Anomalous glassy dynamics in simple models of dense biological tissue

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Abstract – In order to understand the mechanisms for glassy dynamics in biological tissues and shed light on those in non-biological materials, we study the low-temperature disordered phase of 2D vertex-like models. Recently it has been noted that vertex models have quite unusual behavior in the zero-temperature limit, with rigidity transitions that are controlled by residual stresses and therefore exhibit very different scaling and phenomenology compared to particulate systems. Here we investigate the finite-temperature phase of two-dimensional Voronoi and Vertex models, and show that they have highly unusual, sub-Arrhenius scaling of dynamics with temperature. We connect the anomalous glassy dynamics to features of the potential energy landscape associated with zero-temperature inherent states.

Introduction. – How do materials become rigid? In materials that crystallize, rigidity coincides with increasing structural order and a corresponding broken symmetry. A large class of molecular fluids can, however, be supercooled past this crystallization point, and along this path their viscosity $\eta$ increases sharply with no obvious corresponding changes in the structural order. In practice, a material is deemed a rigid glass when either $\eta$ or $\tau$, the time scale characterizing the relaxation of density fluctuations, exceeds some threshold value [1].

In simulations or experiments, the onset of rigidity is typically identified by plotting relaxation time data in an “Angell plot,” $\log(\tau)$ vs. $T_G/T$ [1], where the glass transition temperature $T_G$ is the temperature at which $\tau$ grows past some threshold. Strong glasses are straight lines on such plots, and fragile glasses strongly curve upwards. In a simple Arrhenius model for activated dynamics, the slope of the Angell plot is the energy barrier $\Delta E$ required for activation, suggesting that fragile glasses are “super-Arrhenius,” with energy barriers that grow as the temperature decreases. This has driven intense experimental and theoretical studies of glassy systems, with a focus on understanding how the growth of $\Delta E$ as the temperature decreases may or may not be a signature of a diverging length scale in the problem [2–4]. Despite these efforts, the mechanisms underlying disordered rigidity, even in very simple systems, are still under active study.

Recent observations of glass-like transitions in dense biological tissues [5–8] may seem even more difficult to explain, given that cells are themselves complex entities. Over the past 20 years scientists have coalesced around simple classes of vertex and cellular Potts models of dense tissues that have been remarkably predictive of cellular structures and mechanics [9–13]. Recently, these models were shown to exhibit some features of glassy behavior [14–16], but are the glass transitions in these models for biological tissues similar to or different from those in simple fluids? This question, which is of clear interest to biophysicists, is also pressing from a fundamental theoretical perspective, as vertex models have several unusual features that may help to shed light on the basic mechanisms for glassy rigidity in non-biological systems.

Even though real cells are far from equilibrium and have many more degrees of freedom than captured in these simple models, understanding the equilibrium behavior of such models establishes a crucial baseline for interpreting the past literature and for future studies of these systems.

Much work in statistical physics has focused on understanding how the $T = 0$ rigidity transition in particulate matter (called the jamming transition) might inform our understanding of finite-temperature glassy behavior [17]. There is significant evidence that the excitations responsible for viscosity in supercooled liquids are
strongly correlated with the vibrational normal modes of the $T = 0$ inherent states [18,19]. Some vertex-like models also have a $T = 0$ rigidity transition [20,21] but the mechanisms that drive rigidity in these systems are very different from those in particulate matter. The jamming transition is often viewed through the lens of “constraint counting,” where the number of zero-energy motions ($N_{dof}$) of the system and patterns of stress the system can support ($N_s$) is balanced against the number of degrees of freedom ($N_{dof}$) and the number of constraints ($N_c$) [22]. Particulate systems undergo a rigidity transition by increasing the number of constraints (particle-particle contacts), which decreases the number of zero energy modes until there are none left. In contrast, vertex-like models can rigidify not by changing the number of constraints, but by changing the pattern of stresses the system can support [23], resulting in exotic mechanical states at zero temperature [24] and scaling laws that are different from those in particulate systems [25]. Given this, it is natural to wonder whether their glassy dynamics is similarly unusual.

