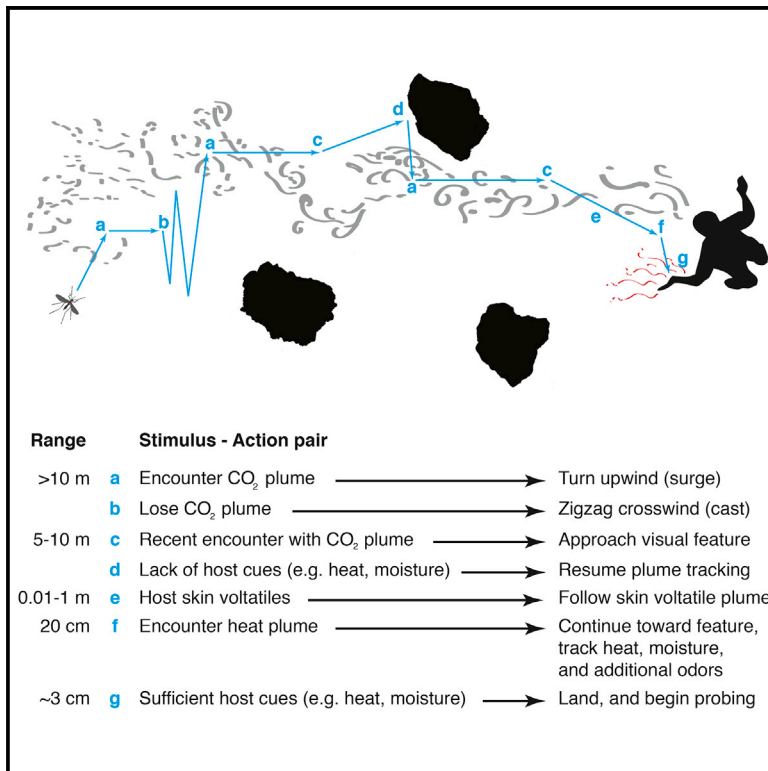


# Current Biology

## Mosquitoes Use Vision to Associate Odor Plumes with Thermal Targets

### Graphical Abstract



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### In Brief

To find human hosts, mosquitoes must integrate sensory cues that are separated in space and time. To solve this challenge, van Breugel et al. show that mosquitoes respond to exhaled CO<sub>2</sub> by exploring visual features they otherwise ignore. This guides them to potential hosts, where they use cues such as heat and humidity to locate a landing site.

### Highlights

- A mosquito's perception of CO<sub>2</sub> triggers a strong attraction to visual features
- A mosquito's attraction to thermal targets is independent of the presence of CO<sub>2</sub>
- Olfaction, vision, and heat trigger independent host-seeking behavioral modules
- Interactions among behavioral modules underlie multimodal sensory integration



