body fossils of a very distinct centipede clade (Devonobiomorpha) are found at the Gilboa site near New York, dated 390 MYA (Middle Devonian), which suggest the contemporaneous existence of other lineages [15]). A comparable chronology applies to millipedes [16].

On the whole, this exemplary analysis of an arthropod genome provides interesting answers to questions that had not been anticipated when the species was nominated for sequencing, but has failed to find answers to questions one would have easily formulated before the study was initiated. Chipman *et al.*'s study is arguably the single most important advance towards understanding the genomic basis of sensory adaptations to terrestrial (and subterranean) life in any arthropod lineage. It has also provided important evidence to link the evolution of juvenile hormone signaling to the emergence of that key diagnostic trait of arthropods, the exoskeleton. This can be concluded even in the light of the still limited sample of arthropod taxa for which completely sequenced genomes are available. Other results, perhaps eventually of comparable importance, however, will only be understood when further genomes become available to allow meaningful comparisons.

Still, the darkest side of myriapod biology remains, with all its attractiveness — the question of segmentation, and its relationship with the epimorphic vs. anamorphic mode of post-embryonic development. Progress in this area is likely to derive more from a continuing dissection of the molecular control mechanisms of embryonic patterning than from additional sequenced genomes. Phenotypically major changes (in segment number and/or variation, and in developmental modus) within the myriapods may perhaps result from minor genetic and a fortiori minor genomic modifications [17]. But resolving this issue is at the moment a challenge for the future.

References

1. Chipman, A.D., Ferrier, D.E.K., Brena, C., Qu, J., Hughes, D.S.T., Schröder, R., Torres-Oliva, M., Znassi, N., Jiang, H., Almeida, F.C., *et al*. (2014). The first myriapod genome sequence reveals conservative arthropod gene content and genome organisation in the centipede *Strigamia maritima*. PLoS Biol. *12*, 11.
2. Chipman, A.D., Arthur, W., and Akam, M. (2004). Early development and segment formation in the centipede, *Strigamia maritima* (Geophilomorpha). Evol. Dev. *6*, 78–89.
3. Brena, C., and Akam, M. (2012). The embryonic development of the centipede *Strigamia maritima*. Dev. Biol. *363*, 290–307.
4. Brena, C. (2014). The embryoid development of *Strigamia maritima* and its bearing on post-embryonic segmentation of geophilomorph centipedes. Front. Zool. *11*, 58.
5. Brena, C., and Akam, M. (2013). An analysis of segmentation dynamics throughout embryogenesis in the centipede *Strigamia maritima*. BMC Biol. *11*, 112.
6. Chipman, A.D., and Akam, M. (2008). The segmentation cascade in the centipede *Strigamia maritima*: involvement of the Notch pathway and pair-rule gene homologues. Dev. Biol. *319*, 160–169.
7. Brena, C., Chipman, A.D., Minelli, A., and Akam, M. (2006). Expression of trunk Hox genes in the centipede *Strigamia maritima*: sense and anti-sense transcripts. Evol. Dev. *8*, 252–265.
8. Kettle, C., Arthur, W., Jowett, T., and Minelli, A. (1999). Homeotic transformation in a centipede. Trends Genet. *15*, 393.
9. Enghoff, H., Dohle, W., and Blower, J.G. (1993). Anamorphosis in millipedes (Diplopoda): the present state of knowledge with some developmental and phylogenetic considerations. Zool. J. Linn. Soc. London *109*, 103–234.
10. Janssen, R., and Damen, W.G. (2006). The ten Hox genes of the millipede *Glomeris marginata*. Dev. Genes Evol. *216*, 451–465.
11. Janssen, R., Budd, G.E., Damen, W.G., and Prpic, N.M. (2008). Evidence for Wg-independent tergite boundary formation in the millipede *Glomeris marginata*. Dev. Genes Evol. *218*, 361–370.
12. Janssen, R., Prpic, N.M., and Damen, W.G. (2004). Gene expression suggests decoupled dorsal and ventral segmentation in the millipede *Glomeris marginata* (Myriapoda: Diplopoda). Dev. Biol. *268*, 89–104.
13. Janssen, R., Damen, W.G., and Budd, G.E. (2012). Expression of pair rule gene orthologs in the blastoderm of a myriapod: evidence for pair rule-like mechanisms? BMC Dev. Biol. *12*, 15.
14. Jeram, A.J., Selden, P.A., and Edwards, D. (1990). Land animals from the Silurian: arachnids and myriapods from Shropshire, England. Science *250*, 658–661.
15. Shear, W.A., and Bonamo, P.M. (1988). Devonobiomorpha, a new order of centipeds (Chilopoda) from the Middle Devonian of Gilboa, New York State USA, and the phylogeny of centiped orders. Amer. Mus. Novitat. *2927*, 1–30.
16. Wilson, H.M., and Anderson, L.I. (2004). Morphology and taxonomy of Paleozoic millipedes (Diplopoda: Chilognatha: Archipolypoda) from Scotland. J. Paleontol. *78*, 169–184.
17. Minelli, A., Chagas-Júnior, A., and Edgecombe, G.D. (2009). Saltational evolution of trunk segment number in centipedes. Evol. Dev. *11*, 318–322.

