How and why *Caenorhabditis elegans* uses distinct escape and avoidance regimes to minimize exposure to noxious heat

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Introduction

Each and every biological and biochemical processes are affected by temperature. Animals have developed many strategies to achieve thermoregulation and limit exposure to extreme temperatures that could be deleterious for their survival, growth, and reproduction. For small ectotherms, like the nematode *Caenorhabditis elegans*, thermoregulation is achieved through locomotion.¹ Worm ability to produce directed behaviors in spatial gradients of temperature has already been known for several decades.² The thermotactic behaviors that *C. elegans* uses to navigate toward a preferred temperature when navigating in an innocuous temperature range have been extensively studied.³⁻¹⁸ Positive and negative thermotaxis refer to the mechanisms through which animals move toward higher and lower temperatures, respectively, when navigating toward their preferred temperature. These mechanisms have been described through a biased random walk model.^{11,13} In this model, animals produce runs and punctual turns. Animals move in straight lines during runs, until they perform a turn, and restart in a random direction. In this biased random walk, animals use environmental information to bias their movement. For example, in the case of negative thermotaxis, animals perform longer runs when they move toward the cool side of a gradient, and shorter runs when they move toward the hot side. With this behavior, animals will drift down the temperature gradient. It was proposed that worms monitor the temporal changes in temperature due to their self-movement in

Minimizing the exposure to deleterious extremes of temperature is essential for animals to avoid tissue damages. Because their body temperature equilibrates very rapidly with their surroundings, small invertebrates are particularly vulnerable to the deleterious impact of high temperatures, which jeopardizes their growth, fertility, and survival. The present article reviews recent analyses of *Caenorhabditis elegans* behavior in temperature gradients covering innocuous and noxious temperatures. These analyses have highlighted that worm uses two separate, multi-componential navigational strategies: an avoidance strategy, aiming at staying away from noxious heat, and an escape strategy, aiming at running away after exposure. Here, I explain why efficient escape and avoidance mechanisms are mutually exclusive and why worm needs to switch between distinct behavioral regimes to achieve efficient protective thermoregulation. Collectively, these findings reveal some largely unrecognized strategies improving worm goal-directed navigation and the fascinating level of sophistication of the behavioral responses deployed to minimize the exposure to noxious heat. Because switching between avoidance and escape regimes circumvents constraints that are valid for navigation behaviors in general, similar solutions might be used by worms and also other organisms in response to various environmental parameters covering an innocuous/noxious, non-toxic/toxic range.

Keywords: thermal nociception, thermal hysteresis, thermotaxis, behavior, behavior simulation, avoidance, TRP channels, neuropeptides, orthokinesis, klinokinesis

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Figure 1. Speed, withdrawal rate, and steering rate as a function of temperature in heating and cooling situations. (A–C) Real profiles as recorded in wild-type (N2) worms. Curves upon heating (red) or cooling (blue) form hysteresis loops. (D–F) Manipulated profiles in which the thermal hysteresis effects are artificially inactivated. Heating and cooling curves overlay as the average of both curves. These artificial profiles have been used as inputs in worm behavioral simulations to evaluate the contribution of the thermal hysteresis effects. (G–I) Manipulated profiles in which the dynamic tuning effects are artificially inactivated by using constant values for heating and cooling curves, respectively. The average thermal hysteresis effects over the temperature range are maintained. The area between heating and cooling curve is the same as the one in the corresponding real profiles (in A–C, respectively). These artificial profiles have been used as inputs in worm behavioral simulations to evaluate the contribution of the dynamic tuning effects.

the gradient to modulate the probability of performing turns.¹¹

In addition to thermotaxis in the innocuous range of temperature, *C. elegans* can detect and respond to noxious temperatures in several ways. When their head is exposed to an acute noxious heat stimuli, worms execute a withdrawal response, consisting in a short period of backward locomotion, a reorientation maneuver called omega turn, and a restart of forward locomotion in a new direction.¹⁹ When their tail is exposed, animals transiently accelerate.¹⁹ When the acute noxious heat stimuli only affects the mid-part of the body, worms produce probabilistic responses that consist either in forward locomotion, backward locomotion, or

pausing.²⁰ A growing number of studies provide information on the genes and neurons controlling these behaviors.^{19–23} However, what was essentially left aside so far is the investigation of how these different behavioral responses, and potentially others, are integrated when worms execute long-range navigation in a changing thermal landscape.

