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REVIEW

Pheromones and signature mixtures: defining species-wide signals and variable cues for identity in both invertebrates and vertebrates

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Abstract Pheromones have been found in species in almost every part of the animal kingdom, including mammals. Pheromones (a molecule or defined combination of molecules) are species-wide signals which elicit innate responses (though responses can be conditional on development as well as context, experience, and internal state). In contrast, signature mixtures, in invertebrates and vertebrates, are variable subsets of molecules of an animal's chemical profile which are learnt by other animals, allowing them to distinguish individuals or colonies. All signature mixtures, and almost all pheromones, whatever the size of molecules, are detected by olfaction (as defined by receptor families and glomerular processing), in mammals by the main olfactory system or vomeronasal system or both. There is convergence on a glomerular organization of olfaction. The processing of all signature mixtures, and most pheromones, is combinatorial across a number of glomeruli, even for some sex pheromones which appear to have 'labeled lines'. Narrowly specific pheromone receptors are found, but are not a prerequisite for a molecule to be a pheromone. A small minority of pheromones act directly on target tissues (allohormone pheromones) or are detected by non-glomerular chemoreceptors, such as taste. The proposed definitions for pheromone and signature mixture are based on the heuristic value of separating these kinds of chemical information. In contrast to a species-wide pheromone, there is no single signature mixture to find, as signature mixtures are a 'receiver-side' phenomenon and it is the differences in signature mixtures which allow animals to distinguish each other.

Keywords Pheromone · Signature mixture · Behavior · Recognition · Learning · Individuality

Abbreviations

2MB2	2-Methyl-but-2-enal
AOB	Accessory olfactory bulb
AOS	Accessory olfactory system
*c*VA	*cis*-~~Vinyl~~ acetate cis-vaccenyl acetate
DHB	(*R,R*)-3,4-Dehydro-*exo*-brevicomin
ESP1	Exocrine gland-
GC	Gas chromatography
HPLC	High-performance liquid chromatography
MHC	Major histocompatibility complex
MOE	Main olfactory epithelium
MOS	Main olfactory system
MOT	Medial olfactory tract
MTMT	(Methylthio)methanethiol
MUP	Major urinary protein
OR	Olfactory receptor protein
OSN	Olfactory sensory neuron
SBT	2-*sec*-Butyl-4,5-dihydrothiazole
VNO	Vomeronasal organ
VNS	Vomeronasal system
VR	Vomeronasal receptor protein

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Introduction

It is 51 years since the start of modern pheromone research, with Butenandt's first chemical identification of a

pheromone in 1959, the silk moth's Bombykol, and the coining of the word 'pheromone' itself (Karlson and Lüscher 1959). Since then, pheromones have been found in species from almost every part of the animal kingdom (Wyatt 2003, 2009). Invertebrates and vertebrates, in a wide range of habitats, are similar to each other in the ways they use chemical communication; the parallels in uses and sensory processes are numerous, even if we are not always sure whether this is by convergence or shared ancestor.

However, there is still a debate about what pheromones are and are not in chemical communication, particularly in mammals. I think the problem continues to be the distinction between a *pheromone*, a molecule produced, for example, by all male mice, and what I propose we call a *signature mixture*, an individual male's distinctive mix of molecules, which a female mouse learns and uses to recognize him as a particular individual. The colony odors of social insects are also signature mixtures, learned by nestmates. Pheromones occur in a background of molecules which make up an animal's chemical profile consisting of all the molecules extractable from an individual (Fig. 1).

Pheromones are molecules that are evolved signals which elicit a specific reaction, for example, a stereotyped behavior and/or a developmental process in a conspecific (Table 1). The same pheromone (or parts of it) can have a variety of effects, depending on the context or the receiver (explored in more detail below). So for example, the male pheromones of mice, dehydro-*exo*-brevicomin and 2-*sec*-butyl-4,5-dihydrothiazole, appear to have the releaser effects of eliciting aggression from other males and attracting females, as well as the developmental (primer) effects of inducing estrus in mature females and accelerating puberty in young females (Novotny 2003). Similarly, the honeybee queen's mandibular pheromone attracts males during her nuptial flight, a releaser effect, but when she is queen of her own nest, the mandibular pheromone plus additional components act as the queen retinue pheromone: a primer signal to the worker bees, her daughters, that she is present and laying eggs (with the effect that the workers do not themselves lay eggs) (Slessor et al. 2005).

Signature mixtures are the subsets of variable molecules from the chemical profile (Fig. 1) that are learnt by other conspecifics and used to recognize an organism as an individual or as a member of a particular social group, such as a mongoose family group or ant colony (see Table 1). 'Signature' is used as it implies individuality. A key difference between pheromones and signature mixtures is that in all taxa so far investigated it seems that signature mixtures need to be learnt (see below) (Wyatt 2003).

It is worth remembering that the original definition of pheromone was proposed in 1959 when only a single pheromone had been chemically identified. It is a tribute to Karlson and Lüscher that the definition has held up so well