Department of Biology, University of Padova, I 35131 Padova, Italy.
E-mail: alessandro.minelli@unipd.it

http://dx.doi.org/10.1016/j.cub.2015.01.018

Multisensory Perception: Pinpointing Visual Enhancement by Appropriate Odors

Multisensory contributions to perception are well studied, but their underlying brain mechanisms are poorly understood. A new study has exploited advances in fly optogenetics to pinpoint mechanisms that enhance responses to visual motion in the presence of ecologically relevant odors.

David C. O'Carroll

Odor is a rich source of information, but is notoriously difficult to localize. In the fad-prone cinema industry of the 1950s, patented systems like "Smell-O-Vision" and "AromaRama" attempted to enrich our cinema experience with elaborate mechanisms to release odors at key points in the plot to coincide with more easily localized visual and sound cues. Though never a mainstream success, such systems exploit a key principle of multisensory integration. In nature, sensory stimuli are rarely encountered alone, so cross-modal interactions provide a key to resolving ambiguities in any one modality. But precisely where and how this modulation occurs in the brain is much less well understood. A study published recently in *Current Biology* by Wasserman *et al.* [1] provides insight into this question from the vinegar fly, *Drosophila melanogaster*, which spends its day finding food or mates by navigating odor plumes.

The search for odor is coupled to powerful visual reflexes in insects [2]. Visual cues provide a fixed reference for zig-zagging search as the animal flies in and out of an

invisible odor plume. In *Drosophila*, the presence of ecologically relevant odors was recently shown to increase the strength of gaze-stabilizing optomotor reflexes [3] that may help keep the animal aligned within the plume during free flight [4]. In their new study, Wasserman *et al.* [1] first confirmed that elements of the fly motion-detecting machinery that drive these optomotor reflexes are necessary for odor tracking behaviour. They measured their turning reflexes in a flight simulator where they could combine odor cues with visual stimuli (Figure 1A). They compared the normal behaviour in the presence of odor with genetically manipulated flies in which they inhibited two classes of neurons, T4 and T5. These neurons were recently confirmed as key elements of local motion detection in flies and are pre-synaptic to wide-field motion 'collating' horizontal system (HS) neurons known to mediate turning responses to horizontal motion [5]. The T4T5 blocked flies were able to detect and orient towards the odor plume normally, but were then unable to sustain plume tracking as long as control flies. Indeed they found the behaviour of the T4T5 blocked flies was similar to that of normal flies deprived of visual motion cues by flying in an arena with blank grey walls.

Having shown that local visual motion signals derived from T4 and T5 are required to stabilize the flight heading within the odor plume, Wasserman *et al.* [1] turned their attention to possible mechanisms for this cross-modal interaction. They found that a recently identified collating neuron, Hx, appears to take inputs from T4 and T5 in a similar manner to HS neurons. But unlike HS, Hx shares expression of a transcription factor (Odd-Skipped) with a number of higher-order olfactory neurons [6], making it a likely candidate for cross-modal interactions. The authors exploited this Hx-specific transcription factor to express a fluorescent protein (GCaMP6m) that can be induced to glow at the high intracellular concentrations of Ca^{2+} typically associated with neuronal excitation. Using a two-photon microscope (Figure 1), they were then able to confirm that Hx is excited primarily by motion from the front of the visual

