"Wandering companionless/Among the stars that have a different birth" (*12*).

How does the model match the observations? The predominance of tightly bound, small-separation binaries at low masses agrees well with predictions. Indeed, the overall trend with total mass suggests a phenomenon related to gravitational binding energy. However, and this is where LHS 2397a and its ilk are important, so far there is no indication of the sharp decrease in binary frequency at the lowest masses that would be expected if most brown dwarfs are planetary and thus single. Observations indicate that luminous [that is, young (*7*)] brown dwarfs occur at a frequency of 20% or more, rather than the predicted <5%.

For the moment, therefore, the more radical suggestion that most brown dwarfs form as planets do, rather than as stars do, remains unsupported observationally. A definitive answer requires further observations of larger numbers of fainter, low-mass brown dwarfs, currently possible only with the Hubble Space Telescope.

References and Notes

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7. Stars and brown dwarfs are classified according to their temperature. The Sun, a G dwarf, has a temperature of 5500 K. M, L, and T are the coolest classes. M dwarfs have temperatures in the range 4000 to 2100 K, with masses below ~0.5 solar masses; L dwarfs fall between 2100 and 1300 K; T dwarfs are cooler still. For stars, lower temperature equates to lower mass. Brown dwarfs are initially class M, but they evolve rapidly through L to T. Almost all late-type (cool) M dwarfs are low-mass stars, as are many early-type L dwarfs, but the majority of late-type L dwarfs and all T dwarfs are substellar-mass brown dwarfs.
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PERSPECTIVES: ATOM OPTICS

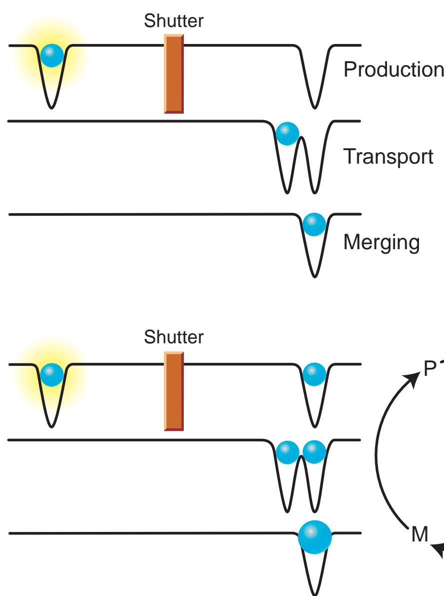
Continuous Progress on Atom Lasers

Tilman Pfau

In 1960, Theodore Maiman demonstrated the first pulsed optical laser, using a synthetic ruby crystal as the laser active material and a flash lamp to achieve population inversion by optical pumping. Just 6 months later, Ali Javan invented the first continuous optical laser. In his HeNe gas laser, collisions of electrically excited He atoms with ground state Ne atoms produced the inversion required for continuous laser operation. Just 1 day after its realization, the laser was used to transmit a telephone call. Similar lasers are still widely used, with applications ranging from precision spectroscopy to material processing.

Today, optical lasers abound, and the sights have been set on atom lasers, which exploit the wave properties of matter. In a gas, individual atoms are usually in distinct states of motion, whereas atom laser operation requires them all to be in the same state. This is achieved in a Bose-Einstein condensate (BEC), in which many atoms are trapped in the minimum energy quantum state (*1*). After experiments demonstrated the phase coherence of these giant matter waves (*2*), the atom traps were combined with controllable leaks to release a coherent beam of atoms from the trapped condensate. Pulsed atom lasers comparable to q-switched (*3*) and mode-locked lasers (*4*) were reported. But it proved difficult to move from pulsed to continuous operation. Improving control over the leaks delivered atom laser beams for up to 100 ms from a single condensate (*5*), but replenishing the reservoir was a major obstacle in moving from pulsed to continuous operation.

Many sophisticated ways to achieve continuous pumping of atom resonators have been discussed (*6–9*). Most of these ideas are based on optical pumping between various internal and external states of the atoms. However, none of them could demonstrate high enough pump rates to overcome the intrinsic losses and achieve laser action. The main problem is that reabsorption of the scattered photons by neighboring atoms gives rise to a loss mechanism that cannot be overcome by the gain due to the pump.



Condensate on demand. Bose-condensed atoms are now available in a continuous reservoir of atoms. Losses due to background gas collisions are compensated by replenishing the reservoir with condensed atoms from a production chamber. The condensates are transported, trapped, and merged with optical tweezers.

The step that seemed straightforward in the case of optical lasers, from pulsed to continuous pumping and operation, thus remained beyond reach for atom lasers. Even 7 years after the first BEC experiments, no true analog of a continuous laser has been reported.

Chikkatur *et al.* have now resolved the quest for a continuously operating reservoir of condensed atoms with a surprisingly simple concept (see page 2193 of this issue) (*10*). Instead of combining laser cooling and storage of the BEC in one spatial location, they store the condensate in a separate vacuum chamber while producing another one.

In their sophisticated apparatus, the authors can transport a condensate over 30 cm from a production chamber to a storage chamber, separated from the former by a mechanical shutter (see the figure). With this setup, they can produce a second condensate in the production chamber while the first one is stored in the dark storage chamber. They then move the second one to the storage chamber, where they merge the two condensates. This sequence can be repeated many times, providing a continuous reservoir of condensed atoms.