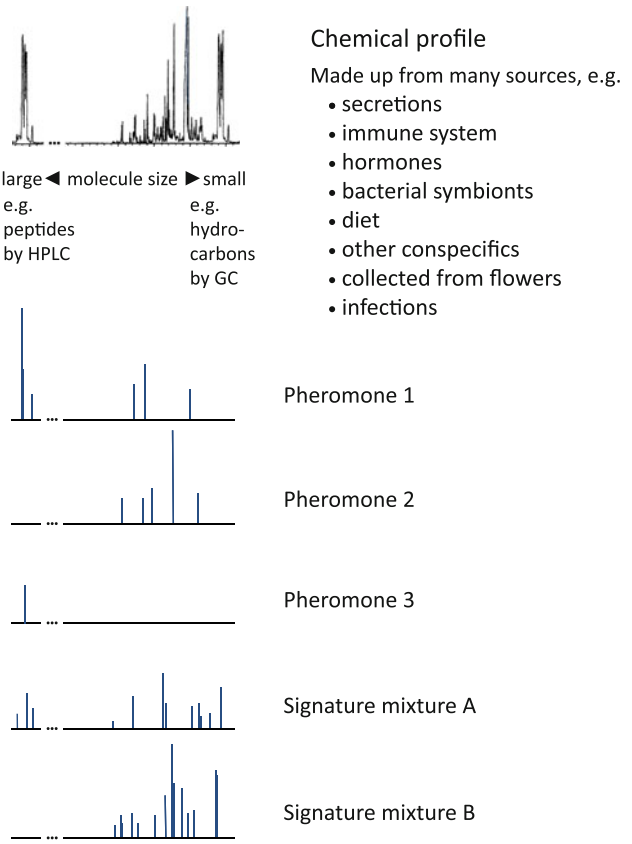

Fig. 1 Pheromones occur in a background of molecules which make up the chemical profile consisting of all the molecules extractable from an individual. The chemical profile (*top*) is an imaginary trace from an imaginary column (at one end is high-performance liquid chromatography (HPLC) with large proteins, at other end is gas chromatography (GC) with small volatile molecules). Each peak represents at least one molecule. The profile could have come from any kind of animal, invertebrate or vertebrate. Much of the chemical profile is highly variable from individual to individual. The sources of the molecules in the chemical profile include the animal itself as well as its environment, food, bacteria, and other individuals, etc. It is this complex background which makes identifying pheromones so challenging in many organisms. The pheromones could include sex pheromones or ones related to life stage or caste. The pheromones would be the same in all individuals of the same type in a species, dominant male, worker ant forager, etc.; that is, they are anonymous, common across the species. As examples, I have included some possible kinds of pheromones that are known from organisms (not necessarily in the same species): a specific combination of large and small molecules (Pheromone 1), a combination of small molecules (Pheromone 2), or a particular large molecule by itself, such as a peptide (Pheromone 3). The signature mixtures (A and B) are subsets of variable molecules from the chemical profile that are learnt for distinguishing individuals or colonies. Different receivers might learn different signature mixtures of the same individual. For example, a male might learn a different signature mixture of their mate from the signature mixture of the same female learnt by her offspring. Hypothetically the male might learn different signature mixtures for the same female in different contexts, say immune-system associated molecules in one context and more diet influenced molecules in another. In other words, signature mixtures may be a 'receiver-side' concept. The layout of the figure is inspired by Fig. 1 of Schaal (2008)

Table 1 Definitions of pheromone and signature mixture

1. Pheromone: molecules that are evolved signals, in defined ratios in the case of multiple component pheromones, which are emitted by an individual and received by a second individual of the same species, in which they cause a specific reaction, for example, a stereotyped behavior or a developmental process

   (Modified after Karlson and Lüscher 1959)

2. Signature mixture: a variable chemical mixture (a subset of the molecules in an animal's chemical profile) learned by other conspecifics and used to recognize an animal as an individual (e.g. lobsters, mammals) or as a member of a particular social group such as a family, clan or colony (e.g. ants, bees, mongoose)

   (Derived from Wyatt's 2005 'signature odor' and Johnston's 'mosaic signal' (*sensu* 2003 and 2005))

A note on the terminology: in Wyatt (2003, pp 2–4) I included signature mixtures within the definition of 'pheromones'. I now think it is more helpful to separate signature mixtures as their characteristics seem to be different, in particular their variability and the need for learning. I considered a number of terms as alternatives to 'signature mixture'. For many readers 'signature odor' implies volatile molecules. 'Chemical signature' and 'chemical profile' are already used, sometimes interchangeably, in many social insect papers to include all the molecules extracted from an insect, including both the variable molecules and pheromones. Signature mixtures are the subsets of variable molecules from the chemical profile that are learnt for distinguishing individuals or colonies. Johnston's 'mosaic signal' (*sensu* 2003, 2005) is effectively the same as signature mixture but in the evolutionary literature 'signal' implies an evolved production which may not be the case

(Wyatt 2009). It is not surprising that it has needed to be modified since. Karlson and Lüscher did not anticipate the individual variation and learning that underlies signature mixtures, which only became clear later as mammals and social insects in particular were chemically investigated further.

Definitions matter only because they can provide useful generalizations and predictions. My purpose in separating pheromones from signature mixtures is pragmatic and based on the heuristic value of separating these kinds of chemical information. When we say something is a pheromone, the reader can anticipate that it is a molecule (or particular combination of molecules) that will be found, for example, in all sexually mature females. There may be variation in quantities of pheromone for example (see below), but not in ways that allow an individual sexually mature female to be recognized as that individual. In Hölldobler and Carlin (1987)'s terms the pheromone signal is anonymous. In contrast, if a phenomenon, such as a male mammal recognizing his mate by smell, relies on a signature mixture, there would be little point in searching for a single combination of molecules eliciting the phenomenon that is characteristic of all females in the species: it is because each female has a different signature mixture that he can learn his mate's signature mixture and recognize her, distinguishing her from other females.

Signature mixtures may be a 'receiver-side' concept. Different receivers might learn different signature mixtures of the same individual. Hypothetically, a receiver might learn different signature mixtures of the same individual in different contexts (see legend to Fig. 1 for more detail).

Pheromones and signature mixtures compared

What are the distinguishing characteristics of pheromones and signature mixtures? It is not the innateness of responses to pheromones, though this is common to most if not all pheromones. Nor is it the specificity of pheromone receptor proteins. Instead, the distinguishing characteristics of signature mixtures are the combination of a requirement for learning and the variability of the cues learnt.

Overall, as I explore in the rest of this paper (see below for further detail and explanation of terms), many of the presumed differences between pheromones and signature mixtures are not supported when examined in detail (Table 2). Too often we have generalized from studies of pheromones in model systems. For example, studies of male moths and their response to female sex pheromone show highly specialized receptors for pheromone and dedicated brain areas specific for pheromone processing. However, other pheromone processing in insects may be by less specific receptors, without dedicated glomeruli in the brain. Narrowly tuned specialized receptors and dedicated glomeruli are not a prerequisite for a pheromone (e.g. Wang et al. 2008).

Similarly, there was an assumption by some scientists in the 1990s onwards, using mice as a model system to study mammal pheromones, that (a) pheromones would be exclusively detected by the vomeronasal olfactory system (VNO), and that (b) all molecules detected by the VNO were pheromones. As explored below, it is now confirmed that (i) pheromones are detected by both the VNO and the main olfactory system (MOS), depending on species and pheromone, (ii) the VNO also responds to other odorants, and (iii) there is extensive integration of inputs from the two olfactory systems.

