sensory systems are weighted and at which stage the combination takes place is still under investigation. But it seems that, at least in the fly, such integration occurs quite early on in the visuo-motor pathways, which helps the animal to keep its gaze level and remain stable in the air during rapid movements but also when slowly drifting.

What is the point in studying the ocelli and other insect sensory systems? There are two answers to that question. For one, using sensory information to control balance and gaze, or to produce other meaningful behaviour, is a common theme amongst all animals, including humans. As I just mentioned, the control of balance and gaze has to work at different speeds — which is true for flies and humans. For instance, flies and humans keep their gaze aligned with the external horizon, which tremendously simplifies the processing of visual information. This is because the connections in the visual system are wired up in a way that assumes a certain orientation of the world when it is projected onto our eyes. Deciphering text when all the words are printed upside-down takes considerably longer than reading upside-up. Although this is an extreme example, it nicely illustrates how important it is to keep the visual environment in its natural upside-up orientation. We do it by moving our head and our eyes relative to our body, while flies can move only their heads to solve the same task. And yet, there are general functional principles that are similar in flies and humans. For slow gaze stabilization, we both use visual information; and for fast stabilization we exploit mechanosensory signals. The big advantage of studying comparatively simple animals such as flies is that we already know a lot about the neural circuits supporting gaze stabilization. We even know the individual neurons that combine ocellar and compound eye signals by name; these play a cardinal role in stabilization reflexes, in general. So, studying the neural mechanisms underlying stabilization reflexes in flies, where both the behavioural and neuronal performance can be quantified, may well help our understanding of how the same task is solved in more complicated animals, such as humans.

The other reason why it is interesting to study ocelli and other sensory systems in insects is because biological systems control gaze and flight in a fundamentally different way from man-made technical systems designed to achieve the same goal. Technical systems, say in aircraft control, use only a small number of highly accurate sensor measurements in combination with heavy super-computing to come up with command signals to ensure flight stability. Biological systems follow an entirely different approach: they take thousands of local, often noisy, signals and combine the information in a task-specific way, so that the combined outcome can be used immediately for control purposes. They replace the heavy super-computing stage with clever signal integration. A detailed understanding of exactly how the nervous systems of insects do this may inspire the future design of control engineering architectures.

Where can I find out more about ocelli?

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Primer

The natural history of antibiotics

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Selman Waksman first used the word *antibiotic* as a noun in 1941 to describe any small molecule made by a microbe that antagonizes the growth of other microbes. From 1945–1955 the development of penicillin, produced by a fungus, along with streptomycin, chloramphenicol, and tetracycline, produced by soil bacteria, ushered in the antibiotic age (Figure 1). Today, the evolution of antibiotic resistance by important human pathogens has rendered these original antibiotics and most of their successors largely ineffective, and if replacements are not found, the golden age of antibiotics will soon come to an end.

Understanding the success and failure of antibiotics requires understanding their natural history — the origins, evolution, and functions of the molecular medley that has played such an important role in human health. Studying their natural history could also result in new strategies to find novel antibiotics and delay resistance to existing ones.

Assembly from readily available parts

Antibiotics do not look like the familiar molecules in beginning biochemistry texts; they usually do not even resemble each other. In spite of these apparent differences, they are assembled from the same types of building block through enzyme catalysed reactions that closely resemble those used in making proteins, fatty acids, and polysaccharides. For example, penicillin is derived from a tripeptide of three amino acids, two of which are proteinogenic (cysteine and valine) and one of which is an intermediate in lysine metabolism (α-aminoadipate) (Figure 1). In conventional polypeptide biosynthesis, tRNAs bring the correct amino acid building block to a mRNA template and peptide bonds are formed to generate an amino-acid chain with the mRNA-encoded sequence. Some peptide precursors to antibiotics are biosynthesized this way,

