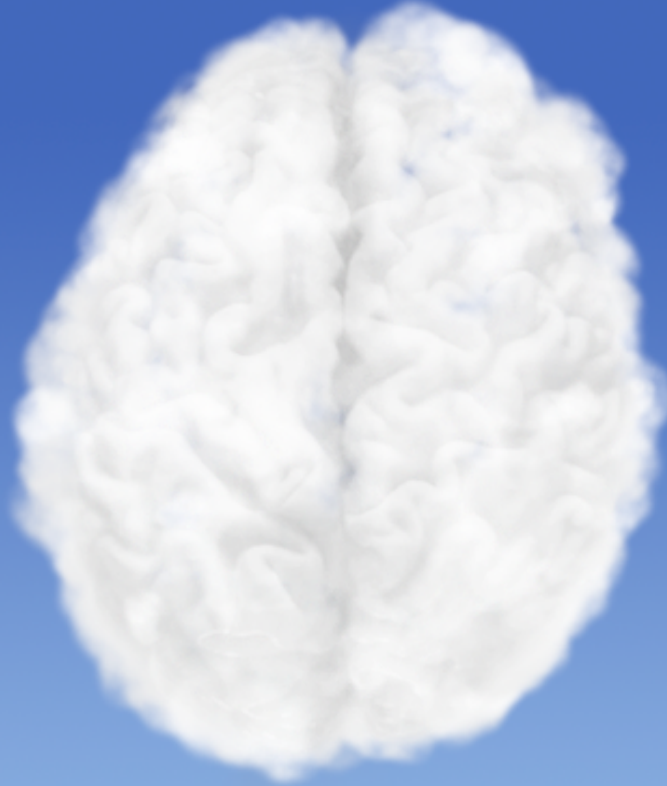


# Brain Clouds

The Science of Collective Phenomena and the Brain



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Can you explain how the brain works while standing on one foot?

No, not even while standing on two feet. However, a brief overview of what we do know about the brain is a sensible place to begin.

The human brain contains  $10^{11}$  neurons (1, 2), which are specialized cells thought to be its computational units. Approximately one fifth of these neurons are contained in the outermost layer called the cortex (1, 3, 4), which is heavily folded and gives the brains its characteristic wrinkled appearance (Fig. 1). The brain also contains glial cells, which according to some investigators outnumber neurons 10:1 (5). However, the extent of their role in computation is not entirely clear. Together, these cells are densely packed within the brain's modest volume of approximately  $1350 \text{ cm}^3$  (1). Neurons utilize an electrochemical potential across their outer membrane to code for information, discharging electrical spikes analogous to a digital code (6).

Similar to other systems containing large numbers of individual units, the interactions between neurons impact the more global properties of the brain. Neurons within the cortex are densely connected, with the average neuron making  $10^4$  direct connections, called synapses, with other neurons (1, 3, 4). Synapses are neuronal junctions with well-defined structure that couple neurons via chemical and electrical signals (7). This coupling can be inhibitory or excitatory, and the strength of the interaction can be modulated on time scales from milliseconds to hours, and perhaps longer (8, 9). It is thought that memory is primarily the information stored in the spatial pattern of these synaptic strengths, and that learning is the process of optimizing these interactions as the result of experience (7). Together memory and learning influence perception, behavior, and cognition. Despite our universal fascination for the brain, our knowledge in this area is remarkably superficial. We hypothesize that these complex phenomena are represented in the brain by evolving patterns of collective neuronal electrical activity. Understanding the physics of these spatiotemporal patterns, as well as their role in both normal and diseased brain states is the primary research focus of ICNDE.

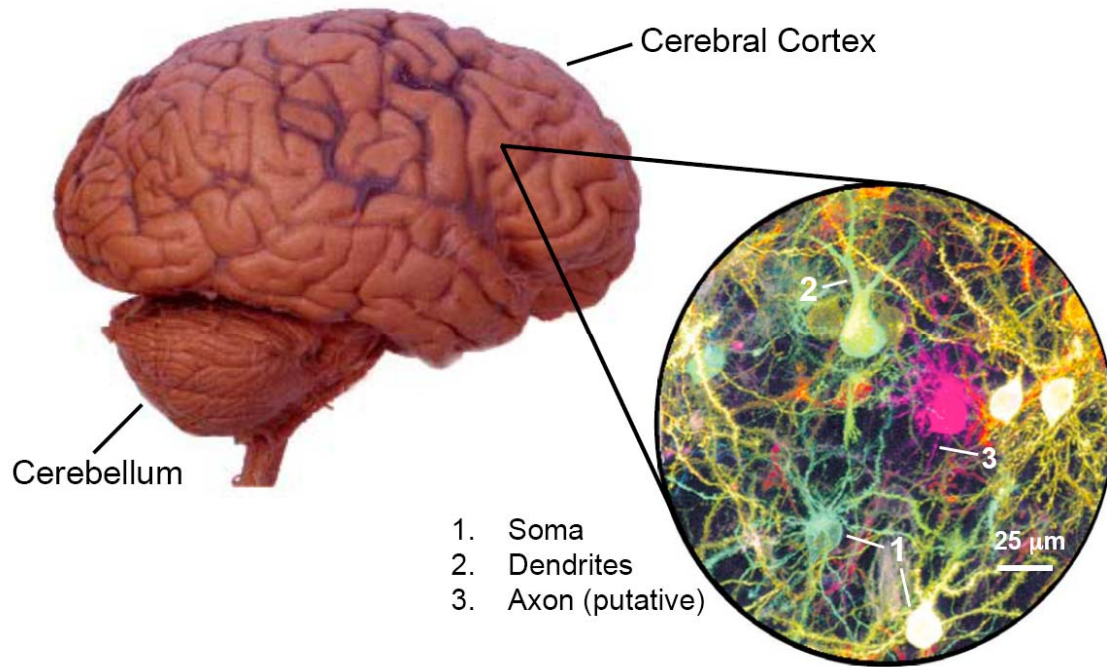


Figure 1 *Macroscopic and Microscopic View of the Brain*. **A** Lateral view of the human brain with emphasis on the two most evolutionary recent structures, the cerebral cortex and the cerebellum. Together they contain the vast majority of the brain's  $10^{11}$  neurons, which are visualized in **B**. A subset of neurons are labeled by a technique developed by Gan et al. (10) where a combination of fluorescent dyes with different colors are used to promote visualization of individual neurons. The large teardrop shaped structures are neuronal cell bodies, or somas. Dendrites are input cables to the soma and are identified as tapering branched structures. They become thin far from the soma and difficult to distinguish from axons, which are the uniformly thin output cables. The small protrusions seen along these cables represent synaptic structures.

How do neurons communicate with each other?

Neurons, similar to other cells have an electrical potential across their outer membrane, where the inside of the neuron is about -70 mV with respect to the extracellular space. This voltage fluctuates in response to the injection of current from the synapses of connecting neurons, which we discuss below (Fig. 2). If the voltage exceeds a threshold, around -50 mV, a population of voltage sensitive protein pores or channels, embedded within the membrane open and allow Na<sup>+</sup> ions to flow into the cell. This inflow of positive ions increases the membrane voltage further, peaking around +30 mV. However, this current is short lived and is followed by the outflow of positive K<sup>+</sup> ions, resulting in a narrow voltage spike called an action potential (3, 11). The “flow” of current through the channels is actually ions diffusing down existing concentration gradients, which are maintained by ion pumps that run continuously.

The membrane containing the voltage sensitive pores extends from the cell body or soma to an output cable called the axon, which propagates the action potential as a traveling wave. The axon bifurcates many times, with the terminus of each branch forming a synapse with a connecting postsynaptic cell. Typically cells in the brain are connected by a small number of synapses, as few as one (12-14). The terminus of the axon, called the synaptic bouton, is filled with 40 nm vesicles that are packed with small signaling molecules called neurotransmitters. The action potential arrives at the bouton and triggers several protein mediated events (Fig. 2), the first of which is the influx of Ca<sup>2+</sup> ions (7, 15). These events culminate in the fusion of a single vesicle's membrane (16) with the outer membrane of the bouton, and the release of the neurotransmitter molecules into the extracellular space. This vesicle fusion and release of neurotransmitter, called exocytosis, can only occur at a specialized section of the bouton's outer membrane. This region, known as the active zone, contains the proper protein machinery required for vesicles to bind to the synaptic membrane and undergo membrane fusion (15, 17). The membrane of the postsynaptic or connecting cell is directly opposed to the active zone, with a 20 nm gap between the two membranes. The neurotransmitter diffuses across this gap or synaptic cleft, where it binds to a variety of protein receptors embedded in the postsynaptic membrane. A subset of these receptors are also channels, and upon binding to neurotransmitter, temporarily allow particular ions to flow in or out of the postsynaptic cell (3). The resulting pulse of postsynaptic current and corresponding voltage propagate along input cables called dendrites, towards the soma of the postsynaptic cell. Depending on the class of the presynaptic neuron and which neurotransmitter it releases, the voltage contribution in the postsynaptic neuron is either positive (excitatory) or negative (inhibitory). In the root of the axon, near the soma, the electrical contributions from many synapses are thought to add up in an linear fashion like an account balance (18, 19). If the resulting voltage increases sufficiently to reach threshold, then the postsynaptic cell fires an action potential and the signal propagates along the axon to another set of synapses.

