

constitutes consistent, but not compelling, evidence of the whereabouts of the last slice of missing baryons.

Beyond the satisfaction of balancing the baryon budget, what would observations of the warm and hot IGM reveal about the universe? The number of absorbers that Danforth and Shull have found agrees with the number of filaments that simulations predict. Those simulations, and their underlying assumptions, will be tested further as the sensitivity of observations and the

power of computers improve.

Observations of the nearby IGM could also help astronomers tackle one of their most pressing and difficult problems: the role of feedback in galaxy formation. One expects the formation of large-scale structure to heat the IGM as galaxies form, but not necessarily to enrich it. The presence of stellar material deep in the IGM suggests that galaxies could influence the formation of other galaxies by expelling hot, energetic gas into the IGM.

Fourteen billion years after the Big Bang, the universe remains a violent place.

Charles Day

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Statistical mechanics elucidates constraints on the ultimate accuracy of biochemical sensing

Some biochemical interactions are akin to detecting a sporadic signal against a noisy background.

In biology textbooks, the way proteins work is often depicted by what looks like a set of puzzle pieces. A small piece, a regulator molecule, say, fits into a large piece, an enzyme, say. The enzyme's shape then changes to one that fits snugly around a medium-sized piece, the enzyme's substrate.

Those cartoons are meant to convey the exquisite specificity of biochemical reactions. Of the myriad reactions inside a cell, a given enzyme catalyzes just one. Not surprisingly, the picture doesn't tell the whole story. What's missing is the physical setting.

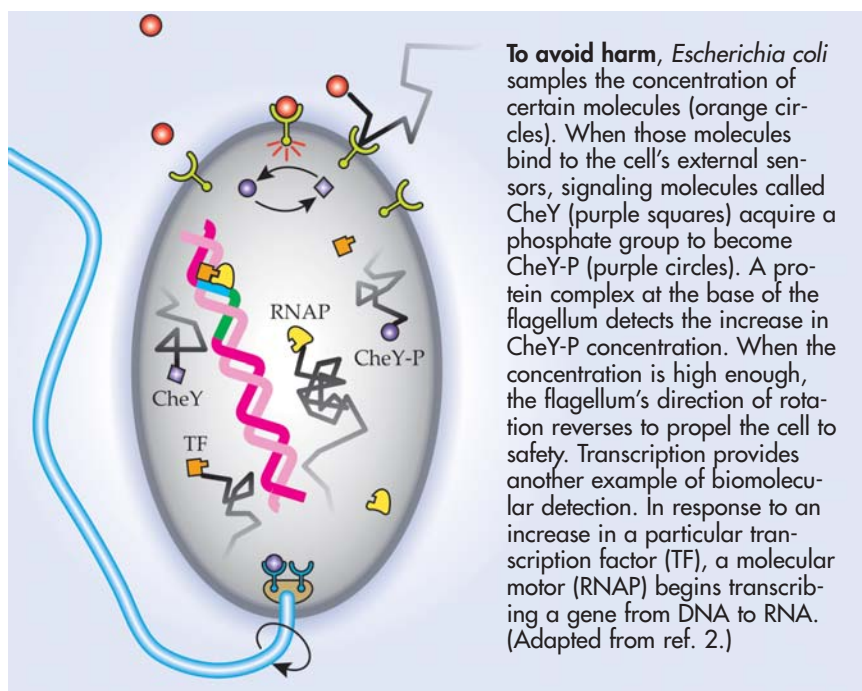
"In the world of a cell as small as a bacterium," wrote Howard Berg and Edward Purcell in a classic 1977 paper,¹ "transport of molecules is effected by diffusion, rather than bulk flow; movement is resisted by viscosity, not inertia; the energy of thermal fluctuation, kT , is large enough to perturb the cell's motion."

Under those conditions, the turning off of genes by transcription factors or the response to caffeine molecules of a neuron, just two examples, both resemble the sampling of a signal. Although the detector, the protein, responds more or less promptly to its target, fluctuations in its environment limit its accuracy.