The kinds of molecule that have evolved to be pheromones and those that are learnt for signature mixtures can overlap (Fig. 1). For example, cuticular hydrocarbons form the majority of molecules in signature mixtures used for colony recognition by many social insects (van Zweden and d'Ettorre 2010), but some particular hydrocarbons are species-wide pheromones (Liebig 2010). The small molecule mouse pheromones appear in a background of similar

Table 2 Comparing the features of pheromones and signature mixtures

	Pheromone	Signature mixture
Stimulus	A species-wide molecule (or particular defined combination of molecules)	A combination of molecules, not a single molecule. Combination of molecules varies between individuals or colonies. Possible 'receiver-side' effect: there may not be one signature mixture for each individual, as different conspecifics (receivers) may learn different subsets of molecules in the individual's chemical profile (Fig. 1)
Type of signal	Anonymous (independent of the source individual)	Variable (allows recognition of an individual or group such as a colony)
Molecule size	Any size or type, depending on habitat and phylogeny	Any size or type, depending on habitat and phylogeny
Source	Make self or acquire/modify. Usually genetically based	Make self or acquire/modify Use chemical mixtures, genetically based or from the environment or a combination
Learning	Little requirement for learning of the signal molecule(s). Innate, stereotyped, or hardwired (with the caveat of developmental constraints)	Cues learnt
Response	Elicits a stereotyped behavior and/or physiological response. May be context dependent	Learnt and can be used to distinguish individuals or groups (can lead to stereotyped response e.g. aggression). May be context dependent
Olfactory receptor proteins	Some (e.g. moth sex pheromones) have high specificity olfactory receptor proteins (and the "labeled lines" and "dedicated glomeruli" that result) Many other pheromones do not have highly specific ORs	Low specificity, broadly tuned receptors
Processing	Mostly combinatorial across glomeruli	Combinatorial across glomeruli
Detection system (olfaction or taste or act directly)	Mostly by glomerularly organized olfactory system(s) A minority of pheromones by other chemosensory routes e.g. taste. Allohormone pheromones act directly on tissues or nervous system	Glomerular olfactory system(s)
In vertebrates with a vomeronasal system	Detection by the VNS or main olfactory system or both, depending on pheromone and species	Detection by the VNS or main olfactory system or both, depending on species

molecular weight compounds, some of which may be used by mice as part of the signature mixture(s) used to distinguish one another as individuals (Novotny 2003; Schaal 2008).

One generalization that may stand is that all signature mixtures are processed by the combinatorial processes of olfaction rather than taste. I should explain that I am using olfaction here and elsewhere in this paper to mean detected by olfactory sensory neurons connected to the glomerular olfactory system—so chemosensory stimulus of such neurons by the touch of an ant's antennae on cuticle of an ant, while called "contact" chemoreception in the insect literature, is effectively olfaction; it is not a question of volatility or distance of communication. Underwater, or if passed to the nose of a terrestrial mammal (e.g. Haga et al. 2010; Roberts et al. 2010; Spehr et al. 2006), the molecules can be large peptides or proteins and still processed by olfaction. While almost all pheromones are similarly processed by olfaction, a minority of pheromones in invertebrates are processed by taste (gustation) or other chemosensory systems excluding olfaction (see below). Some pheromones both in vertebrates and in invertebrates may act directly on the brain or other organs (see below). Both in invertebrates and in vertebrates gustatory receptors come from different families of receptors from olfactory receptors, and link to the brain in different ways from the olfactory pathways.

Pheromones are usually secreted by an organism, but I have changed the verb in the definition to emit rather than

secrete (Table 1) because as long as they are a consistent signal across a species, pheromones could for example result from bacterial fermentation of secreted precursors (perhaps the case for our own armpits), or even be collected, as for example from flowers by male orchid bees in species-specific ways (Eltz et al. 2008).

Molecules in signature mixtures can be produced by the organism itself, acquired from the shared local environment, or other organisms. Examples of genetically controlled cues produced by the individual include, in mammals, odor cues related to the major histocompatibility complex (MHC) or lipocalin major urinary proteins (MUPs) (Hurst 2009; Kwak et al. 2010). Cues can also be acquired from the environment, for example from diet or the products of gut or scent gland microbes. In social insects, the signature mixtures (colony labels) are determined partly by the insect's own genes, but also by sharing molecules with other colony members, the environment (e.g. nest, food), or molecules from the queen which could include heritable and environmental factors (Breed and Buchwald 2009; van Zweden and d'Ettorre 2010).

A social insect colony's shared label is constantly changing (van Zweden and d'Ettorre 2010). The signature mixtures of mammal family groups also change as their diet and bacterial flora changes. This constant change is another reason for treating signature mixtures differently from pheromones.

Pheromones elicit stereotyped but conditional behavior and/or physiological response

Responses to pheromones are characterized by being innate, but the response can be conditional on early experience when growing up or the context of the signal, for example internal hormone levels in the receiver. Innate does not mean unconditional or invariant.

Generally speaking, pheromones do not require learning: they seem to be 'innate', 'hardwired', predisposed, or 'work out of the box', notwithstanding the crucial general caveat that all seemingly 'innate' behaviors may have developmental and environmental requirements for full expression (Bateson and Mameli 2007). Just as a mammal's visual cortex does not form correctly if the eyes do not receive visual stimuli during critical periods after birth (Hensch 2004), normal responses to pheromones may not develop unless species-specific conditions are met, which usually occur as a matter of course in normal development. For example, female mice reared without any contact with males, are attracted to male soiled bedding when adult, but do not apparently respond to volatile male odors (presumably including small molecule pheromones, see below) until after contact with such bedding (Moncho-Bogani et al. 2002). This was only revealed by experiments which prevented the normal exposure that would be experienced by developing mouse pups in the nest. While a role for development in establishing species-specific signals may seem surprising, it is found in some birds: great tit *Parus major* young become sexually imprinted on the wrong species if reared by blue tit *P. caeruleus* parents (though the effect does not happen with the reverse cross-fostering) (Slagsvold et al. 2002). On a shorter time scale, prior exposure for some days to the female pheromone(s) in the premoult urine of the shore crab *Carcinus maenas* primes his later sexual behavioral responses, such as cradling when he is later exposed to the female premoult urine (Ekerholm and Hallberg 2005). In some cases the changes in behavior have been tracked to effects at the periphery of the sensory system: for example, the behavioral response of young worker bees to queen mandibular pheromone depends on exposure to the pheromone soon after pupal emergence, via an effect on dopamine receptor gene expression in the olfactory sensory neurons (Vergoz et al. 2009).

Variation in response to pheromones

The conditionality of responses to pheromones can depend on a great variety of factors, some external such as the time of day, others internal. Johnson and Li (2010) discuss a variety of those affecting the response of fish to their pheromones.

Response may depend on age or developmental stage. For example, freshly eclosed males of the moth *Agrotis ipsilon* do not respond to female pheromone. Full responsiveness develops over days, due to juvenile hormone sensitive changes to the central neurons in the male antennal lobe, the primary olfactory center (review Anton et al. 2007). The response of fish to their alarm pheromone grows in amplitude and specificity with developmental stage (size) rather than age itself (Døving and Lastein 2009).

