TOWARDS PLASMA-LIKE COLLISIONLESS TRAJECTORIES IN THE BRAIN

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ABSTRACT

Plasma studies depict collisionless, collective movements of charged particles. In touch with these concepts, originally developed in the far flung branch of high energy physics, here we evaluate the role of collective behaviors and longrange functional couplings in brain dynamics. We develop a novel, empirically testable, brain model which takes into account collisionless movements of charged particles in a system, the brain, equipped with oscillations. The model is cast in a mathematical fashion with the potential of being operationalized, because it can be assessed in terms of McKean-Vlasov equations, derived from the classical Vlasov equations for plasma. We also provide insights into the possible role of the overrated extracellular neuronal space in generating and transporting the charged particles which display such a collective behavior. A plasma-like brain also elucidates cortical phase transitions in the context of a brain at the edge of chaos and describes the required order parameters. In sum, showing how the brain might exhibit plasma-like features we go through the emerging concept of holistic behavior of nervous functions.

Plasma, the fourth state of matter in addition to gas, fluid and solid, is an electrically neutral medium, where the overall movements of unbound positive- and negative-charged particles are due to long-range electromagnetic forces able to keep the system globally neutral (Sturrock, 1994). In the short length of dozens of microns (a distance called Devbe length), the particles are subject to Ohmic interactions. Otherwise, when plasma dimensions are much bigger than the Devbe length and the movements occur outside the corresponding Devbe sphere, electrons and ions move in guise of a unique body, giving rise to collective motions and an electric field called ambipolar. When charges move, they generate electric currents equipped with magnetic fields and, as a result, they are affected by each other's fields. This governs their collective behavior and many degrees of freedom (Figure 1). Such collective motions are described by the Vlasov equation, i.e., a differential equation assessing time evolution of distribution function of a plasma consisting of charged particles with long-range interactions. Vlasov (1938) modified the collisionless Boltmann equation and, by linking the distribution functions for electrons and positive ions, introduced a novel equation describing time evolution of the plasma distribution function. Such differential operators could be also described in curvilinear coordinates, such as cylindrical, or spherical (Goldston and Rutherford, 1995), or toroidal. Classically used for the description of plasma dynamics, collisionless medium behavior is a common feature of many dynamical systems and can be assessed in terms of the so called McKean-Vlasov equations, derived from Vlasov equations for plasma (Kotelenez and Kurtz 2010). A fully Lagrangian approach to collisionless continuity equations has been recently introduced too (Osiptsov and Rybdylova, 2011). Such equations describe countless dynamical systems, from aircraft motion in dusty atmosphere, to condensation in near-sonic flows, from dust explosions in coal mines, to needle-free delivery of powder drugs, from hypersonic gas flows to large scale mass distribution in the Universe, from traffic jams to flock of birds (Osiptsov and Rybdylova, 2011; De Buyl et al., 2011).

The *plasma-like* concept of dynamical systems' collisionless collective behavior might be used also for the description of brain functions. Here we show how nervous activity displays collective behaviors and long-range connections. We also provide a model cast in a mathematical fashion which is operationally assessed and empirically testable.

Furthermore, Vlasov equations are able to predict features of nonlinear systems. It allows us to describe, in a brain at the edge of chaos, collective nervous dynamics in terms of bifurcations and the corresponding order parameters. We also provide insights into the possible role of the extracellular neuronal space in generating and transporting charged particles, which follow trajectories displaying such a collective behavior.



Figure 1. Examples of different trajectories of collisionless particles' collective movements in plasma (Modified from Cheng and Gamba 2012). A slight change in just one or two parameters may give rise to completely different patterns.