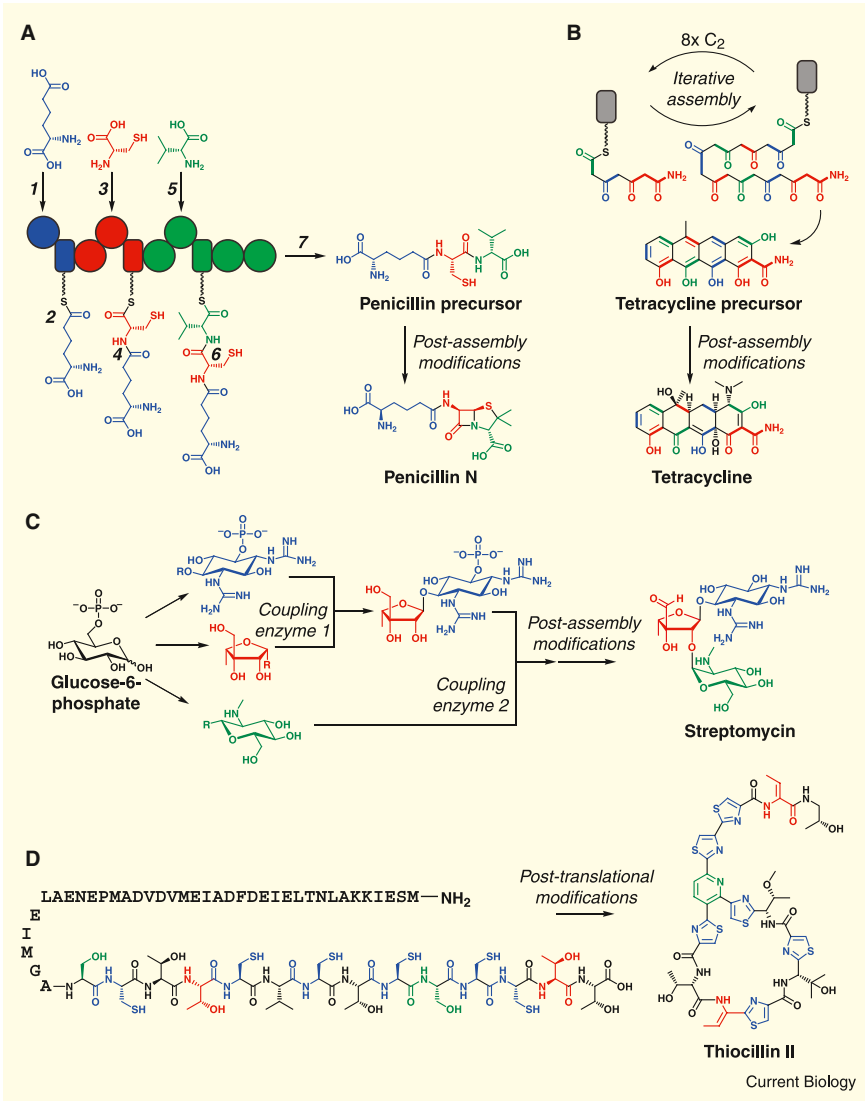

Figure 1. Antibiotic biosynthetic pathways.

(A) Penicillin. Each shape represents a separate protein domain, and the domains are organized into three modules (red, blue, and green) that comprise a single ten-domain protein. (1) α-aminoadipate is selected and activated by the blue module. (2) Activated α-aminoadipate is loaded onto the the blue module. (3) Cysteine is selected and activated by the red module. (4) Cysteine is linked to the red module and then coupled to the α-aminoadipate linked to the blue module, forming a peptide bond and translocating the chain to the red module. (5,6) The process repeats with valine on the green module. (7) The chain is released. Post-assembly modifications convert the penicillin precursor into penicillin N. (B) Tetracyline. The enzymes iteratively couple C2 building blocks (colored red, green, and blue) to synthesize a long chain. Three enzymes cyclize the polyketone chain into a precursor with four fused rings, and post-assembly modifications convert the precursor into tetracycline. (C) Streptomycin. Three different sets of enzymes convert the primary metabolite glucose-6-phosphate into the three building blocks of streptomycin, colored blue, red, and green. Two coupling enzymes link these building blocks, and post-assembly modifications turn the nascent trisaccharide into streptomycin. (D) Thiocillin. The last fourteen amino acids of a 52-residue peptide undergo thirteen post-translational modifications — including cleavage of the 38-residue 'leader peptide' — to become thiocillin.

and the ribosomally encoded peptide undergoes enzyme catalysed post-translational modifications to produce the final antibiotic (Figure 1).