Responses to pheromones may be conditional on the physiological state of the receiving animal. For example, in male hamsters, brain circuits involved in responses to female pheromones are not active unless testosterone levels in the blood are above a threshold value (Wood and Swann 2000). This mechanism provides an internal monitor of readiness to mate because only sexually mature, well-fed males produce sufficient testosterone levels. In some moth species, the response of the male to female sex pheromone is shut down in the antennal lobe for 24 h after he has mated, a period he needs to replenish his accessory gland proteins (Anton et al. 2007).

Pheromones can prompt associative learning of other odors in the environment. For example, alarm pheromone prompts fish to learn the odors of predators in the water at the time (reviews: Døving and Lastein 2009; Johnson and

Li 2010). Later they will react with an alarm response to the predator odor alone. In a similar way, mammary pheromone facilitates rabbit pups' learning of their mother's odors and these will then elicit suckling too (Schaal et al. 2009). In mice, contact with the protein pheromone darcin, a single atypical MUP isoform in male urine, stimulates the female mouse to learn the male's volatile individual signature mixture (Roberts et al. 2010). In these examples the pheromone-prompted learning has the advantage of flexibly tuning behavior.

The responses of both male and female mammals are facilitated by experience. In the mouse and hamster, for virgin males the vomeronasal organ (VNO) is essential for response to female pheromones, stimulating investigation and mounting. However, sexually experienced males no longer need the VNO input to stimulate copulation as they have learned other odor cues associated with females, detected by the main olfactory system (MOS) (Hurst 2009). Maternal behavior elicited by pheromones in a number of mammals, including sheep and mice, has elements of learning. More specific cues, usually olfactory, are needed by animals giving birth for the first time, whereas more experienced (multiparous) females appear to have learned a wider range of associations (Lévy and Keller 2009).

The majority of animals use pheromones

Pheromones have been identified from species in every animal phylum and it is likely that the majority of species across the animal kingdom use them for communication of various kinds (Wyatt 2003, 2009). Some taxa, such as the Crustacea make extensive use of pheromones, but as yet few have been chemically identified (Breithaupt and Thiel 2010). The pheromones of another neglected group, birds, are also now getting the attention they deserve. Sexual behaviors in many bird species seem to be influenced by olfactory inputs and molecules with possible chemical communication roles have been identified in birds (reviewed in Caro and Balthazart 2010; Hagelin and Jones 2007).

Despite early doubts (e.g. Beauchamp et al. 1976), there is good evidence that mammals do indeed have small molecule pheromones that fit well with the original definition (Brennan and Zufall 2006; Wyatt 2003). The many small molecule mammal pheromones include the rabbit mammary pheromone 2-methyl-but-2-enal (2MB2) (Schaal et al. 2003), male mouse pheromones, such as (methylthio)methanethiol (MTMT) (Lin et al. 2005), (*R, R*)-3, 4-dehydro-*exo*-brevicomin (DHB) and 2-*sec*-butyl-4,5-dihydrothiazole (SBT) (Novotny et al. 1985), and Asian elephant pheromones including frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane) and (Z)-7-dodecen-1-yl acetate (Rasmussen et al. 2003).

Part of the problem for early work on mammal chemical ecology was the large number of compounds that were identified from gland extracts and moreover the way that the complex mix of compounds, the chemical profile, varied so much between individuals of the same species—which led to the doubts that pheromones would be found in mammals (Beauchamp et al. 1976). Wilson (1970) noted the similarity between the complex individual mixtures in mammals and the colony odors of social insects which vary between colonies. The resolution of what one might call the 'mammal problem' is that, in addition to having pheromones, vertebrates and invertebrates also have variable chemical mixtures best seen as signature mixtures rather than pheromones (Fig. 1).

The molecules used as pheromones and signature mixtures reflect function and habitat as well as phylogeny

Large and small molecules are used as signature mixtures and pheromones, in part depending on habitat and the range of communication. We know more about the molecules used as pheromones—in part because the relative uniformity helps experimental investigation, in contrast to the variation between different individuals' signature mixtures (e.g. the challenge of MHC odortypes (Kwak et al. 2010)) though we know for example that cuticular hydrocarbons are important parts of signature mixtures in social Hymenoptera, used at short range (van Zweden and d'Ettorre 2010). Aquatic and terrestrial animals use small molecules for longer distance communication, for example the sex pheromones of moths, lamprey sex pheromones and the small molecules of mouse pheromones. Underwater, large molecules can be used so long as they are soluble, so for example peptides are used as pheromones in animals as diverse as the sea-slug mollusk *Aplysia*, nereid worms and, among vertebrates, by newts and frogs (Altstein 2004). Terrestrial organisms may use peptides too, for close communication with physical contact, for example when mice sniff urine marks or each other directly. Mammal major urinary proteins (MUPs) can be pheromones when they are species-specific isoforms (for example ESP1 (Haga et al. 2010) and darcin in mice (Roberts et al. 2010)). Highly polymorphic MUPs can contribute to mouse signature mixtures along with polymorphic tear exocrine gland-secreting peptides (Hurst 2009; Kimoto et al. 2007). Though the molecules are not known, lobsters can recognize each other chemically at a distance underwater (Atema and Steinbach 2007).

The same small molecules occur in a number of insects and vertebrates (Kelly 1996; Wyatt 2003); for example

variations of the terpene brevicomin are used by male house mice and some bark beetle species (Novotny 2003), and the Asian elephant female pheromone, (Z)-7-dodecen-1-yl acetate is a component of the female pheromone blend of some 140 species of moth, and the Asian male elephant's pheromone frontalin is also used by some bark beetles (Rasmussen et al. 2003). The use of the same molecules may reflect some constraints on the number of low molecular weight molecules that are volatile, stable and relatively non-toxic. Animals also share a common ancestry and thus their biochemical pathways, which will also shape the range of molecules available for evolution to act on.

Within a particular taxon some molecules may tend to be used, due either to common ancestors or functional constraints or both. For example, the female pheromones of moths tend to be multicomponent combinations of related short chain fatty acids, ketones, aldehydes and alcohols (Cardé and Haynes 2004) and, as mentioned above, cuticular hydrocarbons are important for signature mixtures used in colony recognition in social Hymenoptera (van Zweden and d'Ettorre 2010). Species may share a pheromone if there is no evolutionary pressure for it to be species-specific, which might explain for example, why larval lampreys of different species appear to release a common pheromone to which adults of other lamprey species are attracted (Fine et al. 2004).

Like invertebrates, vertebrates also use some multicomponent pheromones. For example, the pheromones brevicomin (DHB) and thiazole (SBT) in the urine of male mice (*Mus musculus*) synergistically provoke aggressive behavior in conspecific males if offered together (they also need to be presented in mouse urine; simply dissolved in water they have no effect (Novotny et al. 1985)). Similarly, in the goldfish, while each of two female prostaglandin pheromones, F2α (PGF2α) and 15-keto-PGF2α, have similar effects on male behavior when presented singly, both are needed together to stimulate a gonadotropin surge in males (Sorensen and Stacey 1999). Other examples are mentioned in later sections.