# Mosquitoes Use Vision to Associate Odor Plumes with Thermal Targets

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## SUMMARY

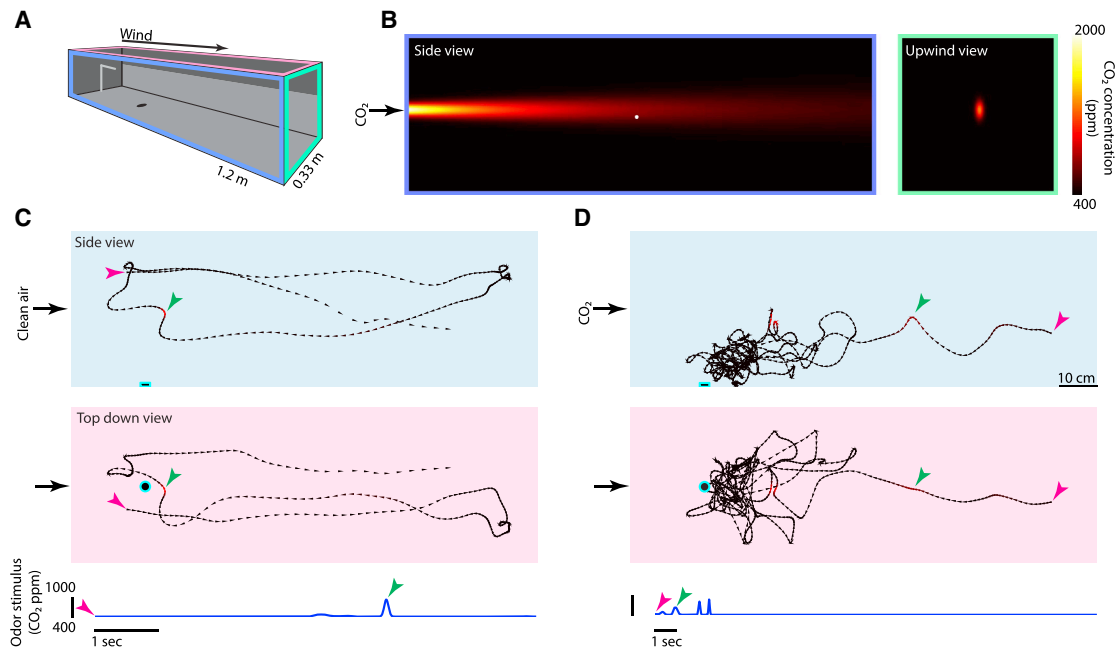
All moving animals, including flies [1–3], sharks [4], and humans [5], experience a dynamic sensory landscape that is a function of both their trajectory through space and the distribution of stimuli in the environment. This is particularly apparent for mosquitoes, which use a combination of olfactory, visual, and thermal cues to locate hosts [6–10]. Mosquitoes are thought to detect suitable hosts by the presence of a sparse CO<sub>2</sub> plume, which they track by surging upwind and casting crosswind [11]. Upon approach, local cues such as heat and skin volatiles help them identify a landing site [12–15]. Recent evidence suggests that thermal attraction is gated by the presence of CO<sub>2</sub> [6], although this conclusion was based experiments in which the actual flight trajectories of the animals were unknown and visual cues were not studied. Using a three-dimensional tracking system, we show that rather than gating heat sensing, the detection of CO<sub>2</sub> actually activates a strong attraction to visual features. This visual reflex guides the mosquitoes to potential hosts where they are close enough to detect thermal cues. By experimentally decoupling the olfactory, visual, and thermal cues, we show that the motor reactions to these stimuli are independently controlled. Given that humans become visible to mosquitoes at a distance of 5–15 m [16], visual cues play a critical intermediate role in host localization by coupling long-range plume tracking to behaviors that require short-range cues. Rather than direct neural coupling, the separate sensory-motor reflexes are linked as a result of the interaction between the animal's reactions and the spatial structure of the stimuli in the environment.

## RESULTS

To study host-seeking behavior in *Aedes aegypti*, we released mated females in a wind tunnel with 40 cm s<sup>−1</sup> laminar flow and recorded over 20,000 flight trajectories (mean length >6 s)

using a three-dimensional real-time tracking system [17] (Figure 1A). We projected a low-contrast checkerboard pattern on the entire floor of the tunnel and placed one high-contrast spot 20 cm from the upwind end (Figure S1A). After allowing the mosquitoes to acclimatize for 1 hr in clean air, which contained a background CO<sub>2</sub> level of 400 ppm, we introduced a CO<sub>2</sub> plume with a peak concentration of 2,500 ppm for 3 hr during the mosquitoes' circadian activity peak. In separate experiments, we measured the CO<sub>2</sub> concentration at 65 points in the tunnel and constructed a spatial model of the plume (Figures 1B, S1B, and S1C). When combined with our three-dimensional tracking, the plume model made it possible to reconstruct the olfactory experiences of the mosquitoes along each individual trajectory [1] (see the Experimental Procedures for additional details). In control experiments, in which we injected clean air instead of CO<sub>2</sub>, the female mosquitoes did not exhibit plume-tracking behavior (Figures 1C, 2A, and S1). In the presence of the CO<sub>2</sub> plume, the female mosquitoes showed stereotypical cast and surge behavior in response to CO<sub>2</sub> concentrations greater than 500–600 ppm (Figure S2), as has been reported previously [11, 18].