Amino acid-derived antibiotics are more frequently produced by modular metabolic pathways in which the templating function of the mRNA is embedded in the order of the modules, and specialized carrier proteins in each module perform the selection function of the tRNAs (Figure 1). The first module in the pathway selects the amino-terminal amino acid (α-aminoadipate in penicillin), and the last module selects the carboxy-terminal amino acid (valine). The last module also releases the tripeptide chain, so that auxiliary enzymes in the pathway can carry out the functional equivalent of post-translational modifications, which are typically quite extensive.

While tRNAs select from a pool of standard (proteinogenic) amino acids, the nonstandard amino acids found in penicillin and other antibiotics need to be synthesized by specialized enzymes in a just-in-time fashion. The proteins of the penicillin pathway fall into various functional categories: enzymes that make nonstandard building blocks such as α-aminoadipate; enzymes that form the modules that select and stitch these building blocks together; enzymes that modify the peptide into the functional antibiotic; regulatory proteins that ensure the pathway is expressed under appropriate conditions; and resistance proteins that prevent the would-be producer from getting killed. In bacteria and fungi, the genes for all these proteins are usually found on a continuous stretch of DNA. Penicillin biosynthesis mimics protein biosynthesis in important ways, but the macromolecules that carry out the two processes are related only in function.

Tetracycline's biosynthesis is closely related to fatty acid biosynthesis, but in this case (distantly) related enzymes carry out both processes (Figure 1). Tetracycline's core is assembled from a starter unit (malonamyl-CoA) and eight two-carbon fragments. Streptomycin is assembled from sugar monomers by close relatives of the sugar linking enzymes that make the common polysaccharides. Of course, the sugar building blocks of streptomycin are more exotic than those of cellulose or chitin, and, as was the case for α-aminoadipate in penicillin biosynthesis, they require specialized pathways for their production from glucose. The enzymes that make these unusual sugars are also relatives of enzymes used in primary metabolism.

Antibiotic biosynthesis is modular, just like the biosynthetic pathways of more familiar biological molecules like proteins and DNA. The startling array of antibiotic structures arises from a more exotic set of starting materials and more extensive modifications of the polymeric core.

Modular biosynthetic pathways

The long linear pathways that nature uses to assemble antibiotics contrast

with the laboratory syntheses chemists devise for similarly complex molecules. Efficient laboratory syntheses tend to avoid long linear reaction sequences, because they involve both the logistical difficulties inherent in having a long supply chain and the likelihood of low overall yields — a ten-step sequence with a 90% yield in every step results in a 35% overall yield. In a microbial cell, the catalytic proficiency of enzymes can push the yield of any step sufficiently close to 100% to tame the arithmetic demon that governs overall yields.

The modularity of the pathways — one module per subunit from the beginning to the end of the molecule — enforces a long linear sequence of reactions, and nature favors modularity to expedite the evolution of molecular diversity. Antibiotics are made by highly evolvable pathways. Consider the penicillin pathway. Each of its modules consists of three protein domains: one to select an amino-acid building block; one to activate it; and one to insert it into the growing chain. Three of these modules synthesize the tripeptide core of penicillin, and the sequence of the peptide chain is determined by the sequence of the modules. Vancomycin, which these days is invariably described as the 'antibiotic of last resort', has seven modules. There are many instances where two pairs of antibiotics produced by these modular pathways differ by the insertion, deletion, or replacement of a module.