In this manuscript we focus on 2D vertex-like models that represent a dense tissue as a tiling of space, in which each tile corresponds to a coarse-grained representation of a cell. In vertex models the cells are polygons (or more generally, d-dimensional polyhedra), and the vertices of the polygons are the degrees of freedom. Recent work has identified an alternative for modeling tissue, taking each cell to be a local Voronoi volume [15,26]. The degrees of freedom, thus, are the Voronoi cell centers, with some evidence suggesting that cell nuclei position themselves at the centers of Voronoi cells defined by their surrounding neighbors [27,28]. In both of these vertex-like models, the degrees of freedom are controlled by an energy functional which specifies quadratic constraints tethering each cell to some preferred generalized volume and surface area (e.g., cross-sectional area and perimeter in 2D).

Unlike particulate jamming, which is marginally stable precisely at the transition density [17,22], the 2D Voronoi model at $T = 0$ is always at the marginal point, with precisely balanced constraints and degrees of freedom [21]. The 2D vertex model, on the other hand, has a bona fide $T = 0$ rigidity transition [20]. Although the $T = 0$ behavior of these two models seems quite different, the 2D Voronoi model has a nearby avoided critical point that may be in the same universality class as that of the vertex model. We find strong similarities in their finite-temperature dynamics, which suggests that they may both be dominated by that critical point.

Our goal is to study these models’ glassy behavior and compare it to the observations made in simple molecular fluids. Strikingly, we show that these models have very unusual fluid-phase dynamics, with no crossover to standard Arrhenius or super-Arrhenius glassy dynamics even when $\tau_a \gg 1$. In the 2D Voronoi model this can be associated with a low-energy vibrational mode spectrum very different from that seen in particulate matter, which we relate to the marginal $T = 0$ phase of the model.

Models and methods. –

**Voronoi model.** We perform dynamical simulations where the forces on each degree of freedom are computed in terms of the Voronoi tessellation derived from the instantaneous cell positions. We note that recently a “Voronoi liquid” has been proposed where a force is defined that moves each Voronoi position towards the centroid of the Voronoi cell to which it belongs [29,30]. Here we study the biologically motivated forces described by gradients of the vertex energy functional described below; it would be interesting to understand any relationship between these two different models. A dimensionless version of the standard vertex energy functional is [15,20,31]

$$e = \sum_{i=1}^{N} \left[ k_A (a_{i} - a_{0,i})^2 + (p_i - p_{0,i})^2 \right].$$

Here $N$ is the total number of cells, $a_{i}$ and $p_i$ are the area and perimeter of cell $i$, and we have chosen the unit of length so that the average area of the cells in the simulation ($\langle a \rangle = 1$). The “preferred” or target values of these geometric quantities are $a_{0,i}$ and $p_{0,i}$, and $k_A$ governs the ratio of the area stiffness to the perimeter stiffness of the cells.

We use a recently developed hybrid CPU/GPU software package, cellGPU, to simulate overdamped Brownian dynamics of the vertex and Voronoi models [32,33]. The positions of the cells are updated at each time step according to $\Delta r_{ia} = \mu f_{ia} \Delta t + \eta_{ia}$. Here $\Delta t = 0.01 \tau$ is the integration time step simulated, $\tau$ is the time unit given by the inverse friction coefficient $\mu$, $f_{ia}$ is the force acting on cell $i$ in direction $a$, and $\eta_{ia}$ is a normally distributed random force with zero mean and $\langle \eta_{ia} (t) \eta_{ib} (t') \rangle = 2 \mu T \Delta t \delta_{ia} \delta_{ab}$ [34]. The temperature $T$ sets the scale of translational noise applied to the cells at each time step.

Initial works studying the Voronoi model have focused on monodisperse systems, but just as in particulate settings there are model parameter regimes in which monodisperse Voronoi packings have a tendency to crystallize into hexagonal ground states [21,35]. To maintain our focus of the disordered solid regime, we work with bidisperse mixtures of cells with different preferred geometric quantities. Inspired by disk packings that frustrate the hexagonal lattice [36], we choose a 50 : 50 mixture of $N = 1024$ cells with $a_{0,a} / a_{0,b} = 4/3$ for cell types $\alpha$ and $\beta$. We then scale the preferred perimeters of the cells so that the dimensionless target shape parameter $q_0 \equiv p_{0,i} / \sqrt{a_{0,i}}$ is identical for all cells.

