ly, the apparent correlation between antigenicity and mobility may reflect the fact that antibodies are not made to the rigid regions, especially for proteins, such as the hemoglobins and cytochrome c, the functions of which have maintained throughout evolution.

However, myohemerythrin and the coat protein of a plant virus such as TMV should be completely foreign to animals and less likely to be subject to complications from tolerance effects. In fact, Lerner and his colleagues deliberately chose myohemerythrin for this very reason. Nevertheless, they point out that, even if the preferential recognition of flexible areas is a fortuitous result of tolerance, it may still help antibodies carry out their functions by directing them to target areas that are capable of adjusting to give a better fit to antibody structures.

Lerner, Ian Wilson, who is also at Scripps, and their colleagues plan to further test the hypothesis that mobility is an important factor in antibody binding in an experiment to be conducted with Sydney Brenner, who is at the MRC's Cambridge Laboratory. Brenner has suggested another possible explanation for the observation that antibodies to peptides so frequently recognize the intact proteins. Because the immune system evolved to recognize proteins, he suggests, it may be fundamentally biased to produce antibodies that recognize conformations that actually exist in proteins.

The investigators have recently performed a computer search to identify a set of peptide sequences, containing at least a half-dozen or so amino acids that occur in unrelated proteins. The idea is to make antibodies to the peptides and see whether they can recognize the proteins that contain the peptides. If Lerner is correct, an antibody to a given peptide may recognize different proteins that contain the peptide even though its conformation may vary among them. But if Brenner is correct, an antibody should bind to different proteins only if the peptide segment has the same conformation in all of them.

Whether other types of interactions between proteins also involve binding to flexible sites is unclear. Lerner notes that there is a fundamental difference between antigen-antibody interactions and those between enzymes and their substrates or hormones and their receptors. "Enzymes have been honed over millions of years of evolution to do one thing," he says. "The immune system has evolved to handle all comers."

Mobility in the form of the relatively large conformational changes that play a role in enzyme activation or inhibition is well known. But the type of mobility implicated in antibody-antigen recognition is much more localized and restricted in scope. Pinpointing such subtle changes when protein substrates interact with their enzymes may be difficult. So far the x-ray crystallographers have solved the three-dimensional structures of only about 25 proteins to a resolution sufficiently high to calculate temperature factors. X-ray diffraction studies of pairs of interacting proteins may also help locate local mobility changes but these are at a very early stage of development. However, antibodies themselves may prove useful as probes of backbone flexibility. Arthur Olson of Scripps asserts, "Immunology is turning out to be one of the tools for exploring mobility." Modern nuclear magnetic resonance methods may also help in this regard.

Finally, the mobility work may facilitate the development of vaccines from synthetic peptides by helping in the selection of those peptides that elicit antibodies that react strongly with the parent protein. The main problem at the moment is the small number of proteins for which temperature factors can be calculated. These do not include proteins of pathogens for which researchers are trying to devise new vaccines. Meanwhile, Klug suggests, selecting peptides from the loops or turns of the target molecule, which are likely to be mobile, may prove more helpful than relying on other possible indicators of antigenicity such as hydrophilicity.—**Jean L. Marx**

**Additional Reading**

1. E. Westhof, D. Altschuh, D. Moras, A. C. Bloomer, A. Mondragon, A. Klug, M. H. V. Van Regenmortel, *Nature (London)* **311**, 123 (1984).
2. J. A. Tainer, E. D. Getzoff, H. Alexander, R. A. Houghton, A. J. Olson, R. A. Lerner, W. A. Hendrickson, *ibid.* **312**, 127 (1984).
3. D. C. Benjamin *et al.*, *Annu. Rev. Immunol.* **2**, 67 (1984).