The most salient result of our experiments, however, was the influence of odor on the attractiveness of the visual object. When the female mosquitoes were exposed to clean air, they explored the ceiling and walls of the wind tunnel but rarely approached the visual feature. By contrast, when mosquitoes were exposed to the CO<sub>2</sub> plume, they spent much of their time exploring the dark visual feature on the floor of the wind tunnel, despite its location approximately 10 cm below the CO<sub>2</sub> plume (Figures 1D, 2B, and S1 and Movie S1). The attraction to this visual feature persisted through the entire length of the 3-hr CO<sub>2</sub> presentation (Figure S3). During these exploratory bouts, the mosquitoes hovered near the visual object at a distance of approximately 3 cm. These results are, to our knowledge, the first direct observation of odor-gated visual attraction in mosquitoes. In previous unpublished experiments, however, Richard Dow came to similar conclusions using trap assays without access to detailed knowledge of either the animals' trajectories or the structure of the odor plume [10]. In experiments in which we provided both a bright-white and a dark-black object on a gray background, the mosquitoes only explored the dark object (Figure 2C), consistent with trap assays using wild mosquitoes [19–21]. In contrast to the female mosquitoes, males vigorously explored the visual feature in clean air (Figure 2D). In the presence of CO<sub>2</sub>, the males did not show any qualitative behavioral changes compared to their clean air responses and did not



**Figure 1. Wind Tunnel, CO<sub>2</sub> Plume, and Example Flight Trajectories**

(A) Wind tunnel used in our experiments. Color borders indicate top, side, and upwind views used in subsequent panels.

(B) Heatmap of a turbulent-flow, particle-diffusion model of the CO<sub>2</sub> plume based on 65 measurements in the wind tunnel; see the [Experimental Procedures](#) and [Figure S1](#) for details. The white dot indicates a mosquito, drawn to scale.

(C) Example flight trajectory in clean air. The two colored arrowheads show synchronized points across side and top views. The spacing between the points (33-Hz intervals) indicates the animal's speed.

(D) Example flight trajectory in the presence of a CO<sub>2</sub> plume, showing the mosquitoes' stereotypical behavior exploring the high-contrast object after sensing CO<sub>2</sub>.

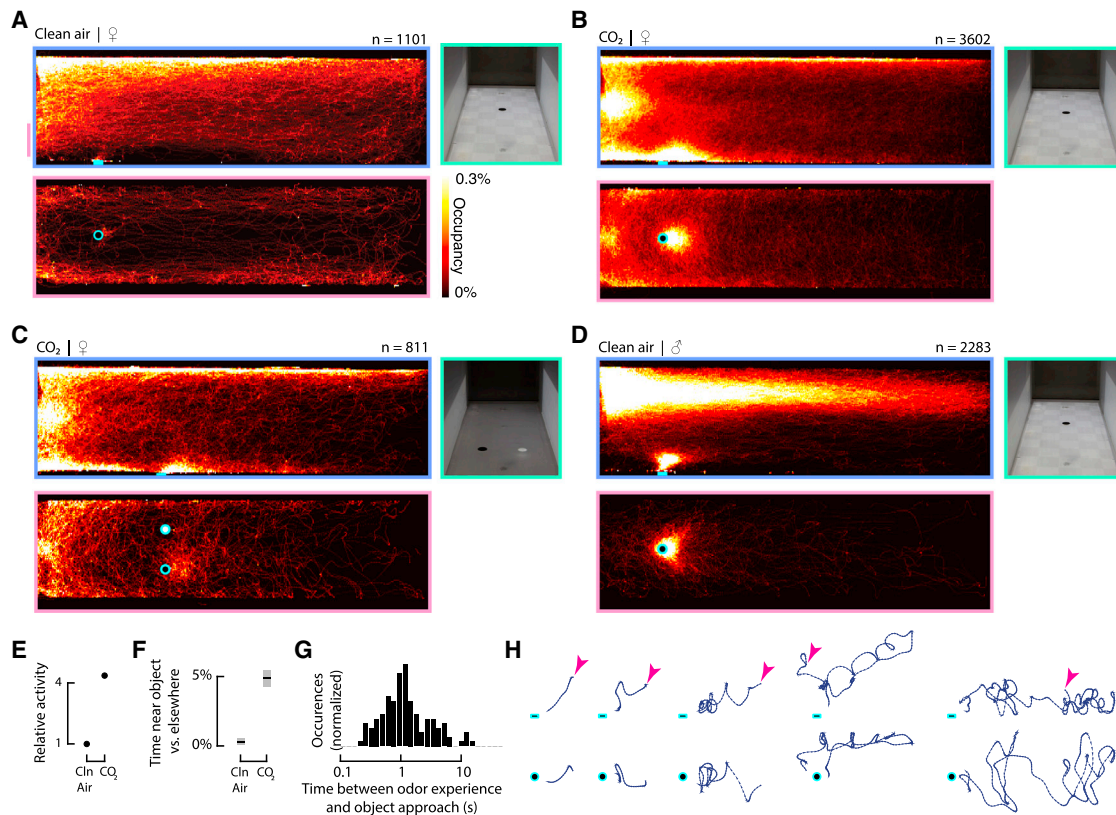
In both (C) and (D), an estimate of the animal's instantaneous CO<sub>2</sub> (or control) experience is plotted below and color-coded within the trajectories using the scale in (B). See also [Figure S1](#) for additional trajectories and [Movie S1](#) for animations.