**Vertex model.** In addition to the Voronoi model, we also simulate a thermal version of the vertex model controlled by the same energy functional, applying thermal noise directly to the vertices of each cell [37]. Unlike the Voronoi model, which takes care of cell-neighbor exchanges by continuously updating the Voronoi tessellation, in vertex models one must explicitly handle rules for how cells undergo “T1,” or neighbor-exchange, transitions. Here we implement a scheme in which T1 transitions
occur whenever two vertices are closer than some threshold value, which we take to be \( t_c = 0.04 \).

For every Voronoi or vertex model state point \((q_0, T)\) of interest we run 100 independent simulations. All simulations are thermalized at their target temperature for \(10^4\tau\) before recording data, and we perform simulations of maximum length \(10^5\tau\). Below we restrict our analysis to systems with a characteristic relaxation time \(\tau_\alpha \lesssim 10^4\). We find qualitatively similar low-temperature behavior in the vertex and Voronoi models, so below we focus on the Voronoi model results. Vertex model data can be found in the supplemental material [supplementary material.pdf](SM).

**Dynamical properties of the glassy phase.** – We begin by characterizing the relaxation time as a function of temperatures and preferred shape using the decay of the self-overlap function [38]. This function measures the fraction of cells that have been displaced by more than a characteristic distance \(b\) after a time \(t\),

\[
Q_b(t) = \frac{1}{N} \sum_{i=1}^{N} w(|r_i(t) - r_i(0)|),
\]

where \(r_i\) is the vector position of cell \(i\), \(w\) is a window function, \(w(r \leq b) = 1\) and \(w(r > b) = 0\). The cutoff \(b\) plays a very similar role to a choice of \(q\) when looking at the decay of the self-intermediate scattering function,

\[
F_s(q,t) = N^{-1} \langle \sum_i e^{iq(\langle r_i(t) - r_i(0) \rangle)} \rangle .
\]

Below we follow convention and look only at the decay of the larger cell species, and choose \(b = \sqrt{\alpha q}/2\). Figure 1 illustrates the behavior of \(Q_b(t)\) for the bidisperse Voronoi model at moderately low preferred shape parameter, \(q_0 = 3.75\), with \(F_s(q,t)\) shown in the SM. Just as in simple fluids the onset or relaxation is delayed as the temperature decreases, but there is a much less pronounced plateau in the decay of the scattering function compared to a standard glass former.

One can also define a characteristic scale by looking at the four-point susceptibility, \(\chi_4\), shown in fig. 1. Letting \(\delta F_s(q,t)\) be the difference between the instantaneous value of the scattering function and the mean, one has \(\chi_4 = N(\delta F_s(q,t)\delta F_s(q,t))\), where \(\chi_4\) is evaluated at \(q\) corresponding to the maximum of the static structure factor [39]. The growth of the peak of \(\chi_4\) as the temperature is lowered, often interpreted as a measure of the size of collectively rearranging regions, is again reminiscent of a standard glassy system and suggestive of a slowly growing length scale that goes from sub-cell scale to \(\sim 2 \sqrt{\alpha q}\).

From the decay of the overlap function we define the characteristic relaxation time of the system, \(\tau_\alpha\), via \(Q_b(\tau_\alpha) = 0.2\), i.e., the time at which most of the large cells have been displaced by a magnitude of order their own size. One can define a structural order parameter, \(\langle q \rangle = \langle p_\alpha / \sqrt{\alpha q} \rangle\), and in the vertex model it was shown that this is an excellent indicator of the \(T = 0\) rigidity transition [40]. The inset to fig. 2 combines these dynamical and structural data, where the mean shape of the cells is encoded in a heat map and a line corresponds to a dynamical transition at which \(\tau_\alpha = 10^4\). There is a significant decoupling between the dynamical transition and a structural transition defined purely by measuring static structural properties of the system. In this sense the Voronoi model fits neatly into the standard paradigm of glass-forming liquids, and this decoupling is in keeping with the expectation based on the work in the athermal limit of the monodisperse model [21].