PLASMA-LIKE FLUXES IN BRAIN: THE RATIONALE

In the true plasma, the particles' collective behavior is governed by: a) the reciprocal influences among the nearby charged particles embedded in a Debye sphere, and b) by the plasma parameter lambda, e.g., the average number of particles in the sphere. The spontaneous formation of spatial features takes place on a wide range of length scales, on the boundary of a metastable state. We would not call brain function with the term *plasma*, but we will use instead the term *plasma-like*. The reason of our terminological choice is that, in true plasma, long-range correlations are preserved in order to avoid the large, disruptive electromagnetic fields which develop in presence of net charge. Instead, in brain we are in front of nearly neutral charges, e.g., a quasi-neutral state with slow to moderate electromagnetic fields and forces. Nevertheless, a similitude between brain and plasma collective dynamics is feasible, because, on temporal scales slower than plasma frequencies (about 10^{11} Hz) and at room temperature, plasma may be thought as a neutral fluid in which spontaneous electric fields are null. This description fits with the features of human brain, that is equipped with a ratio between excitatory and inhibitory neurons collectively equaling the zero (Haider et al., 2006; Lombardi et al, 2012; Xue et al, 2014) and with long-range correlations. Experimental and theoretical clues allow us to conjecture that collisionless particles movements occur in the brain and that some nervous activities could be mediated by long-range extracellular flows (Linkenkaer-Hansen et al, 2001; Vuksanovic and Hövel, 2014). It has been proposed that fluxes occurring in the complex intracellular web of molecular interactions could represent a universal feature of metabolic activity in living cells (Almaas et al, 2016). By implementing a flux balance analysis of the metabolism of an Escherichia coli strain, Almaas et al. (2016) showed that, whereas most metabolic reactions have low fluxes, the overall activity of the metabolism is dominated by reactions characterized by very high fluxes. Cells respond to changes in growth conditions by reorganizing the rates of selected fluxes, predominantly within such a high-flux backbone. Li et al. (2015) suggested the presence of specific band-limited mechanisms of interregional oxygen correlation, driven by rhythmic or pseudo-oscillatory mechanisms. Traveling waves in humans may underlie processes involved in cortical activity's global coordination. For example, Alexander et al. (2016) evaluated whole head MEG, recorded during an observer-triggered apparent motion task. Episodes of globally coherent activity occurred in the delta, theta, alpha and beta bands of the signal in the form of large-scale waves, which propagated with a variety of velocities. Their mean speed at each frequency band was proportional to temporal frequency, giving a range of 0.06 to 4.0 m/s, from delta to beta. The wave peaks moved over the entire measurement array, during both ongoing activity and task-relevant intervals. Direction of motion was more predictable during the latter. It means that a large proportion of the cortical signal measurable at the scalp occurs as large-scale coherent motion. (Alexander et al., 2016).

Equations describing collisionless movements have been already used in the evaluation of large neuronal networks. Taking into account nets' specificity, topology, spatial extension and resulting space-dependent delays, Touboul (2012) developed a neural model based on stochastic analysis methods. He analyzed the collective behavior of mean-field limits of large-scale, spatially extended stochastic neuronal networks with delays. He assessed networks of firing-rate neurons, equipped with linear intrinsic dynamics and sigmoidal interactions. The asymptotic regime of such systems is characterized by integral-differential McKean-Vlasov equations. The latter are similar to usual neural field equations, but, because they incorporate noise levels as a parameter, they allow analysis of noise-induced transitions (Touboul, 2012). Deriving tractable reduced equations of biological neural networks in order of capturing the macroscopic dynamics of neuronal sub-populations has been a long-standing problem in computational neuroscience. Delarue et al. (2015) proposed a reduction of large-scale multi-population stochastic networks, based on the mean-field theory. They investigated the well-posedness of a networked integrate-and fire model describing an infinite population of neurons which interact with one another through their common statistical distribution. Inglis and Talay (2015) evaluated the convergence of a stochastic particle system that interacts through threshold hitting times towards a novel equation of McKean- Vlasov type. In this novel neurons' network model, a classical noisy integrate-and-fire model is coupled with a cable equation, in order to describe the dendritic structure of each neuron (Inglis and Talay, 2015). Furthermore, Galtier and Touboul (2013) derived, for a wide class of spiking neuron models, a system of differential equations of the type of the usual Wilson-Cowan systems. This system describes the macroscopic activity of populations, under the assumption that synaptic integration is linear with random coefficients. Simulations of the reduced model showed a clear-cut agreement with real networks' macroscopic dynamics (Galtier and Touboul, 2013). In our paper, we will make a slightly different use of the McKean-Vlasov type equations, because they will be encompassed in a more general context: a brain function independent from subtending networks or large neural assemblies.