exhibit any evidence of plume-tracking behaviors. Thus, the influence of CO<sub>2</sub> on the reaction to visual features appears to be a sex-specific behavior associated with blood foraging. In addition to plume tracking and object attraction, CO<sub>2</sub> also elicited a significant increase in the general flight activity of females ([Figure 2E](#)). Averaged across all of the trajectories, the female mosquitoes spent close to 5% of their time near the visual object compared to all other parts of the wind tunnel ([Figure 2F](#)). Normalized for volume, the mosquitoes spent ten times more time near the object than in the rest of the tunnel (8.8%/mm<sup>3</sup> versus 0.88%/mm<sup>3</sup>). They also spent much of their time in the vicinity of the tube through which CO<sub>2</sub> was introduced into the tunnel. Although we tried to minimize the visual signature of this tube, it is likely that the mosquitoes could see it to some degree.

The visual object was placed 10 cm below the plume, at which distance the CO<sub>2</sub> was not detectable using a sensitive meter (LI-6262 CO<sub>2</sub>/H<sub>2</sub>O analyzer, LI-COR), and our spatial model based on measurements within the plume estimated a concentration at the floor that was no different from background levels. Thus, when the mosquitoes approached and explored the visual object, they were not experiencing CO<sub>2</sub> above the background. We calculated the time elapsed between leaving the plume and approaching the visual object for the 126 trajectories that contained continuous, un-fragmented data between these two events ([Figure 2G](#)). Some mosquitoes approached the object immediately after leaving the CO<sub>2</sub> plume, whereas others took

circuitous paths in which more than 10 s elapsed before reaching the object ([Figure 2H](#)). Many of the mosquitoes that approached the visual feature continued to explore the area for another 10 s or more without reencountering the plume (see [Movie S1](#)). These results indicate that attraction to visual features can be triggered by a brief prior exposure to odor and does not require simultaneous experience of the two cues. Our estimates are necessarily conservative because our tracking system cannot reliably maintain the identities of individual mosquitoes over periods longer than 10–20 s.

Odor-induced visual attraction could be one mechanism by which mosquitoes first navigate toward and localize potential hosts, but other cues, such as warmth, might also aid in the final stages of foraging. To investigate the potential interaction between vision and CO<sub>2</sub>-gated thermal attraction described in a previous study [6], we constructed two transparent objects from indium tin oxide (ITO)-coated glass, which could be heated to a desired temperature ([Figure 3A](#)). We could independently manipulate the thermal and visual features of the stimulus by placing a long-pass gel filter over the glass. Such a filter appears dark to the mosquitoes but transparent to our cameras ([Figures 3B and 3C](#)). In each experiment, we presented the mosquitoes with two objects: a dark room-temperature control object and a test object that was either dark or nearly invisible and either room temperature or heated to 37°C ([Figures 3D and 3E](#)). When presented with two dark objects, one of which was warm, the



**Figure 2. CO<sub>2</sub> Triggers Mosquitoes to Explore High-Contrast Dark Objects**

(A) Heatmap showing where female mosquitoes spent their time over a 3-hr period. The top panel shows a side view of the data. The bottom panel shows a top down view of the data over the altitude range indicated by the vertical pink line in the top panel. The right panel shows a photograph of the wind tunnel.

(B) Same as (A), but in the presence of a CO<sub>2</sub> plume.

(C) Same as (A), but in the presence of a CO<sub>2</sub> plume and with a black and a white visual object on the floor of the tunnel.

(D) Same as (A), but with male mosquitoes in clean air. We did not find any qualitative differences in male mosquitoes' behavior in the presence of a CO<sub>2</sub> plume (not shown).

(E) Relative flight activity, measured as the ratio of time mosquitoes spent flying in the presence of a CO<sub>2</sub> or clean air plume compared to their prior activity.