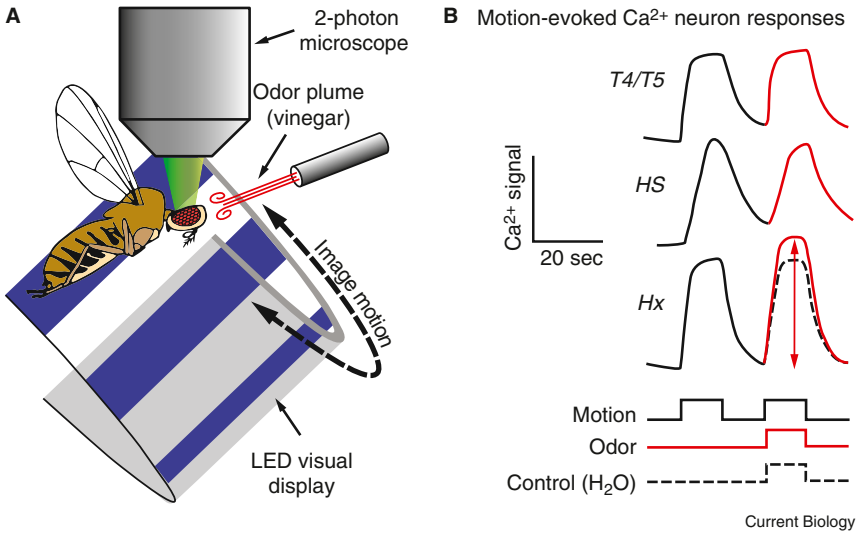

Figure 1. Optical recording from fruitfly neurons.

(A) The fly (*Drosophila melanogaster*) views rotational motion of stripes generated in a panoramic array of light emitting diodes (LEDs). An odorant (vinegar) can be combined with the visual stimulus via a puffer directed across the antennae. The image moves back and forth, while recording either (i) the wingbeat amplitude in loosely tethered flies to determine the overall optomotor (turning) response of the fly to motion, or (ii) the calcium levels in specific neurons in the optic lobes of the brain of restrained flies. (B) Visually evoked responses to motion are measured before and during pulses of odor or a water-vapor control. Long-wavelength (two-photon) excitation then allows Ca^{++} induced fluorescence to be visualized in the living animal and provides a measure of the neuronal activity induced by the visual stimulus. Of 3 neuron types tested, only Hx shows a stronger response to the motion stimulus in the presence of the odor (arrows). ((A,B) adapted from [1].)

field to the back, such as would be experienced during forward progress toward an odor source. When they coupled odor cues with such progressive motion, Hx was more strongly excited than when motion was presented alone (arrows, Figure 1B).

In flies with similar genetic manipulations to express Ca^{2+} indicators in either T4/T5 or HS neurons, Wasserman *et al.* [1] observed no increase in excitation in response to the pairing of odor with the visual stimulus, as seen in Hx. This confirms that the increased response of Hx is not the result of a simple odor-triggered general arousal of activity within the nervous system, but is rather a specific interaction in only a subset of higher order neurons. This is an important point, because a general increase in the gain of all neurons involved in coding motion might not always be appropriate. HS neurons, for example, are known to form part of a negative feedback loop for controlling heading: seeing wide-field motion to the right in both eyes is a sure indication that the fly is rotating excessively to the left and elicits a correcting turn to the right. If the correcting response were too strong, the inevitable delay in the fly detecting its own motion could lead to it overshooting the desired position and start an unstable back and forth oscillation. This is a phenomenon familiar to trainee pilots and computer gamers alike if the controls are too sensitive.

A complication in this interpretation, however, comes from several additional lines of evidence that the mechanism of the odor-induced increase in response of Hx involves modulatory aminergic signaling pathways. Hx neurons appear to receive synaptic input from neurons that release octopamine, a hormone recently implicated in modulation of the strength of responses of both the behavioral response of flies to wide-field motion and the excitation of fly lobula-plate motion detecting neurons, including HS [7]. Again using two-photon imaging of Ca2+ activity, Wasserman *et al.* [1] show that these octopaminergic terminals are indeed activated by odor pulses. At a behavioural level, a null mutation in a vesicular transporter for

monoamines disrupts the ability of flies to track the odor plume, while a rescue of octopamine signaling in these flies is sufficient to restore normal tracking.

These experiments suggest that the cross-modal odor modulation of visual motion responses is driven specifically by octopamine release onto higher-order motion sensitive neurons, rather than by modulation of input pathways such as T4/T5 neurons. Yet given prior work also implicating octopamine as a modulator of the gain of HS neurons, why does odor not lead to an increase in the response of HS neurons as seen in Hx (Figure 1B)? One possibility is that octopamine neurons act via more than one postsynaptic receptor pathway, differentially expressed in higher order neurons. While experimental exogenous application of octopamine might induce modulation of gain in HS neurons also, the odor-mediated release of endogenous octopamine might not be agonistic for all post-synaptic targets. Indeed, this difference between the response of Hx and Hs provides an exciting opportunity for a broader investigation of the subtle ways in which aminergic signaling might be involved in differential cross-modal interactions within the insect nervous system.