Berg and Purcell derived an expression for how accurately a sensor of radius a can determine in time τ the mean concentration c of a target molecule whose diffusion coefficient is D :

$$\Delta c/c = 1/(Dac\tau)^{1/2}.$$

Berg and Purcell's analysis treated the sensor as a sticky sphere: Every target that hits the sensor sticks to it. But real proteins are like flexible scaffolds that fluctuate between two or more metastable configurations. And real target molecules bind and



unbind at different kinetic rates.

In 2005 William Bialek of Princeton University and Sima Setayeshgar of Indiana University incorporated those complications into a reanalysis of limiting sensitivity. Metastability and kinetics, they found, contribute an additional, always positive term to $\Delta c/c$. Berg and Purcell's expression can therefore be thought of as a noise floor: Real systems are less accurate than Berg and Purcell's model; they can never be more accurate.²

Now, Bialek and Setayeshgar have taken a further step toward accounting for the complexities of real biomolecular sensors: cooperativity.³ A cooperative biomolecule consists of two or more identical subunits arranged symmetrically. The binding of one target molecule

to one subunit alters the molecule's configuration and makes binding a second target more favorable. The more subunits a molecule contains, the greater the cooperative boost to binding.

Human hemoglobin, whose job is to scoop up oxygen and ferry it to cells that need it, has four subunits. Cooperative interactions among them result in a steep dependence of the fraction of occupied binding sites on the ambient oxygen concentration. In sensor proteins, cooperative interactions enhance sensitivity. Even a tiny change in concentration will boost the average number of sensors in a particular state. But can cooperative gain, which, in principle, is arbitrarily high, overcome background noise?

To answer that question, Bialek and Setayeshgar applied the fluctuation–dissipation theorem, as they did for their 2005 analysis. According to the theorem, a system in thermodynamic equilibrium will respond in the same way both to a small driving force and to a random thermal fluctuation. From that intuitive proposition, Albert Einstein famously related the dissipative, Brownian motion of a particle to the random, fluctuating knocks the particle receives from the molecules that surround it.

In Bialek and Setayeshgar’s analysis, the fluctuations come from the local concentration of target molecules as they bind and unbind, knocking the

cooperative molecule dissipatively in and out of its various states.

Their analysis is somewhat involved, but, to Bialek and Setayeshgar’s surprise, it yielded a compact formula for $\Delta c/c$. As in their earlier 2005 analysis, including cooperativity adds a second, always positive term. Moreover, the formula is general: It applies to cooperative and noncooperative sensors alike. Whereas cooperativity increases the gain, it doesn’t lower the noise floor.

Experiments that determine $\Delta c/c$ have been done only recently. According to Bialek and Setayeshgar’s formula, the 10% accuracy with which *Escherichia coli* transcribes genes is reached within one minute. That sampling time is consistent

with the time, three minutes, that messenger RNA survives in the cell.

Bialek and Setayeshgar’s formula also predicts, within a factor of three, how often *E. coli* changes direction in response to concentration gradients (see figure). The agreement is historically apt. Purcell first became interested in biochemical sensing when he saw Berg’s movies of zigzagging bacteria.

Charles Day

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Electron-scattering experiments resolve short-range correlations among nucleons

Researchers at Jefferson Lab confirm that high-momentum neutron–proton pairs in a carbon nucleus are 20 times more prevalent than proton–proton pairs.

According to the shell model, the protons and neutrons—collectively known as nucleons—that make up nuclei move independently in discrete quantum orbits and are bound by an average potential created by their mutual attractive interactions. But that picture is too naive. In the 1980s, electron-scattering experiments that knocked protons from both valence and deeply bound nuclear orbitals found only 60–70% of the number predicted by the mean-field approximation.