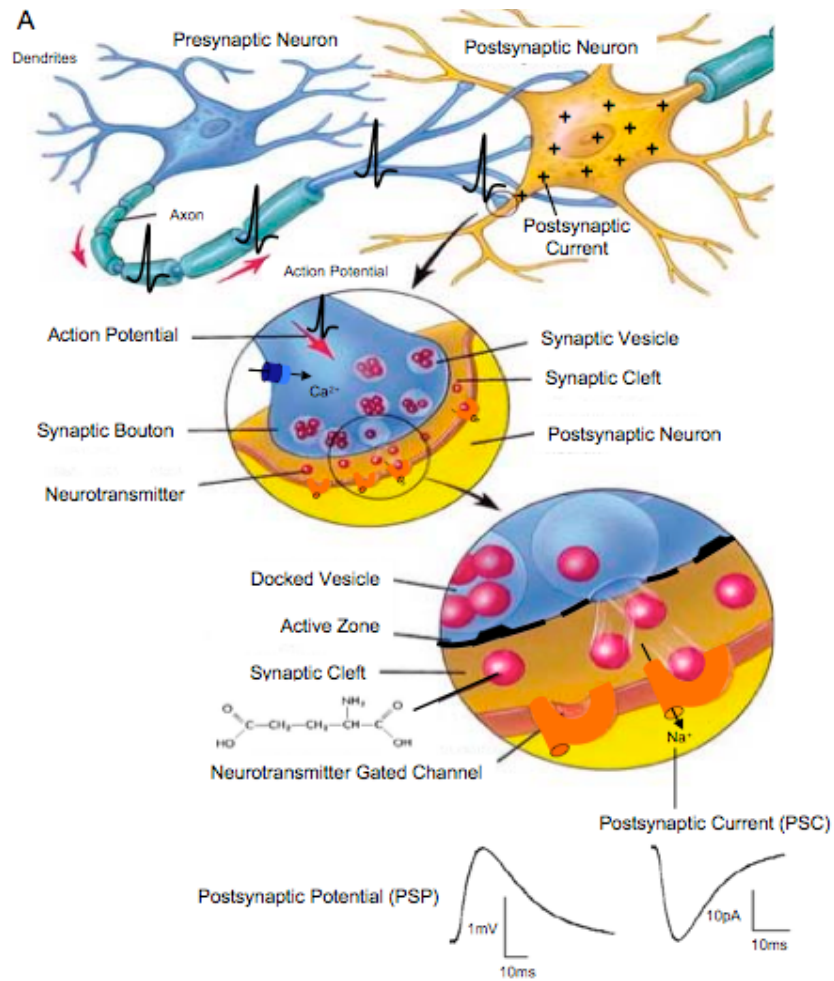


Figure 2 *Excitatory Synaptic Transmission*. A A modified illustration (source unknown) depicting an action potential traveling along the axon of an excited presynaptic cell and entering the synaptic bouton, causing voltage gated  $Ca^{2+}$  channels to open. The influx of  $Ca^{2+}$  initiates a sequence of events that ultimately leads to a docked vesicle to fuse with the cell membrane, releasing neurotransmitter into the synaptic cleft. Here the excitatory neurotransmitter glutamate is shown diffusing across the cleft and binding to glutamate receptors, which can lead to a variety of actions depending on the receptor subtype. One important consequence is the influx of  $Na^+$  ions into the cell, resulting in an excitatory postsynaptic current. Alternatively, the corresponding voltage or excitatory postsynaptic potential can be measured and is displayed to the left.

## Getting Excited About Collective Excitations

Terms can often confuse rather than clarify topics, particularly in those subjects that are complicated and quantitative in nature. To make matters more difficult, much of what is discussed below can be found in a number of different sources under a variety of names including complexity theory, nonlinear dynamics, emergent systems, non-equilibrium statistical mechanics, dynamical systems, chaos theory, swarm intelligence, and attractor networks (20-22). We take what is perhaps a neglected perspective, focusing on the concept of collective excitations, also known as collective modes. We believe that this is not only advantageous from a teaching perspective, but also plays a fundamental role in advancing the disciplines mentioned above. Collective modes are grounded in experiments and make connections with measurable quantities, which ideally should drive theories.

What are collective excitations?

To address this question it is useful to introduce the concept of phase space. Consider a bucket holding 3 liters of water. This bucket contains approximately  $10^{26}$  water molecules. Each water molecule requires an  $x$ ,  $y$ , and  $z$  coordinate to describe its location in the bucket. Likewise, the velocity of each molecule has three components  $v_x$ ,  $v_y$ , and  $v_z$ , and each is required to describe a molecule's motion. These six parameters are independent "degrees of freedom" and form the axes of a six-dimensional volume called phase or configuration space (21, 23) (Fig. 3). This mathematical construction describes the space of possible configurations of a single water molecule, with each combination of location and velocity represented by a point in this volume. To describe the possible configurations for the entire bucket, we need  $6N$  dimensions, where  $N$  is the number of molecules. If we plot multiple points in this space as a function of time we construct a trajectory or path, which describes how the system evolves in time. Although keeping such detailed tabs on all the molecules is not possible, the location and trajectory of the system in phase space in principle contains all the information about the system.

Suppose you put your hand in the bucket and give the water a quick stir. A whirlpool or vortex will form. If we were to plot the trajectory of the system in phase space, we would see something interesting. The trajectory would wind around in a small region, and the vast majority of phase space would be empty. This vortex, represented mathematically by a particular cluster of points in phase space called an attractor (21), is an example of a collective excitation. These attractors can have fascinating mathematical properties, where under typical conditions trajectories cannot escape, but never retrace the same path twice. In addition, attractors have a surrounding region of phase space called a basin of attraction, which acts like a black hole, sucking in any trajectory that enters its boundary (Fig 12). As we will discuss later, this last property is particularly important in biological computations.

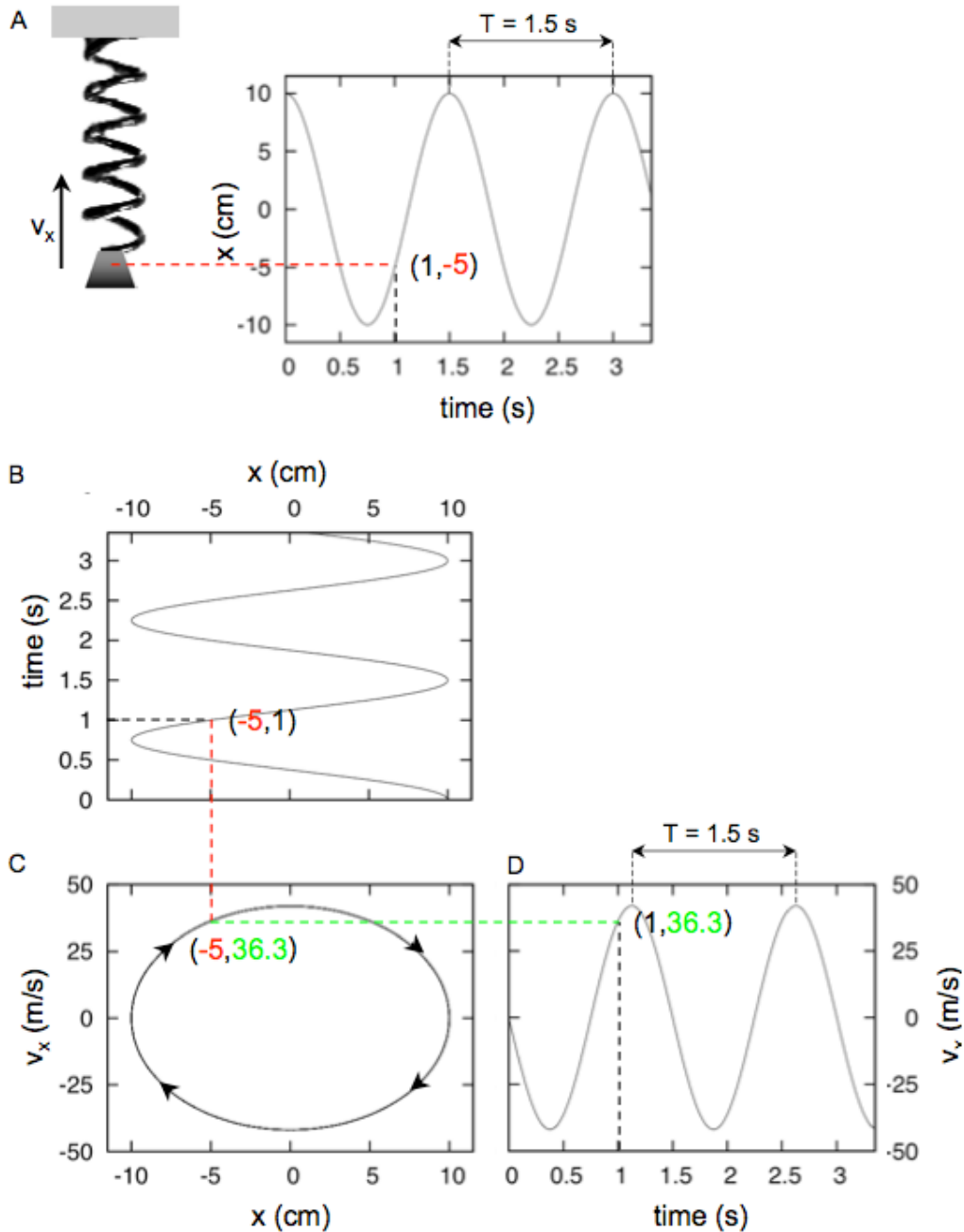


Figure 3 *Construction of Phase Space.* A weight attached to a spring and moving in one dimension is depicted in **A**, where  $x = 0$  marks the position of the weight at rest. Once in motion, the weight's position oscillates up and down indefinitely in the absence of friction. The position, which is one of the two degrees of freedom is graphed as a function of time on the right. A snapshot of the weight at time  $t = 1$  second demonstrates that the weight is at  $x = -5$  cm, which is plotted on the graph. **B** displays the same graph turned on its side. The other degree of freedom is the velocity of the weight, which slows to zero at the top and bottom and is plotted in **D**. At each point in time the values for the position and velocity are plotted on separate axes in the graph in **C** called phase space. This is illustrated for the values at  $t = 1$  second. Repeating this for consecutive time points maps out a trajectory in phase space, which in this case is an oval path that repeats every  $T = 1.5$  seconds. While time is not plotted explicitly in phase space, arrows depict the progression of time along the trajectory.