Some terrestrial vertebrates present their small molecule pheromones together with larger molecules, such as the MUPs used by mice (Beynon and Hurst 2003). The MUPs provide a slow release mechanism for the small molecules and variable MUPs can contribute to the individuality of signature mixtures as mentioned above. Female elephants present their small molecule pheromone in association with an albumin protein (Lazar et al. 2004). In some lizard species, proteins in their marking secretions seem to provide a UV signal (in the lizard's visible range) to attract conspecifics which then detect smaller fatty acid pheromone signals in the marks at short range (Alberts 1989).

Speciation, chemical signals and multicomponent pheromones

Species-specific pheromone signals are important for premating isolation both in vertebrates and in invertebrates (Smadja and Butlin 2009). In moths, each species tends to have its own female sex pheromone consisting of a different combination of compounds (components), in a species-specific ratio (Cardé and Haynes 2004). In some closely related moth species we can see how the different pheromone blends have arisen by particular gene changes that affect enzymes in pheromone biosynthesis, changing ratios of components or indeed which molecules are produced (for example Liénard et al. (2008) and Xue et al. (2007)). The multiple pheromone components are reflected in specialized receptors and a glomerulus for each one in the antennal lobe of the male (see below). Differences in cuticular hydrocarbon blend may mediate incipient speciation in regional races of *Drosophila melanogaster* (Smadja and Butlin 2009).

In contrast to the moth examples above, relatively few vertebrate studies have full identification of the pheromones that differ between species (Smadja and Butlin 2009). The species differences between related newt species are understood as their peptide sex pheromones have different amino-acid sequences (Houck 2009; Woodley 2010). Rodents have substantial species-to-species differences in the compounds used as hormonally dependent male sex pheromones though behavioral details are limited (Novotny 2003). There are multicomponent species-specific odors in fish (Sisler and Sorensen 2008; Stacey and Sorensen 2006). For example, the prostaglandin component of the goldfish female sex pheromone is inactive if presented with the odor of another species (Sorensen et al. 2000).

Variation in pheromone produced between individuals

Just as responses to pheromone can vary between individuals, there can be variation in the quantity of pheromone produced by different individuals. Some of these differences reflect differences in mate quality and influence female choice ("the success of the smelliest" (Wyatt 2009)). For example, female tiger moths (*Utetheisa ornatrix*) choose a male with the most pheromone. His pheromone is derived from the same plant poisons, used to protect the eggs, which he will pass to the female at mating. His pheromone load is correlated with the gift he will give (Conner and Weller 2004; Eisner and Meinwald 2003). In rock lizards the proportion of oleic acid in a male's scent marks is dependent on his body condition (Martín and López 2010). In many mammal species,

production of pheromone is directly related to hormone levels and so scent marks will tend to be honest. Dominant and/or better fed males produce more pheromone and are more attractive to females (Ferkin et al. 1994; Hurst 2009).

There may be changes in the same individual over time as they age. For example, the male European corn borer (*Ostrinia nubilalis*) moth has a 3 component pheromone blend on his hair pencils, used in courtship of females. The proportions of the 3 components change as he ages and females find the blend produced by 4-day-old males most attractive (Lassance and Löfstedt 2009).

A key point about the differences, such as quantities related to male quality or blend changes with age is that they are still anonymous (Hölldobler and Carlin 1987). They indicate, for example, a dominant male or a male that is 4 days old, and not a particular male.

Ultimately, no two animals are identical and pheromone biosynthesis pathways may be controlled by many genes on a complex genetic background so we can expect some differences between individuals (Cardé and Haynes 2004). At the population level such variation underlies signal divergence in incipient speciation (see above). Nonetheless it is practical for us to identify a pheromone blend that elicits a particular behavior for that population despite some individual variation.

Signature mixtures used for individual and colony recognition

In contrast to pheromones, which are a particular molecule or a set combination of defined compounds, signature mixtures (or mosaic signals *sensu* Johnston (2003, 2005)) are variable mixtures of molecules and are used for distinguishing individuals or, in social insects, colonies (Wyatt 2005) (Table 1). A key difference between pheromones and signature mixtures is that in all taxa so far investigated it seems that recognition systems based on signature mixtures all involve learning (Wyatt 2003). Different receivers might learn different signature mixtures of the same individual (see legend of Fig. 1).

Chemical cues are widely used for recognition signatures, perhaps because even the earliest organisms had the receptor mechanisms for receiving and processing the information and perhaps also because of the enormous variety of compounds available, which allows an effectively unlimited number of possible combinations (Wyatt 2003). Kin recognition cues are a subset of signature mixtures which may be any aspect of the phenotype that reliably signifies kinship (Sherman et al. 1997).

Individual recognition by smell is found in many organisms. Lobsters will not fight another individual, recognized by smell, they have lost to in the previous week (Atema and Steinbach 2007). Dominant male mice mark their territories. If an experimenter adds a small urine mark from a resident subordinate, the dominant male soon attacks that individual (Hurst 1993). In some ant species, unrelated founding queens use chemical cues to recognize each other individually (d'Ettorre and Heinze 2005). In many species of mammal, including humans, mates can recognize each other by smell (Schaal and Porter 1991).

Olfactory learning of signature mixtures also occurs at particular sensitive periods in life, a phenomenon termed imprinting (Hudson 1993). In mammals this tends to occur as a young animal, say a young mouse pup in the nest learning the odors, including those related to the MHC, and other characteristics of its siblings so as to avoid them as mates when adult (reviewed by Brennan and Kendrick 2006). Such learning has been demonstrated by cross-fostering experiments with young pups. As an adult, learning occurs when bonding with newly born offspring, as in the case of the now classic system of mother sheep and lambs (Lévy and Keller 2009; Sanchez-Andrade and Kendrick 2009). It also occurs at mating in the female mouse, which remembers the signature odor of its mate, preventing pregnancy block (Brennan 2009). The neonatal imprinting and odor-based recognition of offspring occurs in humans too (Schaal and Porter 1991).

Olfactory imprinting also occurs in social insects. Ants and bees learn their colony odor after emerging as callow adults from their pupae (Breed 1998; d'Ettorre and Moore 2008). In ants, just as mammals, the learning can be demonstrated by cross-fostering a pupa or newly emerged adult: the transferred ant will learn the colony odor of its new hosts (Lenoir et al. 2001).