In fig. 2 we plot the \(\alpha\)-relaxation time data in the Angell plot representation discussed in the introduction, and it reveals strikingly anomalous behavior. Remarkably, the Voronoi model displays *sub-Arrhenius* scaling of the relaxation time as the temperature is lowered. Even though the relaxation time grows to be quite large, the model continues to look closer to a fluid in some ways than to a standard glass. This sub-Arrhenius behavior suggests that either typical glassy energy barriers in the Voronoi model *decrease* in colder glasses, or that a local picture of activated dynamics does not hold; both scenarios are highly unusual in the context of standard glassy materials. The results for the vertex model are qualitatively identical, as we show in the SM. This confirms that the sub-Arrhenius behavior is a generic feature of these vertex-like models.
Fig. 2: (Color online) Angell plot of log relaxation time vs. inverse temperature in the Voronoi model, normalized so that \( T_g \) is the temperature at which \( \tau_n = 10^4 \). The different curves correspond to \( q_0 = 3.725, 3.75, \ldots, 3.9 \) (dark red to light green). Strikingly, in this representation the Voronoi model exhibits sub-Arrhenius scaling of the relaxation time with temperature. We further highlight this by presenting data from a 3D Kob-Andersen mixture of Lennard-Jones particles at density \( \rho = 1.2 \) (black circles, data from ref. [41]). Inset: color map of the mean measured shape parameter, \( \langle q \rangle \), as a function of \( q_0 \) and \( T_g/T \). The dashed red line corresponds to a line of constant \( \tau_n = 10^4 \).

Structural properties of the glassy Voronoi phase. – To better interpret the anomalous glassy dynamics reported above, and to understand the connection between these dynamical results and the \( T = 0 \) behavior of the Voronoi model [21], we investigate the vibrational mode structure of the inherent states of our various thermal configurations. In particular, for equilibrated \( (q_0,T) \) state point configurations we use a FIRE energy minimization algorithm to find a nearby energy minima [42]. We then compute the dynamical matrix, \( D_{ij} = \partial^2 E/\partial r_i \partial r_j \), corresponding to these energy-minimized configurations. The eigenvectors of this matrix are the vibrational modes with frequencies \( \omega_i = \sqrt{\lambda_i} \), where \( \lambda_i \) are the eigenvalues.

We find that the only zero energy modes of the Voronoi model dynamical matrix correspond to the trivial translational modes, so the energy minima are always mechanically stable. This is in contrast with the vertex model, which has a landscape with many flat directions above \( p_c \approx 3.81 \), corresponding to a large number of non-trivial zero modes [13,20]. The inset of fig. 3 plots the result of quenching from a relative high temperature and varying \( q_0 \); consistent with the infinite-temperature quench studies in ref. [21] we find that as \( q_0 \) increases there is an increasing population of low-frequency modes.

The main frame of fig. 3 reveals a structural feature of these energy minima which is also strikingly unusual. The energy minima of colder Voronoi fluids have more low-frequency vibrational modes. This is in stark contrast to the standard picture of the glassy energy landscape, in which the inherent states of glasses prepared at lower temperatures have fewer low-frequency modes available [43]. This does not appear to be a consequence of changes in the local structural order of the inherent states (e.g., local bond-orientational order parameters), which do not show any clear differences in this parameter regime.

In molecular fluids and particulate matter, researchers have begun to establish a connection between the landscape curvature and energy barriers: lower eigenvalue modes typically have lower associated energy barriers [44,45]. Such a connection has not yet been established in vertex-like models, but it is natural to conjecture that the flatter landscape we find at low temperatures may give rise to lower-energy barriers and sub-Arrhenius dynamics. However, we find that the spatial structure of these modes is very different from those in particulate glasses. Specifically, the quasi-localized (QL) low-frequency modes that are common in particulate glasses are not found in the Voronoi model. In fig. 3 we also plot the inverse participation ratio (IPR), \( Y(\omega) \), defined for mode \( u_i \) by

\[
Y(\omega) = \frac{\sum_{j=1}^N |u_j(\omega)|^4}{\left[ \sum_{j=1}^N |u_j(\omega)|^2 \right]^2}
\] (4)

This measures the degree of localization for each eigenmode, where \( Y = 1 \) corresponds to a mode localized to a single cell and \( Y \sim 1/N \) corresponds to a completely
extended mode involving every cell in the system equally. In both jammed [44] and glassy [46,47] particulate systems there is clear evidence that the softest (lowest-frequency) non-plane-wave modes are quasi-localized, involving a core of potentially rearranging particles with an elastic tail. In strong contrast, we see that essentially all of the low-frequency modes in the Voronoi model are collective, much like the disordered modes in the plateau of the density of states in jammed systems. Thus, the density of states supports an interpretation in which the anomalous dynamics result from potentially decreased energy barriers at lower temperatures, and the eigenmode structure suggests that, at least in linear response, localized excitations are not dominating glassy dynamics in these systems.