THE ROLE OF EXTRACELLULAR CURRENTS

We hypothesize that the extracellular electromagnetic fields and currents generated by cortical neuronal spikes and other sources could be equipped with Vlasov-like, collisionless interactions. Such long-range interactions stand for an electrically quasi-neutral brain medium of unbound positive and negative particles. Classically, the relationship between an extracellular potential V_e (measured in Volts) and the current source density (measured in A m⁻²) at a

particular point of brain tissue is given by the Maxwell and Laplace equations (Buszaki et al., 2012). It is believed that multiple currents and sources combine linearly by the superimposition principle. However, if we take into account a plasma-like brain, the classical Ohmic equations are valid just in the narrow spatial limits of the Debye length, while, at a distance >>>Debye sphere, the time evolution of the charged particles' distribution function is not anymore Maxwellian. Long-range interactions take place, which can be mathematically evaluated in terms of collisionless equations. Indeed, a self-consistent collective electromagnetic field is produced by the charged ions, so that the time evolution of long-range interactions among particles could be described by the Vlasov-Maxwell system of equations. In order to evaluate brain functions in a plasma-like context, we need to remove, from the classical Vlasov equation for highly charged plasma, the useless (in our context) term which describes the distribution function for electrons, and to leave just the one for ions. In such a way, we are allowed to describe the dynamics of a brain in guise of a system of charged particles that interact with an electromagnetic field, e.g., the cortical spikes. Concerning the feasible brain counterparts, the proper candidate arises naturally: the nervous extracellular spaces. The extracellular space contains interstitial fluid in contact with cerebrospinal fluid from the ventricular surfaces (Syková and Nicholson, 2008). Within the extracellular spaces, the dominant mechanism of molecular transport is diffusion, constrained by the compartment The brain acts like a porous medium for substances that do not cross cellular boundaries. This geometry. characterization allows the application of well-established diffusion theory already developed in other disciplines. With a suitable statistical treatment, the behavior of a large ensemble of random walks can be described by the equations of macroscopic diffusion. Therefore, a modified diffusion equation could describe the collective trajectories of molecules in the brain (Syková and Nicholson, 2008).

Two extracellular parameters. Extracellular ions concentration dynamics depend not only on transmembrane ionic sources, but also on ionic diffusion along extracellular concentration gradients (Halnes et al. 2015). The contributors to extracellular fields, e.g, the potential generated in the extracellular medium, are numerous: from synaptic activity to fast action potentials, which give rise to the strongest currents; from long-lasting, non-synaptic calcium spikes to intrinsic currents and intrinsic resonance, from spike after hyperpolarization to hyperpolarized down states; from gap junctions, neuron-glia interactions and vascular events, to ephaptic coupling and glial buffering (Wu and Shuai, 2015). Another important factor playing a role in extracellular fields is the nervous geometry and architecture, including the neurons spatial alignment (Buszaki et al, 2012). In particular, diffusion of molecules in brain extracellular space is constrained by two macroscopic parameters, e.g., volume fraction α and tortuosity factor λ (Chen and Nicholson, 2000). The extracellular volume/total tissue volume, e.g., the so called cortical interstitial volume fraction α , has been evaluated to be between 13% and 30% in normal adult brain tissue, with a typical value of 20% which increases to 22% and 24% in sleeping or anesthetized mice and falls to 5% during global ischemia (Xie et al. 2016; Syková et al. 1999). In a free medium, such as an aqueous solution or very dilute gel, $\alpha = 1$. In other disciplines, volume fraction stands for *porosity* (Syková and Nicholson, 2008). The tortuosity of the interstitial space is described by the dimensionless parameter tortuosity $\lambda = (D/D^*)^{1/2}$, where D is the free diffusion coefficient. The magnitude of D* (D* < D) reflects the hindrance imposed by the path geometry and the interactions with the matrix (Nicholson et al., 2011). The λ value is in the range of 1.3–1.8. It has been suggested that plastic *brain compartments* can be detected in the central nervous system, based on the astrocyte brain volume's three-dimensional tiling and on the existence of local differences in cell types and extracellular space fluid and extracellular matrix composition (Marcoli et al, 2015). The development of local voids, e.g., the synaptic gaps able to increase the tortuosity of the extracellular space, is achieved through the plastic structures of the perisynaptic astrocyte processes. The latter are able to modify their morphology within minutes, thus modifying their coverage of pre- and post-synaptic elements (Bernardinelli et al., 2014).