(F) The ratio of the total time mosquitoes spent near the object divided by the total time they spent elsewhere for CO<sub>2</sub> and clean air conditions. Shading shows bootstrapped 95% confidence intervals of the mean.

(G) Time elapsed between when mosquitoes left the plume (conservatively defined here as 401 ppm) and when they approached to within 3 cm of the object.

(H) Example trajectories (top row, side view; bottom row, top-down view) that contributed to the histogram shown in (G), demonstrating the circuitous path many mosquitoes took from the plume to the object. Only the trajectory segments between plume exit (pink arrow) and object approach are shown.

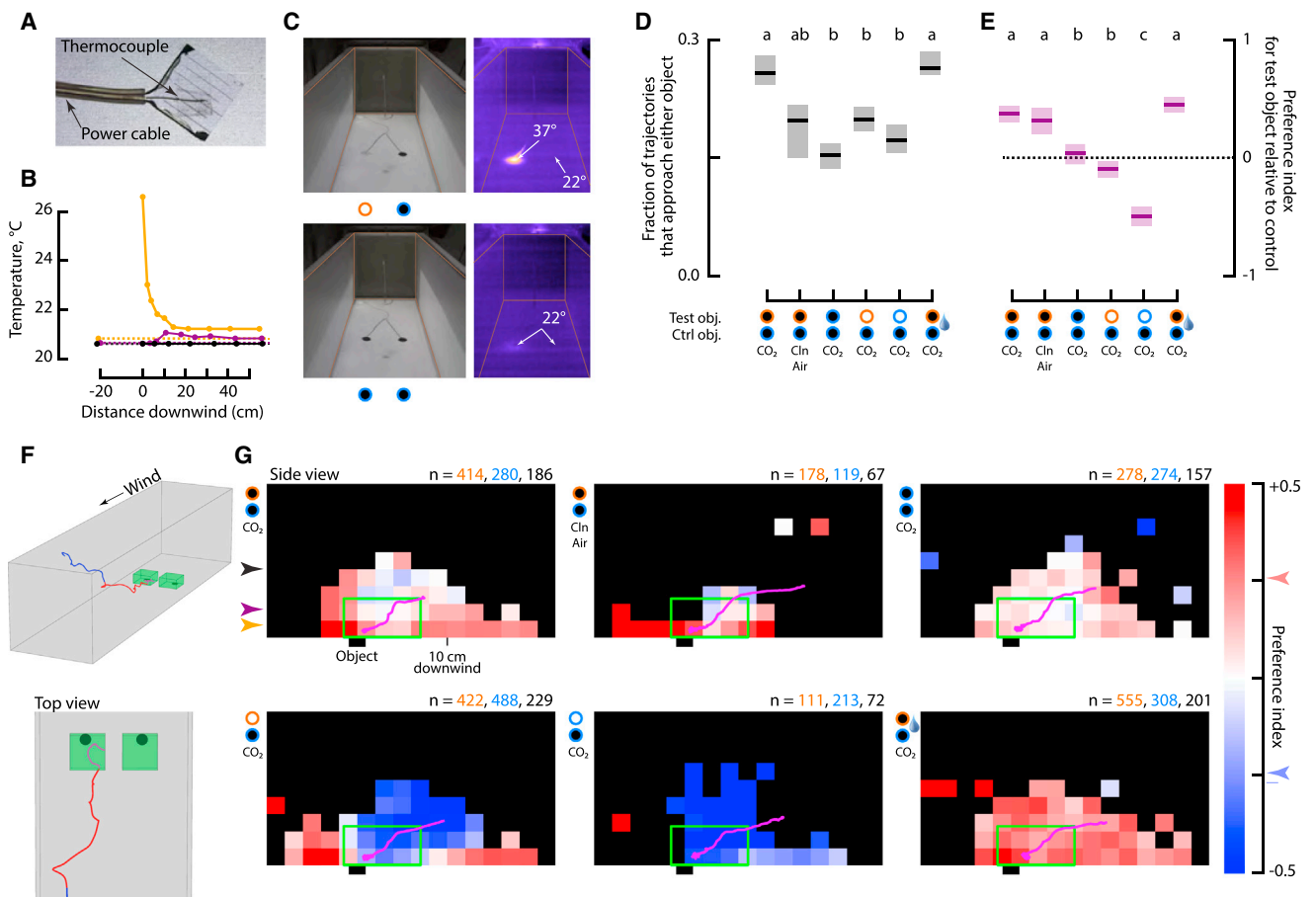
See also [Figure S2](#) for a description of plume-tracking behavior and [Figure S3](#).