Through spatial separation, the authors avoid the inevitable destruction of the reservoir of condensed atoms through absorption of scattered light in the production chamber. Although the pumping mechanism is still pulsed, its repetition rate is faster than the decay time of the resonator. It can therefore

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be used in future experiments, together with an appropriate outcoupler to release atoms continuously from the trap, to obtain a truly continuous atom laser beam. The new approach is technically challenging but conceptually simple. It shows how BECs can be routinely manipulated, transported, and merged. As another milestone in atom optics is passed, what will be next?

It might take longer than just 1 day, but experiments to demonstrate first applications for continuous atoms lasers are under way. Many open questions remain. What are the spectral properties of continuous atom lasers? What is the effect of the merging process on the phase of the BEC? How narrow can the line of an atom laser get? Can it be a precise spectroscopic tool? Will it be possible to produce easy-to-use, compact sources for everyday atom optics applications? Can matter waves also be amplified continuously (*11*, *12*)?

With the experimental results of Chikkatur *et al.*, answers to many of these questions seem to be within reach. Their technically sophisticated but conceptually simple solution to the continuous atom laser problem has been successful where sophisticated concepts have failed. The next challenge will be to extend these concepts and develop "high power" atom lasers.

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PERSPECTIVES: BIOCHEMISTRY

Intramembrane Proteases— Mixing Oil and Water

Michael S. Wolfe and Dennis J. Selkoe

Proteases and peptidases, enzymes that hydrolyze other proteins and peptides, are critical to many normal and pathological events and are often important targets for therapeutic interventions. The last place in the cell to expect enzymes to hydrolyze their substrates is within the hydrophobic environment of membrane lipid bilayers. Nonetheless, several families of hydrolytic enzymes now appear to carry out this seemingly paradoxical process. The latest installment in this continuing saga is reported on page 2215 of this issue by Weihofen and colleagues (*1*). They characterize a hydrolase called signal peptide peptidase (SPP), pinpoint its active site to amino acids within a membrane, and reveal its similarity to presenilin, a hydrolase implicated in Alzheimer's disease.

There are four classes of proteases and peptidases classified according to which amino acid residues in the enzyme catalyze the breaking of an amide bond in the substrate. These classes are the serine/threonine proteases exemplified by the enzymes of the proteasome (the cell's protein degradation factory), the cysteine proteases such as the caspases involved in apoptosis, the metalloproteases exemplified by angiotensin converting enzyme, and aspartyl proteases such as the HIV protease. All four categories contain many examples of fully water-soluble proteases as well as membrane proteases that span the membrane once and have their active sites in the aqueous compartments of the cell.

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Remarkably, the same mechanistic principles seem to apply to the recently recognized multipass intramembrane proteases that traverse the membrane many times and have their active sites buried within the lipid bilayer (see the table). This suggests that there are only a few biochemical solutions to the general problem of how to cut an amide bond. For instance, the S2P family of proteases cleaves membrane-anchored transcription factors involved in cholesterol biosynthesis (*2*), and contains a conserved and essential HEXXH motif that is characteristic of many soluble metalloproteases. Another example is the newly described rhomboid protease family responsible for releasing transforming growth factor–α (TGF-α) from a membrane-bound precursor (*3*). Conserved amino acid residues (asparagine, histidine, and serine) required for activity of rhomboid are reminiscent of the catalytic triad typically found in serine proteases. Indeed, inhibitors of soluble serine proteases also block rhomboid-mediated proteolysis. Both S2P and rhomboid cleave amide bounds within the transmembrane regions of their substrates, and the residues responsible for this hydrolysis are located either within the membrane or at the membrane-cytosol interface. Thus, these two families are members of the rapidly expanding group of intramembrane-cleaving proteases (I-CliPs) (*4*).

Presenilin is the founding member of the aspartic I-CliPs. Presenilin contains eight transmembrane domains and is required for the intramembranous proteolysis of the amyloid-β precursor protein (APP), the Notch and Erb-B4 receptors, E-cadherin, and probably numerous other single-transmembrane substrates (*5*–*8*). This protease activity, called γ-secretase, releases the cytosolic tails of APP and Notch that exemplify part of a new signaling mechanism (*9*, *10*). Processing of APP by γ-secretase also produces the amyloid-β peptide, which plays a central part in the pathogenesis of Alzheimer's disease. Thus, γ-secretase is considered a major therapeutic target. The notion that presenilin contains the active site of γ-secretase arose from the observation that two conserved intramembrane aspartates are critical for both γ-secretase activity and the "presenilinase" activity that cleaves full-length presenilin into its biologically active heterodimeric form (*11*). These data suggest that presenilins are unique intramembranous aspartic proteases that are activated by autoproteolysis.

Aspartyl protease transition-state analog inhibitors of γ-secretase bind directly to both presenilin fragments (*12*, *13*). This finding and the fact that each fragment contributes one of the two key aspartates strongly imply that the active site of γ-secretase resides at the interface of the heterodimeric fragments. However, presenilin heterodimers alone do not constitute γ-secretase. The formation and stabilization of the heterodimers is tightly regulated by other cellular factors (*14*), and these are thought to be integral membrane proteins that combine with the heterodimers to form a large active protease complex. Nicastrin and aph-1 are postulated to be members of this complex (*15*, *16*), but whether these proteins together with presenilin can reconstitute γ-secretase activity remains to be seen.

Although the cumulative evidence strongly suggests that the catalytic component of γ-secretase resides in presenilin, this idea has not been without its skeptics (*17*, *18*). Four apparent inconsistencies have been aired. First is the so-called "spatial paradox": Presenilin is located mainly in the endoplasmic reticulum and Golgi apparatus, whereas γ-secretase cleavage of Notch and APP is thought to take place at or near the cell surface. However, presenilin localization studies used antibodies that do not distinguish between full-length and heterodimeric presenilin or between