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Similarities between action potentials and acoustic pulses in a van der Waals fluid

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An action potential is typically described as a purely electrical change that propagates along the membrane of excitable cells. However, recent experiments have demonstrated that non-linear acoustic pulses that propagate along lipid interfaces and traverse the melting transition, share many similar properties with action potentials. Despite the striking experimental similarities, a comprehensive theoretical study of acoustic pulses in lipid systems is still lacking. Here we demonstrate that an idealized description of an interface near phase transition captures many properties of acoustic pulses in lipid monolayers, as well as action potentials in living cells. The possibility that action potentials may better be described as acoustic pulses in soft interfaces near phase transition is illustrated by the following similar properties: correspondence of time and velocity scales, qualitative pulse shape, sigmoidal response to stimulation amplitude (an 'all-or-none' behavior), appearance in multiple observables (particularly, an adiabatic change of temperature), excitation by many types of stimulations, as well as annihilation upon collision. An implication of this work is that crucial functional information of the cell may be overlooked by focusing only on electrical measurements.

Excitable cells generate a characteristic transient change in transmembrane voltage that propagates along the cell membrane in response to suitable stimuli. The phenomenon was first identified in a frog nerve by Emil du Bois-Reymond in 1843, who called it “negative variation”, later to be termed “action current” (Ludimar Hermann, 1868) and subsequently *action potential* (Blair, Hill and Rushton, among others, 1930s)¹. Cellular excitability was recognized in a large category of cells, including neurons, myocytes, epithelial cells, fibroblasts, glia cells, enteroendocrine cells, pancreas beta cells, as well as non-specialized cells in corals, plants, fungi, Protozoa and possibly even bacteria^{1–11}. Action potentials (APs) are principally associated with behavioral activities of many organisms. Therefore, an understanding of the mechanism of APs, as well as their actions and interactions, constitutes one of the fundamental aspects of biology.

Classically APs are described as a purely electrical phenomenon induced by the flow of specific ions across the cell membrane and down their concentration gradient (sodium and potassium in the original model)^{12,13}. The non-linear electric response is believed to be associated with specialized protein components that coordinate these ionic fluxes. An unavoidable implication of this view is that the phenomenon should only exist in living cells, and could not be identified in non-living systems. However, pulses with similar properties have been observed in non-living soft systems such as lipids and gels^{14,15}. In addition, many experimental facts are neither readily explained nor predicted by the electrical theory of APs. A partial list includes (1) non-electric aspects that co-propagate with the electric pulse¹⁶; (2) the existence of APs in absence of sodium and potassium in the intra- and extracellular solutions¹⁷, and in absence of ion-concentration gradient¹⁸; and (3) ion-channel like current fluctuations in the absence of ion channel proteins¹⁹. Therefore, the classical picture not only is not derived from fundamental physical principles, it also does not satisfactorily describe the observed phenomenology. Alternative approaches, that treat the AP on a more physicochemical basis, have been proposed^{16,20–22}. A common thread of these approaches is that electricity is merely one aspect of the pulse, and it is, therefore, very likely that valuable information is overlooked due to misunderstanding of its mechanism.

One conjecture, which is the focus of this manuscript, is that APs are acoustic pulses that propagate along the lipid interface and cross the phase-transition from the so called *liquid-expanded* to the *liquid-condensed* phase^{20,21}.

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Indeed, experimental observations in lipid monolayers have demonstrated that solitary acoustic pulses can be excited, and that they share many properties with APs. A comparison of key experimental observations between APs and acoustic pulses in lipid interfaces is as follows. (1) APs are not purely electrical waves. Rather, they were identified in multiple observables—electrical, magnetic, mechanical, optical, as well as thermal^{16,23,24}. Acoustic pulses in lipids were also identified in multiple observables (density, pressure, electrical, optical and pH)^{14,25–28}. Particularly, the electric potential difference between the liquid-expanded and the liquid-condensed phase is ~ 100 mV, similar to the amplitude of APs²⁵. (2) The production and absorption of heat during an AP is adiabatic²⁹, and an acoustic description is the natural physical approach for an adiabatic propagating pulse. (3) The time and velocity scales of APs vary by 5–6 orders of magnitude between cells, $\sim 10^{-3}$ – 10^1 s and $\sim 10^{-3}$ – 10^2 m/s, respectively^{7,8,12}. These values are comparable to sound pulses in lipid systems that traverse the phase transition ($\sim 10^{-3}$ – 10^{-2} s and ~ 0.1 – 1 m/s, respectively)^{14,27}. (4) Excitation of an AP is obtained by many types of stimulations: electrical, mechanical (pressure, touch, ultrasound), optical (by shining light), as well as a change of temperature (heating or cooling)^{1,30}. Acoustic pulses in lipids can also be excited by various types of stimulations (mechanical, electrical and chemical (acid as well as solvent))^{14,28,31,32}. (5) Even the less intuitive properties of APs, namely threshold behavior (a sigmoidal response, the so called *all-or-none*)³³ and annihilation upon collision^{34,35}, can be demonstrated as an acoustic behavior near phase transition. Specifically, stimulation was shown to prompt a sigmoidal response of density pulses in lipid interfaces near phase transition²⁷, and these pulses were demonstrated to annihilate upon collision³⁶.

