adds refinement. The community is now working on the third rung, the meta-GGAs, where the kinetic energy density is introduced. The fourth rung approaches the divine functional by treating exchange exactly. For this to work, the exact exchange must be combined with a compatible correlation (*14*). The last rung retains the exact exchange and refines correlation by evaluating part of it exactly. The divine functional must have both exact exchange and exact correlation.

The main strategy in the chemistry community is to refine the use of hybrid functionals. The mix of exact exchange and GGA is usually determined by fitting to selected properties of certain groups of molecules. Anne Chaka (NIST) showed that different mixings are optimal for different properties. Varying the mixing throughout a system was proposed to circumvent this problem. Other speakers explored more radical routes, such as the subsystem functional scheme that divides a system into subsystems and uses different, highly specialized, functionals in these subsystems (*15*). Others include DFT for the Hubbard model (*16*) and phase-space functions and energy densities (*17*).

As usual, the workshop raised more questions than it answered. Is it possible to reach the divine functional? Is any one path more promising than another? To be able to go further, do we need an approach radically different from the two main strategies? There was consensus that at least another order of magnitude improvement in calculated energy differences could be expected from DFT. This would tremendously expand the usefulness of DFT calculations and would enable predictive quantitative results for systems from nanotubes to biopolymers.

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PERSPECTIVES: QUANTUM MECHANICS

To Condense or Not to Condense

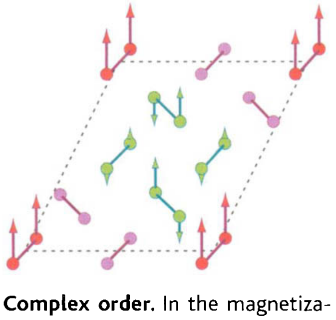
T. M. Rice

In quantum mechanics, particles are divided into two classes: bosons with integer spin and fermions with half-integer spins. As the temperature is lowered, an ideal gas of bosons undergoes a transition to a phase with a macroscopic occupation of the lowest single-particle state. This Bose-Einstein condensation was recently realized in specially prepared dilute atomic gas clouds cooled to very low temperatures (*1*). But under normal circumstances, bosonic atoms form classical crystals, with the exception of ^{4}He, whose light mass keeps it liquid to the lowest temperatures. Its superfluid transition can be viewed as a Bose-Einstein condensation among strongly interacting bosons. Much less attention has been paid to quantum magnets, where the competition between the classical crystalline and the quantum Bose-Einstein condensed ground states of bosons can be observed in another guise.

The starting point is a crystalline array of dimers—pairs of ions with spin $S = 1/2$ that are coupled antiferromagnetically. Dimers made from two Cu^{2+} ions are ideal for this purpose. The ground state of each dimer is a singlet (a state with paired spins) ($S = 0$). The three excited states form a triplet (with parallel spins) ($S = 1$; $S_z = +1, 0, -1$). A triplet excited on one dimer can hop to a neighboring dimer; as a result, the triplet delocalizes in a way similar to electrons that become delocalized in crystals. The ground state of the dimer crystal is a singlet spin liquid with short-range correlations between spins.

Consider now what happens when an external magnetic field, H_z, is switched on. The field does not alter the singlet ground states but leads to a splitting of the triplets, with the component that is parallel to the field lowered linearly with the field. The minimum energy needed to excite this component will be lowered too, and this energy will reach zero at a critical field strength, H_{crit}.

The triplet components with $S_z = +1$ can be regarded as bosons with a hard core repulsion, which prevents more than one boson from being present on a single dimer. The coupling to the magnetic field, which is proportional to the total magnetization, controls the boson density. The z-component of the exchange interactions generates a repulsion between neighboring bosons. The result is a system of interacting bosons whose ground state is determined by the balance between the kinetic energy and the repulsive interactions.



Complex order. In the magnetization plateau of $SrCu_2(BO_3)_2$, with a net magnetization of 1/8 of the saturation value, the spins of the Cu^{2+} ions form a complex pattern: one in eight of the dimers are strongly polarized parallel to the magnetic field, whereas the remaining dimers have a weaker staggered polarization.

CREDIT: ADAPTED FROM (5)

Consider first the case where the repulsive interactions dominate. Here, the bosons will try to minimize the repulsive interactions. This will work best when the boson density per dimer is a simple rational fraction, because the bosons can then form a simple superlattice. In this case there will be a finite energy cost to creating a separated interstitial-vacancy pair in the bosonic superlattice. This causes a jump in the chemical potential versus boson number, which translates as a plateau in the magnetization versus magnetic-field strength at a rational fraction of the saturation magnetization (*2*).

Such plateaus have been observed in a number of systems for some years (*3*, *4*). However, a direct measurement of the magnetic superlattice has only recently been achieved by Kodama *et al.* (*5*), who used a high-field nuclear magnetic resonance (NMR) technique on $SrCu_2(BO_3)_2$. This material is a frustrated two-dimensional lattice of Cu^{2+} dimers and is a realization of a spin model that was solved in zero field by Shastry and Sutherland (*6*).

The frustrated form of the dimer lattice leads to a narrow bandwidth for the triplet ex-

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citations (7), and magnetization plateaus are to be expected as a result. The first of these appears at a value of 1/8 of the saturation magnetization. The required magnetic field of 27 T is quite large but within range of the NMR facility of the Grenoble High Magnetic Field Laboratory. The unique combination of high fields and low temperatures at this facility enabled Kodama *et al.* (5) to observe the magnetic superlattice as a dense series of lines in the Cu NMR spectrum at 35 mK. Analysis of the magnetization in the large supercell implied by the high order of the commensurability (1/8) required a numerical solution of the Shastry-Sutherland model.