What makes collective behavior interesting?

With a slight motion of one's hand one can organize a bucket of randomly moving, seemingly independent molecules into an obedient herd, like a skilled shepherd. However, there is no shepherd, no blue prints, and no conductor telling each molecule where to go. This is one of the hallmarks of collective or emergent behavior: a coherent structure emerges despite the fact that there is no leader that has knowledge of the entire group's activity or a pacemaker that all the molecules follow. Each molecule only senses the activity of its neighbors, and the large-scale pattern emerges from local interactions. Surprisingly, this phenomenon appears to be universal. A large variety of species from electrons and molecules, to cells and even organisms tend to form collective modes (Fig 4).

Although these patterns emerge from local interactions, you would have a difficult time predicting that by observing the behavior of the individual units. If you were to zoom in and observe a single water molecule you would see it move along a straight trajectory for short distance until it collides with another molecule, scattering in a random direction. The time (distance) between collisions is known as the free mean time (path) (23). At times (distances) longer than this the molecules' behavior is entirely unpredictable. Interestingly, collective modes exhibit long time (range) order that is many orders of magnitudes longer (larger) than the free mean time (distance) of the individual units. The long-lived and large-scale order is only evident when you zoom out and view the system at a distance. In the case of the water molecules the free mean time (distance) is less than  $10^{-9}$  seconds ( $10^{-9}$  meters), while the vortex lives for about a second even after you stop stirring, and has a width comparable to the size of the bucket. These microscopic and collective scales differ by more than 9 orders of magnitude!

These emergent properties give these spatial-temporal patterns an identity of their own, somewhat independent of the individual units. For example, suppose there are multiple vortices in the bucket of water (Fig. 4B, 4D). Each vortex contains many water molecules, and each molecule can relocate and belong to either vortex. There exists no one to one relationship between these entities. An interesting illustration of this is the human body. The majority of the cells in your body turn over in just a few years and the molecules even faster (24), yet your identity is remarkably stable. You are nothing but a complex molecular pattern in time and space, a collective mode. Despite this you are as real and well defined as any of the molecules that are within you.

Like the molecules that comprise them, collective modes can have mass, attract or repel each other, collide, and even exchange momentum. Thus, they are sometimes referred to as quasi-particles. In some sense there is nothing quasi about them. Similar to collective modes, particles such as molecules, atoms, and subatomic particles are simply a collection of other particles, often behaving as a single entity. For example, water molecules consist of H and O atoms. Meanwhile, each of these atoms consists of electrons, protons, and neutrons. It is well established that these subatomic particles are made up of a collection fundamental particles called quarks. It is unclear how far this cascade ultimately extends. Regardless, particles on one level of this cascade of increasing complexity are no less defined than those below. They exhibit many of the same properties of the particles that comprise them, in addition to new emergent ones. Returning to the bucket of water, the individual water molecules have mass, charge, and momentum. In addition to these properties, the collection of water molecules also has temperature, compressibility, specific heat, conductivity, and many others that the individual molecules do not.

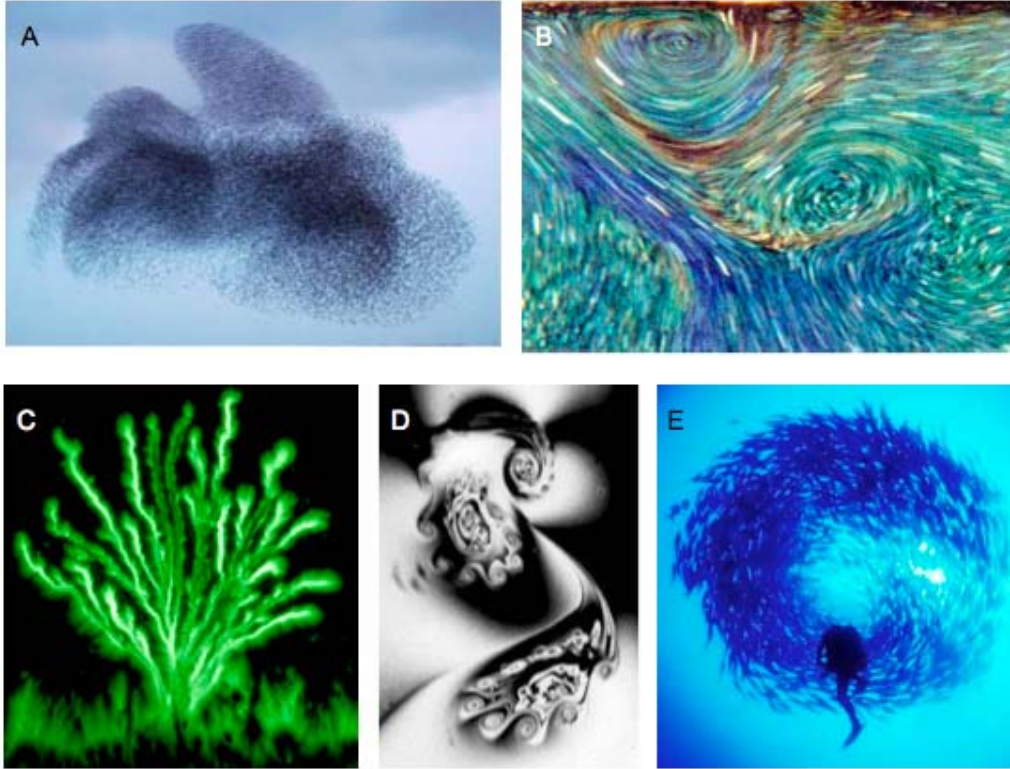


Figure 4 *Examples of Collective Modes*. **A** Thousands of European Starlings are shown forming a large intricate flock (25). **B** A long camera exposure reveals the flow of temperature sensitive liquid crystals in Rayleigh Bernard convection, which occurs when a container of fluid is heated from below (26). **C** Magneto-optical image of magnetic flux density in  $MgB_2$  film displays a branching or “dendritic” type pattern when the film is cooled below 10 K and a perpendicular magnetic field is applied (27, 28). **D** Placing the edge of a razor blade in a flowing thin soap film results in the shedding of a self-similar or fractal vortex pattern. Notice the cascade of vortices of vortices. **E** School of fish organize into a donut shaped formation, which is thought to be protective from prey (29).

What are the necessary conditions to create collective modes?

We suspect that the key ingredients for collective modes are simple: 1) a large number of units that 2) interact with moderate strength and are 3) driven not too far from equilibrium. We can see that the hand exciting the vortex in the bucket satisfies our key ingredients. Meanwhile, its simplicity allows us to build some intuition about collective modes.

1) As the name implies, collective behavior describes the phenomena that occur when large numbers of individual units interact. It is the influence of the masses that elicit behavior that otherwise might not occur in the individuals. An angry mob is an unfortunate but familiar example of collective behavior in humans. In the bucket of water, there are about a million times more molecules than there are stars in the universe. Clearly,  $10^{26}$  molecules is an enormous number, difficult even to comprehend.

2 & 3) The water molecules are attracted to each other due to an asymmetry in the electron distribution within the molecule. The more negative O atom attracts the more positive H atoms from neighboring water molecules, forming what is known as H-bonds. The question of whether this interaction, measured in energy units, between water molecules is weak or strong is somewhat subtle. More precisely, one should ask strong compared to what? Strong compared to some measure of noise or randomness in the system. For a system in equilibrium, the amount of noise is determined by the temperature ( $T$ )\*, which is a measure of the mean kinetic energy of the molecules. This molecular motion is random, and although it provides the energy for processes such as chemical reactions, these processes are only predictable on average. Thermal kicks can drive reactions uphill energetically, which becomes noticeable if small numbers of molecules are involved. To convert  $T$  to the same energy scale as interaction strength, we multiply it by Boltzmann's constant ( $K$ ). Thus, it is useful to describe the interaction strength in multiples of  $KT$ . The H-bond in water is just a few  $KT$  at room temperature. The fact that the two are comparable is precisely what makes water a liquid at room temperature. Liquids are easy to stir and manipulate, yet retain some form when perturbed.