A very similar analysis can be given for the pathways that produce antibiotics like tetracycline, although they are based on acetate-derived building blocks, not amino acids. After the starter unit, each module introduces a two-carbon building block to the growing linear chain (sometimes with a one-carbon side chain; Figure 1). The two-carbon fragment can be processed in a variety of ways to provide distinguishing features to the originally identical building blocks. The result is a lipid-like molecule rather than a peptide, but the modularity that facilitates evolutionary molecular diversification persists. Antibiotics like streptomycin are also assembled in a modular fashion; except the building blocks are sugars and the coupling reactions are the same type that assemble glycogen and cellulose.

Because the modular assembly of most antibiotics mimics the modular assembly of biological macromolecules like proteins, all of the same general evolutionary strategies that provide for protein diversification — mutation, duplication, deletion, and rearrangement — are also used to evolve new antibiotics. The complex suite of antibiotics we see today results from rounds of alteration, selection, and amplification of simpler ancestors.

Antibiotic evolution is complicated by lineage and function

In principle, the evolutionary history of an antibiotic or an antibiotic family, say the beta-lactam family that includes penicillin, should be a wonderful model for the evolution of multigenic traits. There is a clear phenotype — a molecule — and the contribution of each of the gene products to forming the final molecule is increasingly understood. However, tracing a path back from two members of an antibiotic family to a common ancestor, not to mention the more difficult task of tracing the path from an early ancestor to today's family members, is complicated by our current ignorance of both the pedigree of the antibiotic producing genes and the ecological role of the antibiotic in the producer's natural community. The evolutionary history of bacterial genes, especially the genes involved in the biosynthesis of antibiotics and other secondary metabolites, is shaped by horizontal gene transfer. Horizontal gene transfer is undoubtedly the reason that the genes for regulation, resistance and biosynthesis are usually clumped together on a continuous stretch of DNA. As a result, a microbe's secondary metabolite repertoire probably depends more on its neighbors than its ancestors.

Some antibiotic gene clusters are cosmopolitan, while others have cameo roles. One analysis estimated that if 10,000 actinomycetes (the family of soil bacteria that has produced most of our antibiotics and other medically useful molecules) were screened, 2,500 would produce antibiotics. Of these, 2,250 would make streptothricin, 125 streptomycin, and 40 tetracycline. Vancomycin is predicted to be made by one in a hundred thousand; erythromycin, by one in a million; and daptomycin, our newest antibiotic, by one in ten million. Because the soil bacteria that produced so many of our antibiotics live in exceptionally complex multispecies environments, tracing both neighbors and ancestors will be a daunting task. Sequenced bacterial genomes are now appearing with increasing frequency, and it is likely that the genomes of antibiotic-producing microbes will be sequenced at an increased pace in the near future. If the past is any guide, they will reveal that these familiar microbes produce many more molecules than have been found using traditional methods, which will open up great opportunities to tease out the production of the cryptic antibiotics. These new genome sequences will also allow us to make some headway in tracing evolutionary histories, or at least suggest plausible models.

Another problem with tracing the evolutionary history of antibiotics is our current ignorance about their roles in the natural environment. We know what antibiotics can do for us, but what do they do for the producing organism? Without understanding the natural roles of antibiotics, we cannot understand the basis for their evolutionary selection. Most scientists assume that microbes produce antibiotic compounds to mediate interactions with other microbes in their neighborhood. The main evidence for this view is the wide distribution of antibiotic resistance genes: many microbes carry the resistance gene for antibiotics that they themselves cannot produce, from which it follows that resistance genes — and by extension the molecules to which they confer resistance — must have a function.

