

Single atom lases orderly light

Howard Carmichael and Luis A. Orozco

A laser that operates through repeated emission from a single atom is very different from the lasers we know. The beam of light produced has a more orderly photon stream than even the quietest laser.

For many physicists, the fascination of quantum systems comes from their intrinsic fluctuations — those fluctuations always present in any system as a consequence of Heisenberg's uncertainty principle. In quantum systems of practical use (such as lasers and transistors), the intrinsic fluctuations are small enough not to interfere with the function of the device. All of this changes, however, in a miniaturized version of a quantum system, when its size is shrunk down to the ultimate limit. Quantum fluctuations then dominate, and familiar devices such as lasers behave very differently.

The miniaturization of a quantum device requires better control of the elements that form it. Technical fluctuations must be suppressed if behaviour at the quantum level is to be seen. Surprisingly, the emergence of the quantum fluctuations can bring with it a paradox: as the intrinsic fluctuations become dominant, some device characteristics may fluctuate less. As a consequence — and as McKeever *et al.*¹ show on page 268 of this issue — a laser built from a single atom may emit a more orderly photon stream than a conventional many-atom system.

The basic elements of a laser are an amplifying medium (free atoms or a solid-state material) that preserves the phase of an incoming wave, and an optical cavity,

formed by two opposing partially transmitting mirrors. The mirrors force the wave to pass many times through the amplifying medium, increasing its amplification. The medium is pumped in some way (by another laser or an electric current) into an excited state from which its stimulated emission of photons into the laser mode is more favourable than spontaneous emission (which would be a net loss). The interplay creates a threshold for laser action, which begins when the gain, provided by the pumping of the medium, overwhelms the loss from spontaneous emission and mirror transmission.

Single-atom lasers call for a particularly strong coupling between the atom and the photon, as one atom must do the work normally shared by many others. Creating sufficiently strong coupling is not an easy task. For visible photons in particular, a unique set of challenges must be met, arising from the small wavelength of visible light: the atom cannot move more than a fraction of the wavelength, because any such motion introduces noise. But McKeever *et al.*¹ have overcome the technical difficulties. Although one-atom lasers (and masers, the microwave version of lasers) have been demonstrated before^{2–4}, there were always several atoms involved in creating a steady state for laser operation in these systems; the new device

is the first to operate using, as McKeever *et al.* put it, “one-and-the-same atom”. It is a model example of a system in which the quantum fluctuations have been brought to dominance.

The interaction of an electromagnetic field with a single atom has been the subject of long and fruitful theoretical studies, beginning with work in the 1960s by Jaynes and Cummings⁵, and by Paul⁶. Thirty years later, Mu and Savage⁷ explored what might happen were a laser built on this elementary interaction; they questioned popular notions, including the idea that laser light is as ‘quiet’ (free from noise) as any source of light could be. The laser (or maser) principle was first applied on the scale of single atoms in a series of experiments in which a beam of Rydberg atoms — highly excited atoms that emit and absorb microwave — traversed a superconducting microwave cavity. The so-called micro-maser² and a similar device based on two-photon emission³ were developed. These devices achieve maser action with an extremely dilute atomic beam, ideally with no more than one atom at a time in the cavity, although many atoms must traverse the cavity to establish and sustain the maser action. A similar system operating with visible light has also been devised⁴.

McKeever *et al.*¹ have removed the final source of extraneous fluctuations by eliminating the beam of atoms. With a laser trap, they hold a cold caesium atom between the mirrors of a small optical cavity — a cavity so small that the presence of just one photon is enough to enable stimulated emission to overwhelm the spontaneous emission loss. Two lasers pump the atom, which, working alone, amplifies the light through a series of repeated stimulated emissions. Although it emits a directed beam of light, this laser is very different from the lasers we know. The threshold is absent. More fascinating, though, are the fluctuations. The light is quieter than ordinary laser light in two distinct, though interrelated, ways (Fig. 1). First, after a photon is emitted there is a characteristic delay before a second photon is likely to be emitted, with the result that the photon stream is ‘anti-bunched’. Second, the number of photons emitted in a fixed time is more predictable than for an ordinary laser (the distribution is sub-Poissonian). Overall the photon stream is more orderly than that from a many-atom laser.