Despite the striking experimental similarities, a comprehensive theoretical study of acoustic pulses that traverse the phase transition in lipid systems is still lacking. Theoretical modeling was initiated by Heimburg and Jackson, and was focused on solitonic solutions in a small-amplitude analysis of an acoustic model of the membrane interface²⁰. Two main criticisms of the model have been an overestimation of the propagation velocity and the lack of annihilation of pulses. Kappler *et al.* later demonstrated that the viscous coupling between the interface and a bulk fluid attenuates the propagation velocity of interfacial longitudinal waves, and results in a corrected velocity that agrees with experimental evidence³⁷. Still, some observations are not captured by these previous works, including the annihilation of pulses upon collision, as well as a thorough analysis of different aspects of the pulses under adiabatic conditions (e.g., density, pressure, temperature and electrical properties).

Herein, we demonstrate that non-linear acoustic pulses, which annihilate upon collision, arise naturally from a minimum set of well accepted physical assumptions: mass, momentum and energy conservation laws near a phase transition. Our description relies on relatively few and physically measurable parameters and variables. Particularly, no assumptions about the molecular constituents and structure, nor any parameter fit, are required. In spite of its minimalism, the model provides a rich behavior of non-linear acoustic pulses that correspond to experimental results in lipid monolayers as well as to APs in living cells.

Model Description

Our purpose is to investigate the properties of isentropic traveling waves which exist near a phase transition. We therefore consider an idealized ansatz of a one-dimensional compressible fluid with a van der Waals constitutive equation, following the works of Felderhof, Slemrod and Grinfeld^{38–40}. While classically a van der Waals phase transition is between a gas and a liquid, the familiar pressure-versus-volume curves (isotherms) qualitatively resemble the melting transition between the liquid-expanded and the liquid-condensed state in lipids⁴¹. The conservation laws of mass, momentum and energy are written in the Lagrange frame,

$$\begin{aligned}\partial_t w &= \bar{w} \partial_h v, \\ \partial_t v &= \bar{w} \partial_h (\tau_1 + \tau_2), \\ \partial_t E &= \bar{w} [\partial_h (\tau_1 v) + k \partial_h^2 \theta].\end{aligned}\quad (1)$$

Here w , v and E denote the specific volume, velocity and specific total energy of the fluid, respectively. The fluid density is inversely proportional to the specific volume, $\rho = w^{-1}$. The spatial coordinate h (in the Lagrange frame) is related to the x -axis (in the Euler frame) by the cumulative mass of fluid particles⁴²

$$x = \frac{1}{\bar{w}} \int w dh, \quad (2)$$

with \bar{w} a normalization factor that defines the scale of h . In addition, τ_1 and τ_2 represent the stresses in the fluid (see below), k is the coefficient of thermal conductivity and θ is the fluid temperature.

To allow for a continuous transition between the two phases, we follow van der Waals' hypothesis that the energy of a system depends on the gradient of density (the so called *capillarity* term)^{43,44}. A similar definition appears in the Ginzburg-Landau mean field theory of phase transition as well as the Cahn-Hilliard model of coexistence of two phases^{45,46}. The capillarity coefficient is also known as the *gradient-energy coefficient*, and is related to the line tension that arises between two coexisting phases (further clarification is given in the Supplemental Materials). The corresponding stress correction to the dynamics of fluids was developed by Korteweg^{43,47}. Therefore, the expression for stress includes a capillarity term in addition to pressure and viscosity. It is defined as

$$\begin{aligned}\tau_1 &= -p + \zeta \partial_h v, \\ \tau_2 &= -C \partial_h^2 w,\end{aligned}\quad (3)$$

with p the fluid pressure, ζ the dilatational viscosity and C the capillarity coefficient, treated here as constant for simplicity.

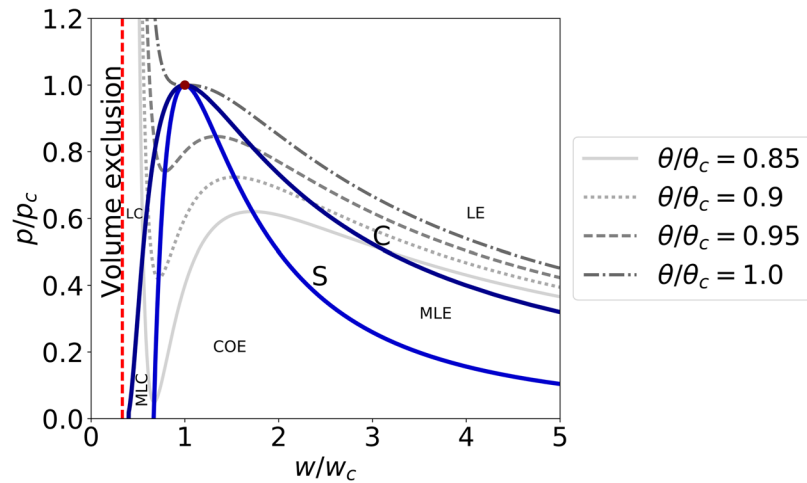


Figure 1. Schematic phase diagram in the w - p plane of the van der Waals model. Four different isotherms, along with the Spinodal (S) and coexistence (C) curves are plotted. The critical point is denoted by a filled circle. LE: liquid-expanded phase, MLE: metastable liquid-expanded phase, COE: coexistence phase, MLC: metastable liquid-condensed phase, and LC: liquid-condensed phase.

