developed by Boss.

Despite these caveats, it should be emphasized that Boss's results provide the first direct evidence that fragmentation can produce hierarchical structures. Whether or not his protostellar cores remain distinct and evolve into actual stars will presumably be determined by future computations. For now, it is worth noting that quadruple-star systems are not uncommon. Their actual frequency is difficult to determine in practice owing to selection effects. Nevertheless, roughly 1 per cent of observed 'stars' may in fact be unresolved quartets¹, implying that

several per cent of all stars reside in groups of four. Many four-star systems with the hierarchical structure seen in Boss's models (distant pairs of tightly-bound binaries) have been detected visually⁸. To the extent that the current simulations continue to be relevant in the face of more detailed calculations, Boss's work may have already explained the formation of quadruple stars such as μ Ori, HR 3337 and ξ UMa. $\square$

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OLFACTION

The strong scent of success

Doron Lancet

WITH their report in *Cell*¹, Linda Buck and Richard Axel may have at last laid a long-standing argument over the mechanisms of smell to rest. They describe the molecular cloning of a large family of proteins, each with seven transmembrane domains and all expressed specifically in olfactory epithelium. In all likelihood these are the long-awaited olfactory receptors.

The words 'long-standing' are appropriate. In the first century BC Lucretius suggested that 'atomic shapes' could underlie the sense of smell, and since then numerous theories of olfaction have been proposed. Some have argued that direct modulation of the lipid in membranes could mediate detection of odours²; on the other

hand, the existence of specific anosmias^{3,4} (the inability to detect particular odorants), and the discovery of an olfactory transduction cascade⁵⁻¹⁰, have made the case for stereospecific protein receptors a strong one. But most receptors are isolated by affinity-related techniques¹¹. In the olfactory system, agonist diversity and lipophilicity, and the lack of defined antagonists, have impeded progress⁷. Receptor identification by way of alternative criteria⁵⁻⁸ such as glycosylation, transmembrane disposition and tissue specificity, or through the isolation of olfactory mutants in *Drosophila*³, has been attempted without success.

Buck and Axel's remarkable discovery is an example of biological prediction come true. Olfaction is mediated by a GTP-binding-protein (G-protein) cascade⁵⁻⁹. It was therefore inferred^{6,8} that olfactory receptors probably belong to the G protein-coupled, seven-transmembrane-domain receptor superfamily. With this notion in mind, Buck and Axel carried out a first screen for rat olfactory receptor clones. They applied the polymerase chain reaction (PCR) to 30 different oligonucleotide pairs, derived from conserved sequences in transmembrane domains 2 and 7. This is an elaborate version of a technique previously used to fish for new G protein-coupled receptors in other systems¹². But as the process often yields a 'zoo' of novel as well as known receptors, a second selection rule had to be formulated.

Among the millions of possible odorants, many are evolutionarily 'unknown' to the organism until they are encountered for the first time.

Olfaction: molecules to network

Olfactory epithelium contains between 10 million and a 100 million sensory cells, and clearly all of them are not equal: they respond to different (though broad and overlapping) ensembles of smells (odorants). With the report by Buck and Axel it becomes possible to uncover the molecular basis for such individuality — most probably, each cell type expresses a subset of the receptor repertoire. Double labelling the sensory tissue with different receptor subtype-specific antibodies or oligonucleotides will help define how many different receptor genes are transcribed in each cell. If the answer is one (that is, clonal exclusion is at work, as in the immune system) then the known broad spectra of individual olfactory cells are wholly attributable to receptor protein 'promiscuity', a model testable by studies of functional expression.

The crudest of the 'labelled lines' premises — that one cell type codes one odour — is largely out of fashion; rather, odour quality is thought to be coded by an 'across fibre' pattern of sensory neuronal firing^{14,15}. It has not been easy to discern this pattern experimentally, presumably because the different sensory cell types form a fine mosaic, with only minor segregation by odour specificity across the epithelial sheet. High-resolution labelling with receptor subtype-specific reagents could reveal the nature and grain of the presumed clonal distribution underlying the expected patterns of function in the epithelium.

A different situation prevails in the olfactory bulb, the first relay in the central nervous system, where individual glomeruli (100- μ m sized clusters of synapses between primary and secondary neurons) show a clear spatial pattern in their responses to a given odorant^{14,15}. Thus, axons from a given sensory cell type may project preferentially to one or a few glomeruli. Such a hardwired projection scheme, possibly rather invariant with time and among individuals¹⁴, embodies a more subtle version of the 'labelled lines' model. The entire pattern across units manifesting such discrete activity is then thought to code an odour.

To ask specific questions about projections to the olfactory bulb, it is necessary to identify unequivocally functional subgroups of sensory neurons. Responses to odours are too broad to be useful, and location in the epithelium is an uncertain guide to function. Now, one might achieve such definition by labelling sensory cells for their unique receptor(s), then find how selective their glomerular projection is. A tempting thought⁵ is that each glomerulus is a unique 'address' for a clone of sensory cells expressing a given olfactory receptor type. The number of glomeruli (about a thousand) is not unlike the extrapolated receptor count.

The synaptic target of a given sensory cell seems to depend on the receptor(s) they express. With the receptors cloned, it will be possible to determine the order of events in development and regeneration: do committed sensory cells recognize their target according to their predetermined receptor specificity, or is it contact with a synaptic target that specifies differentiation and commitment?

D.L.

Schematic view of olfactory neurons in the epithelium and their projection to olfactory bulb. (1) Estimates for the number of odorants range from 10,000 upwards. (2) Receptor proteins of M number of types are carried on (3) N types of sensory neuron; M is currently estimated as 100–1,000, and if clonal exclusion holds then $N = M$. Between stages (3) and (4) — (4) being the 1,000 or so glomeruli of the olfactory bulb — a convergence of some 100,000 sensory cells onto 1 glomerulus has to occur¹⁴. Open questions (?) are whether each neuron expresses more than one receptor type, and whether there is a one-to-one relationship between neuron types and glomeruli. The dual projection of S_2 and S_3 represents output from different individual neurons expressing the same receptor, as each sensory cell is known to synapse in only one glomerulus (cf. ref. 14).