

Self-organization and the physics of glassy networks

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Network glasses are the physical prototype for many self-organized systems, ranging from proteins to computer science. Conventional theories of gases, liquids and crystals do not account for the strongly material-selective character of the glass-forming tendency, the phase diagrams of glasses or their optimizable properties. A new topological theory, only 25 years old, has succeeded where conventional theories have failed. It shows that (probably all slowly quenched) glasses, including network glasses, are the result of the combined effects of a few simple mechanisms. These glass-forming mechanisms are topological in nature and have already been identified for several important glasses, including chalcogenide alloys, silicates (window glass and computer chips) and proteins.

‘Some four thousand years ago man discovered glass in the embers of a fire built somewhere in the deserts of the Near East. A few years from now ultratransparent glass fibers will be transmitting [much, much, much!] more information than copper wires’ [1]. As foreseen 25 years ago, the Internet has indeed revolutionized our world. In this article certain phrases will appear in braces {}; the interactive reader will find background on the {} topics with his or her Internet browser. What was unforeseeable 25 years ago was the discovery of an important new class of *electronic* glasses, namely doped cuprates, exhibiting not only high-temperature (about 100 K) superconductivity, but also ‘strange metal’ transport anomalies right up to the annealing temperature (700 K)—a sure sign of electronic glassy arrest. Theory has identified two new topological phase transitions in network glasses, and a new topological phase characterized by self-organization; it appears that this new phase is also responsible for high-temperature superconductivity in the cuprates. Finally, there is an exciting new bridge between physics and biophysics, based on analysing strain

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in protein networks using methods parallel to those used for strain in network glasses.

Glass is so much a part of our daily lives that we take its properties for granted. The most important glasses (such as window glass) have aperiodic and yet microscopically homogeneous network structures. Glasses are solids formed by slowly quenching melts to temperatures far below their equilibrium melting points, and they can remain in their metastable states indefinitely. Physical glasses (not just network glasses, but also molecular glasses, commercial polymers, the optimized electronic networks of cuprates, and collapsed folded peptide chains of proteins) all share an essential property: they are {space-filling} (or nearly so) *networks*. Mathematicians have studied {space filling} by {sphere or polyhedral packing} in great detail, but the way in which network glasses are connected to fill space is different (much more abstract), and the differences are very important in practice.

The origin of these differences lies typically in skeletal constraints that define the network configuration. Figure 1 shows examples of such constraints, here represented by nearest-neighbour springs for an $N=4$ -membered cluster in $d=2$ dimensions. In real glasses, constraints are imposed not just by nearest-neighbour contacts (bond stretching) (here called σ (strong) forces, as occurs for sphere packing) but also for π forces (bond-bending weaker three-body forces). The radius of a cluster of N atoms increases as $N^{1/d}$, where d is the dimension, and the forces decrease with increasing distance but, at the same time, the number of possible cluster configurations increases as e^N , leading to statistical problems of exponential complexity. These topological problems are well known to mathematicians, who describe them as ‘not polynomial (NP) complete’. (We prefer the description {exponentially complex}.)

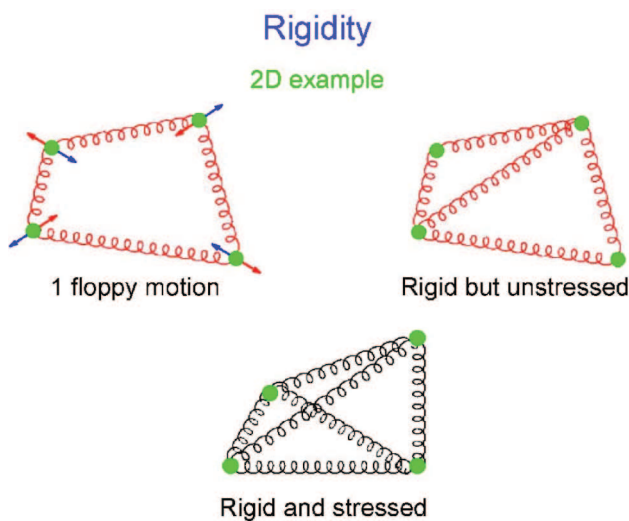


Figure 1. Three examples of elastic network skeletons in two dimensions with nearest-neighbour forces only. A quadrilateral is floppy (isostatic, stressed) with no (one, two) cross braces. Note that there are eight degrees of freedom for the four atoms, but three of these are associated with two translational and one rotational rigid modes. Each spring here is an independent constraint.

A familiar example of an {exponentially complex} problem is the travelling salesman, who should visit randomly placed cities along the shortest path; many combinatorial problems are {exponentially complex}. There are now computer algorithms that have solved problems of 25 000 cities in ‘only’ 70 computer years (parallel processing). However, these graphic methods do not include the physical restriction that the cities form a space-filling megapolitan network, and so they cannot be extended to network glasses or proteins.

The exponentially great simplification brought about by the space-filling network restriction is embodied [1] in a very simple and yet extremely far-reaching idea: the number of interatomic Lagrangian constraints (he and we count the number of potentials and *not* the number of Newtonian forces) N_c that are intact at the glass transition temperature T_g should equal the number N_d of degrees of freedom. There are three possible cases (figure 1). If $N_c < N_d$, the underconstrained glass is ‘floppy’, and it could freely crystallize while, if $N_c > N_d$, the glass would be rigid and stressed and could relieve the stress by crystallizing exothermally (in practice, severely overconstrained materials such as amorphous Si films do not melt; they crystallize explosively when heated). When $N_c = N_d$, the network is rigid and yet stress free. In this ideal case (called ‘isostatic’), the dynamics of the glass are arrested because it is trapped ‘in limbo’ [1]. Intact constraints can be identified in diffraction or optical data as anomalously narrow peaks, but is this idea really correct? Does it ‘miraculously’ identify the optimally space-filling, exponentially small fraction of configuration space that is glassy?