The system of equations is completed with the van der Waals constitutive equations, that qualitatively resemble the transition between a liquid-expanded and a liquid-condensed state in lipids (Fig. 1 and ref.⁴¹)

$$p = \frac{k_B \theta}{mw - b} - \frac{a}{m^2 w^2},$$

$$E = \frac{v^2}{2} + c_v \theta - \frac{a}{m^2 w} + \frac{C}{2} (\partial_t w)^2, \quad (4)$$

with k_B the Boltzmann constant, m the mass of a fluid particle, a the average attraction between particles, b the volume exclusion by a fluid particle, and c_v the specific heat capacity⁴⁸. The phase space contains an unstable region, $\partial p / \partial w > 0$. This region is bounded by the spinodal curve (marked by S in Fig. 1), which satisfies $\partial p / \partial w = 0$. A slightly larger area, governed by the Maxwell equal area rule, describes the region where a coexistence of phases has a lower free energy as compared to a single phase solution (marked by C in Fig. 1). Both curves meet at the critical point (w_c, p_c, θ_c), where the distinction between the two phases disappears. The critical point can be expressed by three parameters: m , a and b (Eq. (S1) in the Supplemental Materials). A detailed list of the 6 variables and 7 parameters of the model is provided in the Supplemental Materials (Tables S1–S2).

The critical point and the fluid viscosity were used to define proper scales (time, length and velocity, respectively)

$$T \equiv \frac{\zeta}{p_c}, \quad L \equiv \zeta \sqrt{\frac{w_c}{p_c}}, \quad U \equiv \frac{L}{T} = \sqrt{w_c p_c}. \quad (5)$$

These scales were used to derive a dimensionless form of the model equations (Supplemental Materials, Eqs (S3)–(S5)), that depends on only three parameters: the (dimensionless) heat capacity, thermal conductivity and capillarity coefficient

$$\tilde{c}_v = \frac{c_v \theta_c}{p_c w_c}, \quad \tilde{k} = \frac{k \theta_c}{p_c w_c \zeta}, \quad \tilde{C} = \frac{C}{\zeta^2}. \quad (6)$$

Dimensionless variables and parameters are hereafter marked with tilde (e.g., $\tilde{x} = x/L$).

A complete set of all of the material constants is not known for any single lipid system, nor for a composite soft interface, for example in biological cells. Therefore, typical values were estimated from experiments with DPPC lipids. The critical point of a two-dimensional DPPC monolayer was identified from isothermal state diagrams (w_c, p_c, θ_c) $\cong (5 \cdot 10^5 \text{ m}^2/\text{kg}, 3 \cdot 10^{-2} \text{ Pa} \cdot \text{m}, 315 \text{ K})$ ^{14,25,30,41}. The order of magnitude of the membrane viscosity was estimated from measurements of shear viscosity, $\zeta \sim 10^{-3} \text{ Pa} \cdot \text{s} \cdot \text{m}^49$. The order of magnitude of the heat capacity was evaluated from experiments at constant pressure, $c_v \sim c_p \sim 10^3\text{--}10^4 \text{ J/kg} \cdot \text{K}$ ^{20,25}. Unfortunately, no direct measurements of the thermal conductivity and capillarity coefficient of lipid monolayers exist. Thermal conductivity was approximated from the evaluation of heat conduction in interfacial water in a lipid system, $k \sim 5 \text{ J/s} \cdot \text{K}$ ²⁰. The capillarity coefficient was estimated from measurements of line tension at the phase boundary, $C \sim 10^{-27}\text{--}10^{-24} \text{ kg}^2/\text{s}^2$ (Supplemental Materials and ref.⁵¹). For typical values of a lipid system, the proper scales are $T \approx 30 \text{ ms}$, $L \approx 4 \text{ m}$ and $U \approx 120 \text{ m/s}$, and the dimensionless parameters are $\tilde{c}_v \sim 10^1\text{--}10^3$, $\tilde{k} \sim 10^2$, and $\tilde{C} \sim 10^{-21}\text{--}10^{-18}$. Although the capillarity coefficient is insignificantly small, a non-negligible value was used for numerical