An appealing possibility is that antibiotics are made by microbes to kill competing microbes, but as early as 1961, Selman Waksman pointed out that the ability of a microbe to produce a small molecule with antibiotic properties when cultured under unnatural conditions in the laboratory does not imply such a function for the molecule in nature. Recently, it has been shown that at concentrations well below those needed to inhibit the growth of other bacteria, antibiotics can modulate the transcriptional profiles of target bacteria. These revelations have caused several scientists to argue that what we call 'antibiotics' are actually signaling molecules that happen to kill bacteria when applied at unnaturally high concentrations. In this view, the products of resistance genes silence messages rather than provide protection. In short, we know little about the ecological role of the molecules we call antibiotics.

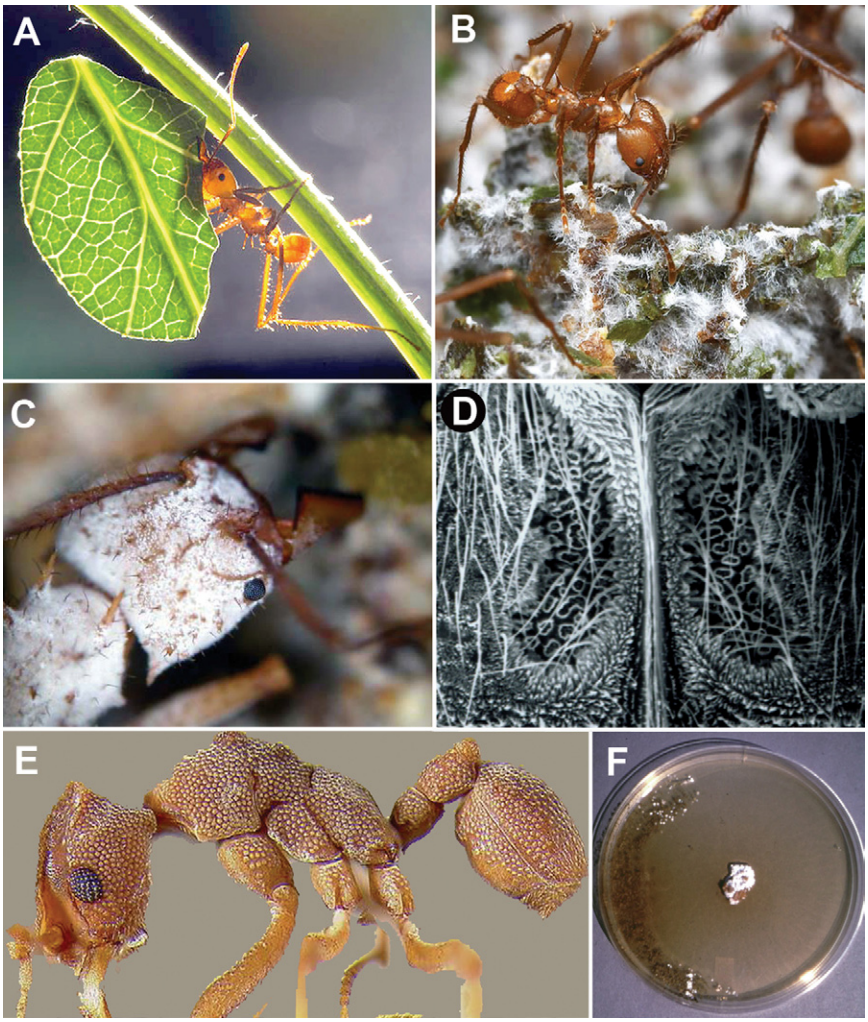

Figure 2. Exploring the natural history of antibiotics by focusing on ancient agriculture in ants.
Fungus-growing ants, including the conspicuous leaf-cutters (A), cultivate fungus for food (B). The ants engage in another mutualism with actinomycetes, which can completely cover the exoskeleton of workers ((C); whitish substance on *Acromyrmex* sp.), or occur within specialized crypts, on the ventral surface of the ants ((D); propleura in *Cyphomyrmex longiscapus*) and can even cover most of the surface of workers ((E); white dots on exoskeleton of *C. longiscapus* represent openings to crypts). The symbiotic actinomycetes produce antibiotics that help protect the garden from specialized parasites in the genus *Escovopsis* ((F); bioassay with bacterium in middle and parasite *Escovopsis* on the left side). (Photocredits: A,B, Alex Wild; C, Ainslie Little.)

