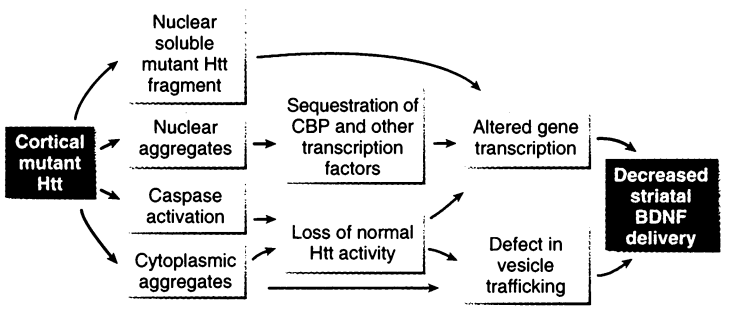
reaches nerve cells in the striatum by anterograde transport (*6*). Zuccato *et al.* show that BDNF mRNA and protein are decreased in the brain cortex of HD patients and of transgenic mice that express human mutant huntingtin (*7*). In the transgenic HD mice, a decrease in cortical BDNF correlated with a decrease in BDNF in the striatum, suggesting that the integrity of striatal cells may be compromised by a drastic reduction in cortical BDNF.



One too many glutamines. Mutant huntingtin (Htt) may decrease production and delivery of BDNF to striatal neurons. The mutant form of huntingtin has a tendency to form aggregates in the nucleus, which could sequester transcription factors needed to switch on BDNF gene expression. Alternatively, such aggregates in the cytoplasm could interfere with the trafficking of vesicles including those carrying BDNF by anterograde transport. However, mutant huntingtin also activates caspases (enzymes that induce cells to undergo apoptosis), which may lead to cleavage of wild-type huntingtin and to a partial loss of its beneficial activities. Black arrows indicate evidence of a causal connection, red arrows indicate connections yet to be proven, and blue arrows indicate hypothetical connections.

Impaired neuronal signaling was originally invoked to explain selective neurodegeneration of striatal neurons in HD (*8*, *9*). The striatum receives abundant excitatory glutamatergic projections from the cortex. Inducing excessive glutamatergic signals by treating rats with excitatory amino acid agonists results in many of the neuropathological changes found in HD, including the selective loss of striatal medium spiny neurons. In this rat model, BDNF prevents the death of striatal neurons (*10*). Depletion of cortically derived BDNF could render striatal medium spiny neurons more sensitive to excitotoxic stress.

How does mutant huntingtin decrease BDNF expression? With a reporter-gene assay, Zuccato *et al.* show that mutant huntingtin reduces transcription of the *BDNF* gene driven by three of the four *BDNF* promoters. Previous reports have implicated dysregulation of transcription in HD pathogenesis (*11*). It has been proposed that transcription factors and accessory proteins could become trapped by mutant huntingtin aggregates. Indeed, CREB-binding protein (CBP), a coactivator for the CREB transcription factor, has been found in nuclear inclusions in HD patient brains (*12*). Depletion of CBP may alter the regulation of many genes including those encoding neurotrophic factors. Intriguingly, *BDNF* gene transcription is known to be regulated by CREB (*13*, *14*). It will be interesting to learn whether CBP is involved in the decreased transcription of BDNF in HD patients.

Zuccato *et al.* propose a different (but not necessarily exclusive) mechanism for HD pathogenesis in which loss of the beneficial effects of wild-type huntingtin could play a part in the selective death of striatal neurons. Wild-type huntingtin in neurons is protective and can block processing of procaspase-9, an enzyme required for apoptosis (*15*). Switching off expression of the normal *hd* gene in the adult mouse brain causes both the striatum and cortex to degenerate (*16*). Zuccato *et al.* demonstrate that overexpression of wild-type human huntingtin stimulates BDNF mRNA expression in cultured neurons and in the brains of transgenic mice. They propose that mutant huntingtin in cortical neurons induces caspase activation that leads to cleavage of wild-type huntingtin and to partial loss of its transcriptional activity (see the figure). This, in turn, would result in a decrease in cortical BDNF production and striatal cell death. In HD patients, however, it is not yet clear whether there is partial loss of wild-type huntingtin activity (*4*). How wild-type huntingtin promotes transcription of the *BDNF* gene is not known—its cytoplasmic localization suggests that it does not affect transcription directly, although a growing list of transcriptional regulators seem to interact with both wild-type and mutant huntingtin (*4*). As wild-type huntingtin is required for efficient vesicle trafficking, it is also possible that mutant huntingtin causes disturbances in the anterograde transport of cortical BDNF, contributing to BDNF depletion in the striatum. Either way, as Zuccato *et al.* point out, the finding that BDNF production is altered in HD hints that BDNF and perhaps other neurotrophins may be valuable therapeutics for treating HD.

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PERSPECTIVES: POLYMER DYNAMICS

Chance Encounters

Thomas P. Russell

When long, flexible chain molecules are tethered to a surface, they can form an exceptionally large number of conformations. However, the probability that a configuration exists depends on an associated energy, which accounts for the stretching of the chain at the interface and the interactions between the chain and the surrounding medium. Consequently, not all configurations are equally probable. It is tempting to think that configurations with a low probability are unimportant, but as Jeppesen *et al.* demonstrate on page 465 of this issue (*1*), some of the least probable configurations nevertheless play an important role in recognition.

As we know from classical rubber elasticity, as a chain is stretched, the chain configuration becomes energetically unfavorable, and the retractive force increases rapidly as the elongation of the chain increases. In the presence of a good solvent, the osmotic pressure counteracts this retractive force. Compressed configurations are then not favored, and the chains will extend from the surface to maximize favorable interactions between the chain segments and the solvent.