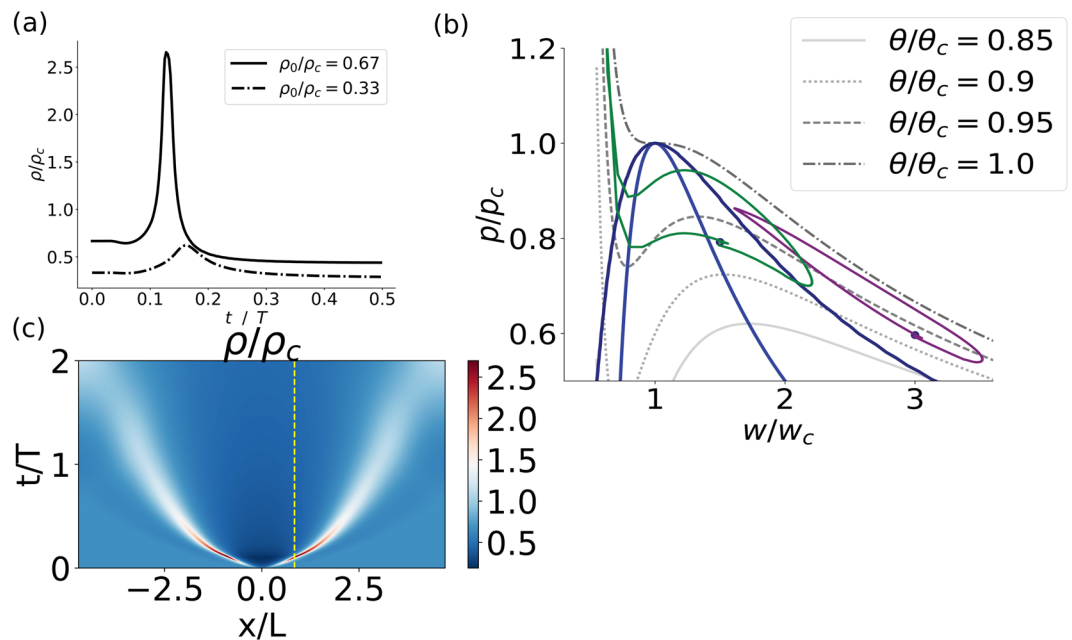


Figure 2. (a) Density pulse as a function of time, as measured at distance $x/L = 1$ from the excitation point, with an initial density of $\tilde{\rho}_0 = 0.67$ (solid line) and 0.33 (dotted-dashed line). (b) A projection of phase space into the w - p plane ($w = \rho^{-1}$). Several isotherms are plotted for reference (shades of grey lines) as well as the coexistence and spinodal curves (dark blue and blue lines, respectively). The trajectory of the two pulses shown in (a) is plotted in green and purple respectively. (c) Density field of the entire fluid as a function of space (x -axis) and time (y -axis) with initial density $\tilde{\rho}_0 = 0.67$. Dashed yellow line marks the solid line solution depicted in (a). Parameters of the model were $(\tilde{c}, \tilde{k}, \tilde{C}) = (600, 100, 1)$, additional initial conditions were $(\tilde{v}_0, \tilde{\theta}_0) = (0, 0.93)$, and excitation parameters were $(\tilde{x}_0, \tilde{t}_0, \tilde{p}_{exc}, \lambda) = (0, 0.1, 300, 0.088)$. Numerical calculation was conducted with 4096 grid points, x -domain $[-3\pi/2, 3\pi/2]$ and $dt = 5 \cdot 10^{-4}$.

reasons ($\tilde{C} \sim 1$) – to avoid sharp gradients in the density field. The use of a non-negligible capillarity coefficient did not show a major effect on our results (Fig. S1).

The system of equations (1)–(4) was numerically solved with the Dedalus open-source code⁵², which is based on a pseudo-spectral method. The model was solved using periodic boundary conditions, and with homogeneous initial conditions, (w_0, p_0, θ_0) in the liquid-expanded phase. Excitation of a pulse was obtained by ‘injecting’ a localized stress (around h_0) with an amplitude p_{exc} for a brief time (t_0) into the momentum flux; i.e., adding the following term into the right-hand-side of the middle Eq. 1

$$\bar{w} \partial_h \left(p_{exc} \Theta(t_0 - t) e^{-\frac{(h-h_0)^2}{2\lambda^2}} \right). \quad (7)$$

Here, Θ is the Heaviside function, and λ is the width of excitation.

Results

We now turn to analyze sound pulses that traverse the phase transition. Upon excitation, distinct pulses were obtained when the initial state of the fluid was near phase transition. Figure 2a (solid line) depicts the shape of a density pulse as measured at distance $x/L = 1$ from the excitation point. The shape of the density pulse was qualitatively very similar to experimental measurements in lipid monolayers¹⁴, as well as to the voltage signal of an AP³³. Because this issue is of particular relevance to the open debate regarding the physical nature of cellular excitability, we further discuss the relation between the interface density and a transmembrane voltage measurement in the Discussion section. In contrast, pulse amplitude was much lower when the initial state was away from the phase transition (Fig. 2a, dotted-dashed line). A projection of the closed trajectory in the w - p plane is shown in Fig. 2b, for the two pulses depicted in Fig. 2a (green and purple curves, respectively). If a trajectory does not cross the phase boundary (dotted-dashed line in Fig. 2a and purple curve in Fig. 2b) the pulse undergoes only a little amplification in density ($\tilde{\rho} \lesssim 1$). The change in density is accompanied by a parallel increase in pressure ($\tilde{p} \lesssim 1$) and temperature. Subsequently, the local state decreases in all three fields (density, pressure and temperature) into a rarefaction state before relaxing back into the initial state. In contrast, once a pulse traverses the phase transition region, the density and pressure evolve non-linearly (solid line in Fig. 2a and green curve in Fig. 2b). At first, a significant increase in density is obtained ($\tilde{\rho} \gtrsim 1$), with almost no change in pressure. Subsequently, as the local state approaches the volume exclusion region, the pressure sharply increases ($\tilde{p} \gtrsim 1$),