Thermal random motion is not the only contribution to noise we must consider. As you stir the fluid, the molecules collide with each other and randomize their motion, analogous to the thermal noise described above. This occurs even if the stirring action is perfectly smooth. One can see this phenomenon with billiard balls. As the number of balls in a combination shot increases, one must be increasingly accurate in striking the cue ball. The errors magnify with each successive collision such that the ball's trajectory becomes unpredictable within a handful of collisions. Although many have tried to define a dynamical or non-equilibrium analog to temperature, this

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\* Temperature is an example of a control parameter, which is like a knob that one turns in an experiment hoping to produce a response in order to learn something about the system. Cranking up this particular control parameter introduces more noise into the system. Some readers may be familiar with entropy, which quantifies a system's degree of disorder by counting the number of microscopic configurations that give the same macroscopic state of the system. In equilibrium, there is a well-defined relationship between entropy and temperature, but this relationship does not hold away from equilibrium where temperature is not well defined. We could have constructed what is perhaps a more rigorous discussion of noise in both equilibrium and driven systems using the concept of entropy. Instead, we introduced the concept of dynamical temperature, extending what for many readers is the more familiar concept of temperature to non-equilibrium states. This has the additional benefit of making connections with other control parameters such as the Reynolds number ( $Re$ ) as well as the concept of phase transitions, which we discuss in the next section.

issue remains unresolved. However, in fluid dynamics the Reynolds number ( $Re$ ) quantifies how vigorous the fluid is mixing (30), and in a loose sense determines the dynamical temperature in hydrodynamic systems. We know from our experience that we must stir the fluid sufficiently hard to excite the vortex to form. Hence we use the term collective *excitation*. However, driving the fluid too vigorously, with a blender for example, would raise the  $Re$  number resulting in turbulent flow and destroy the organized structure of the vortex. This balance is key to the formation of collective modes and is explored in more detail in the next section.

What are dynamical solids, liquids, and gases?

Above we introduced the concept of dynamical temperature, which analogous to thermodynamic temperature quantifies the amount of randomness introduced into a system. Here we extend the temperature analogy further by introducing dynamical solid, liquid, and gas phases. First, let us remind ourselves how the traditional solid, liquid, and gas phases form in water (Fig 5). When the temperature drops below the freezing point and  $KT$  is significantly less the strength of the H-bond, the random motion of the molecules cannot overcome the attractive forces between the water molecules. The result is a phase transition, where the attractive forces align the molecules into an ordered crystal, called ice. Conversely, when the temperature is increased such that the thermal energy of the water molecules exceeds the attractive forces between them, water becomes a gas. Here the molecules scatter off each other and move in entirely random trajectories and the system exhibit no order. As we discussed above, when  $KT$  is comparable to the strength of the H-bond, water exists as a liquid.

We utilize two simple systems to demonstrate that analogous phases occur in dynamical systems (Fig. 5). The first is a soap film preparation developed by Martin et al (31). Here a thin soap film waterfall flows past a comb whose teeth are stuck into the film. As the fluid flows past the teeth, vortices are created similar to our bucket example in the previous section. Rather than stirring the liquid by moving an object in the fluid, vortices are created by moving the fluid past a stationary object. The other system is an example of what is known as a granular system, which in this case consists of a bucket of short metal rods. Instead of stirring the bucket, Blair and colleagues shake it on a vibrating table (32). Surprisingly, simple rods in a bucket also form vortices when agitated properly.

What happens to each system as we change the dynamical temperature, i.e. how fast the soap film flows ( $Re$ ), or how hard we shake the table? Each system undergoes a non-equilibrium phase transition, also called a bifurcation. At low temperature the attraction between units is strong compared to the noisy dynamics, and the system exhibits features analogous to a solid<sup>\*</sup>. In the case of the soap film we see repeating laminar streams of fluid analogous to ordered molecules in

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\* It is useful to introduce the concept of an order parameter, which quantifies how synchronized or orderly units are behaving as a population. A classic example of an order parameter is magnetization, which describes how many of the magnetic spins in a material point in the same direction. In the two non-equilibrium examples above the appropriate order parameters might be the extent of correlation among the velocities of the water molecules in the soap film, or how well aligned the rods in the bucket are. Similar to the magnetic system, cranking up the temperature or  $Re$  creates more noise and lowers the order parameter. However, one should not confuse the values that quantify the cause (control parameter that introduces noise) with those that quantify the effect (order parameter).

a crystal. In the case of the rods, we observe ordered crystalline domains analogous to a metal alloy. Conversely, if the system is driven too vigorously, random collisions will destroy any organization or structure, resulting in a chaotic gas-like phase. However there exists a “Goldilocks” region at intermediate temperature or  $Re$  where the noise and interaction strength are balanced. This is the vortex-rich state where complex, yet orderly structures tend to form. Notice that despite the fact that they are composed of very different individual units with different interactions, the two systems form similar collective modes under the right dynamical temperature. This again demonstrates the remarkable universality of collective modes. Of course, vortices are not the only collective excitations in nature as we explore below.

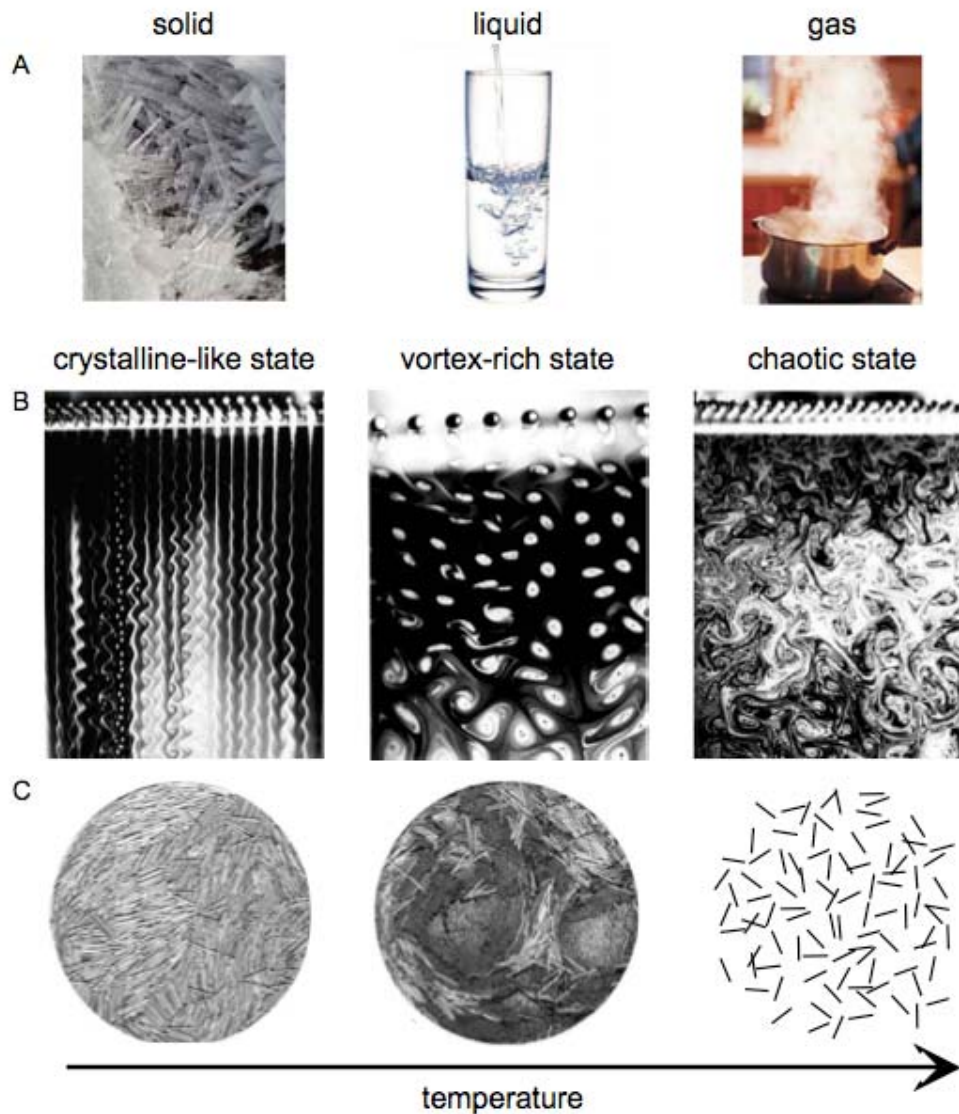


Figure 5 *Dynamical Temperature and Phases*. The different phases of water are depicted in **A**. As the temperature is increased, water changes from a periodic crystal or ice (33), to an intermediate liquid state (34), to a highly disordered gas phase (35). Analogous states exist in the nonequilibrium systems shown in **B** and **C**. In **B**, a thin soap film flows past the teeth of a comb (31). For low  $Re$  or dynamical temperature, synchronous periodic ripples are observed. As the  $Re$  increases more mixing between fluid elements takes place and complex yet ordered vortices form. Finally, at high  $Re$  these ordered structures break down resulting in a chaotic state analogous to a gas. Remarkably similar states can be observed in a vibrating bucket of metal rods (32), shown in **C**. At rest these rods align into a few preferred orientations similar to crystals. As the bucket shakes, noise is introduced into the system and vortices begin to form. Finally, a schematic of a chaotic gas-like state is depicted where the rods begin scattering off each other above the bucket, analogous to gaseous water molecules leaving the pot of water.

## Why did collective excitations evolve in biology?

Through time organisms have evolved to become more complex than their predecessors. The first life forms on earth were likely single self-replicating molecules. Later, single cell organisms similar to bacteria evolved. Assuming that they were similar to their present day relatives, they contained several hundreds to a few thousand genes. This eventually led the way to multicellular organisms with tens of thousands of genes and astronomical numbers of cells. For example humans have ~30,000 distinct genes and  $10^{14}$  cells [*please contribute references*].