# Soft X-ray Laser at Lawrence Livermore Lab

***An extensive battery of diagnostic tests makes Livermore's the first well-documented x-ray laser; Princeton is not far behind***

Researchers from the Lawrence Livermore National Laboratory have claimed success in the long quest to build an x-ray laser. The group made its announcement on 29 October, on the opening day of the American Physical Society's Division of Plasma Physics meeting in Boston. Laser scientists who have examined the Livermore experiments enthusiastically concur with the claim. "There is no doubt at all that they have a laser," says laser pioneer Charles H. Townes of the University of California at Berkeley.

Livermore's laser emitted radiation at 206 and 209 angstroms, with a maximum intensity about 700 times that expected for spontaneous emission (fluorescence) at the same wavelengths in the highly ionized selenium plasma that served as the laser medium. Some physicists prefer the designation extreme ultraviolet (XUV) for this wavelength range.

At the same meeting, scientists from the Princeton Plasma Physics Laboratory reported amplification by a factor of 100 of 182-angstrom radiation from a hydrogen-like carbon plasma. However, Szymon Suckewer, head of the Princeton group, says he would like to see an enhancement of intensity of 1000 before claiming a laser. "Livermore is already there," he adds.

Diagnostics is the strength of the claim of the 27-member Livermore group, which is headed by Dennis Matthews. Previous assertions of x-ray lasing either have been refuted or lie in limbo for lack of corroborating evidence. "Livermore has done exquisitely careful diagnostic tests," says Stephen Harris of Stanford University, who is working on his own version of an XUV laser. Both Harris and Townes are members of a select group of laser experts called in by Livermore to go over the x-ray laser experiment with a fine-tooth comb prior to making a public announcement.

Careful diagnostics are needed because, comparatively speaking, all candidate x-ray lasers have had rather feeble outputs. The key characteristics are the gain coefficient and the length of the laser. The intensity of the laser radiation is proportional to *exp(gl)*, where $g$ is the gain coefficient and $l$ is the length.

When the gain-length product is high, as in commerical visible and infrared lasers, there is no question of whether lasing is taking place because all the measurable radiation is at the laser wavelength. When it is low, radiation due to lasing and that due to spontaneous emission at other wavelengths may have similar intensities.

Lasing occurs when there are more ions (or atoms or molecules, depending on the laser medium) in high-energy quantum states than in low-energy states, the inverse of the usual thermal distribution. With this population inversion, photons spontaneously emitted when ions relax to low-energy states can stimulate the emission of additional photons from ions that have not yet relaxed, which stimulate the emission of still more photons in a kind of chain reaction. The gain is proportional to the population inversion.

Following the lead of earlier would-be x-ray laser makers, the Livermore physicists used a plasma as the laser medium. While it takes extra energy to vaporize a target and generate the plasma, the highly ionized atoms in the plasma offer a plethora of quantum states. The trick is to find a state from which spontaneous emission is inhibited long enough to allow the formation of a population inversion and then to adjust the plasma temperature and density so that this state is preferentially occupied.

Prior to their experiments, which are expensive partly because they use the laboratory's giant Novette glass laser of laser fusion fame as the means of pumping energy into the plasma, the Livermore physicists carried out extensive theoretical work to identify an ion with the requisite quantum states. It was also necessary to design a target configuration that would result in a plasma of uniform density and temperature.

The physicists chose the well-characterized neon-like selenium ion, whose 10 electrons in the lowest energy (ground) state are in a $1s^2 2s^2 2p^6$ configuration, where 1 and 2 refer to the principal quantum number ($n$) and $s$ and $p$ are orbital angular momentum quantum numbers. Electron collisions result in the population of several excited states.

When electron spin is included, it turns out that there are several $1s^2 2s^2 2p^5 3p$ excited states from which lasing transitions can begin and $1s^2 2s^2 2p^5 3s$ excited states at which they can end. Using an elaborate computer analysis devised by Peter Hagelstein of the Livermore group, the physicists concluded strong lasing transitions were possible at 183, 206, and 209 angstroms. The 183 transition was predicted to have the highest gain of the three.