The one theoretical exception which does not require learning for kin recognition is the Green Beard Effect, proposed by Hamilton (1964) and named by Dawkins (1976). It is a system of three linked genes that code for something distinctive (e.g. a color or smell), the genetic ability to recognize it in others, and a genetically determined appropriate response. Dawkins hypothesized linked genes that gave the owner a green beard and prompted the green-bearded individual to look after others with green beards. There is one animal example, in the fire ant *Solenopsis invicta* which responds to variation at a single gene, *General protein-9* (*Gp-9*) (Gotzek and Ross 2009), though this has been questioned (Leal and Ishida 2008). There are no vertebrate examples that I am aware of.

Perception: vertebrates and invertebrates are more similar than different

All signature mixtures, and almost all pheromones, whatever the size of molecules, are detected by olfaction

(as defined by receptor families and glomerular processing), in mammals by the main olfactory system or vomeronasal system or both.

Despite an enormous diversity of antennae and noses, animals perceive chemical signals and cues in basically the same way. Olfactory receptor proteins (ORs) are exposed in the membrane of olfactory sensory neurons (OSNs; some authors term these olfactory receptor neurons ORNs). Both in vertebrates and in invertebrates, the OSNs are organized so that those expressing the same olfactory receptor protein converge on the same glomerulus (neuropil) on each side of the brain (Hildebrand and Shepherd 1997; Su et al. 2009; Touhara and Vosshall 2009) (for a good diagram of the parallels of glomerular organization in invertebrates and vertebrates see Fig. 5 in Vosshall and Stocker (2007)). Whether this common glomerular organization is due to a common ancestor, or instead a uniquely logical response to the demands of olfactory processing, will remain unclear until developmental genes for neuropils in protostomes and deuterosomes are identified (Strausfeld and Hildebrand 1999). The only notable exceptions to glomerular organization, apart from those animals with no nervous system, are the nematodes (Eisthen 2002) and some homopterans including aphids (Kristoffersen et al. 2008).

In contrast to the common glomerular organization they share, insects and chordates have unrelated olfactory receptor protein families and different transduction mechanisms, which suggest that their ORs, at least, have evolved independently (Benton 2009; Kaupp 2010; Nakagawa and Vosshall 2009). This reinforces the idea that membrane receptor proteins of many different kinds can be co-opted for chemosensory roles if they interact with important odorants for that species.

A key element of the common glomerular organization is the similar functional organization of synaptic circuitry in the olfactory bulb of vertebrates and the antennal lobe of insects and in the processing of olfactory information at the next relay levels, in the primary olfactory cortex of vertebrates and protocerebrum of insects (Christensen and White 2000; Eisthen 2002; Hildebrand and Shepherd 1997; Touhara and Vosshall 2009). In vertebrates, the olfactory sensory neurons synapse in glomeruli with secondary neurons called mitral/tufted cells which project their axons to the olfactory cortex. In insects, the analogous secondary neurons synapsing in the glomeruli are the projection neurons which project their axons to the higher brain regions of the mushroom body and the lateral horn of the protocerebrum.

In terrestrial vertebrates the principal system for general odor reception is the main olfactory system though the VNO also responds to some general volatile odorants. Depending on the species, pheromones and individual recognition cues may be detected by the MOE or the VNO, or both; the integration of the inputs from both systems higher in the brain is now well established (inputs and integration are reviewed by Baum and Kelliher 2009; Brennan and Kendrick 2006; Keller et al. 2009; Munger et al. 2009).

Combinatorial olfactory coding of pheromones and signature mixtures

The processing of all signature mixtures, almost all general odors and most pheromones, is combinatorial across a number of glomeruli, even for some sex pheromones which appear to have ‘labeled lines’.

Both in invertebrates and in vertebrates most olfactory receptors are broadly tuned so that any odor molecule will stimulate a number of receptors and their associated glomeruli, giving a combinatorial code of glomerular stimulation characteristic for that odor molecule (Hallem and Carlson 2006; Kaupp 2010; Malnic et al. 1999). So for example, hypothetically a molecule might stimulate the olfactory receptors on OSN types 1, 3 and 25. A different molecule might stimulate OSN types 2 and 44. This combinatorial processing allows organisms to discriminate and distinguish innumerable molecules, including ones never encountered before.

Some receptors are so narrowly tuned to a particular molecule that, at normal concentrations, just one glomerulus is stimulated, giving the impression of a ‘labeled line’ (Christensen 2005). These may not be different from ordinary olfactory responses except in the difference between the specificity of the receptors and thus the sensitivity of those olfactory sensory neurons in relation to others in the olfactory system (Christensen and Hildebrand 2002). There is no compelling evidence for a functional distinction of generalist versus specialist receptors in insects (Kaupp 2010). If the concentration of pheromone is raised high enough, many less specific olfactory sensory cells respond (this characteristic is not shared by VNO receptors which do not broaden their sensitivity with higher concentration (Leinders-Zufall et al. 2000)).

Some of the most spectacular examples of specialized receptors and ‘labeled lines’ are those in the male moth for individual components of female sex pheromones, but even these are processed combinatorially (my only disagreement with Touhara and Vosshall (2009)). Each pheromone component of the female’s multicomponent pheromone is detected by a specialist OSN which feeds into a specialized glomerulus for each component, in a particular part of the antennal lobe, the macroglomerular complex (MGC) (de Bruyne and Baker 2008; Hansson 2002). However, despite the specialization of the receptors, the processing of the information is combinatorial, with key projection neurons

responding to the simultaneous stimulation of key glomeruli representing the key multicomponent blend (Christensen and Hildebrand 2002; Sorensen et al. 1998). All the required components of the blend need to be present in the right ratio (and present in the absence of the distinctive compounds of other sympatric species, which instead turn the male moth away, so he does not waste time flying to a female of another species) (de Bruyne and Baker 2008). This integration is achieved by the projection neurons. A similar arrangement of pheromone components detected by narrowly tuned receptors, stimulating particular glomeruli and then integration of this information for a species specific response to sex pheromone seems to occur in the goldfish (Hamdani and Døving 2007).

The male mouse pheromone exocrine gland-secreting peptide 1 (ESP1) is processed by a highly specific vomeronasal receptor protein (V2Rp5) in the female's VNO (Haga et al. 2010). Stimulation of the V2Rp5 glomeruli gives a sex-specific stimulation to the hypothalamus and results in lordosis, sex receptive behavior, by the female, which in turn leads to more matings with her by males.