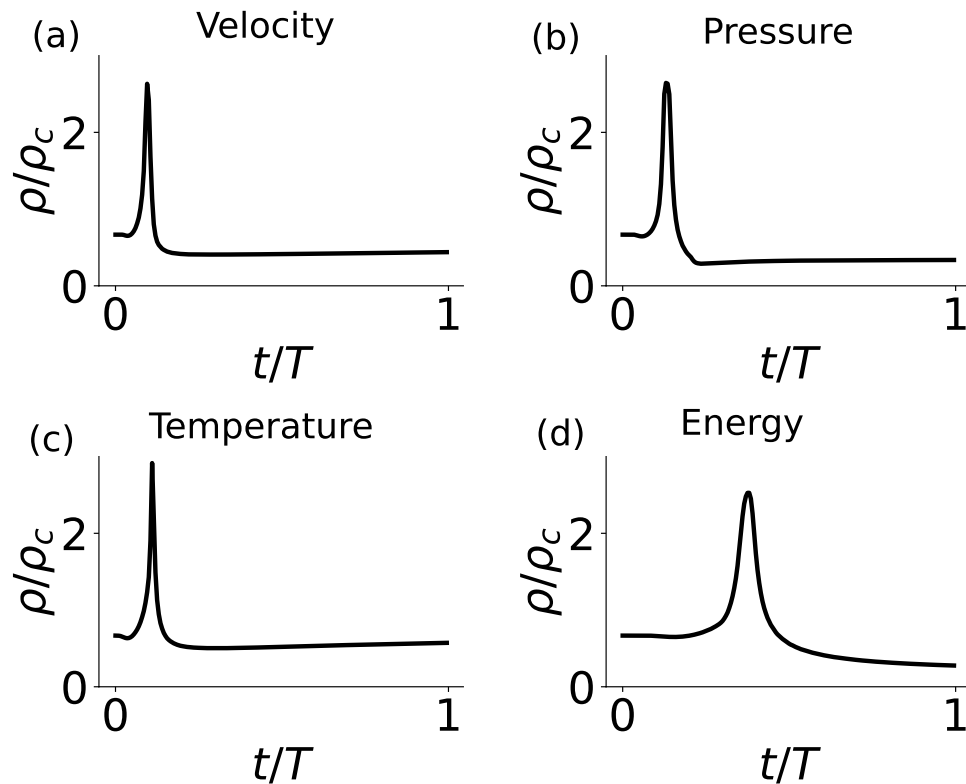


Figure 3. Excitation by a local injection of (a) velocity (middle of Eq. (1)), (b) pressure (upper Eq. (4)), (c) temperature (lower Eq. (4)), and (d) energy (lower Eq. (1)). Excitation parameters were $(A, t_0) = (300, 0.1)$, $(300, 0.2)$, $(3000, 0.1)$ and $(2 \cdot 10^4, 0.2)$, respectively. A is the normalized amplitude of excitation (p_{exc}/p_c , p_{exc}/p_c , θ_{exc}/θ_c and E_{exc}/U^2 , respectively). Density as a function of time was plotted at $x/L = 0.8, 1.0, 0.8$ and 1.4 , respectively.

with only a slight increase in density. A parallel small increase in temperature also occurs. Relaxation follows in a reverse order—a sharp decrease in pressure is followed by a sharp decrease in density into a rarefaction that relaxes back into the initial state.

The solution of the density field across the entire fluid is plotted in Fig. 2c. Following an excitation around $x = 0$ that lasted 0.1 T, two localized pulses were generated, propagating in opposite directions. Their length, time and velocity scales were $\approx 0.5 L$, $\approx 0.1 T$, and $\approx 5 U$, respectively. An important observation is that these pulses did not maintain a constant velocity and shape, and eventually dispersed; i.e., these solutions are neither solitons, nor homoclinic orbits. Nonetheless, the pulses had a distinct shape for a distance of 3–5 times the pulse width. Variation of the duration or width of the stimulation (t_0 and λ in Eq. (7), respectively) did not have much influence on the time and length scales of the pulse (Fig. S2). However, upon increasing the duration of the stimulation (t_0), the pulses maintained a distinct shape for a longer distance (more than 10 times the pulse width, Fig. S2b). The dashed yellow line in Fig. 2c marks the solution that was plotted in Fig. 2a (solid line).

Stimulation by different model variables (velocity, pressure, temperature or energy) was obtained by adding the excitation term $\left[\tilde{A} \Theta(t_0 - t) e^{-\frac{(h-h_0)^2}{2\lambda^2}} \right]$ to other model equations (Eqs (1) or (4)). Figure 3 shows the density pulses that were generated by different ‘types’ of stimulations. The resulting pulses were qualitatively similar.

By increasing the amplitude of excitation, at a given initial state, a non-linear (sigmoidal) response of the density pulse was obtained (Fig. 4a,b). At low amplitudes of excitation the pulse response was qualitatively similar to previous theoretical results obtained in a small-amplitude analysis³⁷. However, at larger amplitudes of excitation the amplitude of the density pulse saturated at $\rho = 3 \rho_c$. The saturation of density is a direct result of the exclusion of volume given by the van der Waals equation (upper Eqs (4) or (S5)). The response resembles experimental observations in lipid monolayers²⁷ as well as voltage measurements of APs in living cells³³.

Figure 4c shows the simultaneous pressure aspect of the pulse. Pressure increases significantly when the system is driven into the liquid-condensed phase. In addition, during the adiabatic compression and decompression, the temperature increases and subsequently decreases (Fig. 4d). Not surprisingly, the temporal width of the temperature aspect crucially depends on the thermal conductivity (data not shown).

