article.

Resting state activity in the brain is not immediately related to any motor task or sensory input. It represents spontaneous activity that is closely related to the functional organization of the neural network and encompasses both, sub-threshold membrane potential oscillations and patterns of neural spiking activity. By assisting spike-timing dependent plasticity (see section 4.d), synchronisation of the sub-threshold activity facilitates reliable and precise adaptation of synaptic strengths [128]. Therefore, the resting state is involved in organization of the neural activity, optimization of the learning process, network development in the brain and is believed to be implicated in higher functions, such as different states of consciousness and focus [129, 130]. Finally, it interacts with external inputs (see section 4.b).

Recent results suggest that the observed resting state patterns indicate a state at which the brain is stable yet responsive. This is summarized as the critical brain hypothesis [131], stating that the brain operates, controlled by a self-organizing process, in a subcritical regime, yet close to the critical point [132], where it is most excitable. Criticality is an umbrella term that denotes the behaviour of a system perched between order and disorder. In the brain, the subcritical regime is considered as unexcitable, whereas the critical regime displays cascades of activity unrelated to any input. Neither regime is favourable for normal brain function and excitations lead to a controlled response only slightly below the critical point.

Evidence suggests that the phase transition associated with the critical point in question is in fact the transition between desynchronisation and synchronisation [133] (see also section 4.a), highlighting once more that synchronisation, a very basic feature of coupled oscillatory systems, is at the very heart of coordination of complex

functions. The mechanism that appears to be responsible for restoring the system to the working point after it has shifted too far into the critical or subcritical regimes is sleep [134], during which resting state activity is pronounced. Curiously, during sleep, the resting state activity couples to the flow of blood and cerebrospinal fluid [135], the latter being driven by the synchronised motion of cilia [136]. This mechanism is hypothesized to facilitate, for instance, waste disposal, and hints at another analogy: throughout this article, spatiotemporal synchronisation of relaxation-contraction oscillations has been pointed out as the driving force behind fluid flow in the slime mould. Here, a quite similar mechanism that is rooted in the spatiotemporal synchronisation of neural oscillations drives fluid flow in the brain.

It is unclear whether self-organized criticality is involved in the dynamics of *P. polycephalum*. Coggin & Pazun [137] indicate that the spectrum of frequencies observed in *P. polycephalum* may constitute a signature of criticality. The authors further support their hypothesis by showing that the oscillating system operates at the edge of chaos (at the boundary between order and disorder), another indication for criticality that has been studied in the context of self-organization in general, and in particular in neural networks [138]. The peculiar power spectrum of *P. polycephalum* has not only been noticed in the context of criticality but also with regard to the anticipatory learning behavior of the slime mould described in section 3.b. Here, it serves as an underlying assumption to the model of Saigusa et al. [57]. Despite its implications, the mechanisms generating the power spectrum are as of now unclear and thus the hypothesis has not been further verified.

How can an oscillatory system be maintained at the edge of chaos? Mechanisms facilitating this include coherence resonance and stochastic resonance [139] that can stabilize a spectrum by noise-induced entrainment and synchronisation, which lead to frequency selection [140,141]. Alternatively, modification of the Kuramoto model to include adaptively controlled coupling leads to a similar effect. The scheme facilitating this adaptive control in dynamical systems that exhibit chaos builds on the self-organized control of unstable periodic orbits through inclusion of a delayed intrinsic feedback [142]. Intriguingly, by application of this scheme to coupled Kuramoto oscillators, Kaluza & Mikhailov [143] were able to generate a system that robustly adapts desired synchronisation levels through feedback control of coupling strengths. This corresponds to the adaptation of synaptic weights in a neural network (see section 4.d), highlighting that the combination of these rather general mechanisms can facilitate learning in addition to maintaining criticality. Recently, these principles of adaptation have been experimentally verified in an artificial system of optically coupled chemical oscillators [144] and have been extended to complex, modular synchronisation patterns [145].

Albeit operating on a slow time scale, the adaptation of coupling strengths is a motive in the structure formation of *P. polycephalum* [146] (section 4.d). It is driven by the oscillatory shuttle streaming and utilized by the organism to adapt to its environment by eventually modifying the topology of its network. Notably, such topological adaptation is another form of maintaining criticality if it stabilizes the system in the vicinity of the percolation phase transition [147]. In networks, percolation is the transition between a low-connectivity, fragmented state and a state with high connectivity, indicated by the existence of a giant component [146]. Due to the slow time scale, percolation appears as a rather unlikely candidate in *P. polycephalum* or Neurozoans, unless the highly dynamic network of flow directions (in the slime mould) or neural activations (in Neurozoans) is considered instead of topologies of veins or neurons [147].

d) Adaptation and computation

Although topological adaptation is a weak candidate for explaining criticality, it is clearly involved in the formation of memory in Neurozoans. Here, it manifests as the adaptation of weights (synaptic strengths) between neurons and is controlled by a mechanism referred to as spike-timing dependent plasticity: connections are promoted if neurons fire in synchrony and demote otherwise. This feedback mechanism for the adaptation of the neural network topology is reminiscent of the current reinforcement model brought forward by Tero et al. [148] which states that veins in the tubular network of *P. polycephalum* are promoted if there is a sufficient volume flow, and demoted otherwise. This oscillatory flow is driven by relaxation-contraction oscillations that organize as a wave [32]. For efficient transport, phase and frequency relationships along a single vein need to be intricately maintained [149,150], indicating that precise control of the spatiotemporal oscillation pattern is required in the slime mould as well.