At the time, some theorists attributed the difference to correlations between nucleons. A rich variety of low-energy nuclear phenomena, including collective rotations and vibrations, shape mixing, and superfluidity, are known to originate in correlations between nucleons separated by several femtometers. But those long-range correlations make up less than half the difference. Short-range correlations (SRCs), on the scale of a femtometer or less, can close the gap, but direct evidence for them has proven elusive. Still, physicists have surmised their presence for decades, not least because short-range repulsion between nucleons prevents the collapse of a nucleus.

One can think of SRCs as transient fluctuations in the local nuclear density when the wavefunctions of two energetic nucleons strongly overlap. For less than a trillionth of a femtosecond, the nucleons approach each other closely enough to form correlated pairs, with local densities close to what’s expected in the core of a neutron star. While short in time, those correlations are ever pres-

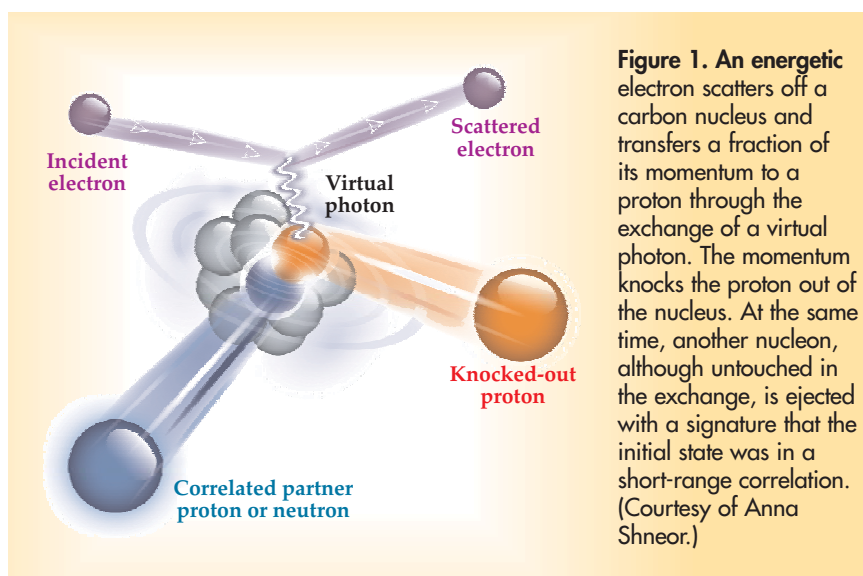


Figure 1. An energetic electron scatters off a carbon nucleus and transfers a fraction of its momentum to a proton through the exchange of a virtual photon. The momentum knocks the proton out of the nucleus. At the same time, another nucleon, although untouched in the exchange, is ejected with a signature that the initial state was in a short-range correlation. (Courtesy of Anna Shneor.)

ent, with a percentage of nucleons paired up at any given time. The development of high-energy accelerators has made observing such pairs possible, primarily because a probe’s wavelength can be made smaller than the nucleon–nucleon distance.

To resolve SRCs, an experiment must transfer to the nucleus momenta near 1 GeV/c, an amount larger than the characteristic Fermi momenta of nuclei. According to Mark Strikman, a theorist at the Pennsylvania State University, momentum-transfer reactions can test two fundamental features of SRCs: First, the shape of the high-momentum component of the nucleon wavefunction is independent of the nuclear environ-

ment; in effect, the bare interaction in a pair is unmediated by the presence of other nucleons. And second, the ejection of one nucleon is accompanied by the ejection of its correlated partner with equal and opposite momentum, leaving the rest of the system nearly unaffected.

Two years ago Strikman, along with Eliezer Piasetzky (Tel Aviv University), Misak Sargsian (Florida International University), Leonid Frankfurt (Tel Aviv University), and John Watson (Kent State University), analyzed the data from a 2003 Brookhaven National Laboratory experiment using the AGS accelerator in which GeV protons were incident on a thin carbon foil. The team found the telltale signs of correlated