In order to be successful, organisms must sense their surroundings, process the information, and plan and execute an appropriate response. This requires that different cells and genes interact with each other. For simple organisms this may have involved small networks that executed simple logic functions (36). An example of such logic might be if receptor *a* senses molecule *A* in the environment, and receptor *b* senses molecule *B*, then begin synthesis of a novel molecule *C* (AND logic). Through competition of resources, organisms evolved to process and respond to increasingly complex situations, requiring more processing units and exceeding the capacity of the small numbers of binary logic networks. This resulted in increasing numbers of molecules and cells, as well as a rapidly growing number of interactions between them to process this information. We know from the previous sections that if the number of interacting units is large, the system will synchronize or freeze unless noise is introduced into the system (link to seizures below). This is what occurs during traffic jams. Drivers typically have well defined behavior and strong interactions between them, such as rubbernecking or slowing down when you see break lights. This interaction far exceeds the noise, which is limited by the geometry of the road and our lawful behavior. As soon as the number of cars exceeds some critical number the system freezes. Completely frozen systems are stuck at a single point in configuration space, exhibit a single response regardless of the situation, and therefore have no information processing capacity. This is of minimal utility to biological systems, which must survive and adapt in rich and continuously changing environments. However, introducing too much noise can degrade the performance of a system, causing it to display unpredictable behavior. For example, sometimes an organism might decide that a plant or prey is poisonous and other times conclude that is delicious. Clearly, many situations require a well-defined response.

Thus, we hypothesize that nature has solved this complexity dilemma by utilizing large numbers of moderately noisy elements to construct collective modes to process information. Here collective modes, not individuals, are the relevant functional biological units. This approach has several advantages. Recall that collective modes are simply patterns that evolve with time. Each mode contains many units, and each unit can belong to multiple modes. This is in contrast to coding schemes that many biologists imagine, where nature simply averages over noisy units \*. This property allows collective modes to maintain much of the complexity inherent in the large number of individual units and their combinations, while avoiding synchrony. The system can still exhibit reliable behavior because each state of the system is represented by a region in phase space, called an attractor, rather than the state of single noisy unit (20). This also has the added advantage that should several units become damaged, the function often remains intact (Fig 6). Next, recall that collective modes are ubiquitous in nature, and emerge without detailed plans,

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\* This suboptimal solution involves taking a tally of the state of many noisy individuals, and implementing a winner take all approach. This eliminates mistakes by noisy components. However, all of the individuals act to execute a single function, acting as one unit and eliminating the advantage of multiple interacting individuals. In addition, the energetic cost of producing multiple noisy units is far greater than a single reliable one.

making it likely that such solutions could evolve spontaneously through natural selection \* (37). Lastly, the properties of attractors and their basins of attraction allow the system to respond spontaneously and appropriately to environmental changes without central oversight.



Figure 6 *Collective Modes are Resistant to Malfunctioning Units.* A radiological image of a patient as described in (38). “He aimed a shotgun toward his symptomatic right eye and fired. Noncontrasted brain CT demonstrated multiple metallic pellets... The patient survived and at discharge exhibited no significant neurologic deficit.”

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\* Stuart Kaufman also argues that systems that are on the “edge of chaos” are more easily optimized by evolution

## Brain Clouds

Does the brain have the necessary ingredients for collective excitations?

Recall our ingredients for collective modes include a non-equilibrium (driven) system containing a large number of interacting units, where the strength of the interactions is balanced sufficiently by noise. The human cortex contains approximately  $10^{10}$  neurons and  $10^{14}$  synaptic connections. In addition to the 20 billion neurons in the cortex, the cerebellum contains another 70 billion neurons (2). Although not as large as Avogadro's number, these are still astronomical numbers.

Like in many non-equilibrium systems, it is difficult to accurately quantify the balance between interaction strength and noise in the brain. Despite this, there is strong evidence that interactions between neurons in the brain are both weak and noisy\*. Neurons in the cortex and cerebellum are connected by a small number of synaptic contacts, often just one (12-14). The strength of these contacts is measured by the amplitude of the postsynaptic voltage, which is quite variable and typically around 1 mV. We can get a feel for this magnitude by comparing it to the threshold for firing, which is approximately 15 mV above the resting voltage. Depending on the cell type, the contribution from approximately 10 to 30 excitatory presynaptic cells must make simultaneous contributions for the postsynaptic cell to fire an action potential (39). This does not take into account inhibitory synaptic inputs that decrease the postsynaptic voltage, balancing excitatory inputs, and potentially quieting the cell†. Even without noise one might conclude that synaptic transmission is not a very strong interaction.

In addition to being weak, synaptic transmission is unreliable and thought to be the dominant source of noise in the brain (39, 40). There is good evidence that not all action potentials that reach the synaptic bouton result in neurotransmitter release, and that not all neurotransmitter release events are triggered by action potentials. It is thought that this unreliable release of neurotransmitter is due to the stochastic nature of vesicle fusion with the plasma membrane, where the probability of fusion is dependent on the internal  $\text{Ca}^{2+}$  concentration and the number of vesicles available for fusion (14, 41). When the cell is at rest and not firing action potentials, the intrasynaptic  $\text{Ca}^{2+}$  concentration is low. Despite being at rest, synaptic release of vesicles can occur with low probability in the absence of action potentials, which is known as spontaneous release (42). Upon arrival of the first action potential after the cell has been at rest for some time, the probability for vesicle fusion is only about 50% (14, 40). This value can decrease with the arrival of additional spikes (14) (Fig 7B). This occurs for two reasons: 1) the probability of release is proportional to the number of vesicles docked at the active zone (Fig. 7C) and 2) during activity vesicles at the active zone are depleted faster than they can be replaced from a reserve pool of vesicles. This results in a depletion of docked vesicles (also known as the readily releasable pool of vesicles) and a subsequent decrease in the probability of neurotransmitter

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\* We should note that much of what we describe here does not hold for the more evolutionary ancient structures of the nervous system, most notably the brain stem and peripheral nervous system. Nor does it hold for the neurons of evolutionarily primitive organisms that lack advanced structures such the cortex and cerebellum. Thus, we don't expect these systems to utilize collective excitations to code for information. For example, *C. Elegans* has exactly 108 neurons, with a well-defined wiring diagram that is identical in all members of the species. These synapses are significantly stronger and more reliable than the central synapses of the mammalian brain. This must be the case for the animal to exhibit reliable behavior with a sparse number of neurons

† However, the effect of inhibition is complex and may even promote synchrony (32).

release, which reaches a steady state value that depends on the stimulus frequency. Surprisingly, a sustained stimulus frequency of 10 Hz results in the transmission of only one in twenty action potentials to the postsynaptic cell. In addition, during activity some vesicle fusion events appear to have little correlation with the timing action potentials. This asynchronous release is yet another manifestation of noisy synaptic transmission (43-45).

There is evidence that the noisy synaptic transmission discussed above is not an inherent limitation that nature could not overcome, but that the machinery in the synapse evolved to be noisy (46, 47), perhaps for the reasons discussed previously (48). The extent of noise is remarkable and is a clue that neural coding is more complicated than the familiar digital coding schemes used in computers. We believe that the brain utilizes collective excitations as its principle computational unit, not individual neurons. We discuss this type of collective phenomenon below.