Calculating the gain requires a specific target design and a detailed knowledge of the temporal and spatial evolution of the plasma after the Novette laser vaporizes the target. The plasma behavior was calculated from a complex computer program originally written for laser fusion analysis. Mordecai Rosen, borrowed from Livermore's large laser fusion collaboration, helped design the target. Called an exploding foil, this type target is commonly used in fusion experiments. In the present case, the foil is a selenium film 750 angstroms thick that is supported by a plastic (Formvar) sheet.

Experiments were conducted in the closing weeks of Novette's operation last summer (a still more powerful Nova is nearing completion at Livermore). Pulses of green (0.53 micrometer) light of intensity $5\times10^{13}$ watts per square centimeter and lasting about 0.5 nanoseconds were focused on one or both sides of the selenium film, which is typically 1.1 centimeters long by 0.02 centimeters wide. The film has to be thin to avoid refraction effects that otherwise bend the x-rays out of the plasma and thereby reduces the stimulated emission.

Livermore physicists made several types of tests. X-rays due to spontaneous emission can come out in all directions, but laser x-rays are restricted to emerging from the ends of the plasma strip because only in these directions is there enough plasma for significant amplification. Hence, any wavelengths appearing only from the ends are candidate laser lines. Brightness is another indicator. From the brightness, it is possible to calculate the effective temperature of the light source. Lines whose sources seem to be hotter than the plasma are candidate laser lines. Pulse length is a third diagnostic. As the amplification increases, pulse length decreases.

Although the predicted 183-angstrom line never appeared, the 206- and 209-angstrom lines passed all these tests. Most observers regard a fourth test as the most conclusive. The Livermore physicists were able to vary the length of the vaporized selenium film. Observing the characteristic exponential growth in amplification as the length grew sealed the case for lasing.

Princeton's x-ray laser experiment runs on a considerably lower budget and has recourse to fewer physicists than Livermore's. It also works quite differently. An infrared (10.6 micrometers) carbon dioxide laser beam focused to a 200-micrometer diameter vaporizes a small portion of a carbon disk, forming a plasma column of fully ionized carbon. A magnetic field confines the electrically charged plasma particles long enough for it to cool before dispersing.

Cooling occurs by the capture of electrons in high principal quantum number orbits with the emission of radiation. This creates a population inversion between quantum states with high and with low principal quantum numbers, thereby giving rise to stimulated emission and lasing. The theoretically predicted and experimentaly observed 182-angstrom emission corresponds to a transition between $n = 3$ and $n = 2$ states.

While this radiation passed many tests for lasing, owing to the geometry of the experiment, Princeton physicists could not change the length of the plasma without changing other variables simultaneously. Hence it was not possible to make the decisive amplification versus length measurement. Said one observer to *Science*, "Princeton's observations are all consistent with laser action but do not prove it, whereas Livermore has proved it."

Suckewer hopes an experiment with newly available x-ray mirrors will overcome any doubts. By reflecting light through the plasma, the length is effectively increased, and the amplification should grow accordingly. Up to now, the lack of mirrors has meant that all the amplification has to come in a single pass through the plasma.

What comes next? The x-ray region of most interest is not that of the very soft (long wavelength) 200-angstrom radiation but considerably shorter. The significance of the new results is that of a proof of principle. Selenium was nearly certain to work, according to theory. Now that it has, physicists are more confident that the complex computer programs that predict likely laser candidates correctly take account of the important physical principles. Although the absence of the predicted 183-angstrom line remains mysterious, they can now go ahead with other ions that are more risky but also more interesting.

Livermore has already obtained evidence for lasing at 155 angstroms with yttrium targets. Matthews told *Science* that it is not at all out of the question to hope for a 30-angstrom laser, which would be of great interest to biologists for making three-dimensional images (holograms) of cells and their contents.

—**Arthur L. Robinson**