In *Drosophila melanogaster*, the male produced pheromone *cis*-~~vinyl~~ acetate (*c*VA) elicits aggregation behavior both in males and in females, but different courtship behavior in males and females (Vosshall and Stocker 2007). Male and female *D. melanogaster* have the same receptors for *c*VA and the same glomerulus is stimulated by the OSNs, but the brain circuits in the target of the projection neurons, the lateral horn, seem to differ between the sexes (Datta et al. 2008). The lateral horn seems to lead mainly to stereotyped responses in contrast to the mushroom bodies which are involved in learning of various kinds (Vosshall and Stocker 2007). General odors, such as food seem to go to a different part of the lateral horn from pheromones (Jefferis et al. 2007).

However, it is not necessary to have 'labeled lines' and 'dedicated' glomeruli to have species specific responses to pheromones. For example, non-sex pheromones in honeybees and ants can be shown to stimulate more general receptors and thus a number of glomeruli (which might also respond to floral or other odors). The activation of these glomeruli (visualized using calcium imaging) and activation of PNs (by calcium or direct recording) in response to pheromones is repeatable, for alarm pheromone in ants (Yamagata et al. 2007) and in honeybees (Sandoz et al. 2007). Presumably it is the integration by the projection interneurons that leads to the appropriate characteristic and stereotyped response to alarm pheromone. In one ant species *Camponotus obscuripes* the alarm pheromone seems to be processed in a particular group of glomeruli (Yamagata et al. 2006), but not in a related ant species *Camponotus floridanus* in which Zube et al. (2008) observed that the patterns of glomeruli activated by pheromonal and nonpheromonal odors were partly overlapping, indicating that processing of these odor classes is not spatially segregated within the antennal lobe. In honeybees the processing of alarm pheromone seems to be by non-specific glomeruli, in a similar and overlapping pattern with the processing of floral scents (Wang et al. 2008).

In fish, groups of glomeruli in particular parts of the olfactory bulb respond to different types of odors. Their mitral cells project to higher brain areas by different tracts: sex pheromones by the lateral medial olfactory tract (lateral MOT), alarm pheromones by the medial MOT, and glomeruli stimulated by food odors via the lateral olfactory tract (Hamdani and Døving 2007). The species specificity of response to alarm pheromone suggests that the fish are responding to a number of molecules and that this is a combinatorial response (Døving and Lastein 2009).

In mammals, as in the *Drosophila* and fish examples, within the main olfactory system there may be some kind of separation between general olfaction and responses to pheromones and other predisposed chemical stimuli that elicit an 'innate' response. For example, the response to urine volatiles in mice was localized to mitral cells in two clusters of MOS glomeruli and within these zones there were mitral cells specifically responding to the male pheromone (methylthio)methanethiol (MTMT) (Lin et al. 2005). These specific responses may work in parallel with more general odor processing across many glomeruli (Lin et al. 2006).

The rabbit mammary pheromone is perceived by the main olfactory system in rabbit pups and stimulates them to suckle, but where in the brain it is processed is not known (Hudson and Distel 1986; Schaal et al. 2003, 2009) though in the rat, mammary odors (as yet unidentified) appear to be processed in specific modified glomeruli (Teicher et al. 1980).

An indication of how innate responses to pheromone might be processed in mammals comes from a study of the innate response to aversive, non-pheromone, molecules in the mouse. The dorsal zone of olfactory sensory neurons in the MOE and their associated glomeruli, which include the glomeruli that process the predator odor trimethyl-thiazoline, can be genetically ablated. This abolished the innate fear response to predator odor and the innate aversion to the odors of spoiled food, yet left the rest of the main olfactory system sufficiently intact for olfactory learning of general odors (Kobayakawa et al. 2007).

Combinatorial processes probably also occur in the AOB. The mouse pheromones brevicomin (DHB) and thiazole (SBT) are detected by narrowly tuned and highly sensitive vomeronasal sensory neurons (Leinders-Zufall et al. 2000). These compounds act together synergistically so presumably the outputs from the glomeruli in the AOB are integrated combinatorially, together with responses to other urine volatiles which are also required. Further

support for idea that AOB units integrate information from distinct components comes from experiments using a new in vivo VNO stimulation technique (Ben-Shaul et al. 2010).

Learning of signature mixtures

Signature mixtures, as they involve learning, may be processed in different glomeruli from pheromones, though not necessarily. The neurobiology of the olfactory imprinting of signature mixtures by adult mammals is well studied in mice (for the Bruce effect, the odors of her mate are learnt in her accessory olfactory lobe) and sheep (the mother learns the odors of her lamb in her main olfactory lobe) (reviewed by Brennan and Kendrick 2006; Lévy and Keller 2009; Sanchez-Andrade and Kendrick 2009). These authors remind us of the importance of the integration of information about individual identity from the VNO and MOE via their combined inputs to the medial amygdala in a variety of mammals. The same molecules, for example MHC peptides, can be processed in parallel by both systems, giving different kinds of information.

We know much less about the detailed neurobiology of learning of signature mixtures in insects and other invertebrates. Individual recognition in lobsters is mediated by olfactory pathways (Johnson and Atema 2005) though currently not enough is known about olfactory processing in lobsters to know if pheromones are processed differently. In social insects, a colony's shared labels are constantly changing and thus the learnt signature mixture has to be constantly reinforced and fine tuned (van Zweden and d'Ettorre 2010). In ants, one study has suggested that recognition of colony members occurs at the level of sensilla on the antennae (Ozaki et al. 2005) though this seems not to be the case in another ant species (Kleineidam and Rossler 2009; Zube et al. 2008). It seems likely that identity learning in social insects will occur in the mushroom bodies, but I am not aware of any detailed studies of this.

Mate choice by MHC

In young mammals, the negative imprinting of familial odors, notably those associated with the MHC, affects their later mate choice (reviewed by Brennan and Kendrick 2006). When adult, mice choose mates with a different MHC haplotype from their siblings, learnt when growing up. The main olfactory system is sufficient for mate choice by olfactory cues which include a complex signature mixture consisting of volatile molecules associated with the MHC (the odortype) and MHC peptides (Restrepo et al. 2006). The processing of the volatile odortypes is combinatorial, demonstrated by mapping c-*fos* activation of glomeruli across the olfactory bulb by urine odors from different strains (Schaefer et al. 2002). The MOE also detects some MHC peptides (Spehr et al. 2006). These gain access to the MOE during the close contact of mouse social interactions. Peptide recognition in the MOE probably occurs in a combinatorial manner too (Spehr et al. 2006). MUP haplotype may also be important in mate choice in mice (Hurst 2009) though Spehr and Munger (2009) remind us that many other mammalian species possess only a single intact MUP gene (Logan et al. 2008) so this may not be generally applicable.