Intriguingly, the analogy not only applies to synaptic plasticity and current reinforcement, but also to memristors, electrical components with a resistance that is based on the history of currents flowing through them. Memristor-based computational models have been successful at modeling learning in *P. polycephalum* in the form of anticipation of periodic events [151] (see also sections 3.b and 4.c), as well as the computation of shortest paths [152]. Indeed, the 'electric circuit analogy' is more general and encompasses hydraulic counterparts for all basic electrical components. In consequence, microfluidic devices can be manufactured that mimic the function of electrical circuits [153], including the generation and control of oscillatory flows [154], thus extending the analogy to alternating currents. This has been widely applied, for instance for the description of oscillatory blood flow in the field of hemodynamic [155]. There it has led to the formulation of the Windkessel model, a motif of electrical networks consisting elementarily of a resistor and a capacitor in parallel. The Windkessel model accounts for the influence of vessel elasticity on pulsatile flows and has been successfully employed to model frequency selection, migration and symmetry breaking in *P. polycephalum* [156]. In neuroscience, the approach of modeling biological transport processes by a corresponding electrical circuit has seen great success, pioneered for instance by the Hodgkin-Huxley model [157]. Intriguingly, the Windkessel model has also been applied by Cabral et al. [158] for modeling the organization of resting state activity (see section 4.c) in the brain in conjunction with the Kuramoto model for synchronisation [158]. Notably, the model of Cabral et al. [158] also requires the interaction between oscillators to be time delayed, an effect which has been first shown to exist in biological systems in *P. polycephalum* [73].

The emergent computational principles of neural systems have broad implications beyond fundamental neuroscientific research. The development of silicon-based multi-purpose computing architecture is facing severe limitations, making bio-inspired innovations indispensable. Neuromorphic computing [159] mimics basic functions of neurons and synapses, paving the way for efficient hardware implementation of deep learning, potentially using memristors [160]. Further, oscillator-based computing [161] seeks to harness the complexity of oscillatory systems for computation. Both can make use of reservoir computing [162], the concept of adapting to the inherent computational powers of naturally or randomly-generated systems instead of tailoring them to the task. Intriguingly, systems have been generated in this fashion that unite oscillatory properties, signatures of criticality, memristivity and learning [163–165]. Irrespective of the details of the implementation, understanding the rules governing how natural oscillatory systems such as *P. polycephalum* process information and learn is paramount to the advance of computing, and any advances are expected to be of mutual benefit.

5. Transdisciplinary Integration of Universal Mechanisms and Concepts.

In this review, we have undergone a journey from the biochemistry of molecular constituents via the physics and the biology of mesoscopic cellular organization to macroscopic behaviour of *P. polycephalum*. We have argued that coordination and interaction of oscillations across a vast range of spatiotemporal frequencies and wave lengths provide a powerful theme of self-organisation in active matter, i.e., life. We have eluded to analogies in pattern formation and dynamics between the human brain and *P. polycephalum* plasmodia linking microbiology with neurobiology employing chemistry, physics, and ecology along the way. Moreover, we pointed out that these analogies likely will turn out to be universal mechanisms, thus highlighting possible routes towards a unified understanding of learning. In order to arrive at this point, we had to immerse ourselves into each other's disciplines. Without the behavioural perspective leading to a clear characterization of foraging in *P. polycephalum*, we could not elevate biological physics from describing basic mechanisms of tubular network dynamics to the far more complex level of correlated foraging behaviour. Reciprocally, the ensuing mechanistic understanding will facilitate a deeper understanding of behavioural traits. Such a transdisciplinary approach towards *P. polycephalum* promises to be fruitful also in the future investigation of basal cognition in comparison to cognitive functions in the human brain. We aim to understand information processing on oscillating networks with variable topology. We have identified synchronisation of oscillators as a basic principle applicable independently of the substrate and specific architecture. This is key, for instance, for the neurobiology of attention [166]. Further concepts needed to describe the ensuing structure formation in driven non-equilibrium systems are provided by stochastic thermodynamics [167] and Bayesian mechanics of a limited set of behavioural states as given by Markov blankets defining the organism through its interface with the environment [168]. Aneural model systems, like *P. polycephalum* and their simple Neurozoan counterparts, like Hydra [169] or *C. elegans* [170], have the crucial property that behaviour is readily accessible by the dynamics of their morphology and/or topology. This macroscopic level can be modelled by a mesoscopic description of the network (and further components) whose parameters are set by microscopic details. For these three systems, details are known to a large extent. A full hierarchical description of behaviour is possible, extending from individual organisms to the collective behaviour of populations made up of small groups, swarms or even complex societies. In the spirit of universal mechanisms, we expect to find similar structures defining traits like habituation, anticipation, decision making, attention, etc., also at this higher hierarchical level, as has been identified, e.g., when comparing *P. polycephalum* with ants [171] or transport networks [50], as well as in the Kelly criterion, a heuristic for optimal asset allocation [172].

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Authors' Contributions

AB, AF and CO laid down the overall plan of the manuscript. AB, AF, CO, LB, HGD and AD contributed to the first draft of the manuscript. AF, CO and AD produced the figures and the movies. AD coordinated the writing of the manuscript. AD and HGD secured funding. All authors gave final approval for publication.

Competing Interests

We have no competing interests

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Figure 1: These pictures illustrate a) a macroplasmodium; the vegetative phase of *P. polycephalum*, b) a sclerotium, the dormant stage, c) a slime mold making a decision between different food sources varying in quality, d) a vein network, e) a magnified vein and d) the nuclei stained with DAPI within the plasmodium.

Figure 2: Oscillations, coupling & synchronization: a) the (instantaneous) phase indicates the state of an oscillator, b) the change of phase is driven by the natural frequency and coupling, c) coupling can be global or local, mediated by a network topology, d-f) states of a random planar network of Kuramoto oscillators, see supp. movies 3&4, d) desynchronization, e) dynamical wave synchronization (local coupling), f) full synchronization (global coupling).