We proceed now to investigate the question of collision between longitudinal pulses. While linear (small amplitude) pulses generally superimpose, these non-linear waves displayed a rich behavior of interaction, annihilation and in some cases even repulsion. The type of interaction between pulses strongly depends on the value of the heat capacity and thermal conductivity of the fluid. Here we provide an example of annihilation of two pulses that were

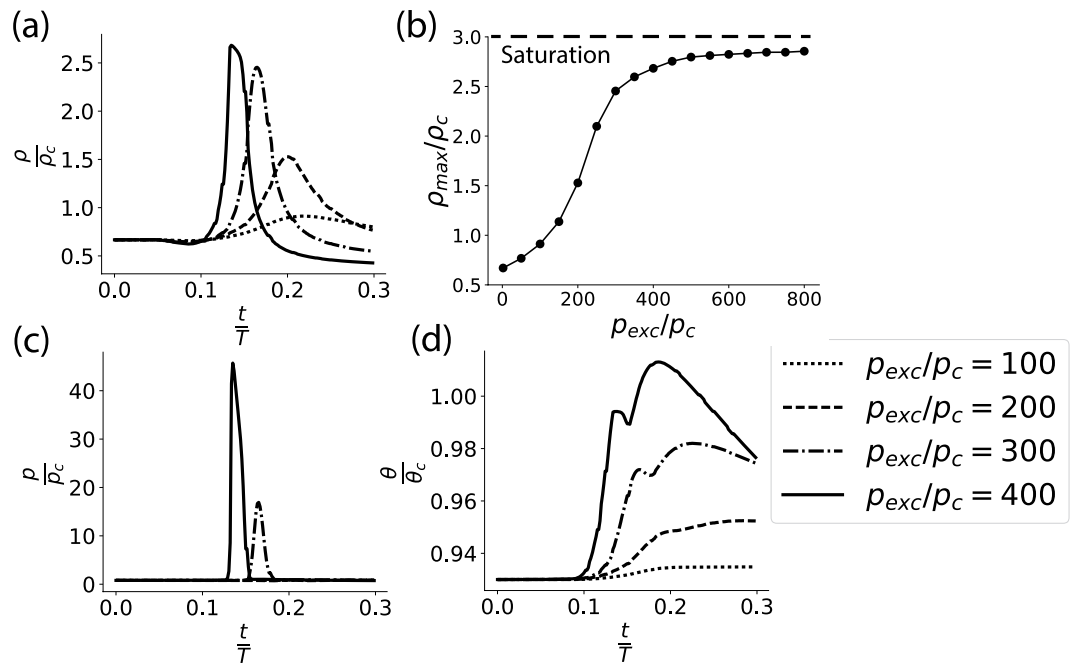


Figure 4. (a) Pulse shape at four amplitudes of the excitation, as reflected by the change of density. (b) Non-linear response of the amplitude of the density pulse (ρ_{max}) to stimulation amplitude (p_{exc}). (c) Pressure and (d) temperature aspects that co-appear with the density pulse. The first two pressure curves are indistinguishable, as the state did not reach the liquid-condensed phase. Initial density was $\tilde{\rho}_0 = 0.67$, and pulse was measured at distance $x/L = 1.2$ from the excitation point. Other parameters appear in the caption of Fig. 2.

excited in a small sized domain. Figure 5 and Movie S1 show the dynamics of the density, pressure and temperature fields before, during and after a collision. The propagation of the pulses is evident in all three fields, and the collision is characterized by a localized increase in amplitude, most dramatically observed in the pressure field.

Discussion

The lipid-based interface is a ubiquitous component of biological cells, and plays a critical role in many cellular functions. Particularly, the discovery of solitary longitudinal pulses that travel along lipid interfaces have stimulated a discussion on the functional role of acoustics in biological systems^{14,20,21,26–28,30,31}. In this paper we continued this line of research and demonstrated that an idealized fluid model near phase transition captures many properties of experimentally measured acoustic pulses in lipid monolayers as well as APs in living cells.

Time, length and velocity scales of density pulses in lipid interfaces. In a small amplitude analysis, the propagation velocity of acoustic pulses is inversely related to the square root of the compressibility^{20,31}. In contrast, the local compressibility of a van der Waals fluid is ill-defined within the coexistence region. Instead, we have shown that the scales of the system are associated with the critical point and the interfacial viscosity (Eq. (5)). Specifically, density pulses that traverse the phase transition region were demonstrated to scale as $\approx 0.1 T$, $\approx 0.5 L$, and $\approx 5U$, respectively (Fig. 2). For typical lipid values, these corresponded to ≈ 3 ms, ≈ 2 m, and ≈ 600 m/s. While the theoretical time scale agrees with measurements (≈ 5 – 10 ms), the length and velocity scales are overestimated by 2–3 orders of magnitude (≈ 1 – 10 mm and ≈ 0.1 – 1 m/s)^{14,27}. Similar estimation of velocity was previously obtained by others^{20,31}. The discrepancy results from our attempt to keep the model simple, and would disappear by extending the model to include the non-negligible coupling to the bulk²⁶. It was previously demonstrated that the viscous coupling between a compressible interface and the bulk attenuates the velocity and length of acoustic pulses by a factor of $\sim \sqrt{1 + \sqrt{\rho_b \eta_b t_p} / \rho_i}$ ³⁷. Here, ρ_b is the bulk density, η_b the bulk viscosity, t_p the pulse duration, and ρ_i the density of the interface. For a typical lipid interface coupled to bulk water, this results in attenuation by 2–3 orders of magnitudes, and agrees with experimental observations in lipids^{31,37}, as well as of APs in living cells^{7,8,12}.