It does quite well (sufficient precision (about 1%) for practical purposes, as confirmed by many experiments), and figure 2a shows the quantitative results [2]. One can construct space-filling, tetrahedrally coordinated models of amorphous Si, disordered in various ways, and then dilute the connectivity of the network by striking out bonds at random until the average coordination number has been reduced from four to nearly two. At this level the network has begun to fall apart into disconnected chain segments, and there are many cyclical (zero-frequency) vibrational modes. In reality, weak additional forces will give these modes a small finite frequency of a few wave numbers and so we shall refer to them as floppy modes. One now adds cross-linking bonds at random, and the number of such floppy modes decreases. Remarkably, that decrease is nearly linear in the average coordination number $\langle r \rangle$, and the latter itself is linear in the number of intact constraints; it extrapolates to zero at the mean-field value of $2.40 = 12/5$ (calculated theoretically from σ and π constraints). More sophisticated numerical simulations [3,4] have shifted the transition to 2.39.

Cyclical, or Goldstone, modes play an important role in theoretical physics; they are usually explained as the result of some kind of symmetry. However, this disordered network has no obvious symmetries and, if one examines the vibrational matrix and counts the number of off-diagonal Newtonian forces generated by the three-body potentials, it is much too large to explain the large number of cyclical or floppy modes for $\langle r \rangle < 2.40$. This ‘counter-intuitive’ behaviour is dramatic evidence for the power of Lagrange’s concept of constraints (he and we count the number of potentials and not forces), here applied in the statistical limit where both N_c and N_d are large, but the fractional difference between them is small. It is fair to say that this idea, as confirmed in figure 1, has revolutionized our understanding of the

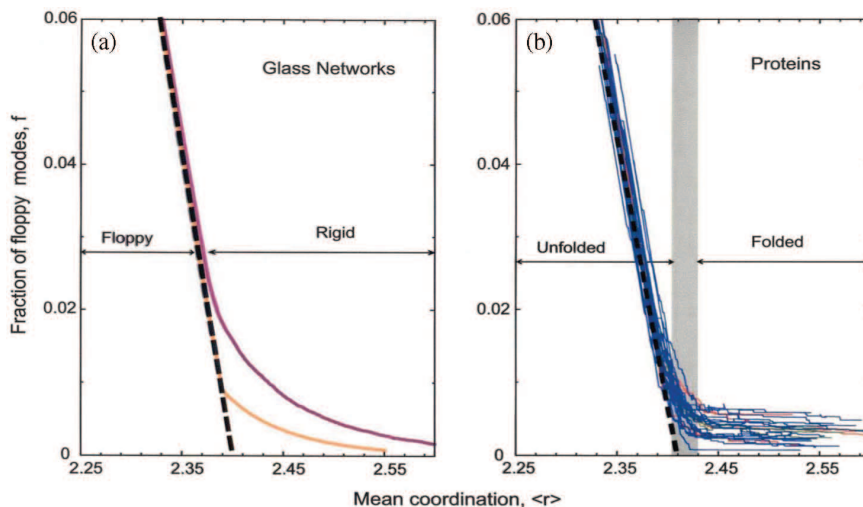


Figure 2. (a) The number of floppy (cyclical) vibrational modes per degree of freedom for a diluted diamond lattice with several thousand atoms. The random case gives a smooth curve, while allowance for the formation of percolative self-organized backbones suggests a first-order transition from floppy to rigid. (b) A similar plot for 20 proteins, each also involving several thousand atoms. The similarity is used to help to calibrate the relative strengths of hydrogen bonds and hydrophobic interactions, and to identify the transition states of the proteins [3].

microscopic nature of glass and other networks of atoms. This idea has sweeping implications; for instance, it shows that all the very common central force (sphere-packing) models of glasses are non-trivially incomplete. Experience has shown that liquids composed of atoms behaving as spheres (for instance, liquid Ar) always crystallize, no matter how rapidly they are quenched, and mixtures of Ar and Ne phases separate and crystallize, again no matter how rapidly they are quenched. Lagrangian constraints have enabled us to resolve the exponentially complex problem of why covalent network formers are so much better glassy materials than many other apparently promising candidates, and they have even told us where to look for the best covalent network formers. The actual calculations require no more than five easy lines of linear algebra.

The first dramatic experimental confirmation of the power of the 'limbo' concept came from Raman and Mössbauer experiments [5] on chalcogenide glass alloys (S and Se cross-linked by As, Ge, Si, Sn, etc.). These glasses form typical predominantly covalent networks, with elemental coordination configurations following the classical '8 - N ' rule of valence chemistry. The experiments examined the bond and site connectivity of the alloys and revealed that some kind of phase transition was occurring near $\langle r \rangle = 2.40$. An example is shown in figure 3 for (Sn, Ge)Se alloys. Replacing Ge (high melting point) with Sn (low melting point) dilutes the π bending constraints, and the 'limbo' composition is calculated to occur at 40% Sn, which is exactly where T_g collapses. Mössbauer site populations exhibit parallel behaviour.