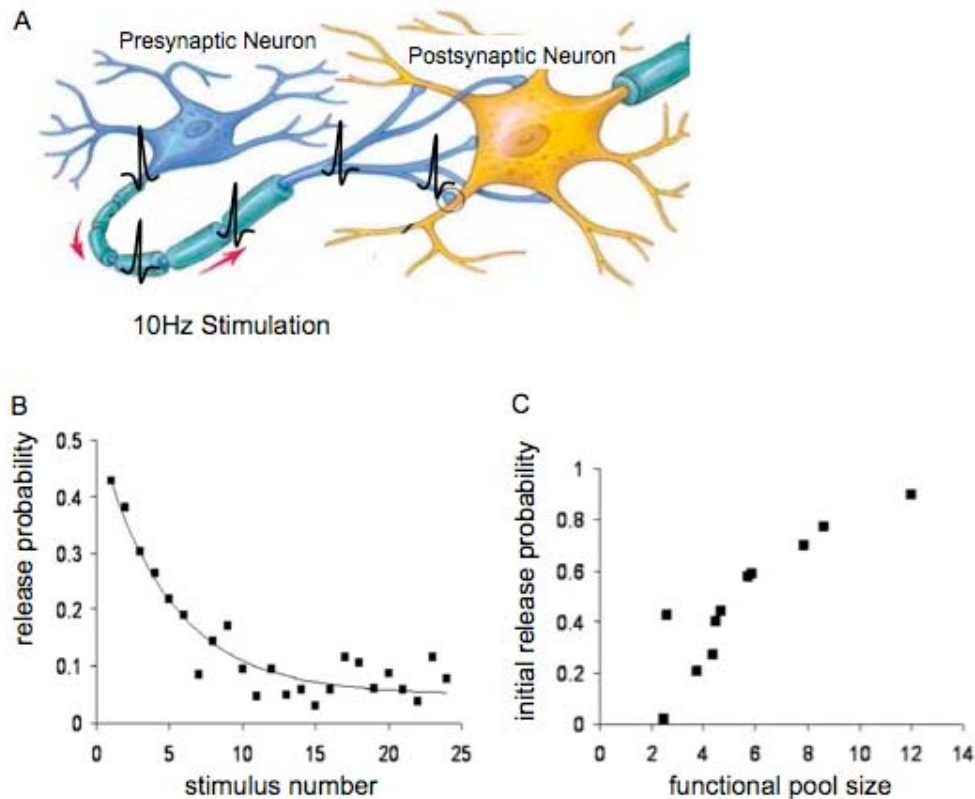


Figure 7 *The probability of neurotransmitter release decreases as docked vesicles are depleted.* **A** Axons from presynaptic neurons were minimally stimulated at 10 Hz by Dobrunz and Stevens (14), while excitatory currents in postsynaptic neurons were measured. **B** The probability of measuring a postsynaptic current, and thus neurotransmitter release, decreases exponentially with each electrical stimulus. In this example, the 15<sup>th</sup> stimulus marks the time where the probability decays by 3 decay constants or  $e^{-3} = 5\%$  of its original value. This empirically defines the point where one readily releasable pool worth of vesicles has been released. This pool is one of multiple functional vesicle pools hypothesized to exist in the synaptic bouton, and is conjectured to correspond to the number of anatomically docked vesicles. **C** By integrating the probability curve in **B** from 0 to where it falls to  $e^{-3}$ , one can measure the functional size of the readily releasable pool. This value is plotted for several synapses on the horizontal axis against the probability of measuring a response to the first stimulus. Notice that the initial probability of releasing neurotransmitter increases with the size of the readily releasable pool.

What are brain clouds?

If you were to zoom in you would see that ordinary clouds consist of countless numbers of ~10 micrometer sized water droplets. These particles are large enough to scatter sunlight giving them their milky white color, but small enough that they stay suspended in the air, being whipped about effortlessly by convective wind currents. Of course lying in the grass looking up at clouds in the sky provides a far more familiar perspective. Clouds can mimic countless numbers of intricate shapes that are so realistic that one might think they were composed (Fig 8). The girth of these majestic forms can rival mountains and are many orders of magnitude larger than the microscopic droplets that comprise them. Enamored by these clouds, we cannot help but stare at them only to find that they take on an entirely different form moments later. What seems to be disappointingly brief is still many orders of magnitude slower than the time over which the droplets' motion randomizes. These are among nature's most beautiful and popular collective modes, and serve as an elegant analogy to what might be occurring in the brain.

Think of the action potential as a particle. Actually, they are somewhat analogous to particles of light called photons. Photons, like action potentials, are traveling wave packets of electromagnetic energy. In addition, both photons and action potentials can be created and destroyed ("annihilated" in physics lingo). Action potentials are created when many postsynaptic voltages are integrated by the soma and their sum surpasses the voltage threshold for firing (3). These neuronal particles travel down the axon and duplicate as the axon bifurcates. Finally, the collection of particles arrives at their respective synapses, rarely onto the same postsynaptic cells, where they can stimulate a cascade of new particles to continue the journey. Alternatively, the particles can be destroyed either by failing to elicit vesicle fusion, or not arriving in concert with a sufficient number of other particles in the postsynaptic cell to cross the threshold. This analogy with particles is useful in that it motivates us to think about what are the free mean path and free mean time of action potentials (link). We show in the appendix that an action potential created in the soma triggers an action potential in only one of its  $10^4$  postsynaptic partners on average. The identity of this excited partner is far from predictable, and like an electron undergoing diffusion in a light bulb filament, the path of our neuronal particle resembles a biased random walk. Each postsynaptic action potential is like a collision, scattering the particle in a random direction. Recall for diffusing particles the free mean time (path) is the typical time (distance) between collisions. For our neuronal particles this would be the time between subsequent action potentials in cells separated by a single synapse, which is on the order of 10 ms. The free mean path is the typical distance that an action potential travels before encountering the postsynaptic cell. The majority of connections are made locally, but detailed data describing the statistics of axon lengths in the brain is limited. *[please contribute references]*

We argue that like ordinary clouds there exist slow large-scale collective modes in the brain. Instead of containing water droplets or molecules, these collective modes are spatial temporal patterns of neuronal particles or action potentials. How slow (large) are these neuronal excitations? Significantly slower (larger) than the mean free time (path) of action potentials, namely much longer than 10 ms (*unknown*). Like clouds, we speculate that the brain has a rich repertoire of spatial temporal patterns that can code for an enumerable number of situations, which is essential for biological computations. Just as it does not make sense to ask what is the temperature of a single molecule, it likely does not make sense to ask what information does a single neuron or a spike code for? Rather, we believe that this is the property of collective neuronal excitations, which we call brain clouds.

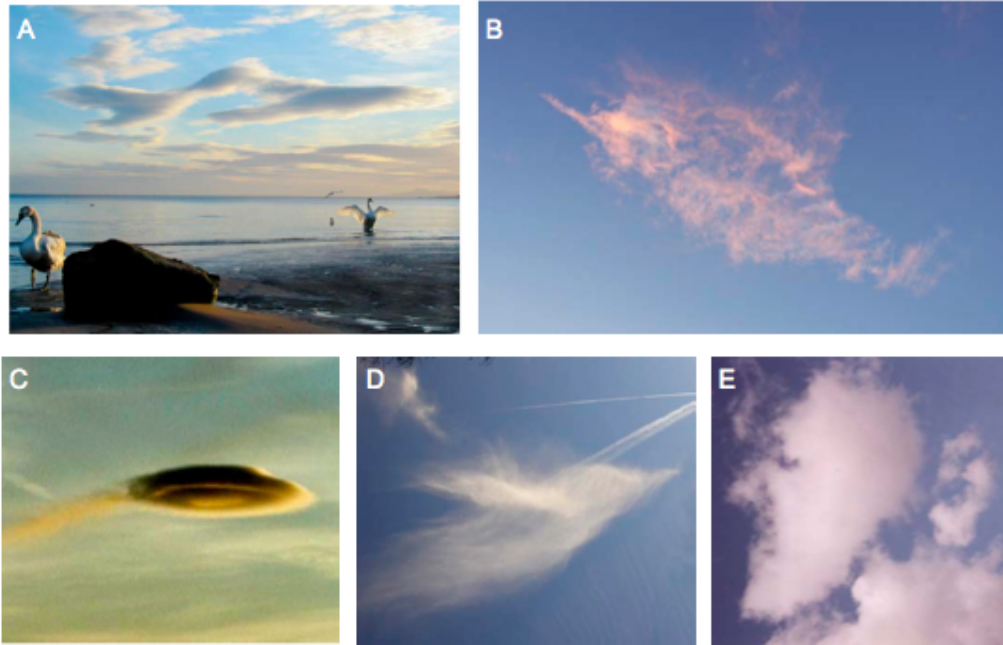


Figure 8 *Clouds can take on a vast number of shapes.* Photos taken by various members of the Cloud Appreciation Society (49). **A** Swan taken by Brett Meikle. **B** Swordfish taken by Ken Fung. **C** Flying Saucer taken by Bob Askew. **D** Humming Bird taken John A. Adam. **E** Face taken by Michael Poole.

Is epilepsy a disease of pathological brain clouds?

Clearly, if brain clouds are the functional units of the brain, then many disorders of thought and cognition from schizophrenia to Alzheimer's might some day be understood in terms of the abnormal function of neuronal collective excitations. However, the study of collective modes may have the most immediate impact on our understanding of seizures and epilepsy. Seizure is the state of abnormal synchronous neuronal firing (50). It can begin in a localized region of the brain and can spread to involve the entire cortex, which contains approximately  $10^{10}$  neurons. During these episodes patients can have severe impairment or loss of consciousness. Figure 9 shows a recording of the electrical activity or electroencephalogram (EEG) of the scalp of a patient experiencing a seizure. Notice the widespread synchronized oscillating electrical signal is reminiscent of the streams of fluid observed in the low temperature state of the soap film. We hypothesize that seizure is the low temperature state of neuronal networks (51). Despite the fact that synapses likely evolved to avoid these neurological traffic jams, seizures still afflict about 1% of humans.

Although we don't know the cause of seizures, the ingredients necessary for collective excitations points us in the right direction. As discussed above, synchrony is inevitable when large collections of reliable units interact. By making synapses unreliable and weak, evolution was able to balance these interactions and avoid synchrony. It is this balance between the strength of neuronal interactions and noise that is likely to be disrupted in patients with seizure.

There are several possible mechanisms for this loss of balance. This is perhaps the reason why seizures can be elicited in laboratory animals using different agents and techniques and occur in patients in a variety of clinical settings (7, 52, 53). Enhanced excitatory drive itself can result from a number of mechanisms including increased neurotransmitter release, increased receptor density, or altered channel conductance (at the synapse and along dendrites). These effects can enhance the amplitude of the excitatory postsynaptic voltage and hence strengthen the interaction between neurons. Glial cells may also be involved by either directly stimulating neurons via neurotransmitter as well as being involved in the modification of neuronal synapses (54, 55). In addition, any mechanism that decreases inhibitory synaptic contributions can potentially strengthen the interactions between neurons. For example, the primary effect of anti-seizure medications such as barbiturates and benzodiazepines is to enhance inhibitory synaptic transmission. Lastly, decreasing the excitability of the neuronal membrane or altering the threshold potential effectively alters the strength of neuronal coupling as well. This is likely the mechanism underlying the anticonvulsant properties of several medications including of phenytoin, lamotrigine, and carbamazepine.

