of MaSC function risks being an oversimplification. Also, can MaSCs turn rogue and act as cancer stem cells? And if so, are miscues by oestrogen and/or progesterone complicit in this Jekyll and Hyde hypothesis?

A notable issue is the relevance of these observations[1,2] to human breast development. Encouraging recent findings[10] suggest that progesterone also has proliferative effects on a human stem/progenitor cell through a paracrine mechanism (one affecting nearby cells). These revelations underscore the presence of an indispensable signalling mechanism that goes far back in evolution.

The present studies[1,2] therefore succeed in uncovering a long-suspected cellular mechanism by which oestrogen and progesterone control the MaSC pool and its regenerative activity. Such findings promise to accelerate the understanding of steroid-hormone control of normal mammary development. They will also provide an exciting conceptual framework — a stem-cell perspective — for the current debate on exposure to steroid hormones and the risk of breast cancer. ■

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1. Asselin-Labat, M.-L. *et al. Nature* **465,** 798–802 (2010).
2. Joshi, P. A. *et al. Nature* **465,** 803–807 (2010).
3. Pike, M. C., Spicer, D. V., Dahmoush, L. & Press, M. F. *Epidemiol. Rev.* **15,** 17–35 (1993).
4. Lambe, M. *et al. N. Engl. J. Med.* **331,** 5–9 (1994).
5. Brisken, C. *et al. Proc. Natl Acad. Sci. USA* **95,** 5076–5081 (1998).
6. Fata, J. E. *et al. Cell* **103,** 41–50 (2000).
7. Jones, D. H. *et al. Nature* **440,** 692–696 (2006).
8. Fernandez-Valdivia, R. *et al. Dev. Biol.* **328,** 127–139 (2009).
9. Gonzalez-Suarez, E. *et al. Mol. Cell. Biol.* **27,** 1442–1454 (2007).
10. Graham, J. D. *et al. Endocrinology* **150,** 3318–3326 (2009).

NONLINEAR DYNAMICS

# Chaotic billiard lasers

A. Douglas Stone

**The chaotic motion of light rays gives microlasers surprising emission properties, enhancing quantum tunnelling by many orders of magnitude and producing highly directional output beams.**

Physicists have worried for some time about what happens when chaos and quantum mechanics meet. Chaos refers to a generic effect of nonlinear forces in classical physics: the final state of a system depends with exponential sensitivity on the initial conditions. In a practical sense, therefore, it is unpredictable — the 'butterfly effect' made famous in fiction and film. Conversely, quantum mechanics is governed by linear equations, but to reproduce classical behaviour on macroscopic scales it must somehow contain the seeds of chaos.

Albert Einstein pointed out in 1917 that the rules then established by Niels Bohr and Arnold Sommerfeld to connect quantum and classical dynamics would be inapplicable if the classical motion had properties that we now term chaotic[1]. For the past few decades, physicists across many sub-fields (nuclear, atomic, condensed-matter and optical physics) have been trying to tease out the signatures of classical chaos in the study of microscopic systems[2]. Writing in *Physical Review Letters,* Shinohara *et al.*[3] demonstrate clearly one such effect — known as chaos-assisted tunnelling — by studying the emission properties of special micrometre-sized lasers.

Shinohara and colleagues' study was motivated by extensive theoretical work in chaos theory relating to 'dynamical billiards'. These are among the simplest and most easily visualized systems for studying chaos, consisting of a two-dimensional enclosure with reflecting walls and negligible friction, in which a point mass is constrained to move in a straight line until it hits the boundary — at which point it obeys the familiar rule that the angle of incidence is equal to the angle of reflection. Of course, real billiard tables have straight sides, so the motion of the ball is rather simple as it bounces off multiple walls. However, unless they are highly symmetrical (circular, for example), other billiard shapes give rise to a mixture of unpredictable chaotic motion, or regular predictable motion, depending on the starting position and momentum of the mass. Physicists and mathematicians going back to Lord Kelvin[4] have learned a great deal about chaotic motion and its onset by studying dynamical billiards because of their varied shape.

It was thus natural for physicists to ask, and to model, what would happen if the billiard was very small and the mass was a quantum particle[5]. How would its quantum wavefunction and quantum dynamics reflect the possibility of chaotic motion in the billiard? A number of clear differences were found compared with highly symmetrical ('non-chaotic') quantum systems, for example pseudo-random behaviour of energy levels and wavefunctions, as well as a new avenue for quantum tunnelling — a process in which a quantum particle mysteriously transits a region that cannot be traversed according to the laws of classical mechanics. The 'quantum billiard' was a wonderful theoretical model, but experimentally it was difficult to find real physical systems to which the model applied. Artificial atoms known as quantum dots have been analysed with some success as chaotic quantum systems, but these systems typically contain many interacting electrons, and the electrons are not confined by 'hard walls' of a known shape so as to make a simple connection to billiards. This situation changed in 1997 when Nöckel and Stone[6] pointed out that certain types of laser cavity are realizations of quantum billiards.