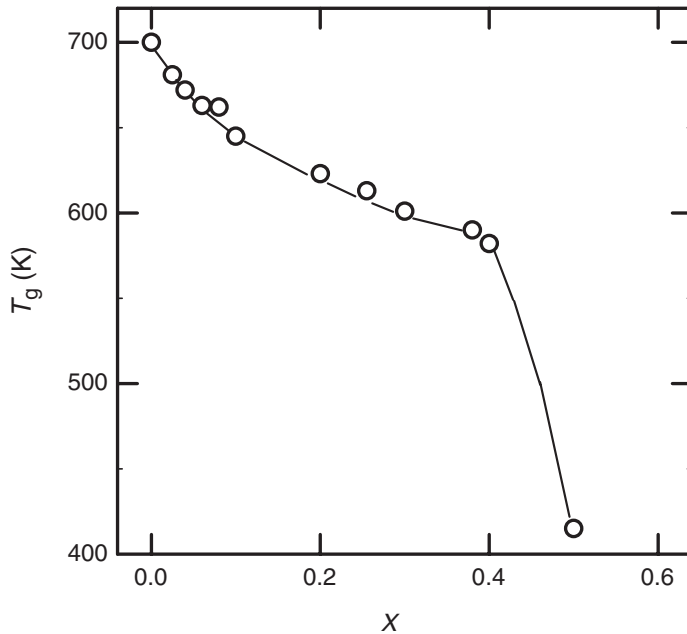


Figure 3. The glass transition temperature T_g in $\text{Sn}_x\text{Ge}_{1-x}\text{Se}_2$ glass alloys. At the predicted critical composition with $x=0.40$ the network softens dramatically [5]. Angular constraints are weak and so are ignored at the Sn ions but are strong and intact for Ge and Se ions.

Subsequent work repeatedly confirmed the existence of the stiffness transition at or very near $\langle r \rangle = 2.40$; later, however, it suggested [6] that there could actually be *two* closely spaced transitions, rather than just the one predicted by mean-field theory for a ‘random’ space-filling network. Between the two nearby transitions is a new glassy phase, the ‘intermediate phase’, which is strictly a *topological* phase. The phase has no special symmetry, but it does have a characteristic connectivity. It is a percolative phase, but the percolation is not occurring on a lattice, and it is not random. At first, one might think that non-equilibrium ‘off-lattice’ percolation behaves identically with equilibrium ‘on-lattice’ percolation, but this is apparently not the case. In a sense this is obvious, as there are two non-equilibrium stiffness transitions, which bound the non-equilibrium intermediate phase, and only one equilibrium critical point, with no intermediate phase. Of course, because this glassy phase is not an equilibrium phase, it is not a true phase in the sense of equilibrium thermodynamics. However, its boundaries with respect to composition are often sharp, justifying the terminology.

Some experiments have identified an equilibrium electronic intermediate phase, and the electronic cases often generate disputes involving complex quantum interactions. However, it appears that the same intermediate phase occurs in insulating network glass alloys, where quantum effects are secondary; in the latter the topological nature of the intermediate phase is unambiguous. The generic similarities between these intermediate phases are striking, and it seems quite probable that they all share a common topological origin.

Specific heat experiments on glasses have traditionally involved a technique called differential scanning calorimetry (DSC) but, when these are modified to include modulation with lock-in detection, one gains in two ways: accuracy is increased by an order of magnitude, and one now measures both the reversible and the non-reversible enthalpy of the glass transition. The new instruments are widely used in industry for quality control, especially of plastics, but are entering research practice only slowly. Figure 4 shows dramatic results for several glass transitions [7]. The non-reversible enthalpy of the transition varies extremely rapidly near the two stiffness transitions, dropping in favourable cases nearly to zero in the intermediate phase, and forming a 'reversibility window'. (Of course, all glass transitions are irreversible; this term is merely a convenient way to describe the very deep recently discovered valley, whose existence had previously not even been suspected.) Also shown is the much shallower (and unremarked) valley in a more traditional quantity, the logarithmic derivative of the viscosity in the melt, extrapolated to T_g , said to measure the 'strength' of the glass (loosely speaking, its resistance to crystallization, which decreases here by a factor of only 2 in the window). The database for chalcogenide alloy glasses includes many different compositions (20–30 for an alloy series) for many alloys (about ten). Overall the window spans a range of $\langle r \rangle$ from 2.28 to 2.52 [8] and is centred on 2.40(3). Clearly the reversibility window defines a glassy 'phase' that will have physical properties quite different from those of glasses with compositions outside the window.

The reversibility window is only one of the remarkable properties of the intermediate phase. It is also often a maximal *plateau* (not peak!) in molar density. (In other words, the result of the space-filling condition is at first an increase in density when chains are cross-linked, followed by a decrease when the network is overconstrained. However, in the strain-free [8] intermediate phase, across a narrow range of compositions the density is nearly constant as percolative strain-free backbones are added to the network. For this reason the intermediate phase can be said to be in isostatic mechanical equilibrium; isostatic is a term borrowed from hydrodynamics to describe the absence of nonlinear strain effects in the intermediate phase.) When one monitors the ageing or relaxation of the glassy network by changes in the non-reversible enthalpy of the glass transition over periods of the order of years (figure 5), there is almost no ageing in the intermediate phase [9] and substantial ageing outside it, a fact of great importance for quality control.

The discrete methods of set theory and topology used to describe glassy networks are also used in computer science. The parallels are more than casual; a 'phase transition' occurs between computable and non-computable problems which closely resembles the stiffness transition. Moreover, again there is an intermediate phase of intermediate (i.e. possible, but very difficult) computability [10]. The meaning of the word 'computability' has often been unclear, but the comparison between glassy networks and Boolean logical networks provides a clear-cut physical basis for the concept.