While all the above mechanisms are feasible and actively being explored, little attention has been given to the role of neuronal noise in seizures. Any mechanism that decreases this noise pushes the system toward synchrony (Fig. 9). As we discussed above the primary source for noise in the brain is unreliable synaptic transmission. Vesicle fusion is a  $\text{Ca}^{++}$  dependent stochastic process that involves dozens of proteins. There is evidence that the structural protein actin actually inhibits neurotransmitter release, and that chemicals that depolymerize actin increase the probability of neurotransmitter release (47). One can imagine that actin or other proteins involved in maintaining unreliable vesicle fusion could be altered in some forms of epilepsy. Alternatively, the mechanisms that regulate the availability of vesicles have a significant impact on the reliability of neurotransmitter release. Studies show that proteins in the bouton actually hinder rather than accelerate the movement of reserve vesicles to the active zone (46, 56). Mutations or pharmacological alterations in these proteins could make the brain more susceptible to seizure and may be involved in epilepsy (57). Interestingly, it was recently discovered that the target of

the antiepileptic drug Levetiracetam is the vesicle protein SV2A (58). The function of this protein is not well understood, and it would be interesting to explore if SV2A is involved in the trafficking of synaptic vesicles.

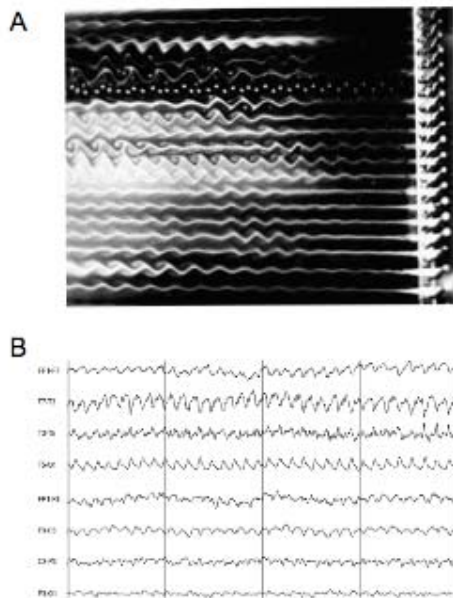


Figure 9 *Seizure is a low temperature state.* **A** Image of the same thin flowing soap film displayed in 5B, turned on its side, demonstrating synchronous periodic ripples at low Re number or dynamical temperature. **B** Four seconds of EEG recorded from a patient experiencing a seizure (courtesy of Dr. Mark Scheuer). Notice that the electrical activity appears as synchronous periodic waves analogous to the low temperature state in A.

What empirical evidence do we have that brain clouds exist?

While photons reach our retina at the speed of light and our optic nerve conducts visual information to the brain in tens of milliseconds, it takes on the order of hundreds of milliseconds to seconds for the brain to form perceptions. The slower extreme of this spectrum is highlighted by simple experiments where human subjects are asked to look at ambiguous stimuli. The Necker cube is a classic example and is demonstrated in Figure 10. The visual stimulus is a two-dimensional schematic of a cube that has two possible orientations. Typically, only one orientation is perceived at a time and one's perception of the cube flips spontaneously. However, the typical timescale for switching is on the order of seconds (59). While there are certain states in the neurons such as molecular phosphorylation cascades that can take on the order of seconds, this phenomenon is unlikely to be explained on the single neuron level. We hypothesize that the neurological basis for these long-lived perceptions are collective neuronal excitations or brain clouds. As described above these are long-lived states, much longer than the microscopic time scales of action potentials that are often implicated in the coding of information in the brain.

In addition to being long-lived, brain clouds are large excitations. Evidence for large-scale excitations for even simple sensory stimuli are shown Figure 11 (60). Here an elementary movement of a single rat whisker results in excitation of not only the contralateral (opposite side) primary sensory cortex as expected, but also spreads to the motor and other areas of the contralateral cortex. Interestingly, this simple sensory stimulus also results in activation of the ipsilateral (same side) cortex. It remains unclear how these temporal-spatial patterns of neuronal activity code for whisker position and related sensory information.

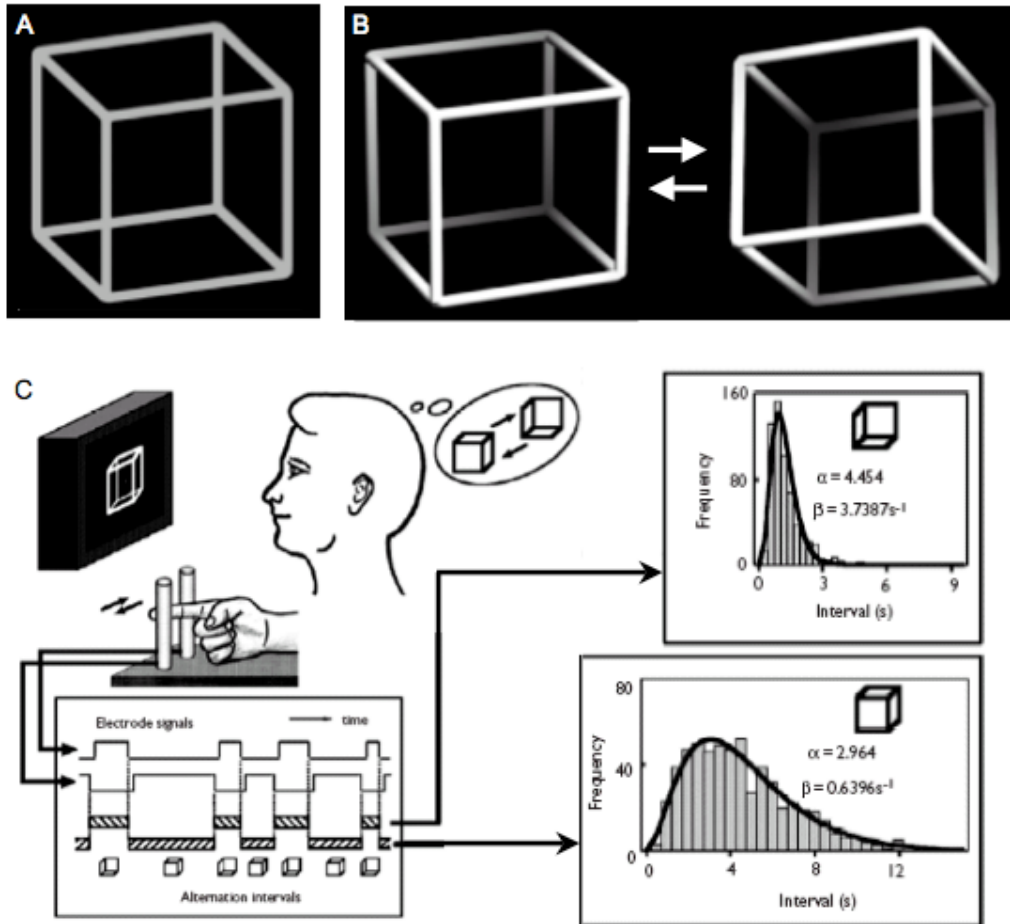


Figure 10 *Evidence for long-lived perceptual states in humans.* **A** Schematic of a Necker cube adapted from Murata et al. (59). This two-dimensional drawing has two possible three-dimensional interpretations as depicted in **B**. **C** Experiments using human subjects that report what they perceive by touching one of two electrodes show that their perception of the cube switches randomly between the two interpretations with a characteristic time scale of seconds, and is governed by a well known probability distribution.

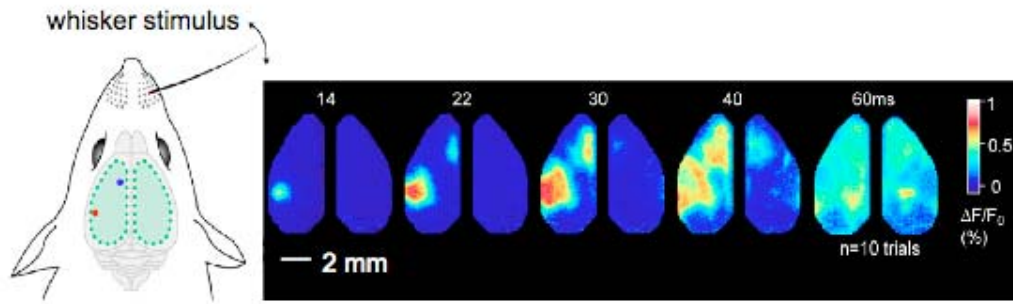


Figure 11 *Large-scale neuronal excitations are elicited for even simple stimuli.* A schematic demonstrating the sensory stimuli used in experiments by Ferezou et al. (60) is shown on the left. Here a single whisker on the right side of the face of the mouse is deflected. This results in large areas of the mouse cortex being excited as seen on the right. Here the neuronal activity is proportional to the fluorescence intensity emitted from voltage sensitive dyes imbedded in the neurons.

What is the role of brain clouds in perception?

Consider the task of identifying a predator such as a lion. Although unlikely, assume that there are neurons that fire in response to particular features of the lion. For example, let us assume that there is a neuron that fires when whiskers are observed, and another for the mane, and yet another for paws, etc. Together the activity of these neurons can be represented by a point in phase space (20). If the visual stimulus is such that the position of the system in phase space lies within the basin of attraction for the lion attractor, then the trajectory will be pulled into that attractor (Fig. 12A). Thus, the image of the lion will excite the proper collective mode that corresponds to that perception.