The spectra could be well fit by the magnetization pattern shown in the figure. One in eight of the dimers is strongly polarized parallel to the external field. But the magnetization pattern is much richer than a simple polarization of 1/8 of the dimers. This more complex pattern can be attributed to the high magnetic polarizability of the singlet ground state of the dimer lattice. As a result, the dilute superlattice of spin triplet dimers is accompanied by a background magnetic polarization. The transition into the superlattice state as the field is increased appears to be first order, which favors an interpretation of it as a crystallization of a dilute bosonic fluid.

Turning our attention back to the quantum ground state, which appears when the kinetic terms dominate, new results on another set of copper salts, $KCuCl_3$ and $TlCuCl_3$, have recently been obtained. Initially, their crystal structure seemed to imply that the dimers formed the rungs of ladders with only weak interladder interactions. However, a detailed mapping of the energy dispersion of the triplet excitations showed a fully three-dimensional network of exchange interactions (8).

These salts do not show magnetization plateaus but instead show a continuous rise starting at a threshold magnetization value and ending at the saturation magnetization. The Bose-Einstein condensed state in the intermediate range is characterized by a coherent superposition of the singlet and $S_z = +1$ triplet component on each dimer (9). This generates a staggered magnetization transverse to the external field.

The phase in the complex superposition determines the orientation of staggered moments in the *xy*-plane. Elastic neutron-scattering measurements observe a staggered magnetization with long-range ordering with a finite ordering temperature (10). Recently, Ruegg *et al.* (11) examined the dynamics of the condensate by inelastic neutron scattering and observed a mode with linear dispersion above the threshold magnetization. As shown by Matsumoto *et al.* (12), this mode can be nicely interpreted as the well-known collective oscillation (or Goldstone mode) of the Bose-Einstein condensate.

As these recent experiments illustrate, quantum magnetism in a magnetic field offers exemplary systems for exploring the competition between the classical and quantum ground states for interacting bosons—a subject of current research also for the dilute atomic bosonic clouds.

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PERSPECTIVES: CANCER BIOLOGY

A Matter of Dosage

Riccardo Fodde and Ron Smits

Knudson's classic two-hit model of tumorigenesis stipulates that mutation of both alleles of a tumor suppressor gene is needed to trigger tumor formation (1). This recessive nature of tumor suppressor genes has been challenged by a growing number of reports (see the table) including recent papers in *Science* and *Nature Genetics* (2–4). These studies show that mutation or loss of a single allele may be sufficient to exert a cellular phenotype that leads to tumorigenesis without inactivation of the second allele. This gene-dosage effect is called haploinsufficiency and has been demonstrated by at least two different experimental approaches. Individuals or mice carrying a heterozygous mutation that inactivates only one allele of a tumor suppressor gene exhibit an increased incidence of tumors, a subset of which develop without loss or mutation of the second normal allele (5, 6).

Enhanced online at www.sciencemag.org/cgi/content/full/298/5594/761

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Alternatively, haploinsufficiency can modify cancer risk in humans or mice that either already carry a heterozygous mutation in a separate tumor suppressor gene (known to comply with Knudon's two-hit model) (7) or that have been challenged by exposure to radiation or viruses (8). Tumors influenced by haploinsufficiency usually have a later age of onset when compared with those caused by inactivation of the second allele (loss of heterozygosity).

Although it is well documented that gene-dosage effects cause developmental defects in model organisms and in certain inherited human diseases, their importance in tumor biology has been overlooked. Morphogen gradients modulate cell proliferation, differentiation, and apoptosis in developing organisms. Exposure to different doses of these diffusible factors is rate-limiting for the determination of cell fate. Likewise, in the presence of a heterozygous loss-of-function mutation in a tumor suppressor gene, fluctuations in gene dosage below tissue-specific thresholds may interfere with the control of fundamental cellular processes (see the table). This results in either the direct triggering of tumorigenesis or modification of the cellular environment so that additional mutations or epigenetic changes in other genes can successfully promote tumor growth (see the figure).

Some tumor suppressor genes are "gatekeepers," that is, they carry out a crucial cellular function that when abrogated leads directly to tumorigenesis. However, there also exists a subset of tumor suppressor genes that are "caretaker" genes involved in DNA repair or chromosomal segregation. Haploinsufficiency at these caretaker genes may result in defective DNA repair and increased genetic instability leading to somatic mutations in other tumor suppressor genes and oncogenes. The recent *Science* and *Nature Genetics* papers (2–4) support the notion of DNA repair haploinsufficiency.

Bloom syndrome is a rare recessive disorder characterized by a predisposition to a broad spectrum of tumors. It is caused by loss-of-function mutations in the *BLM* gene, which encodes the DNA repair enzyme recQ helicase. Gruber *et al.* (2) genotyped two large series of colorectal cancer patients of Ashkenazi Jewish ancestry and showed that carriers of the BLM^{Ash} founder mutation had a significantly increased risk of developing large-bowel tumors. However, they did not analyze whether the second normal allele was mutated in the colorectal cancers. Thus, they could not discriminate whether the increased colorectal cancer risk was