The discovery of a new inorganic phase in glasses, with a nearly reversible, nearly non-ageing character, opens new vistas for understanding non-equilibrium behaviour. Internal strain fields govern this behaviour; traditionally such off-lattice strain fields have defied our best efforts to achieve quantitative understanding. They are not

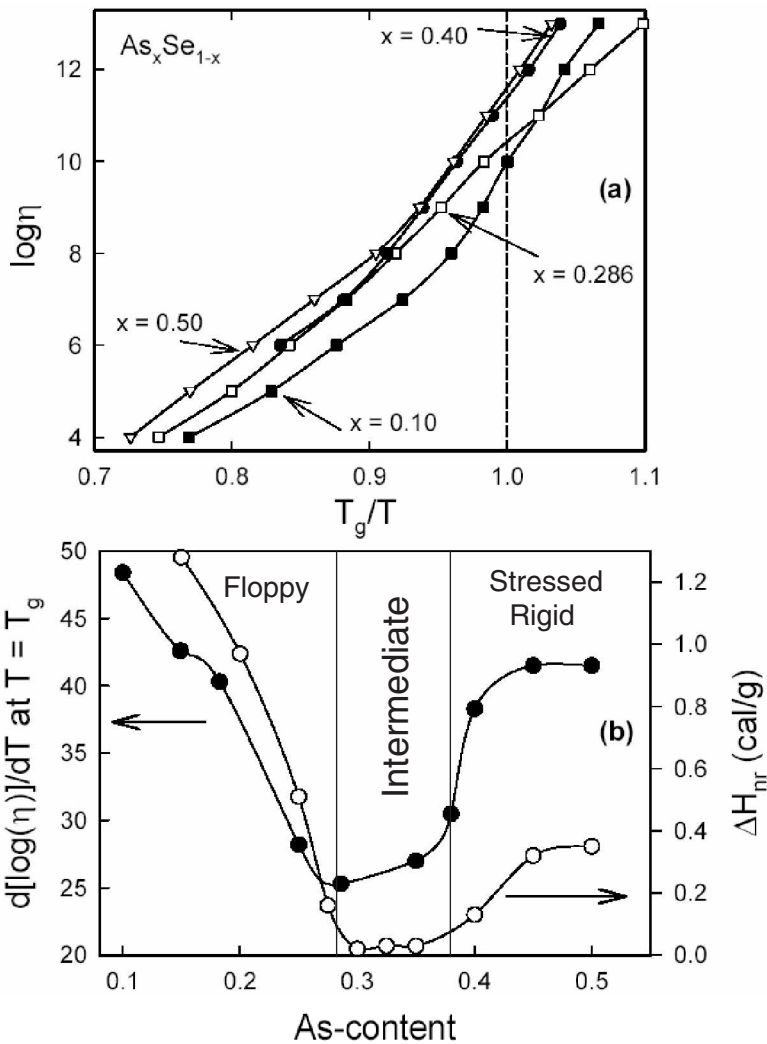


Figure 4. (a) Viscosity $\eta(T)$ of four $\text{As}_x\text{Se}_{1-x}$ glass melts as a function of temperature; a rare example of a glass alloy system for which such complete viscosity data are available. (b) Comparison of $d[\log(\eta)]/dT$ at T_g with the non-reversible enthalpy ΔH_{nr} of the glass transition as functions of x , as measured by modulated DSC. The latter are available for many alloys. Note the different base lines. The former drops by a factor of 2 in the window, whereas the latter drops by a factor of more than 10 (nearly to zero). Thus the reversibility window is resolved much more accurately by the modern method (modulated DSC), enabling its identification, and giving accurate estimates of its compositional boundaries [7].

only long range, but also non-local. They are easy to understand in the context of covalent crystalline heterointerfaces, where the lattice framework makes it easy to treat elastic misfit and {misfit dislocations}. Similarly in metals there are {shape memory alloys} whose properties are based on the presence of two microphases,

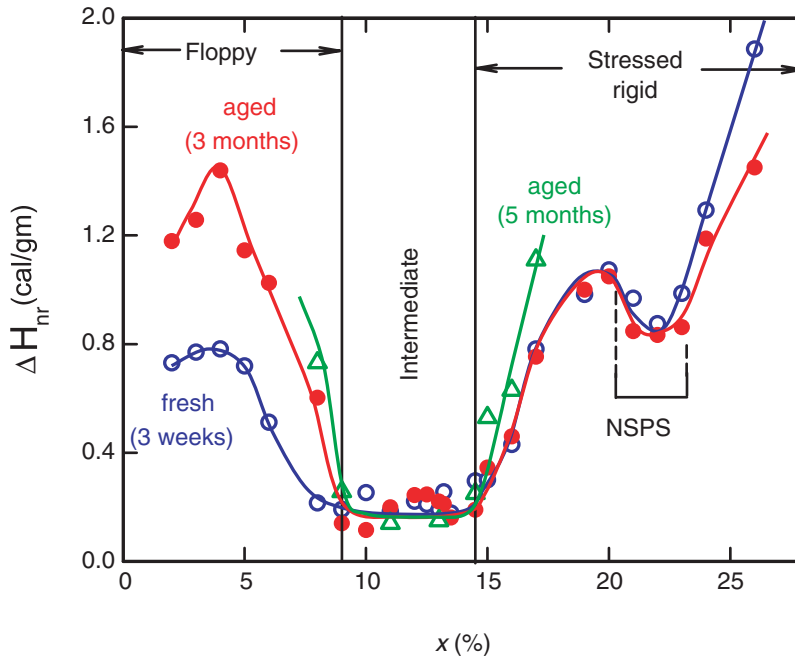


Figure 5. The special nature of glassy networks in the non-reversibility window is brought out in spectacular fashion by studying the ageing of ΔH_{nr} at temperatures well below T_g for periods of the order of months. Within the window, there is very little change but, outside the window, ageing causes large increases in ΔH_{nr} . Nanoscale phase separation of P_4Se_4 and P_4Se_3 molecules from the backbone results in the feature labelled NSPS. The alloy studied here is $Ge_xP_xSe_{1-2x}$ [9].

one stiff, and the other soft. Are there other applications of these very general concepts?