Recent data suggest that extracellular flows are good candidates for collisionless movements in the brain. It has been proposed that the extracellular space and matrix are the main players in the intercellular communication in nervous networks. Indeed, the latter depends not only on wired communication channels, such as chemical/electrical synapses and ephaptic transmission, but also on diffusion of signals in extracellular spaces (Marcoli et al, 2015; Tozzi, 2015). Therefore, liquids such as extracellular fluid, cerebro-spinal fluid and blood, have a role in handling information through a so called *volume transmission mode* (Agnati et al., 2010), characterized by the diffusion of signals in physically poorly delimited extracellular pathways. Signals are transported by diffusion and convection along energy gradients, allowing a widespread intercellular communication that occurs through the meshes of the extracellular matrix and the cerebrospinal fluid (Agnati and Fuxe, 2000). Theoretical studies elucidated how, contrary to the common belief, diffusive currents are of comparable magnitude with Ohmic currents and their apport must not be neglected. Sustained periods of neuronal output up to 84 seconds modify local extracellular ion concentration by several mM (Halnes et al. 2015). Furthermore, the quite slow diffusive currents could induce local changes in the extracellular potential, in the order of a few tens mV. In neurophysiological studies, extracellular signals - as measured by local field potentials (LFP) or electroencephalography - are of foremost importance. Pods et al., (2013) introduced a threedimensional model exploiting the cylinder symmetry of a single axon embedded in extracellular fluid, based on the Poisson-Nernst-Planck equations of electrodiffusion. The propagation of an action potential along the axonal membrane was investigated by means of numerical simulations. Special attention was paid to the Debye layer, the region with strong concentration gradients close to the membrane. They focused on the evolution of the extracellular electric potential and found a peculiar up-down-up LFP waveform in the far-field. This electrodiffusion model showed another signal component stemming directly from the intracellular electric field. Depending on the neuronal configuration, this might have a significant effect on the LFP (Pods et al., 2013).

The well-known changes in extracellular space diffusion parameters could affect the movement and accumulation of neuroactive substances and thus impact upon neuron–glia communication, synaptic and extra-synaptic transmission. (Syková et al. 1999). Changes in extracellular space volume and/or geometry may affect the clearance of metabolites and toxic products and impact upon the diffusion of neuroactive substances, leading to changes in synaptic and extra-synaptic transmission, neuron–glia communication and ionic homeostasis. Recent studies in brain slices show that, when osmolarity is reduced, λ increases and α decreases. In contrast, when osmolarity increases, α increases, but λ attains a plateau. The latter is easily explained, when we take into account that the brain cells' shapes change non-uniformly during the shrinking or swelling induced by osmotic challenge. The non-uniform cellular shrinkage produces residual extracellular space that temporarily traps diffusing molecules, thus slowing macroscopic diffusion. (Chen and Nicholson, 2000). Pan et al. (2014) confirmed, through microelectrode arrays recordings in cultured neurons, that extracellular action potentials' signal amplitude depends on the impedance of micro-tunnels.

BUILDING A PLASMA-LIKE MODEL FOR BRAIN ACTIVITY

Here we introduce modified Vlasov equations lacking its *classical* term of free electrons. The so-called McKean-Vlasov equations display other moments, instead of the mean charge such as number density, flow velocity and pressure ones (Dawson and Vaillancourt, 1995; Chayes and Panferov, 2010; Kotelenez and Kurtz, 2010). These variables, described in terms of means of main observables, are functions just of position and time. In such a way, a selfconsistent collective field comes into play, representing brain long-range behavior. We hypothesize an extracellular space containing collisionless particles, e.g., chemical ions (**Figure 2**). The particles' trajectories in neural extracellular spaces are dictated by two factors: their electrical interactions (positive and negative charges) and the medium density. The latter is correlated with the parameter tortuosity λ . In this context, the role of the spikes internal to neuronal axons could solely be to modify the above mentioned currents in the extracellular space, which is the 15% of the total brain volume. Therefore, the currents of the extracellular space display collective, plasma-like long range trajectories, partially depending on the intra-axonal changes in ion fluxes during spikes.