Typical laser cavities are formed by arrangements of mirrors, which trap the light that is generated by pumping an atomic gain medium with some external energy source, often an electrical current. The pumped gain medium then amplifies the light as it bounces back and forth in the cavity before eventually escaping. However, the push for small on-chip lasers to enable integrated optical circuits has given rise to new, cylindrically shaped laser cavities, in which the light is almost completely trapped by total internal reflection. If such cylindrical

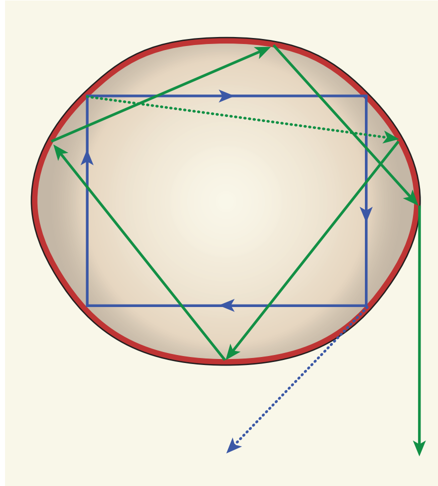

**Figure 1 | Cross-sectional shape of the 'asymmetric resonant cavity' microlaser of Shinohara and colleagues[3].** The laser is 'pumped' by an electrical current so that most of the light rays generated follow a rectangular periodic orbit (blue), which is totally internally reflected according to the usual law of specular reflection in ray optics. Conventional 'quantum tunnelling' would lead to light emission at the corners of the rectangle (dashed blue arrow; similar processes would occur at all four corners). But the authors[3] find that light is actually emitted by 'chaos-assisted tunnelling', whereby the light rays violate the specular reflection law of ray optics by a small amount (dashed green arrow; again a similar process would occur at each corner) and subsequently obey ray optics along a chaotic trajectory (green; simplified for clarity) until they escape by refraction at points far from the corners of the rectangle and near to the horizontal axis of the asymmetric resonant cavity. All of the emission occurs in four highly directional beams approximately parallel to the vertical axis of the cavity, in contrast to the output directions at approximately 45° to that axis expected from conventional tunnelling.

cavities are smoothly deformed so that their cross-section is roughly oval-shaped (Fig. 1), the result is an 'asymmetric resonant cavity' (ARC), in which a thin cross-sectional slice contains the gain medium, and photons bounce around within this slice, behaving like quantum particles in a two-dimensional billiard of the corresponding shape. However, there is one crucial and interesting difference: the photons can sometimes refract out at the boundary instead of reflecting back in, so these systems are leaky quantum billiards. How would their behaviour differ from the corresponding 'classical behaviour', which in the case of light means the behaviour expected from ray optics?

Surprisingly, in many cases the chaotic, classical motion of light rays can be used to predict how these laser cavities will emit light, with little need to take into account quantum effects[6,7]. For these cavities, the periodic ray orbits that are intended to trap the light are unstable, and chaos carries rays away, causing them to fall below the angle of total internal reflection and refract out in a surprisingly regular manner[7]. The work of Shinohara *et al.*[3] provides a dramatic exception to this classical ray mechanism for emission, and shows how chaos and quantum effects can work cooperatively.

In their experiment, a specific shape of ARC microlaser was designed that had a periodic ray orbit in the shape of a rectangle (Fig. 1); only light in the vicinity of this orbit would be strongly amplified owing to the authors' pumping scheme. Unlike previous ARC cavities, this rectangular orbit was stable, meaning that rays close to it would not behave chaotically, but would remain in the orbit's vicinity indefinitely, undergoing an oscillatory motion. Moreover, the angles of incidence at the bounce points of the ray orbit were all larger than the critical angle for total internal reflection, so that no light rays would escape the laser at all if ray optics were valid for this system. Not to worry, quantum mechanics steps in here and tells us that there is some small probability that a photon can 'tunnel' out of the cavity, despite the law of total internal reflection for rays. So an experienced quantum physicist would not be surprised to find some weak emission of light near the bounce points of the orbit, in the tangential direction (Fig. 1).

But that is not at all what is seen in Shinohara and colleagues' set-up[3]. Instead, the light escapes far from the bounce points and ends up travelling in several highly directional beams perpendicular to the major axis of the ARC. This is because chaos alters familiar quantum behaviour. A light ray travelling on or near to the rectangular orbit is unaffected by the chaotic motion that it would undergo if it could get just a little further away. But the photon 'wavefunction' has some small chance of sneaking further away, into the 'chaotic sea'. In fact, this small chance is still much larger than the probability that the photon will tunnel directly out of the cavity, because it involves a smaller violation of classical mechanics. However, once the photon makes this small quantum detour, it is quickly carried out of the cavity by chaotic motion, causing it to fall rapidly below the critical angle for total internal reflection. This process, called 'chaos-assisted tunnelling', was predicted many years ago[6,8,9], but has been observed in only a few experiments[10,11], and in none as dramatically as in the experiment of Shinohara and colleagues[3].