Consider window glass first; it may well be the material most responsible for modern civilization. Window glass is based on silica (SiO_2), but the melting point of SiO_2 is much too high for practical processing. So soda (Na_2O) is added to reduce the melting point at the eutectic, but the Na_2O creates non-bridging O dangling alkali ends ($-Si-O-Na$) that are reactive. Empirically it was found that adding lime (CaO) zips up these ends and makes window glass chemically stable. Can topology calculate how much Na_2O (x) and CaO (y) should be added to SiO_2 ($1-x-y$) to form window glass? It can! Na_2O is strongly ionic; so one has to modify the classical valence rules to recognize, as prescribed by Pauling, that there is only one resonating valence bond or Na ion. (Pauling's rules are also valid for complex materials such as the cuprates, discussed below.) Two conditions are needed to determine x and y . The first condition is global: the strain-free 'limbo' condition, while the second condition is local (for space filling by $Si-O-Si-O\cdots$ rings, the average number of rings passing through a cation should be the same as in crystalline SiO_2 , namely six). These two conditions are illustrated by the ternary phase diagram (figure 6); they give $x=0.16$ and $y=0.10$, in perfect agreement with commercial practice [11].

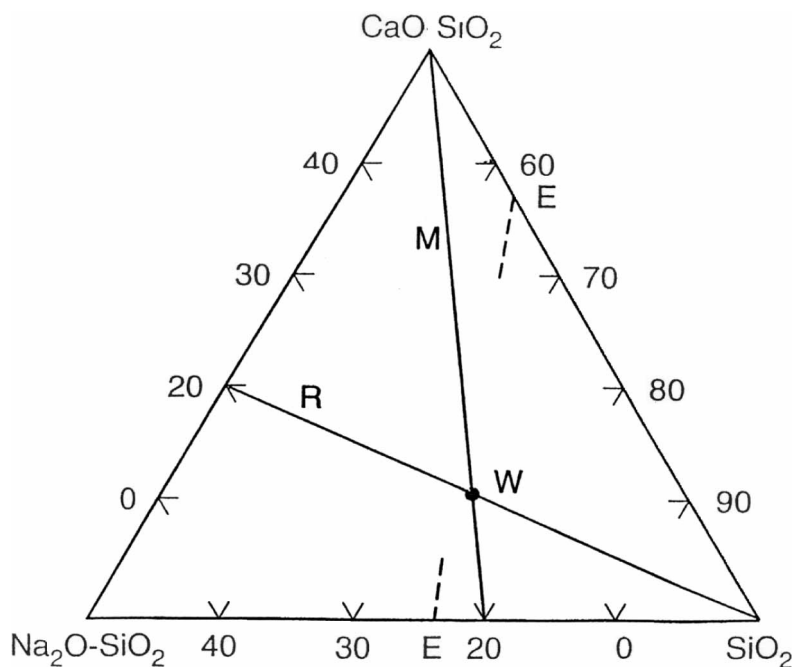


Figure 6. A ternary phase diagram for SiO_2 - Na_2O - CaO glass alloys. The line labelled M is the mean-field line for a global stress-free network, while the line labelled R represents the local topological condition of constant ring size. The dashed line segments labelled E are eutectics. The lines M and R intersect at W, which is the composition of window glass.

If the optimal composition of *ternary* SiO_2 - Na_2O - CaO mixtures to form window glass is determined by *two* topological conditions, what determines the optimal compositions of *binary* glasses, for instance sodium silicates? The two factors, global and local, compete, but the overall data pattern suggests that the global (stress-free network) condition dominates, with the local (space-filling) condition having only a secondary influence. Thus, as we saw above, the optimal average coordination number in chalcogenide glass alloys spans the range from 2.28 to 2.52 [8], but the average (over many binary alloys) is still the global or mean-field value 2.40(3). In effect the local geometrical factors cause deviations that average to zero over many different kinds of local packing, a gratifyingly simple result.

While window glass is very old, the next example is essential to modern electronics. A trick question is: why is it that computer chips are usually made from Si, rather than Ge? Ge has many electronic advantages, including higher carrier mobilities, lower Joule heating, etc. The reason is that electronic factors are usually secondary to a crucial materials factor, the perfection of the native oxide interface with 'the world outside', $\text{M}:\text{MO}_2$. For $\text{M}=\text{Si}$ this interface is nearly ideal, and the question is: how and why does crystalline Si form a nearly ideal interface with glassy SiO_2 ? The ideality of the $\text{Si}-\text{SiO}_2$ interface corresponds to a defect level near 10^{-4} , while simple misfit considerations (similar to those used for crystalline heterointerfaces) would lead one to expect defects levels of 10%.

{High- k dielectrics} (SiO_2 films doped with Zr or Hf) are now technologically interesting: what are their minimal defect densities? Topology explains the perfection of the undoped interface in terms of an SiO monolayer; it turns out that, when the constraints are calculated carefully, and allowance is made for breaking of π constraints involving non-resonant O–Si–Si interlayer bonds, this monolayer is actually isostatic, that is strain free, which means that it can be ideal. Moreover, the theory [12] enables one to identify the relevant chemical variables for both the defect (charge trapping) density (figure 7), which is the main factor limiting transistor speed, and the dielectric constants of the Zr- or Hf-doped films (figure 8).

The electronic applications of topological network theory are very interesting, but they involve a variety of quantum factors that the interested reader can study elsewhere [13]. There are a few points of general significance. Efforts are often made to describe the metal–insulator transition in semiconductor impurity bands, the intermediate phase of high-temperature superconductors and sometimes even the