It has been recently proposed that mental operations, such as spontaneous activity and mind wandering, follow constrained, topological donut-like trajectories along preferential functional brain railways, shaped in guise of a torus (Tozzi and Peters, 2016). In order to describe how do such trajectories move on the torus, the plasma-like brain model is very helpful. If we depict brain intracellular and extracellular fluxes as taking place on a sphere (**Figure 3**), we notice that the collisionless trajectories can be described as movements in the extracellular space. If we now take into account equations on a n-torus, we can describe the time-evolution of probabilistic distribution of densities and their free energy functional (Chayes and Panferov, 2010). Such treatment in terms of collisionless movements on a torus can be assessed through th McKean–Vlasov equation, that describes the time-evolution of a density $\rho = \rho(x, t)$, where $x \in T^d_L$, the *d*-dimensional torus of scale *L*. The equations states that:

$\rho t = \Delta x \rho + \theta L^d \nabla x \cdot \rho \nabla x (V * \rho).$

where ρ is the density, θ the interaction (coupling) strength, e.g., the underlying density of the fluid, *L* is the torus scale, d the torus dimension, V the interaction potential, * the convolution in x. L^d stands for the volume factor. The term ∇ denotes the divergence or the curl (rotation) of a vector field defined on a multi-dimensional domain. We now need to evaluate the brain counterparts for the terms of the above mentioned equation. The value $\rho(x, t)$ has a probabilistic interpretation which we relate to particle or fluid brain extracellular density, and thus depends on the tortuosity factor λ . The value *V* stands for the extracellular interaction potential.

It is assumed that ρ integrates to one. The dynamics is a gradient flow (with respect to a certain distance in the space of probability measures) for the *free energy* functional F. It means that, in touch with a long tradition of studies quantifying brain energy (Friston 2010; Sengupta et al., 2013), our model is also able to quantify the required dynamics and free energy functional. Indeed, the dynamical equation can be recast into the form:

$$d/dt \ \mathsf{F}_{\theta}(\rho) = \int \mathrm{T}^{\mathrm{d}}_{\mathrm{L}} \rho \left| \nabla \log \rho / \mathrm{e}^{-\theta L dV * \rho} \right|^2 dx.$$

For further mathematical details, see Chayes and Panferov (2010).

For such dynamical system, we expect the following behaviour:

- a) Weak convergence to equilibrium, e.g, the phase space density tends towards a time-independent measure.
- b) Particles oscillate with smaller and smaller amplitude, but their speed, due to energy conservation, does not reach the zero.
- c) Some particles will get accelerated to larger speeds, so that the time-independent limiting phase space density will not have anymore compact support.

Summarizing, we require a sort of McKean-Vlasov equation for collective behavior of particles, which takes into account the following (brain) system features:

1) a spherical phase space, or alternatively, a torus, donut-like structure.

2) the presence of ions, but not of free electrons, which are at charge equilibrium, e.g., positive charges=negative charges.

3) the density value of the medium embedded into the sphere.

4) the presence of *obstacles* to free movements into the sphere, consisting in ramifications that correspond to the so called λ coefficient.



Figure 2. Our model predicts that the trajectories and the behaviour of the iones (charged particles) embedded in the extracellular space can be described collectively, due to reciprocal long-range interactions. The upper part of the figure depicts the extracellular space, the lower one the intra-axonal neuronal compartment. The rest and spike potentials values depicted in Figure refer to the inner membrane potentials. When the potential is at rest, a negative intra-neuronal potential occurs. When a spike potential takes place, the ions concentration is reverted and the extracellular space displays a negative potential. The background Figure roughly describes the extracellular collective movements taking place in the brain. The charged particles move according the equations of the collisionless movements. The shape of the collective movements of the charged particles (the brain extracellular ions) depend on two factors: the viscosity of the extracellular medium and the coefficient lambda (which depicts the *tortuosity* of the ever-changing extracellular space).



Figure 3. An oversimplified model of McKean-Vlasov collective movements. In **Figure 3A**, the brain, depicted as a rigid ball, contains charged particles, e.g., the ions embedded in the extracellular and intracellular neural medium. The larger intracellular neuronal compartment (inner circle), consisting on about 85% of the brain volume, is surrounded by the thinner extracellular space (outer circle). Both at rest and during spike potentials, the extracellular charged particle movements are constrained by their electric interactions and display a collective, long-range plasma-like trajectories. The collective movements in the extracellular space can be described in terms of trajectories along a donut-like torus surface, excluding the central *hole* where intracellular currents take place. **Figure 3B**, just as an example, illustrates a simulation of the particle movements in a very small zone of the extracellular compartment, which might be compared to movements on a flat plane. This plot might be retrospectively compared with previous EEG or fMRI studies, in order to achieve a comparison between theoretical patterns and real data.