Advantages of studying less complicated microbial environments

If our ability to unravel the natural history of antibiotics is frustrated by the complexity of their producers' environments, a logical recourse is finding simpler systems in which microbes produce antibiotics. At a minimum, the likelihood of finding useful new molecules would increase by moving our search away from explored environments. For example, investigations of marine environments have provided many microbial-produced novel small molecules. While these molecules are likely to contribute new human therapeutic agents, the ecology of their marine habitats is not understood well enough to trace antibiotic phylogeny and/or function. In contrast, insect–bacteria mutualisms — a symbiotic association in which each of the participants receives a net benefit — appear quite tractable for functional and evolutionary analyses. An especially attractive system is the multilateral symbiosis among fungus-growing ants, the fungus they cultivate for food, and the bacterial symbionts that help protect the ants' fungal crops (Figure 2).

The relationship between fungus-growing ants and their food fungus first originated some 50 million years ago in the Amazon Basin. As the name suggests, these ants cultivate fungus for food in specialized gardens, typically underground. The relationship between ants and their food fungus is an obligate mutualism: the ants cannot survive without their fungal partner, and the fungal partner cannot survive without the ants. When new queens leave their parent colonies, they carry a fragment of the fungus with them to the site of the new colony. Both ant and fungus have prospered: from a single pair of founding species this initial symbiosis has evolved to include more than 230 species of ants and diverse fungal strains. In the leaf-cutter ant genus *Atta*, the most derived members of the fungus growers, a single colony can harbor millions of workers and persist for more than a decade. Leaf-cutter ants use fresh leaf substrate to cultivate their fungal partner, and their copious foraging activities make them one of the dominant herbivores of the Neotropics. The phylogeny of the ants and their fungal partners is largely known, and the evolutionary history of the food fungus broadly parallels the ant phylogeny — they have undergone diffuse co-evolution for tens of millions of years.

The ants engage in a second mutualism with bacteria that belong to the same order of bacteria (actinomycetes) that produce so many of our clinically used antibiotics (and anticancer agents). In this system, all of the known ant-associated bacteria belong to the genus *Pseudonocardia*, and the association between the ants and their bacterial symbionts appears to be an ancient one. The strongest evidence for their long-standing association is the elaborate morphological adaptations that the ants have evolved for housing their bacteria (Figure 2). Different ant genera have different types of modification, and the structures housing the bacteria are connected to glands, which are thought to produce nutrients that support the growth of the bacteria. Ants are highly specialized for their bacterial symbionts, and experiments to replace an ant's bacterial symbiont with that from another ant have not yet been successful. These ant-associated bacteria produce antibiotics, which are as yet poorly known, that protect the ants' fungal gardens from microbial

pathogens. Experimental studies crossing the presence/absence of the bacteria with the presence/absence of a specialized garden pathogen — a fungus in the genus *Escovopsis* — have shown that ants with antibiotic-producing bacteria are better able to protect their fungal gardens from disease. These studies are among the best evidence that at least some antibiotics suppress infections in nature.

The ant–fungus–bacteria mutualism is an ancient system whose evolutionary histories can be deduced by traditional molecular phylogenetic studies. Once these histories have been established and the associated antibiotics have been identified, there will be a wealth of data to trace both the evolution of these small molecules and their function. These studies could also reveal how the ant-bacteria system has maintained itself over tens of millions of years without running out of antibiotics to combat the inevitable development of antibiotic resistance by their microbial pathogens. In short, we can learn a lot from bugs — both the six-legged and microbial varieties.

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A neural basis for unique hues?