Orderly photons do come at a price — a rather small flux of less than 100,000 photons per second, and continuous operation for less than one second. But new directions are opened up. In the quantum future, single-atom lasers might form circuit components for manipulating quantum information.

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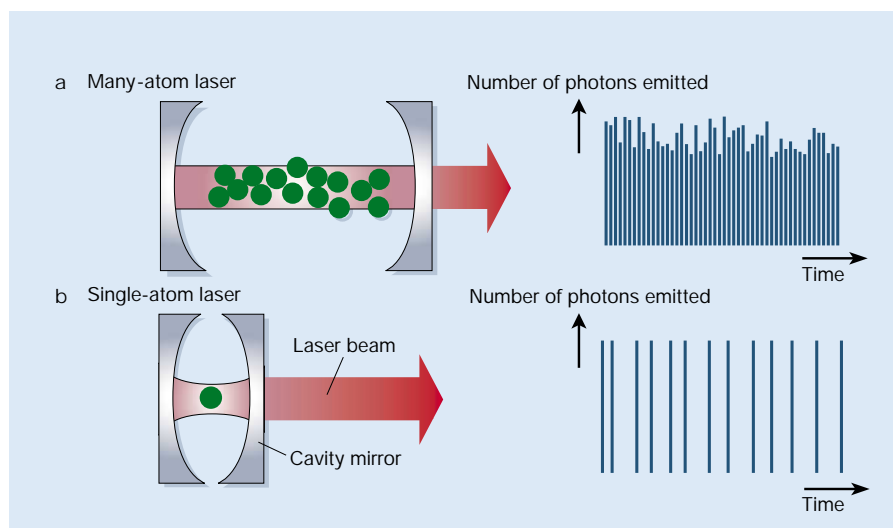


Figure 1 Photons to order. a, In a conventional, many-atom laser, stimulated emission of photons from atoms inside a mirrored cavity generates an intense beam of radiation. If the make-up of the beam is analysed over time, the flux of photons is seen to fluctuate considerably. b, In the single-atom laser demonstrated by McKeever *et al.*¹, the photons are ‘anti-bunched’, spread out over time. But the number of photons emitted over a given time interval is more predictable than for the many-atom laser.

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Cancer

Cues for migration

René Bernards

Lack of oxygen causes the cells of certain tumours to spread to new locations. It also activates a homing mechanism that enables the migrating cells to target specific organs.

The ability of tumour cells to metastasize — to spread to other parts of the body — is perhaps the main reason that certain types of cancer are often fatal. But how do tumours acquire this characteristic? Starving tumour cells of oxygen seems to be one trigger for metastasis, and researchers are beginning to uncover the molecular pathways that underlie this phenomenon^{1,2}. Writing on page 307 of this issue, for instance, Staller and co-workers³ reveal that a gene called *CXCR4* is activated by the lack of oxygen, and that this activation causes tumour cells to migrate and to home in on a specific set of organs.

Highly aggressive tumours rapidly outgrow their blood supply, leaving the cells starved of oxygen — a condition known as

hypoxia. Tumour cells adapt to hypoxia by increasing their synthesis of a protein named HIF (hypoxia-inducible factor), which in turn binds to and activates several genes⁴. The proteins encoded by these HIF-responsive genes have a variety of functions. Some increase tissue oxygenation — such as vascular endothelial growth factor (VEGF), which stimulates the outgrowth of new blood vessels — and some enhance cellular glucose uptake and metabolism to allow energy generation when oxygen is scarce.

Our understanding of how levels of HIF are upregulated during hypoxia is growing rapidly⁴. The protein encoded by the von Hippel–Lindau tumour suppressor gene (pVHL), which is frequently mutated in cancer, is central to this process. The normal

VHL protein is part of a complex that, when oxygen is abundant, targets the α -subunits of HIF (HIF- α) for degradation. Recognition of these subunits by pVHL depends on a modification of HIF- α that can occur only in the presence of oxygen. When oxygen is scarce, this modification does not occur and so HIF- α escapes destruction, causing an increase in HIF levels and enhancing expression of the hypoxia-inducible genes. Mutations of the *VHL* gene produce an effect rather like hypoxia — mutant forms of pVHL found in cancer cannot destroy HIF- α , and as a result, the hypoxia-inducible genes are persistently activated⁴ (Fig. 1).