ELUCIDATING NERVOUS PHASE TRANSITIONS

The brain is sometimes described as a complex, non-linear system, formed by a large number of interacting and interdependent components which exhibit emergent properties, spontaneous self-organization and sensitivity to initial small changes (Bak et al, 1987; Tognoli and Kelso, 2014; Papo, 2014; Afraimovich et al., 2013). It has been proposed that the brain operates at the edge of chaos (Deco and Jirsa, 2012), near a critical regime, where the maximum information function lies between randomness and regularity (de Arcangelis and Herrmann, 2010; Zare and Grigolini, 2013). The treatment of nervous dynamics in terms of collisionless movements on a torus helps in elucidating both the claims that phase transitions occur in brain and their potential mechanisms. Furthermore, it allows us to predict which is the control phase parameter required in order to achieve the predicted nervous criticality. Touboul (2012) analyzed the collective behavior of mean-field limits of large-scale neuronal networks, characterized by a very intricate stochastic delayed integro-differential McKean–Vlasov equation. The authors identified, through bifurcation analysis, several qualitative transitions in the mean-field limit due to noise. In particular, stabilization of spatially homogeneous solutions, synchronized oscillations, bumps, chaotic dynamics, wave or bump splitting were exhibited, arising from static or dynamic Turing–Hopf bifurcations (Touboul, 2012). It means that noise can be used in the evaluation of longrange collisionless nervous trajectories in nonlinear systems. In such a vein, Chayes and Panferov (2010), who studied the McKean–Vlasov equation on the finite tori of length scale *L* in *d*-dimensions, were able to derive the necessary and sufficient conditions for the existence of a phase transition (Gates and Penrose 1970). They found indications pointing to critical transitions at the value θ^l of the interaction parameter θ described above. They showed that the uniform density is dynamically stable for $\theta < \theta^l$ and that a *critical* transition occurs at $\theta = \theta^l$. They also showed that, under generic conditions such as *L* large, $d \ge 2$ and isotropic interactions, the phase transition is discontinuous and occurs at some $\theta_T < \theta^l$. In sum, McKean-Vlasov equations allow us to hypothesize the possible modalities of brain phase transitions and to elucidate their control parameters.

CONCLUSIONS

In the last century, Golgi's model of *functional sincythium* has been discarded in favor of Waldeyer's theory of neuron. Further developments led to the modern concept of spike transmission encompassing also the nervous message. However, suggestions dating back to Angelo Mosso (1896) hypothesize nervous mechanisms other than neuronal electric spikes (Tozzi 2015, Marcoli et al. 2015) and recent developments start to unveil that the brain displays a *holistic* behavior (Friston, 2010), acting like a system with long-range interactions.

Here we suggest that changes in a small number of extracellular parameters might lead to long-range nervous interactions. A large repertoire of brain functions and activities (Andrews-Hanna) could be grounded on collective brain phenomena. Indeed, a plasma-like nervous behavior fits very well with the description of the consciousness and might also be responsible of maintaining perceptions, memories and thoughts. This approach, when implemented in a proper lattice or network, might provide a testable alternative to the well-consolidated neural models based on binary logic, such as McCullogh-Pitts neuron and Hopfield networks, or on nonlinear interactions (Tozzi et al. 2016). By an operational point of view, in order to give testable previsions, we need to ask whether it is feasible to use McKean-Vlasov equations in the evaluation of EEG and fMRI patterns of spontaneous and evoked brain activity. It would not take a big effort to compare the nervous trajectories of the real temporal patterns described by previous studies with the theoretical results suggested by collisionless equations.

Furthermore, taking into account trajectories in nervous spaces, we could be able to predict whether they will fall in the suggested donut-like torus. For example, we speculate that, when particles fall into the torus conformation (where two antipodal particles cannot never meet or become closer, due to their recurrent rotations) the correlated psychical activities could be either repetitive patterns of movements or thoughts, or preserved memories, or mind wandering, or unsure perceptions, in which different ideas are not properly melted together.

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