Dispersion of shape and propagation velocity. According to the classical electrical description, APs are pulses that maintain a stable shape and a constant propagation velocity along an ‘infinitely’ long cell (a homoclinic orbit)¹². Similar characteristics were also suggested by the acoustic soliton model²⁰. Surprisingly, a validation of this hypothesis, by physiological measurements of velocity and shape at more than two sites, was hardly investigated, presumably due to the small cellular size. However, recent experiments have showed, using a multi-electrode array, that the propagation velocity as well as the shape of an AP are not constants during propagation. Rather, a clear trend of decrease in velocity and amplitude, as well as an increase in width, was observed^{53,54}. These findings are in accord with our results, that do not preserve a constant velocity and shape, and eventually disperse. We have, nonetheless, demonstrated that distinct pulses were maintained at distances up to 1–10 times the length of a pulse (Figs 2c and S2b). Interestingly, the length of many excitable cells is of similar

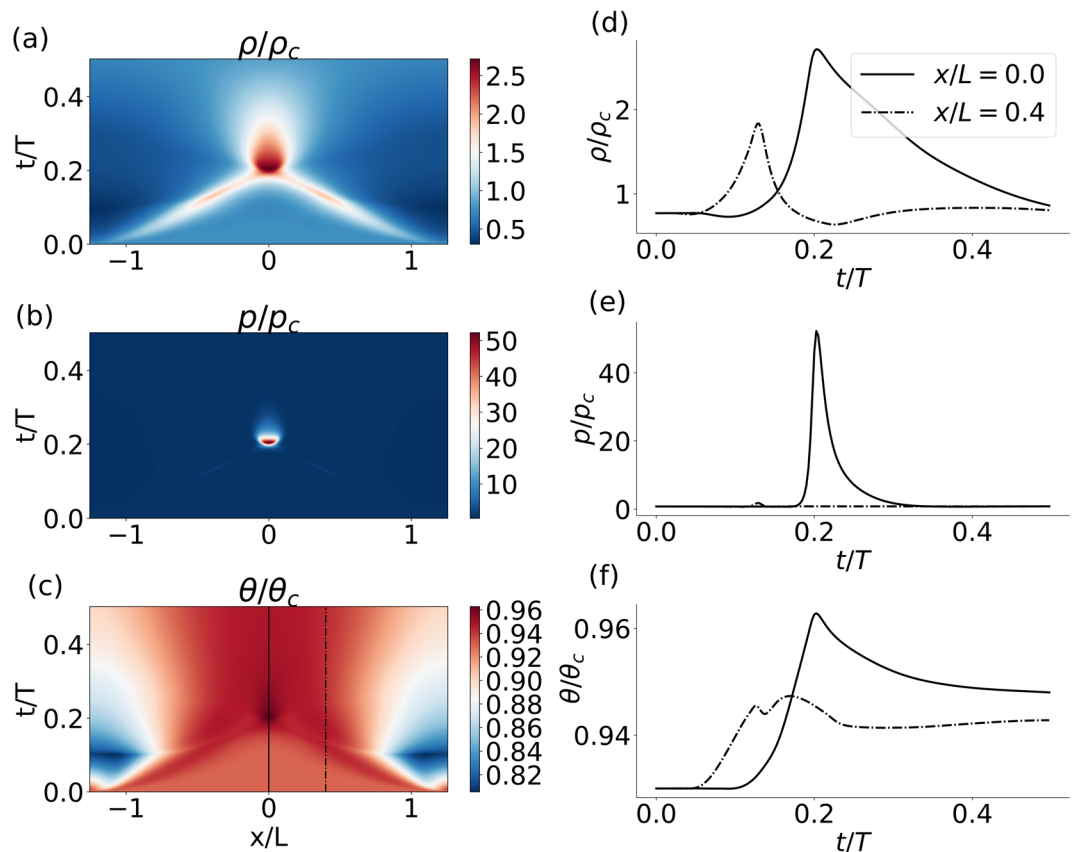


Figure 5. Collision between two pulses as appeared in the (a) density, (b) pressure and (c) temperature fields. x - and y -axis represent space and time, respectively. A local description of the (d) density, (e) pressure and (f) temperature is plotted as a function of time at the collision point ($x/L = 0$, solid line) and at some distance away from it ($x/L = 0.4$, dashed-dotted line). The location of these solutions in space is marked in (c) by solid and dashed-dotted line, respectively. Fluid initial density was $\bar{\rho}_0 = 0.77$. Excitation was conducted at $\tilde{x}_0 = \pm 0.4\pi$. Numerical calculation was performed with 8192 grid points, and the x -domain was $[-0.4\pi, 0.4\pi]$. Other parameters are similar to those given in caption of Fig. 2.

order. For example, in *Loligo Pealei* squids the length of a giant axon is 3–5 times the length of an AP (the axonal length is 10–20 cm, and the estimated length of an AP is ≈ 4 cm (the pulse duration is ≈ 2 ms and the propagation velocity is ≈ 20 m/s)^{12,55}). Because the characteristics of APs over distances of the order of the pulse size were scarcely investigated, it may be worth to examine these properties in a future work.