Worms Use Multiple Behavioral Mechanisms to Navigate in Noxious Heat Thermogradients

In Schild and Glauser,²⁴ we recently reported a comprehensive study of *C. elegans* behaviors when navigating in thermogradients covering the innocuous-noxious

temperature continuum. We wanted to know what behavioral mechanisms are recruited, how these mechanisms are affected by temperature and temperature changes, and how they are integrated to minimize worm exposure to noxious heat. The work focused on the behavior of starved worms. Indeed, we and others had previously shown that starvation for a few hours markedly reduced, if not completely abolished, negative thermotaxis.^{10,21} We reasoned that starvation would remove one layer of behavioral complexity, permitting to focus on “purer” avoidance behaviors, independently of temperature preferences. The Multi-Worm Tracker developed by Swierczek and colleagues²⁵ was used to analyze movies of wild-type worms (N2) crawling in spatial temperature gradients, as well as in isothermal environments at constant temperature, upon heating, or upon cooling in temperatures ranging from 20–32 °C. Results showed that worms engage three very distinct behavioral responses to direct their navigation toward cooler temperatures. First, worms modulate their speed. Second, they use withdrawal responses coupled with sharp reorientations as described by Wittenburg and Baumeister.¹⁹ Third, they use another very distinct turning behavior in which moving worms progressively reorient, that we have named steering. This behavior resembles the shallow turn behavior previously proposed to control worm two-dimensional navigation in isotropic environments.²⁶ Withdrawal and steering events represent two types of turns that occur according to a stochastic pattern. The magnitude of the angles taken during these turns is not random, with withdrawals leading to sharp reorientations and steering events producing shallower turns. The directions taken during these turning events did not appear to be influenced directly by the gradient direction. However, as detailed below, the rate at which withdrawal and steering events occurs is controlled by temperature and temperature changes.

Thermal Hysteresis: The Importance of Temperature Changes

Speed, withdrawal rate, and steering rate are affected by temperature and

temperature changes, which is particularly visible if one represents them as a function of temperature in heating vs. cooling situations (Fig. 1A–C). Strikingly, the heating and cooling curves do not overlap. For example, the rate of withdrawals upon heating rises progressively with temperature values, whereas it remains low over the full spectrum of temperature upon cooling (Fig. 1B). The steering rate upon heating initially rises and then declines, whereas it is constantly lower at any temperature upon cooling (Fig. 1C). Although the shapes of the curves differ, withdrawal and steering rates in a given temperature interval are systematically higher if temperature increases, as compared with if temperature decreases. This type of asymmetric thermal dependency is reminiscent of cases in physics, where the state of a system as a function of a given parameter depends on the history of the values taken by this parameter. The McGraw-Hill Dictionary of Scientific and Technical Terms defines thermal hysteresis as follows, “A phenomenon sometimes observed in the behavior of a temperature-dependent property of a body; it is said to occur if the behavior of such a property is different when the body is heated through a given temperature range from when it is cooled through the same temperature range.”²⁷ This definition perfectly matches our situation with worm behaviors.

One can wonder then how do thermal hysteresis properties in withdrawal, steering, and speed help worms reducing exposure to noxious heat? Withdrawal and steering events are two types of turns. In a strict parallel to the biased random walk described above for negative thermotaxis, increasing the turning probability when worms move toward higher temperatures and suppressing it when worms move toward cooler temperatures, is sufficient in a temperature gradient to shorten the duration of runs toward the hot side and lengthen the duration of runs toward the cold side. The net result is a drift of worms toward cooler temperatures. With respect to speed, the thermal hysteresis effect was observed for a large stretch of temperatures (Fig. 1A). However, its polarity was inverted as compared with turns (Fig. 1B and C),

such that animal speed is decreased upon heating, but increased upon cooling. This difference is sufficient to promote worm drift toward lower temperatures. To better grasp the impact of speed thermal hysteresis, one could consider again the random walk model. Let's imagine there is no turning bias, such that turns occur at a constant rate, independently of temperature. In that case, the average duration of runs toward the cool and the hot sides will be equal, but the distance covered will be longer toward the cool side (because animals move faster) and shorter toward the hot side (because animals move slower).

All these observations led to the conclusion that worm-directed navigation in temperature gradients spanning noxious temperatures can be described by a biased random walk, where the bias originates from thermal hysteresis in two independent types of turning events and in speed.

The mechanisms described above imply that worms have some sort of memory of the past temperatures in order to determine if temperature is decreasing or increasing. The next question was about the size of the relevant retrospective time window. The data have shown that temperature changes over as little as a few seconds were sufficient to induce those thermal hysteresis properties for speed, steering, and withdrawals.²⁴ Potentially, the implicated mechanisms might even occur over a shorter period; however, it was not possible with these behavioral readouts to reliably test shorter time periods. Collectively, these results have shown that worms do not need to integrate very long term history to produce behavioral responses helping them navigating toward cooler temperatures. These observations do not however rule out that longer term adaptation processes may be implicated as well.

Figure 2. Simulations of *C. elegans* drift kinetics in a temperature gradient. Worm navigation was simulated in a 2.7 °C/cm linear temperature gradient as previously described.²⁴ For each simulation, the position of 5500 worms was scored during 2 h, with a starting temperature of 30 °C. For each time point, data are expressed as the average temperature experienced by worms. (A) Comparison between simulated worms with empirically determined behavioral parameters (Wild-type worms) and simulated worms for which the thermal hysteresis effects are abolished as shown in Figure 1D–F (No thermal hysteresis). (B) Comparison between simulated worms with empirically determined behavioral parameters (Wild-type worms) and simulated worms for which the dynamic tuning effects are abolished as shown in Figure 1G–I (No dynamic tuning).