female mosquitoes showed a significant preference for the warm object ( $p < 0.01$ ). Although fewer mosquitoes approached either object in clean air, those that did showed a preference for the warm object that was not different than in the presence of a CO<sub>2</sub> plume ( $p < 0.01$ ), indicating that CO<sub>2</sub> does not appear to directly gate the attraction to warm objects. Significantly more mosquitoes approached the warm high-contrast object than the warm nearly invisible object. This result shows that attraction to visual features increases the probability of localizing a warm object. However, more mosquitoes found the warm nearly invisible object than a room-temperature nearly invisible object, indicating that thermal signals can provide an independent source of information about the location of potential hosts.

The data shown in [Figure 3E](#) provide only a simplified view of the behavioral algorithm used by the mosquitoes. To indicate how the visual and thermal cues influence behavior on a finer

spatial scale, we constructed a preference index as a function of tunnel position for the 2 s before the mosquitoes approached either object ([Figures 3F](#) and [3G](#)). On average, mosquitoes initially approached the objects without encountering the heat plume, which was only detectable 2–3 cm above the floor of the tunnel ([Figure 3B](#)). The mosquitoes that approached the object from just above the floor did, however, show a preference for the warm object from as far away as 20 cm.

Water vapor from rapidly evaporated perspiration has been attributed as another cue mediating host-seeking behavior in mosquitoes [12]. To investigate the possible role of water vapor on host localization in combination with visual and thermal cues, we placed a small petri dish containing a moist KimWipe over each glass pad in combination with the infrared pass filter that provides the visual cue. In this case, mosquitoes showed a significantly stronger response to the warm object at altitudes



**Figure 3. Visual Stimuli Provide an Intermediate Cue, Linking Long-Range Olfactory Cues and Short-Range Heat Sensing**

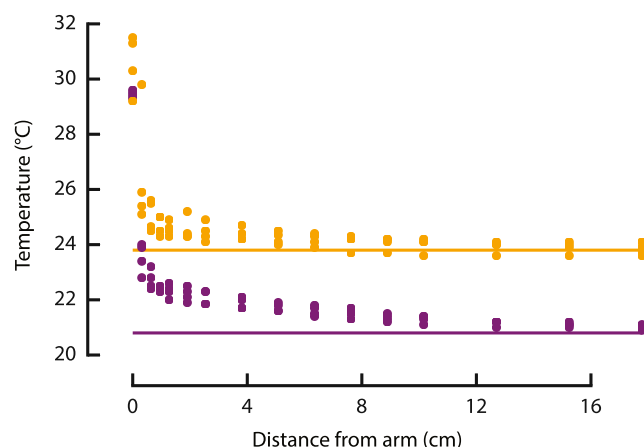
(A) Photograph of the ITO-coated glass pad.  
 (B) Measurements of the thermal plume created by the heated glass pads at altitudes of 0.5, 2.5, and 6.5 cm, colored orange, purple, and black, respectively.  
 (C) Photographs and thermal images of the stimuli in the wind tunnel.  
 (D) Mean fraction of trajectories that entered an  $8 \times 8 \times 4$  cm<sup>3</sup> volume above and downwind of either the left or right object (see F). Shading indicates 95% confidence intervals. The letters at the top indicate significantly different groups (Mann-Whitney U test with Bonferroni correction,  $p = 0.01$ ).  
 (E) Mean preference index for the test object versus control object with 95% confidence intervals. Statistics were calculated as in (D).  
 (F) Sample trajectory entering one of the test volumes (green) used in (D) and (E). The trajectory is color-coded red for the 2 s prior to when it entered the volume.  
 (G) Spatial representation of preference index prior to when mosquitoes entered either test volume shown in (F). For each trajectory, we selected the segments 2 s prior to when they entered either volume, in addition to the portions spent inside the volumes (red region of the trajectory shown in F). We then calculated the preference index for each  $2 \times 2$  cm<sup>2</sup> rectangular region as the amount of time spent on the side of the wind tunnel of the test object compared to the control object, divided by their sum. We then calculated the mean preference index for each  $2 \times 2$  cm<sup>2</sup> region across all trajectories and its 95% confidence interval. Colors indicate preference index for regions where the 95% confidence interval was smaller than 0.5 (out of the total range of  $-1$  to  $+1$ ); the regions with higher uncertainty are shown in black. Blue or pink colors that are more saturated than the arrows on the scale bar represent regions where the mosquitoes showed a statistically significant preference for one side or the other. The average approach trajectory for all the mosquitoes in each trial is shown as a magenta line. Because the average approach trajectories to the two objects were indistinguishable, this line shows the average approach of all trajectories for simplicity. The light-green box shows a side view of the volumes shown in (F). The colored arrows indicate the altitudes at which the temperature of the air was measured in (B). The number of trajectories that approached the test (orange), control (blue), or both (black) objects is indicated in the top right of each panel.