There is one last puzzle with the authors' observations. Why doesn't the chaotic motion of the photon lead to essentially random transmission in all directions? The reason is that the full pseudo-random behaviour of chaotic billiards develops only after many bounces. As noted above, it has previously been shown[6,7] that highly directional emission is typical from these leaky chaotic cavities, and that the favoured emission directions can be predicted from the study of few short, unstable periodic orbits in the chaotic sea. This 'unstable manifold' theory[7] was used by Shinohara *et al.*[3] to explain the origin of the brightest emission points near the major axis of the ARC (Fig. 1) and the highly directional beams perpendicular to this axis seen in the experiment. It is this directional emission property that has motivated the study and design of ARC microlasers as potentially useful on-chip light sources for integrated optical circuits[12,13]. Studies such as that of Shinohara and colleagues exemplify the gratifying confluence of fundamental and technological interest in these systems. ■

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1. Einstein, A. in *The Collected Papers of Albert Einstein* Vol. 6 (transl. Engel, A.) 434 (Princeton Univ. Press, 1997).
2. Gutzwiller, M. C. *Am. J. Phys.* **66,** 304–324 (1998).
3. Shinohara, S. *et al. Phys. Rev. Lett.* **104,** 163902 (2010).
4. Lord Kelvin *Phil. Mag.* **2,** 1–40 (1901).
5. Heller, E. J. *Phys. Rev. Lett.* **53,** 1515–1518 (1984).
6. Nöckel, J. U. & Stone, A. D. *Nature* **385,** 45–47 (1997).
7. Schwefel, H. G. L. *et al. J. Opt. Soc. Am. B* **21,** 923–934 (2004).
8. Davis, M. J. & Heller, E. J. *J. Chem. Phys.* **75,** 246–254 (1981).
9. Tomsovic, S. & Ullmo, D. *Phys. Rev. E* **50,** 145–162 (1994).
10. Dembowski, C. *Phys. Rev. Lett.* **84,** 867–870 (2000).
11. Steck, D. A., Oskay, W. H. & Raizen, M. G. *Science* **293,** 274–278 (2001).
12. Gmachl, C. *et al. Science* **280,** 1556–1564 (1998).
13. Yan, C. *et al. Appl. Phys. Lett.* **94,** 251101 (2009).

BLOOD-VESSEL FORMATION

# Bridges that guide and unite

Thomas Schmidt and Peter Carmeliet

**To form new blood vessels, the endothelial tip cells of two existing vessels come together by the process of anastomosis. But how do they find each other? Macrophages seem to provide a bridge and mediate their union.**

Many primitive organisms lack blood vessels, and oxygen simply diffuses to their innermost cells. Blood vessels arose in evolution when organisms outgrew the physical limits of oxygen diffusion. They are lined with endothelial cells and branch by sprouting — sending out specialized endothelial cells called tip cells at the forefront of the sprout that navigate to their target[1]. Previous studies have mainly focused on understanding how tip cells initiate vessel sprouting; so nearly nothing is known about how these cells fuse with neighbouring sprouts to form a perfused vessel. Writing in *Blood*, Fantin *et al.*[2] report that, contrary to expectation, tip cells lack the precision to find, recognize and fuse with other tip cells. Instead, macrophages, phagocytic cells of the immune system, serve both as what we would like to call 'bridge cells' and as guidance posts to precisely position tip cells in preparation for accurate fusion.

Fantin and co-workers show that, precisely when tip cells are about to fuse — a process referred to as anastomosis — tissue-resident macrophages are located in the vicinity of vessel branches. Further, the absence of macrophages or blockage of their function impairs vessel fusion and thereby angiogenesis, the formation of new vessel circuits (Fig. 1, overleaf). For aficionados in the field who had expected that tip cells would perform this job without external help, these findings not only shed light on a fundamental aspect of angiogenesis, but also highlight the growing evidence for a link between macrophages and angiogenesis.

Indeed, macrophages can regulate the growth and remodelling of blood and lymph vessels in quite different ways. As their name (Greek for 'big eater') reflects, they can inhibit angiogenesis by initiating a cell-death program in endothelial cells and engulfing the dying cells[3], and they can also inhibit angiogenesis more generally; the macrophages that carry out these processes are of the type termed M1 (ref. 4). Another type of macrophage, called M2, promotes angiogenesis by releasing pro-angiogenic factors such as VEGF and VEGF-C, and thereby induces tip-cell formation[4,5]. The macrophages that Fantin and colleagues describe are polarized towards the M2 type.

Disease is another setting in which macrophages affect vessel formation. In tumours, they excessively stimulate angiogenesis, leading