In the new study, Staller *et al.*³ searched for genes that are regulated by pVHL. They introduced *VHL* into renal carcinoma cells (which lack a normal copy of this gene) and then, using DNA microarray analysis, they looked for changes in the activity of thousands of other genes, under non-hypoxic conditions. Unexpectedly, they found that normal pVHL dramatically reduced the production of a receptor protein called CXCR4. This receptor binds chemokines — secreted proteins, rather like growth factors, that allow migrating cells (immune cells, for example) to navigate to specific organs⁵. The binding of chemokines to receptors such as CXCR4 on the surface of migrating cells stimulates both cell adhesion and motility, and causes the cells to move towards the source of the chemokine.

But how does pVHL regulate the production of CXCR4? As the authors expected, it does so by downregulating HIF. The authors found a functional HIF-binding site in the regulatory region of the *CXCR4* gene. They also found that cells containing normal pVHL produced more CXCR4 when exposed to hypoxia. So *CXCR4* seems to be a bona fide hypoxia-inducible gene.

The connection between CXCR4 and hypoxia is revealing, because several studies have indicated that 'chemoattraction' through CXCR4 contributes to organ-specific metastasis in certain forms of cancer. For instance, human breast cancer cells often contain high levels of CXCR4, and these cells preferentially metastasize to sites that produce large amounts of the chemokine SDF-1 α (the binding molecule, or ligand, of the CXCR4 receptor), such as the lungs and bone marrow⁶. In fact, *CXCR4* is part of a small set of genes that cooperate to promote bone metastases from breast cancer⁷.

But why does hypoxia induce CXCR4? Presumably, it doesn't matter to a tumour cell where it migrates. An answer to this question can be deduced from the characteristics of mice that are genetically engineered to lack this gene. Such mice show defects in the branching and/or remodelling of certain blood vessels⁸. So the activation of CXCR4 in blood-vessel cells might be part of an integrated hypoxic response that allows

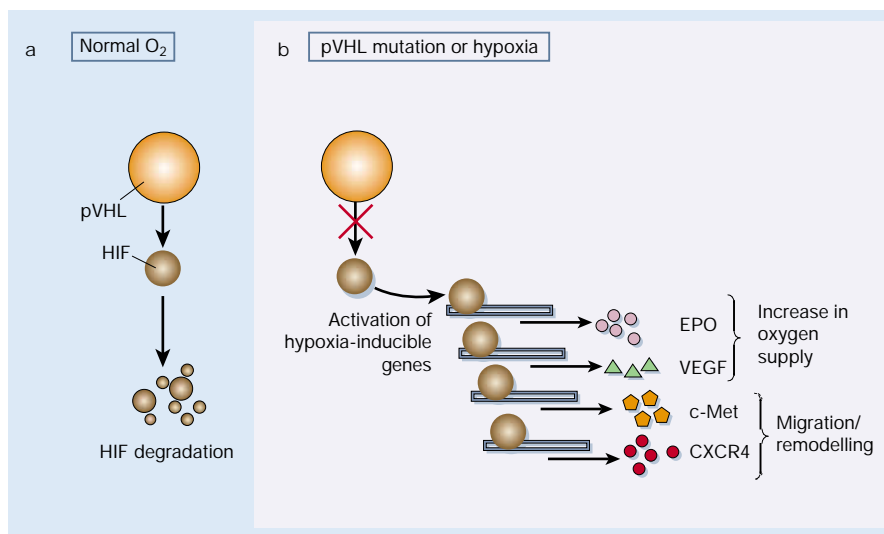


Figure 1 The hypoxic response. **a**, Under conditions of normal oxygen, the von Hippel–Lindau tumour suppressor protein (pVHL) modifies the protein HIF, which leads to its destruction. **b**, When oxygen is scarce (hypoxia), or when pVHL is mutated, HIF accumulates inside cells and activates the expression of certain genes. This triggers two complementary responses. First, tissue oxygenation is stimulated through the activation of genes such as VEGF (which stimulates the outgrowth of new blood vessels) and erythropoietin (EPO, which stimulates the production of red blood cells). Second, tumour cells are stimulated to move away from the site of hypoxia through the activation of genes such as *c-Met*, which enhance cell motility and invasion. Now, Staller *et al.*³ show that the gene *CXCR4* is also activated by HIF. CXCR4 not only stimulates migration, it also enables tumour cells to home in on specific, distant organs.