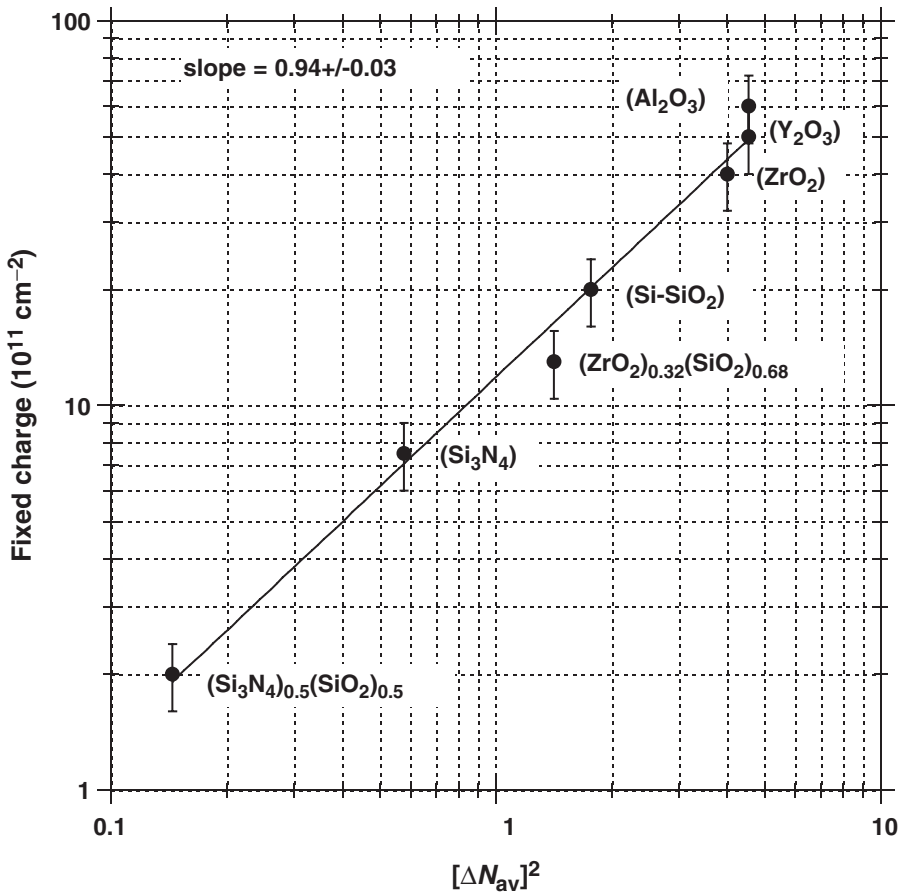


Figure 7. Fixed charge (trap density) at Si–dielectric interfaces for dielectrics of technological interest [12]. Here N_{av} is the average valence number of the dielectric and $\Delta N_{av} = N_{av} - 2.67$.

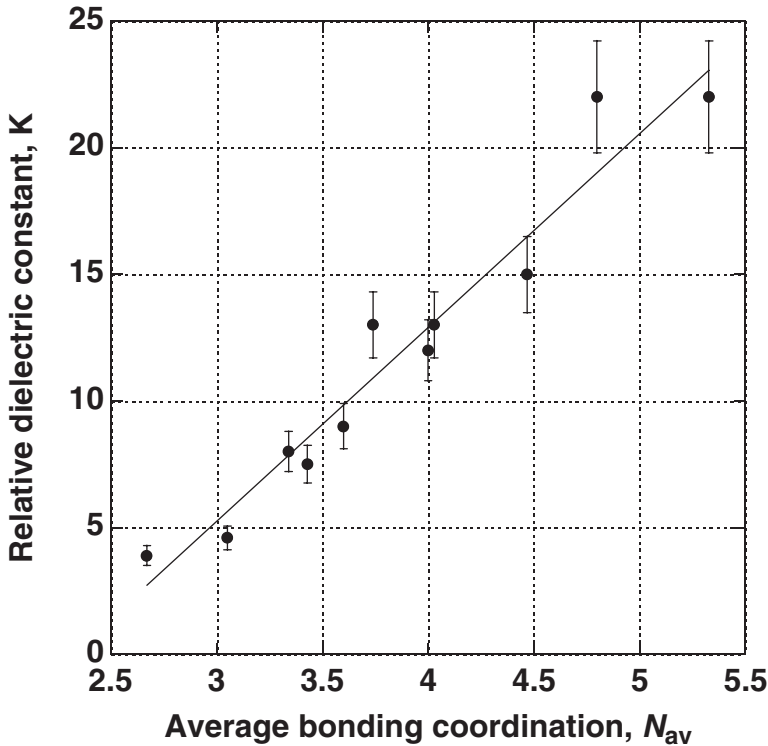


Figure 8. Dielectric constant k for many Zr- and Hf-doped dielectrics relative to SiO_2 . Here N_{av} is the average valence number of the dielectric [12].

molecular glass transition in terms of a *single* continuum phase transition and its associated critical point, but experiment does not support these efforts based on mean-field models. There are definitely two well-separated impurity band transitions, one electronic and one thermal, and there is an intermediate phase between them with scaling properties different from those predicted by continuum critical point theory. In the cuprates all the experimental evidence, including the isotope effect, supports a picture of three-dimensional glassy percolation along topological paths determined by minimizing strain and maximizing dielectric screening energies associated with dopants located *outside* the ubiquitous CuO_2 planes. The latter are crucial primarily for architectonic, and not electronic reasons; they are isostatic (strain-free) planar networks (much like the SiO monolayers discussed above), and they stabilize a soft network that would be otherwise insulating because of the {Jahn–Teller} effect.