J.D. Mollon

The four perceptually simple colors — red, green, yellow and blue — are a challenge to neuroscience, because no one has found cortical cells that represent color in terms of these ‘unique hues’ [1]. The chromatically selective cells at early stages of the primate visual system do not map on to the unique hues [2,3]. Recently, however, Stoughton and Conway [4] have reported that the peak sensitivities of color cells in posterior inferior temporal cortex do cluster near the unique hues. The authors plot their results as a polar histogram: at each position on a hue circle, they show the number of cells that are maximally excited by that hue. There are three peaks in the histogram: one (the largest) falls close to unique red and another falls close to unique blue, while the third (less well-defined) lies in the yellow-green region. In fact, however, if the stimuli used in the experiment are plotted in a physiological color space, they form not a circle but an obtuse triangle. The peaks identified by Stoughton and Conway [4] fall at the apices of this triangle. Because these stimuli maximize the ratios of cone signals, they would maximally excite cells earlier in the visual system. So Stoughton and Conway’s polar plot does not in itself show that cells of the posterior inferior temporal cortex represent unique hues, nor that they differ qualitatively in their behavior from chromatic cells at an earlier level.

The stimuli were presented to the monkey on a CRT and the individual chromaticities were obtained by

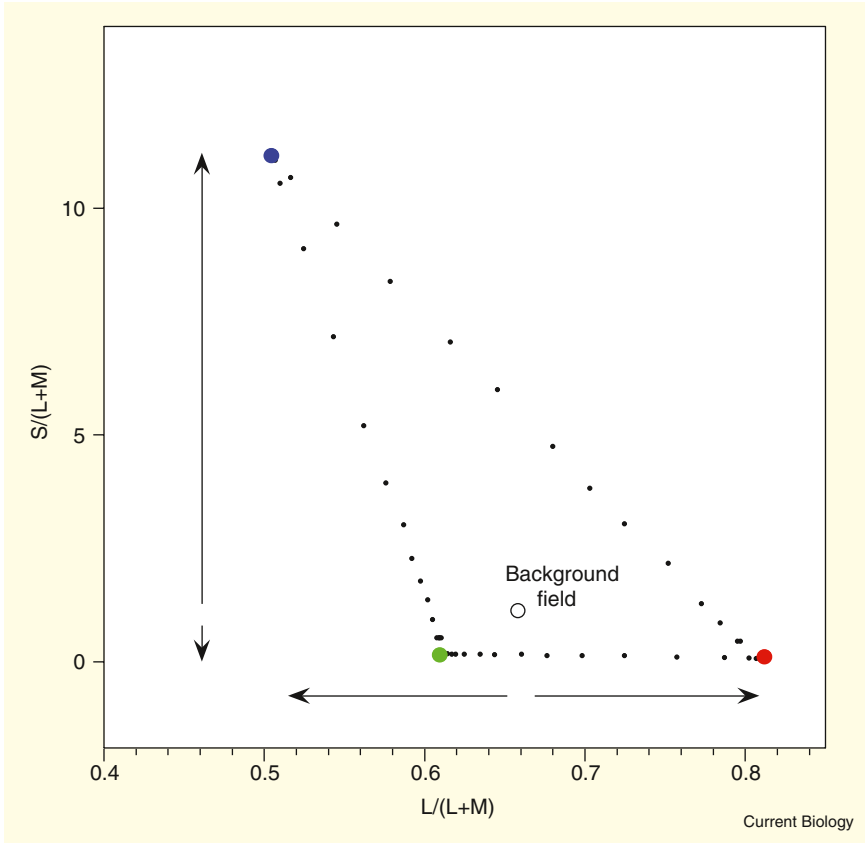

Figure 1. Stoughton and Conway’s [4] equiluminant stimulus set (small black points) re-plotted in the chromaticity diagram of MacLeod and Boynton (1979).

The colored dots show the chromaticities of the three phosphors of the CRT used in the experiments. Open circle: chromaticity of the white background present during the measurements. The arrows indicate the maximum available modulations on the two axes of the diagram. Scaling of S axis as in [8].