Voltage signal of acoustic pulses. We now turn to examine the effect of density changes on a transmembrane voltage measurement. Changes in electric properties, such as capacitance and resistance, are unavoidable during propagation of acoustic pulses in soft materials^{32,56}. Furthermore, the surface potential of some lipid monolayers differ by ~ 100 mV between the liquid-expanded and the liquid-condensed phases, the same order of magnitude as the electric aspect of an AP²⁵. To quantify these changes, we explore a simple extension to the model; a standard electrophysiological measurement across a lipid interface. For the moment we ignore any transmembrane current of ions, and focus on currents following solely from voltage changes generated by the layer itself. The conservation of charge requires

$$\frac{d}{dt}(\mathbb{C}V) = 0, \quad (8)$$

with \mathbb{C} the local capacitance of the material, and V the local transmembrane voltage. The equation implies an inverse relation between the voltage and the material capacitance

$$\frac{V}{V_i} = \frac{\mathbb{C}_i}{\mathbb{C}}, \quad (9)$$

with V_i , \mathbb{C}_i the initial voltage and capacitance, respectively. The capacitance of the system can be associated with the area, thickness and relative permittivity of the material (A , d and ϵ , respectively)

$$C \approx \varepsilon_0 \varepsilon \frac{A}{d}, \quad (10)$$

where all variables (including ε) depend on the local thermodynamic state of the membrane⁵⁶. Replacing the area term with the density of the membrane, we obtain a linear relation between the voltage and the local density

$$C \propto \frac{\varepsilon}{d\rho} \Rightarrow V \propto \frac{d\rho}{\varepsilon}. \quad (11)$$

Thus, a propagating density pulse (Fig. 1), if detected by a voltage sensor, should display a distinct shape that includes a depolarization, repolarization and hyperpolarization phase, similar to measurements of APs. However, a voltage pulse is expected to display a sharper non-linear response (a threshold) as compared with the density pulse (Fig. 4a,b). This is because the relative permittivity and thickness are also state dependent, the former decreases and the latter increases as the pulse traverses into the condensed phase^{25,57,58}. On top of these results, one could include the resistance of the soft system to transmembrane ionic currents, which is governed by a state dependent permeability^{19,59}. In conclusion, the electric potential difference across a lipid interface responds non-linearly when acoustic pulses travel along the interface.

The realization that APs may be acoustic pulses, that carry electrical changes as they travel, should have significant implications for the field of neuroscience. For decades the field has placed much focus on measurements and analysis of electric signals in nervous-systems of many organisms. However, it is possible that crucial computational information goes unnoticed when the state of a neuron is simplified into a *raster plot* data (a digital-like uniformity of zeros and ones that represent events of APs). Let us describe one plausible scenario. In Fig. 4 we have demonstrated that at large excitation amplitudes very similar density pulses can be excited with a significantly different pressure signature. Thus, a voltage sensor, sensitive to density but not to pressure, would not resolve between different pressure signatures that could induce different cellular responses, and result in a considerably different computational scheme as compared to the classical electrical picture.

Model extensions. The evidence that the reported pulses do not emerge from a fine-tuned model, but rather result from an idealized description of a soft system, emphasizes the generality of the phenomenon. This, however, should only be viewed as a first step. To treat pulses in soft systems more accurately, further extensions to the model are required. (1) The parameters of the system; specifically, viscosity, heat capacity and thermal conductivity, are state dependent and not constants^{20,60,61}. This is particularly evident near a phase transition and should modify the detailed properties of the nonlinear pulses. (2) The van der Waals constitutive equation is not an accurate representation of the state diagram of soft materials, lipids in particular. For example, in DPPC the volume exclusion appears at $\approx 0.8 w_c$ ^{25,30,41}. This is quantitatively different from the van der Waals equation, where the volume exclusion occurs at $w_c/3$. These differences clearly influence the properties of the pulse. For example, the saturation amplitude of the density pulse would be $\rho_{sat} \approx 1.2 \rho_c$ instead of $\approx 3 \rho_c$. (3) The viscoelastic properties of lipids are more complicated than simply considering a capillarity term. Particularly, effects of state dependent rigidity and distortion of the lipids as well as embedded proteins clearly modify the dynamic response to lateral compression^{49,62}. (4) No effect of geometry was considered in this work (boundary conditions, extension to two- or three-dimensions, coupling to bulk). (5) The parameters that describe the material (critical point, thermal conductivity, etc.) are very likely influenced by additional components that were not considered here. For example, pH, ions, as well as embedded proteins. (6) In order to provide a detailed analysis of electrophysiological measurements, a more accurate description of the electro-mechanical coupling is necessary. For example, we did not address space- and voltage-clamp experiments in this paper¹². (7) Our description is based on a mean field approximation. Therefore, thermodynamic fluctuations were not accounted. In particular, the model does not describe current fluctuations that were experimentally measured in non-living soft systems as well as in living cells¹⁹. To accommodate for state fluctuations, an analysis of the thermodynamic susceptibilities is necessary. These aspects should be considered in a future work.

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Author Contributions

M.M. and M.F.S. devised the project and the main conceptual ideas. M.M. performed the computations. M.M. and M.F.S. wrote the manuscript.

Additional Information

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