Because better samples are now available, as well as synchrotron beams with higher intensity and better resolution, there is now a growing wave of evidence [14] for strong electron–phonon interactions in the cuprates; these also reflect enhanced interactions of carriers at the Fermi energy with disordered (glassy) dopants. This suggests that topological models of soft hosts and glassy dopants will play an increasingly important part in developing genuine understanding of the physics of high-temperature superconductivity. Many studies of older intermetallic

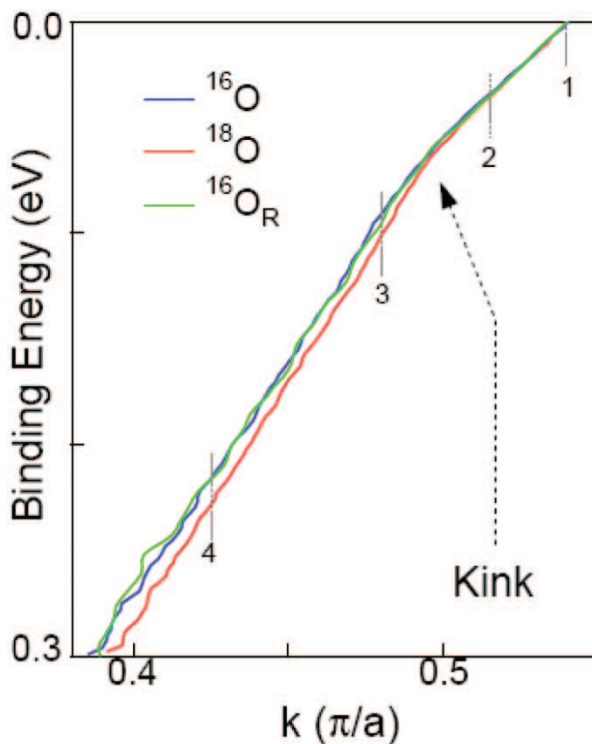


Figure 9. Isotope shifts measured by angle-resolved photoemission. There is a kink in the dispersion curve near 70 meV; above this kink (points 1 and 2, closer to the Fermi energy, set equal to 0) the isotope shift is small, and below it (points 3 and 4) the shift grows linearly. These shifts are inexplicable using polynomial methods (e.g. conventional polaron theory).

superconductors (such as NbN and Nb₃Sn) showed that the same strong electron-phonon interactions that produce high-temperature superconductivity also cause lattice instabilities that limit the attainable temperatures. Just as these limits are reached, one finds anomalies not only in vibrational dispersion curves, but even in the lattice constants themselves.

The most striking recent data [15] concern the effect on dispersion of quasiparticle states near the Fermi energy on replacing ¹⁶O with ¹⁸O (figure 9). Because of glassy arrest of the dopant configuration during sample annealing, the observed isotope effects on phonon fine structure in the cuprates show many anomalies. In particular, there is a kink in the dispersive curves at the Debye energy. Between this kink and the Fermi energy, the quasiparticle dispersion is almost unaffected by isotope exchange, but outside this band the effects are large. Moreover, the same separation into 'rigid' and 'soft' sets of states is seen when the dopant concentration is varied. Conventional quasiparticle (Landau Fermi-liquid) theory also predicts separate behaviours above and below the Debye energy, but the 'rigid' and 'soft' sets of states are reversed! This tells us that 'free'-particle models of any kind are inadequate, and that we are indeed dealing with a nanoscopic glass. High-resolution scanning tunnelling microscopy has observed similar two-phase separation into

larger gaps and smaller gaps [16]. Such behaviour is readily explained by the topological methods of constraint theory. The ‘rigid’ (soft) states below (above) the Debye energy are spectroscopically narrow (broad), which is much the same condition as was used to identify intact and broken constraints in network glasses.

Self-organized isostatic backbones immersed in soft matrices, even in space-filling inorganic networks, are strongly suggestive of the native states of proteins in water, collapsed by a combination of hydrophobic interactions in their cores and hydrophilic interactions nearer their surfaces [17]. Figure 2b shows the strong similarities in network topologies of proteins and glasses. Protein structures exhibit a high density of local close packing, characteristic of densely packed spheres, involving the side groups of the peptide chains.

Sphere-packing models [18], of course, include only σ (main-chain) interactions, whereas the dynamic properties of proteins near their transition states must be determined by primarily π (bending or shear) interactions. This suggests using hydrogen bonds and side group (amino acid) contacts to index protein structures near their transition states [3]. One begins with a mechanical model of the completely collapsed, static protein structure determined by diffraction and molecular dynamics (the ‘native’ state) and dilutes the connectivity by cutting hydrogen bonds and hydrophobic ‘tethers’, starting with the weakest. In this way, one arrives at the transition state, defined as a maximum in the free energy and the state at which non-trivial floppy modes first occur in significant numbers. (Just as with glasses (figure 2), this state occurs very close to an average coordination number of 2.40, which provides a model-independent topological *definition* of the transition state.)

This leads us to a paradox; paradoxes often occur in exponentially complex problems. Native structures are determined by combining structural information from diffraction with relaxation of the structure according to molecular dynamics potentials. In particular, the diffraction data are resolution limited and generally do not determine hydrogen bonding configurations. Thus a dynamic simulation technique is used to obtain the full *static* structure. However, for typical proteins containing 100 or more amino acids, the simulations of protein *dynamics* cannot be carried out for much more than tens of nanoseconds, whereas in reality protein (or glass transition) dynamics usually evolve over milliseconds. More generally, such difficulties are *characteristic* of {exponentially complex} physics, and they can be used to ‘prove’ that proteins cannot have evolved without some kind of special help; for a typical protein with $N \approx 100$ amino acids, there are about 10^{300} possible combinations of the sequences formed from 20 amino acids that determine the protein; this number of possible combinations could not have evolved haphazardly. (Biochemists call this {Levinthal’s paradox}.)

What is this special help that made the creation of proteins possible? In the intermediate state, which is presumably the state in which proteins are formed, the peptide chains are strain free. Mathematicians in a subfield called ‘graph theory of rigidity’ have studied the flexibility and rigidity of mechanical networks, following the first work of Maxwell [19] on scaffolds. Their work shows that, when two strain-free networks are interlaced, the combined network is also strain free. This simple additivity or closure condition has a startling effect on the combinatorial complexity of proteins; instead of being exponential in the number N of peptide units in the protein, the complexity is probably about N^2 , but nearly linear in N practically. Thus

placing protein dynamics, including protein formation, in the intermediate (strain-free) phase resolves {Levinthal's paradox} in principle, even though there may still be questions about the reliability of native structures and hydrogen bonds for any particular case. It also explains the origin of the mysterious and not easily quantified {folding funnels} that are popularly used to explain the evolutionary origin of protein functionality and reversibility [20].