Pregnancy block (Bruce) effect

Male mouse urine contains a complex mixture of pheromones with primer effects on female reproductive state, including the ability of an unfamiliar male to block pregnancy (the Bruce effect) (Brennan 2009; Brennan and Kendrick 2006). When she mates, the individual signature mixture of her male mate is learnt in her accessory olfactory lobe. This memory prevents his pheromones from eliciting the pregnancy block. Thus, there are two distinct kinds of chemical information, a male testosterone-dependent pheromone(s) (the same for all males) as yet unidentified (though it is of low molecular weight; Peele et al. 2003), and the male's variable individual signature mixture including his urinary odortype and peptides related to the MHC. MHC peptides from a non-stud male of a different haplotype can induce pregnancy block (Boehm and Zufall 2006; Brennan and Kendrick 2006) and can be detected directly by the V2R receptor-expressing zone of the vomeronasal epithelium (Leinders-Zufall et al. 2004). However, there is still the problem that MHC peptide ligands have yet to be identified in mouse urine so there may yet be another class of individuality chemosignals in addition to the MHC peptides and MUPs (Brennan 2009).

From studies of urine stimulation of VNO slices, He et al. (2008) concluded that individual information, even allowing distinction of littermates, is encoded by the combinatorial activation of VNO neurons, presumably by complex mixtures including other molecules as well as peptides. The peptide detecting VSNs themselves show combinatorial activation with overlapping specificities (Leinders-Zufall et al. 2009).

Atypical pheromones detected or acting by other chemosensory systems

In invertebrates a minority of pheromones are detected by other, non-glomerular chemosensory routes. For example, the cuticular hydrocarbons important as species-specific pheromones in *Drosophila* are detected in courtship by gustatory receptors present on the male front legs (Vosshall and Stocker 2007). Male crayfish (*Orconectes rusticus*) appear to be able to detect female odors with their main

chelae (claws) using their non-glomerular distributed chemosensory system (Belanger and Moore 2006).

Some pheromones are passed directly to another individual, as anticipated by Karlson and Lüscher (1959) in their example of termite caste-controlling pheromones with primer effects passed by mouth around the colony. In the red-sided garter snake (*Thamnophis sirtalis parietalis*), prostaglandins in the male's semen contribute to making her unresponsive to other males (Mason 1993). The *Drosophila* sex peptide transferred with the seminal fluid changes the female's behavior by activating specific chemosensory neurons in her uterus and oviduct (Hasemeyer et al. 2009). The term *allohormone* has been proposed for such molecules which bypass external sensory organs and have their effects directly (proposed by Koene and ter Maat (2001, 2002), argued against by Ruther and Steidle (2002)). I think allohormones, if the term is seen to be useful, should be used as a subclass of pheromone. Such an approach would avoid calling similar salamander peptide pheromones different things depending on their route of transmission: for example, peptide pheromones are wafted in currents by aquatic newt species, deposited on the openings to the VNO in some terrestrial salamanders mating on land, and in one species, directly injected into the blood stream of the female (via skin piercings made with 'vampire' canines) (Houck and Reagan 1990; Houck 2009). The injected peptide would thus be an allohormone pheromone.

Evolution of signature mixtures and pheromones

Chemical cues are sensed by all organisms, from bacteria to the most complex animal: generalist olfactory receptors (see below), derived from membrane bound receptor proteins, are broadly tuned so that almost any molecule will stimulate some receptors (Hallem and Carlson 2006; Malnic et al. 1999).

In an earlier section, the evolution of signature mixtures was discussed in the context of response to cues that are a reliable statistical indicator of kinship or group membership. Alternatively, signature cues may simply be mixtures sufficiently stable and individually different to enable one to recognize the same individual on another occasion.

How do chemical cues evolve into pheromone signals? For example, hypothetically if there are molecules associated with mature females about to lay eggs, then mutant males better able to detect these will find her first and gain more matings. Over generations this would result in selection for increasing sensitivity to the female's molecules (with multiple copies of such receptors) and changes in the receptors for greater specificity. If there is a benefit to the female then there will be selection to release more of the molecules. Such a scenario has been suggested to explain the evolution of fish sex pheromones which appear to have evolved from initial 'spying' by males of the hormones leaking out of females, and then evolution of increasingly specialized systems for detecting and responding to these molecules and release of the molecules as part of a chemical duet (Stacey and Sorensen 2006). Ultimately these molecules became pheromones: full signals, with both production and reception as evolved features, in a process known as ritualization (Maynard Smith and Harper 2003). The best understood endpoint is perhaps represented by moth sex pheromones (with specialized enzyme pathways and structures for release in the female moth, and specialized receiver systems (from receptors to specialized glomeruli) in the male (Cardé and Haynes 2004)). In the case of fish, hormones themselves can be pheromones (termed hormonal pheromones) though in many animals the original function of the molecules used as pheromones can only be speculated (Wyatt 2003).

In contrast to pheromone signals, only the receiver's response to cues is evolved. For example, the CO_2 released by an animal as it breathes can be used as a cue by a blood sucking insect to find its host. The mosquito's response is certainly evolved (and indeed it has highly specialized receptors to detect CO_2), but the release of CO_2 by the host did not evolve to have the effect of attracting mosquitoes so it does not count as a signal.

As with all evolutionary processes, the current situation in a particular species may be at any point on the theoretical pathway in the evolution from cue to signal so we might expect the definition of pheromones and the distinction of pheromone signals from cues to be problematic in some species.

The chemical signature mixtures used by vertebrates and invertebrates may best be seen as cues rather than signals: although the response is highly evolved, the emitted molecules may not be evolved specially for this function. For example, the variability of the MHC is likely to be driven by its immune-system function and so the analogy might be of human fingerprints, not evolved for purpose of individual recognition but we can use them for recognition in crime identification. However, it is possible that complexity of cues used in individual recognition might be selected for ease of recognition (Tibbetts and Dale 2007) though we have no evidence of this in chemical signature mixtures yet. The variety of cuticular hydrocarbons in social Hymenoptera (van Zweden and d'Ettorre 2010) and the co-expansion of MUPs and vomeronasal receptor proteins in some mammals could be indicative (Chamero et al. 2007). One way to investigate this might be to compare related species that live solitarily or socially to see whether the social species have more complex signature mixtures.

Conclusions

Distinguishing between signature mixtures and pheromones (Table 1) could help, for example, guide research strategy in future studies and help clarify understanding of what we have discovered so far. Karlson and Lüscher (1959) ended their paper introducing 'pheromones' by throwing the definition open for discussion, hoping that it would prove itself in practice, which 50 years on, it certainly has. In a similar spirit I would welcome comments and suggestions for improving the ideas presented here.

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