The trick of course is to set up phase space to have the proper topology, where points in phase space corresponding to stimuli from different perceptions land in the basins of attraction for the correct collective mode (Fig. 12B). It is the interactions between particles that determine how points in phase space evolve. Recall, that learning is thought to be the optimization of synaptic strengths with experience. Thus, much of the learning involves adjusting the strengths of synapses, called synaptic plasticity, so that different stimuli can be properly classified. This process not only shapes the basins of attraction, but also likely the collective modes themselves in order to optimize this task. Although we know much about synaptic plasticity on the level of the individual synapses (7, 8, 61), we are far from a complete picture of how large collections of neurons adjust the population of synaptic strengths to achieve the goal above [Hopfield or Reinhart and McClelland references].

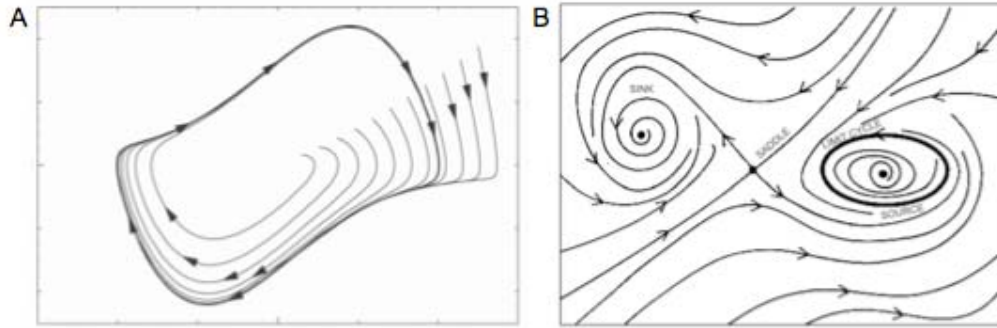


Figure 12 *Attractors have a basin of attraction that traps nearby trajectories. A* A phase diagram of a limit cycle adapted from (62), where nearby trajectories both inside and outside the cycle gravitate to the attractor. Once on the limit cycle attractor, trajectories never escape and move about the cycle indefinitely. *B* An example of a phase diagram containing multiple attractors and their basins of attraction (63). The initial conditions, i.e. where the trajectory starts in phase space determines the final state of the system. Attractor neural networks model sensory stimulus as an initial point in phase space, and each attractor as a different perception.

Can brain clouds form hierarchical networks?

One deficiency with the above description is that it does not explain how the features themselves are properly identified. For example, how does the brain know that we are looking at whiskers? One might conjecture that these features are themselves perceptions with corresponding collective modes that becomes excited via the mechanism described above. This of course begs the question: how are the features that are essential to whiskers like their white color and linear shape coded? Are there collective modes for those as well? If so, how do they interact with each other to produce the ultimate perception of the lion?

As we discuss above collective modes take on their own identity. Their emergent properties do not prevent them from interacting with each other as cohesive units. Just as vortices can scatter of each other and exchange momentum, brain clouds can act as modular units combining to perform higher order computations and coding. In fact, one can imagine collective excitations of collective excitations (see Figure 3D). This is likely the case for more complicated perceptions such as the lion. Collective modes representing whiskers, paws, and manes are the individual units that make up the higher order collective mode that represents the lion.

Clearly, a hierarchical theory of perception is an oversimplified view, and other key processes must be involved in perception (50, 64, 65). As is often the case with simple theories, the brain cloud hierarchy hypothesis stimulates more questions than it answers. We pose a few of these questions below, and pose even fewer answers.

Where does the cascade of brain clouds terminate?

Once again, the answer likely lies in the physiology of synapses. Recall that collective modes require large numbers of moderately noisy interacting elements. Compared to the cortex, the peripheral nervous system emerged earlier in the evolution of multicellular organisms. Accordingly, synapses of the peripheral nervous system are considerably stronger and more reliable than their counterparts in the cortex and cerebellum (12, 13) [*please contribute peripheral synapse references*]. For example, some simple reflexes are mediated by a single spinal cord synapse, which are both fast and reliable. In vision, photons of light are not represented by collective excitations of photoreceptors in the retina. Rather, each photoreceptor can sense as few as a single photon and subsequently excite nearby neurons. The retina contains a few neuronal layers that process this input, eventually sending information about contrast at each location in the visual field along the optic nerve to other areas of the brain. However, because the numbers of neurons per visual area or receptive field is small \* and their interactions are strong, this information is unlikely to be coded for by collective excitations. We hypothesize that as sensory information is propagated to other parts of the brain and higher order features are extracted, a transition in coding schemes occurs. This transition parallels the change that occurred in evolution discussed above (link), where complex features became coded by collective excitations of action potentials rather than action potentials themselves. Whether this transition is abrupt and where its exact location is in the cascade of sensory formation is not know.

How do brain clouds code for time varying stimuli?

Recall that brain clouds contain both spatial and temporal components and therefore in principle have the capacity to code for time varying information. For example, how do brain clouds code for a musical melody or speech? There exists no satisfactory answer to this question and a review of the literature on this topic is beyond the scope of this introduction. We leave the interested reader to explore alone with some suggested references as a guide [*please contribute references*].

How does attention shape brain cloud formation?

Count the number of times the letter F appears in the following passage.

FINISHED FILES ARE THE  
RESULT OF YEARS OF SCIENTIFIC  
STUDY COMBINED WITH THE  
EXPERIENCE OF YEARS.

There are six 'F's. Those who have not seen this demonstration before often skip the 'F's in the three instances of the word "OF" above. This example is illustrative of the way attention affects our perceptions. Typically, we do not identify or even see individual letters when we read words. The word seems to take on an identity of its own, appearing as an identifiable pattern somewhat independent of the letters that comprise it. This transition of viewing the word as a collection of individual letters to an identifiable pattern is illustrative of the consolidation that occurs during

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\* Receptive fields as small as 10 um in width were measured near the fovea of the monkey retina [*need concrete reference*]. This corresponds to the diameter of a single cell body. The retina has a thickness of a few hundred microns. Assuming the cells are closed packed, this gives an estimate of a few dozen cells per receptive field.

learning. One might even guess that a child who is still learning to read might perform better at the counting task above than a mature reader. This phenomenon motivates a set of interesting questions:

- 1) Does there exist a hierarchy of brain clouds for reading? For example are there brain clouds that code for letters, while words are represented by higher order collective modes?
- 2) If so, are the brain clouds for the individual letters excited during reading, but somehow do not result in our awareness of the letters that they code for?
- 3) Alternatively, if brain clouds representing letters are not excited while reading, how do we switch back and forth between reading and letter counting?
- 4) How is the hierarchy of brain clouds modified to optimize reading?

The physics of attractors inspires another related question regarding brain clouds and attention. Attractors are typically stable structures, where trajectories are trapped in a region of phase space once they enter. In order to code for a new perception, the system must be perturbed to move to another basin of attraction. This occurs if the environmental stimulus changes and moves the system to a different region of phase space. However, what happens if the stimulus doesn't change? Is the brain frozen in the last attractor? What happens if the stimulus changes while we are still actively perceiving the scene? How do we maintain the perception and the corresponding brain clouds as we are being bombarded by other stimuli, referred to as the cocktail party effect? The answer to these questions and those above likely lies in the mechanism of attention. Are there internal timing mechanisms that gate our perception and mark the start and end of brain cloud formation and break up the world into discrete time windows for perception (50)? How do we shield brain clouds from distracting sensory inputs during these time windows? These are key questions that must be addressed if the hierarchal picture of perception is to be fully understood.

How can we approach the study of brain clouds?

Imagine you are an alien with exquisite vision but no auditory sensation, and you are sent to Earth to study human beings. One of the first things you notice is that they can communicate through relatively long distances without looking at each other, via a seemingly empty space. Being the intelligent intergalactic traveler that you are, you realize that the space between them is not vacant, but is filled with a gas that must be transmitting their messages. You zoom in and start to track individual air molecules. You find that each appears to changing directions every  $\sim 10^{-15}$  seconds. They scatter off each other and move in random directions, even when the creatures' lips appear to be communicating the same message repeatedly. How can these seemingly random molecules that never seem to get anywhere be transmitting anything useful? Then you step back and observe the collection of air molecules at a distance. There are slower patterns of large density waves containing uncountable number of molecules that travel between the humans. You realize that these collective modes, which we know as sounds waves, are the relevant structures for communication, not the individual molecules.

This approach lies at the heart of what is known as soft condensed matter physics, a branch of physics that studies a variety of phenomenon in fluids and gels. This approach is known as the hydrodynamic method, which was described by Harald Pleiner as:

*“The hydrodynamic method is based on the observation that in most condensed systems there is only a small number of slow, long living (and long wavelength) processes compared to the huge number of fast, microscopic degrees of freedom, which can be discarded in a description of the macroscopic behavior”.*

The experience of the neuroscientist is much like that of the alien, frustrated and confused by the noisy behavior of individual neurons. To make significant progress, we believe that one should take a hydrodynamic approach to the brain, focusing on collective neuronal excitations.

While hydrodynamic theories are macroscopic, they are built on statistical descriptions that require experimental observations of large numbers of individual units, as well as coarse-grained measurements at a variety of spatial scales. For neuroscience, this poses significant technical challenges. We describe the experimental approaches and techniques that ICNDE has planned to address some of these challenges in the next chapter ([link](#)).

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