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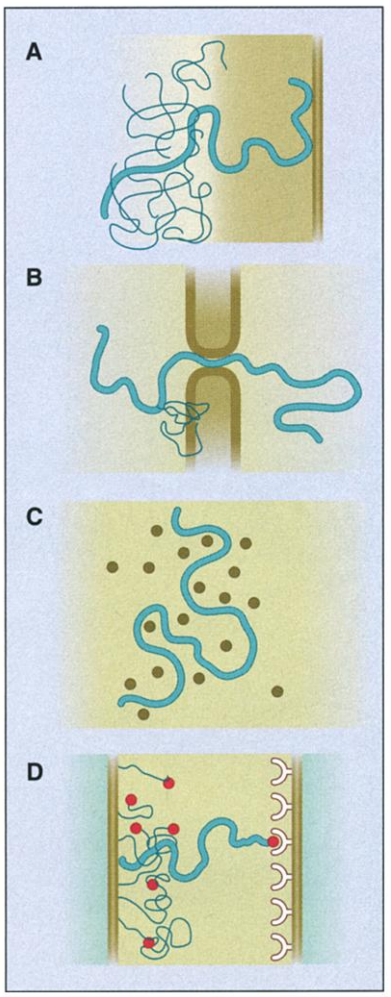
If we replace the solvent with a polymer, as is the case at the interface between two polymers, a similar situation exists, although the entropic contribution to the free energy of mixing is reduced because of the high molecular weights of both components. At equilibrium, the balance between these forces causes the polymer chains to assume an average configuration.

Numerous studies have evaluated the equilibrium properties of polymer interfaces, polymer brushes, polymer stabilized suspensions, adhesion promoters, and filled polymer systems, which all depend on the average configuration of the chains at the interface (*2*–*7*). For example, the interfacial width between two polymers describes the average interpenetration between two polymer layers. The interpenetration in turn dictates adhesion between the polymers, that is, the force required to pull the layers apart. In the case of colloidal suspensions, the average configuration of chains anchored to a particle surface defines a minimum separation distance between the particles, which prevents aggregation or precipitation.

Polymer chains at interfaces are not static but dynamic and are constantly probing different ensembles of configurations. We know that excursions of the chains into very high-energy states must exist, but these events are exceptionally difficult to detect, because they are so infrequent and short-lived. However, although the equilibrium states of polymeric systems depend largely on the average configuration of the chains, the ability of chains to test and adopt energetically unfavorable states is manifest in many kinetic processes. In the case of surface reconstruction, for example, a system is driven from one equilibrium state to another by a change in the surface or interfacial energy (*8*). The pathway by which the reconstruction occurs may require the diffusion of chains through domains where unfavorable segmental interactions occur, but overall reduction in the free energy allows these excursions to occur.



Chains in motion. (**A**) A polymer chain diffuses through a second polymer during a surface reconstruction in response to a change in surface interactions, (**B**) a single chain diffuses through a narrow pore, (**C**) a polymer is entropically trapped by physical barriers, and (**D**) one of many end-functionalized polymers anchored to a surface samples a high-energy configuration and interacts with a surface decorated with complementary functional groups.

Similarly, if a long chain molecule must diffuse through a pore having a diameter comparable to that of a segment, the entropy of the chain poses a substantial barrier to this diffusion. Even though only a few configurations of the chain will allow passage of the macromolecule through the pore, eventually, after countless attempts, a configuration occurs where there is sufficient penetration to allow complete passage of the chain through the pore (*9*).

Conversely, macromolecules may be prevented from sampling all possible configurations, for example, in a gel or a medium with fixed obstacles. This causes an entropic confinement of the chains, which increases with the length of the chain. Such restrictions of configurational states forms the basis of several molecular separations processes (*10*, *11*).

But what occurs when there is no applied force that drives the chains to high-energy configurations? In principle, the macromolecules must sample all configurational states, even those that cost a large amount of energy, but proving this point has been difficult.

Jeppesen *et al.* (*1*) have devised a very clever, quantitative means of probing the configurational dynamics of long chain molecules at equilibrium anchored to a surface, the ability of the chains to sample rare, high-energy configurations, and the importance of these configurations to recognition processes. The authors placed ligands on the ends of chains anchored to one surface and introduced a second surface to which receptor sites are attached. They found a strong attractive force between the surfaces. This force occurred abruptly when the separation distance between the surfaces is much larger than the average radius of gyration of the anchored chains, which defines the average volume occupied by a chain.

The probability that the tethered chains stretch to such distances without application of an external force is miniscule. Nonetheless, by combining direct force measurements as a function of separation distance for chains of different length with simulations and theory, Jeppesen *et al.* (*1*) have been able to see the effects of the rare, highly extended chain configurations and the chance encounters of the chain ends with the adjacent surface (see the figure). With sufficiently strong binding sites on the ends of the chains, the highly extended configurations are trapped, and the elastic, retractive force of the chains that span between the two surfaces pulls the surfaces together at distances far greater than the equilibrium radius of gyration.

The beauty of this work lies in its simplicity and the absence of any applied external force to achieve the highly extended configurations. Nature dictates that these configurations must occur, however infrequently or energetically unfavorable. Not only do Jeppesen *et al.* (*1*) demonstrate that these chance events occur, but they also show how such rare excursions of the tethered chains may play an important role in long-range biological recognition processes. In many ways, the encounters between the chain ends and the recognition sites are "as vessels starting from ports thousands of miles apart pass close to each other in the naked breadths of the ocean, nay, sometimes even touch in the dark (*12*, p. 353)."

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