of 6–8 cm, rather than the narrow 2-cm region above the floor in which mosquitoes responded to the heat plume without H<sub>2</sub>O ( $p < 0.01$ ) (Figure 3G). These results suggest that the secondary effect of increased humidity over a warm object may be a more important cue than the temperature of the object itself. This behavior would help mosquitoes differentiate warm radiant objects, such as dark rocks heated by the sun, from animals, which increase the humidity around them when perspiring [12].

To determine the spatial scale over which thermal cues could realistically be detected by a mosquito, we measured the tem-

perature downwind of a human arm in our laminar flow wind tunnel at ambient temperatures of 20.8°C and 23.8°C (Figure 4). These temperatures are representative of the typical range in Rio de Janeiro, Brazil [22] during the months of highest Dengue fever transmission by *Aedes* [23]. At a distance of 10–15 cm, the difference between the heat plume and ambient temperature falls below 0.2°C, the detection threshold for *Aedes* [13]. Although mosquitoes can only see with an angular resolution of 4°–8° [16], this would still allow them to detect a human arm at 30–50 cm, three times the distance at which they might detect





**Figure 4. Thermal Signature of a Human Arm**

Temperature downwind (0.4 m/s) of a human arm measured at two different ambient temperatures (orange and purple). Horizontal lines indicate the ambient temperatures.

a heat signature. In still air conditions, such as those found in a home, the heat plume would most likely dissipate even more quickly. Thus, visual features are likely to provide useful cues over a much greater distance than thermal plumes.

## DISCUSSION

In our experiments, we deliberately created a simple continuous odor plume so that we could register it with the mosquitoes' reactions. Under more natural conditions, however,  $\text{CO}_2$  would move with the wind in intermittent packets of high concentration interspersed with background air [24]. The intermittent structure of natural plumes will cause an animal to experience a brief puff of odor, and then nothing for seconds, or even minutes [24–26]. Visual cues, however, are constant and effective from any angle, regardless of wind direction and turbulence. After experiencing a short  $\text{CO}_2$  exposure, mosquitoes may encounter a visual feature that might be the odor's source. It thus makes sense that the attraction to visual features is triggered by a brief encounter with a chemical cue but persists for many seconds following the exposure. This feature of the behavior is a natural consequence of the physics of natural plumes and makes clear predictions for the time constants of the underlying neural circuits. The time course of the  $\text{CO}_2$ -induced visual attraction that we observed is similar to that recently demonstrated for a change in the gain of the optomotor response in *Drosophila* following exposure to an attractive odor [27]. Odor-gated attraction to visual features has also been observed in other insects such as fruit flies [1] and hawk moths [28], which suggests that this type of behavioral coupling may be a general and ancient strategy employed by insects for food search. Many vertebrates also track intermittent odor plumes to locate food [4, 5], suggesting that they, too, must integrate chemical and visual cues with long interaction delays, as opposed to the 100 ms timescales typically considered in multimodal sensory integration [29].

Our results are consistent with a scheme in which host-seeking behavior emerges from a simple series of reflexes that are sequentially triggered according to the spatial scale over