A special algorithm [4], based on graph theory, called the {pebble game} identifies the rigid or overconstrained regions of a mechanical network and separates them from the soft regions. (Similar games are popular in computer science for solving hierarchical problems by variational techniques. Note that, in games, one attempts to maximize gain while minimizing risk. In the pebble game, connectivity is maximized while minimizing strain energy.) This leads to realistic pictures of the dynamic behaviour of proteins (such as the protein HIV protease shown in figure 10). Because of the Lagrangian simplifications inherent in restricting the structure to the intermediate phase, the calculations required to obtain such pictures take only minutes on a personal computer, even for very large proteins. Main-chain flexibility appears also to be critical to protein–ligand (drug) interactions (called docking), as illustrated in a study of binding of a candidate 'drug' molecule to a 165-amino-acid protein [21].

There have been many workshops and conferences devoted to the 'unconventional' topological topics discussed here [22, 23]. The general reader, however, may find it easier to assess the significance of the topological phase by considering it in the

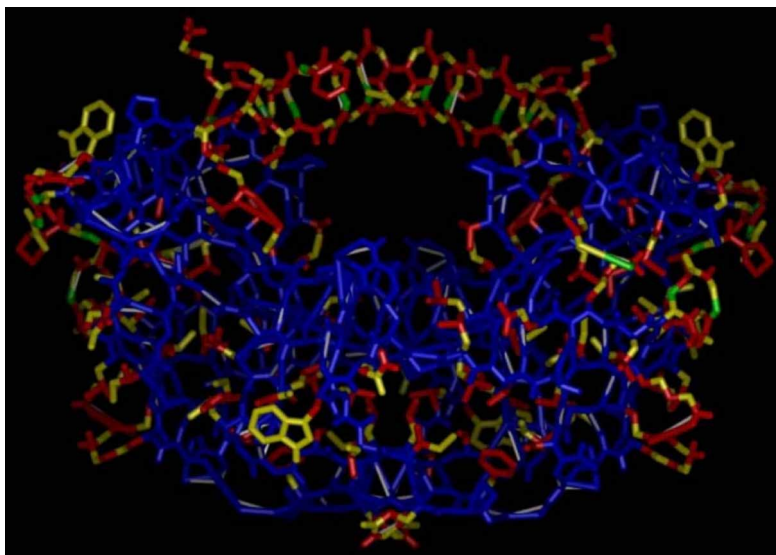


Figure 10. The protein HIV protease is a homodimer containing about 200 amino acid residues. It can be separated into flexible parts (shown in red, yellow and green) and a rigid core (shown in blue) using algorithms based on the pebble game [4]. The function of HIV protease can be inhibited by pinning the flaps at the top by the binding of an appropriate ligand.

context of the phase diagrams of impurity band materials. For a long time it was supposed that there was only one transition with increasing doping in these materials, the insulator–metal transition. According to one-electron energy band theory, homogeneous (undoped) crystals are insulators if there is a gap in energy between occupied and unoccupied discrete energy bands indexable by integers. Similarly, in metals, one has a Fermi surface defined by a continuum of states, so that topologically speaking the insulator–metal transition is one from integers to the continuum.

This kind of topological transition was first discussed in an entirely mathematical context by Cantor [24]; his ideas immediately created controversies. The great French mathematician Henri Poincaré described Cantor's theory of infinite sets as a malady, from which mathematics would someday be cured. In response, the equally famous German mathematician David Hilbert said 'no one would expel us from the paradise that George Cantor has opened for us'. Cantor had proved that the number of real numbers is infinitely larger than the number of integers; moreover, he conjectured that there was no set with an infinite 'size' *between* the integers and the reals. This is called the continuum hypothesis. (One might think that the rational numbers are just such a set, but Cantor showed that there are just as many rational numbers as there are integers.) Hilbert [24] identified Cantor's continuum hypothesis as the first of his list of 23 conjectures to be solved in the twentieth century and, while about half of the others have been proved, it now appears that the continuum hypothesis, which everyone had believed to be true, is still unprovable and must be treated as an independent axiom [24]. Physically this means that some disordered materials exhibit intermediate phases because of strong local fields, while others do not, because they are well described by mean-field theory.

In classical treatments of dynamically balanced granular materials, one finds qualitative differences between systems that depend on the validity of the continuum hypothesis. If it is valid, mean-field variables are continuous and smooth functions of space and time and are independent of the averaging length and time scales. Otherwise, the average variables may be discontinuous and scale dependent, but the same average balance equations hold within the framework of calculus of generalized functions [25]. The correspondences here with the physics of insulator–metal quantum transitions are quite striking. Homogeneous insulator–metal transitions apparently conform to Cantor's continuum hypothesis; there are no intermediate phases between the metal and the insulator, just as he had assumed that there were no intermediate sets between the integers and the reals. However, impurity band transitions take place in an intrinsically inhomogeneous medium, and in this rich context there *is* an intermediate phase, with a topological connectivity not describable by mean-field theory. There is also an intermediate phase in network glasses, but these are not in equilibrium. However, the intermediate phase associated with impurity band transitions apparently is in equilibrium. Its existence confirms the opinion of Paul Cohen, who was awarded the Field Medal for his work on set theory and the continuum hypothesis [24]. (It also suggests that any theorem whose proof involves the continuum hypothesis is valid only in the mean-field approximation and is not applicable to intermediate phases.) The fact that it is this intermediate topological phase that is also responsible for high-temperature superconductivity in the cuprates helps to explain why the latter has proved so resistant to the development

of theory [26]. In fact, one could even go so far as to say that Bednorz and Müller's discovery has provided the 'cure' requested by Poincaré.

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