Regardless of the outcome of future work to reconcile these findings, the study by Wasserman *et al.* [1] provides clear evidence for a mechanism that dynamically enhances sensory perception in a contextually appropriate manner. In humans, congruent odor cues have been shown to facilitate perception of color or shape based visual cues, just as the inventors of Smell-O-Vision had hoped to exploit in their 1950s experiments in multisensory cinema. Until recently, however, no similar effect was known for motion, which is primarily processed in the visual dorsal stream, a subdivision of the cortex that shares many properties in common with the fly lobula plate [8]. Another recent study, however [9], showed that olfaction can indeed bias visual motion perception in humans. It remains to be seen whether such cross-modal interactions in the human dorsal stream also involve aminergic modulation, as now shown in the fly.

References

1. Wasserman, S.M., Aptekar, J.W., Lu, P., Nguyen, J., Wang, A.L., Keles, M.F., Grygoruk, A., Krantz, D.E., Larsen, C., and Frye, M.A. (2015). Olfactory neuromodulation of motion vision circuitry in *Drosophila*. Curr. Biol. *25*, 467–472.
2. Kennedy, J.S., and Marsh, D. (1974). Pheromone-regulated anemotaxis in flying moths. Science *184*, 999–1001.
3. Chow, D.M., Theobald, J.C., and Frye, M.A. (2011). An olfactory circuit increases the fidelity of visual behavior. J. Neurosci. *31*, 15035–15047.
4. Duistermars, B.J., and Frye, M.A. (2008). Crossmodal visual input for odor tracking during fly flight. Curr. Biol. *18*, 270–275.
5. Maisak, M.S., Haag, J., Ammer, G., Serbe, E., Meier, M., Leonhardt, A., Schilling, T., Bahl, A., Rubin, G.M., Nern, A., *et al.* (2013). A directional tuning map of *Drosophila* elementary motion detectors. Nature *500*, 212–216.
6. Levy, P., and Larsen, C. (2013). Odd-skipped labels a group of distinct neurons associated with the mushroom body and optic lobe in the adult Drosophila brain. J. Comp. Neurol. *521*, 3716–3740.
7. Suver, M.P., Mamiya, A., and Dickinson, M.H. (2012). Octopamine neurons mediate flight-induced modulation of visual processing in Drosophila. Curr. Biol. *22*, 2294–2302.
8. Clifford, C.W.G., and Ibbotson, M.R. (2002). Fundamental mechanisms of visual motion detection: models, cells and functions. Prog. Neurobiol. *68*, 409–437.
9. Kuang, S., and Zhang, T. (2014). Smelling directions: Olfaction modulates ambiguous visual motion perception. Sci. Rep. *4*, 5796.

Department of Biology, University of Lund, Sölvegatan 35, S-22362 Lund, Sweden.
E-mail: david.o_carroll@biol.lu.se

http://dx.doi.org/10.1016/j.cub.2015.01.021

Tumor Biology: With a Little Help from My Dying Friends

Apoptosis is an essential form of cell death underlying daily tissue regeneration. In tumor biology, apoptosis resistance is a well-established hallmark of cancer that is targeted by therapeutic approaches. A new study assigns a hitherto-underestimated function to this 'deadly friend': apoptotic cells promote tumor growth, accumulation of tumor-associated macrophages, and angiogenesis.

Kirsten Lauber[1,*] and Martin Herrmann[2]

Being a central opponent of cell proliferation, apoptosis plays a pivotal role in tissue homeostasis. Apoptotic cells are swiftly removed by phagocytes and stimulate wound-healing responses, along with the production of anti-inflammatory cytokines [1]. *In situ*, apoptotic cells are commonly associated with macrophages, which have a tissue-remodeling, angiogenesis-promoting phenotype that is also known of tumor-associated macrophages (TAMs). Accumulation of TAMs has been reported to correlate with poor prognosis in various human malignancies, and the contribution of TAMs to cancer progression has been extensively explored [2]. The mechanisms orchestrating the accumulation, differentiation and polarization of TAMs are still poorly understood, but the association of intra-tumoral apoptosis, TAM accumulation, and disease aggressiveness suggests a functional interconnection [3].

In a new study in this issue of *Current Biology*, Ford *et al.* [4] examine the impact of apoptosis on tumor cell proliferation and tumor growth in transplantation models of lymphoma and melanoma. They report that human Burkitt lymphoma cells overexpressing the anti-apoptotic proteins Bcl-2 or Bcl-x_L showed significantly delayed tumor growth compared with their wild-type counterparts after transplantation into immunodeficient SCID mice. Tumor cell proliferation *in vivo* was strongly impaired, although basal apoptosis was reduced and proliferation *in vitro* was increased. These rather surprising observations suggest that inhibition of spontaneous apoptosis interferes with non-tumor cell autonomous mechanisms that favor tumor growth *in vivo*. Transplantation experiments with the λ-Myc lymphoma model further strengthen this conclusion: depletion of apoptotic cells from the inoculum strongly attenuated tumor growth, whereas