which the sensory cues can be detected. In the presence of an attractive odor such as  $\text{CO}_2$ , mosquitoes become more active, following the plume upwind using an iterative sequence of cast and surge reflexes. The distance at which mosquitoes first detect the  $\text{CO}_2$  plume created by a human has not been precisely measured. However, a study that artificially released  $\text{CO}_2$  at 4 l/min (roughly equivalent to that produced by a large bovine) found that the plume was detectable above background at a distance of 60 m in a riverine habitat [30]. The results reported here show that the detection of  $\text{CO}_2$  triggers the exploration of high-contrast visual features, and a human figure would become visible to mosquitoes at distance of roughly 5–15 m [16], depending on the lighting conditions. This behavior will direct mosquitoes toward a potential host, at which point heat, humidity, and other olfactory cues [15, 31–35] may guide the final approach and the decision whether or not to land. At these intermediate distances, human skin volatiles are likely to play an important role, as demonstrated in a recent study which showed that when presented with separate plumes of  $\text{CO}_2$  and human skin volatiles, *Aedes* followed the skin volatiles rather than the  $\text{CO}_2$  [15]. This might direct mosquitoes to an appropriate landing site on the body surface—such as the feet or ankles—rather than following the  $\text{CO}_2$  plume to the mouth. In the same study, exposure to a  $\text{CO}_2$  plume did not induce mosquitoes to land on dark beads, whereas they did land on beads coated with human odor [15]. The most likely explanation for the discrepancy between these prior observations and our own results is that the visual contrast generated by the small dark beads on a dark background may have been insufficient to elicit the visual attraction that we observed.

In our proposed scheme, the behavioral modules employed by mosquitoes to find a host are both independent and interacting. The modules are independent from one another in the sense that mosquitoes may bypass individual steps in the sequence. For example, if mosquitoes happen to fly near a warm object without having previously encountered  $\text{CO}_2$ , they may still approach the object and land. The behavioral modules may also interact with one another indirectly. For example, the influence of  $\text{CO}_2$  on both arousal and visual feature attraction will greatly increase the probability that mosquitoes come close enough to a host to detect its thermal plume.

For a human hoping to avoid being bitten by a mosquito, our results underscore a number of unfortunate realities. Even if it were possible to hold one's breath indefinitely, another human breathing nearby, or several meters upwind, would create a  $\text{CO}_2$  plume that could lead mosquitoes close enough to you that they may lock on to your visual signature. The strongest defense is therefore to become invisible, or at least visually camouflaged. Even in this case, however, mosquitoes could still locate you by tracking the heat signature of your body provided they get close enough. The independent and iterative nature of the sensory-motor reflexes renders mosquitoes' host seeking strategy annoyingly robust.

## EXPERIMENTAL PROCEDURES

### Animals

Mosquitoes (*Aedes aegypti*, standard laboratory Rockefeller strain [18, 36]) were raised in groups of 100 and were cold-anesthetized to sort males from

females after they cohabitated for 6–8 days. At this time, more than 90% of the females have typically mated, as indicated by their developing embryos. Three hours prior to their subjective sunset, we released 20 females into the wind tunnel. Two hours prior to sunset, the CO<sub>2</sub> plume (or air in control experiments) was automatically switched on for 3 hr. The wind tunnel and tracking system have been described in detail previously [1, 17].

### CO<sub>2</sub> Plume Calibration

In order to calculate the olfactory experience of each trajectory, we measured the CO<sub>2</sub> concentration inside the wind tunnel at 65 different locations with a LI-6262 CO<sub>2</sub>/H<sub>2</sub>O analyzer (LI-COR) and constructed a model based on particle diffusion in turbulent flow (see the [Supplemental Experimental Procedures](#)).

### Trajectory Analysis

Details on the tracking software [17] and general camera setup for this particular system [1] are provided elsewhere. Because our tracking system is unable to maintain identities for extended periods of time, individual traces were considered independent for the sake of statistical analysis. We restricted all of our analysis to trajectories that were at least 150 frames (1.5 s) long. The average length of the trajectories was approximately 6 s, with some trajectories reaching 85 s. In total, we collected over 20,000 trajectories over the course of our experiments.

Data for the heated object experiments in [Figure 3](#), as well as in [Figure 2A](#), were collected with 60 individual mosquitoes over three trials per experimental condition, yielding between 1,101 and 3,433 trajectories for each condition. Data in [Figure 2B](#) were collected with 120 individuals over six trials, yielding 3,602 trajectories. Data for [Figures 2C](#) and [2D](#) did not require statistical analyses and were collected with 20 individuals over one session due to equipment access constraints, yielding 811 and 2,283 trajectories for the two conditions.

### SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, three figures, and one movie and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2015.06.046>.

### AUTHOR CONTRIBUTIONS

F.v.B. carried out all the experiments and analyzed the data. All authors contributed to the experimental design, and interpretation of the data. F.v.B. and M.H.D. together produced the figures and wrote the manuscript, with help from J.R. and A.F.

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