**Discussion.** — Through extensive Brownian dynamics simulations we have demonstrated that the low-temperature fluid phase of vertex-like models have very unusual dynamics. Although the characteristic relaxation time in the disordered phase grows as the temperature is decreased, this growth is slower than exponential in the inverse temperature. We further studied the inherent states of the 2D Voronoi model after thermalization at many different temperatures; this data was consistent with the unusual dynamics observed and revealed that colder glasses were in characteristically softer energy minima.

We show in the SM that replotting fig. 2 on a log-log scale suggests that the relaxation time of the Voronoi model has a power-law form even for $\tau_0 \gg 1$. The larger-$q_0$ state points show a scaling of $\tau_0 \sim T^{-3/2}$ over the entire range of temperatures studied, whereas simulations at lower $q_0$ are perhaps crossing over from power-law scaling at high temperatures to another form at very low temperatures. As seen in fig. 2, though, we never observe a clean Arrhenius scaling over any substantial range of $T$.

Such a power law scaling has been observed in geometrically frustrated versions of the two-dimensional XY model [48] and attributed in part to the phenomenon of avoided criticality. It may be fruitful to think of the Voronoi model behavior in terms of an avoided critical point [21]. The $T=0$ Voronoi model does not have an unjamming transition, but it is close to models that do, either by taking $k_A \rightarrow 0$, by moving from flat space to a space of non-zero Gaussian curvature so that disordered Voronoi geometries can satisfy all of their energetic constraints, or by removing the constraints that every cell adopts a Voronoi geometry (i.e., by studying a vertex model). In the SM we also provide data for the dynamics of the vertex model evolving according to the same energy functional, and show that the low-temperature dynamics are similar.

Although for large $q_0$ there appears to be power-law rather than activated dynamics, we have been, as yet, unable to find an accompanying diverging length scale in the model. At zero temperature we have observed that the mechanical rigidity transition is completely collective, with no signature of growing regions of mechanically stable cells. An important question, then, is whether such a static length scale can be observed and used to formulate a better theoretical understanding of these cellular models — certainly the apparent absence of activated dynamics suggests that they may be more easily understood than typical glassy systems. This is particularly interesting in light of the slow growth of the peak of $\chi_4$ seen in fig. 1, which suggests the possibility that nonlinearities are a key to understanding structural length scales in this model.

The statistics of the linear properties of the energy landscape that the Voronoi model explores at different temperatures, i.e., the vibrational mode frequencies and their spatial structure, is quite striking. The fact that lower-frequency modes are available to the system at colder temperatures suggests that residual stresses —which are the mechanism of zero-temperature rigidification in the vertex model and underconstrained versions of the Voronoi model [49], as well as in crystalline Voronoi models [23]— may also be crucial to understand the finite-temperature behavior of these models. We speculate that these unusual dynamics may be a signature of broad classes of residual-stress-rigidified systems, such as underconstrained Mikado models with strain-controlled rigidity transitions [50].

We also find that the low-frequency modes are collective, rather than the quasi-localized modes typically seen in particulate glasses. In conventional glasses the QL mode frequencies are known to strongly correlate with the scale of the energy barriers to motion in the direction of those modes [44,51], which makes the modes a natural way to understand the rearrangement dynamics that drive structural relaxation. The fact that we do not observe such QL modes suggests that either the cellular rearrangements are fundamentally less local in the Voronoi model, or that the tight connection between linear and non-linear behavior seen in particulate settings may not hold here. Future research should resolve precisely this issue and provide an understanding of whether the energy barriers associated with collective modes evolve with temperature in the same way that barriers associated with QL modes do. Natural approaches include either directly studying the statistics of the energy barriers in the model or by using machine-learning methods to infer such features [52,53].

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