Figure 3. *C. elegans* integrates multiple behavioral mechanisms to navigate in temperature gradients covering innocuous and noxious temperatures. Scheme illustrating the temperature ranges at which each behavioral mechanism is engaged by worms, in order to achieve efficient avoidance and escape. Thermal hysteresis effects have specific contributions at different temperatures and represent the main motile force for worm locomotion toward lower target temperatures. Dynamic tuning effects affect the full temperature range and primarily determine the time needed by worms to drift toward target temperatures. The figure summarizes data obtained with starved animals.

Avoidance Vs. Escape: Different Situations Require Different Tools

From the temperature profiles depicted in Figure 1A–C, it is noticeable that the magnitude of the difference between the heating and cooling curves varies as a function of temperature. In other words, the degree of thermal hysteresis for each behavioral parameter varies according to the position of the worm along the innocuous-noxious continuum of temperature. Intuitively, this tells us that some behavioral mechanisms might be preferentially used in different regions of the temperature spectrum. To put numbers on these intuitions, Monte Carlo simulations of worm navigation in temperature gradients were used to test the efficiency of each behavioral mechanism at different positions in the gradient. Simulations of real worm behavior were compared with simulations where the thermal hysteresis-based mechanisms were disabled alone or in combinations. To disable the thermal hysteresis effects, we implemented thermal profiles where the heating and cooling curves are artificially superimposed. These situations are illustrated in Figure 1D–F. Through these manipulations, simulated worms behave the same regardless of whether they head toward cooler or warmer temperatures. Their behavior is then only affected

by the absolute temperature value they experience at a given instant, but not by the changes in temperature caused by their movements. This means, for example, that the speed of animals will be higher if they are on the hot side of the gradient as compared with the cool side, but that, at a given location, their speed will be the same if they move toward the cold side or the hot side (Fig. 1D). The results of these simulations reported in Schild and Glauser²⁴ confirmed that speed and steering modulations mostly impact behavior at low temperatures, when worm's goal is to stay away from noxious temperature; whereas withdrawal responses primarily impact behavior at high temperatures, when worm's goal is to run away from noxious heat. The term avoidance was used to refer to behaviors that help animals staying away from noxious heat prior to exposure, and the term escape was used to refer to behaviors aiming at running away from noxious heat after exposure. Thus, worms use different sets of thermal hysteresis-based strategies for avoidance or for escape purposes. In the next paragraph, I will discuss additional parameters that are distinctive of avoidance and escape regimes, and that significantly impact worm behavior efficacy.

If one sets aside the thermal hysteresis effects and concentrates on the general impact that temperature has on speed, it

is quite clear that speed globally rises with temperature from 22–28 °C (Fig. 1A). Fast moving animals around 28 °C produce also globally straighter trajectories (with less steering overall) than at 22 °C (Fig. 1C). Thus, speed and steering rate are not only affected by temporal changes in temperature; they are also continuously adjusted according to the temperature absolute values. We refer to this latter phenomenon as dynamic tuning. It might not be immediately evident, but these dynamic tuning properties also contribute to reduce worm exposure to heat. Indeed, low speed and curvy trajectories at lower temperatures limit the “diffusion” of worms and favor avoidance since worms tend to stay where they are. Conversely, high speed and straight trajectories at high temperature favor rapid escape down temperature gradients. This behavior is also helpful if animals are trapped in a local spot of high, homogenous temperatures, since high speed and straight trajectories will increase worm dispersal and will shorten the time needed to find an escape route.

Computer simulations were used again to evaluate the importance of dynamic tuning processes on escape and avoidance performances. Simulations of real worm behavior were compared with simulations where each of the dynamic tuning-based mechanisms were disabled alone or in combination. To blunt dynamic tuning, heating and cooling values were set as constants over the full temperature range. These situations are illustrated in Figure 1G–I. Through these manipulations, worms can still respond to temperature changes, but the differential responses will not be modulated according to their position along the innocuous-noxious continuum. Results of these simulations reported in Schild and Glauser showed that the dynamic tuning of speed and steering significantly contributes to minimize worm exposure to noxious heat.²⁴ Thus, worms have good reasons to develop complex temperature-dependencies of specific navigational behaviors as depicted in Figure 1A–C, and not like in Figure 1D–I. In theory, worms could be even better at minimizing the exposure to noxious heat if (1) they moved faster at high temperature and (2) they were simply

immobile at innocuous temperature. With respect to the first point, there are obvious physiological limitations in how fast worms can move. With respect to the second point, we should keep in mind that the present analysis focuses on starved worms navigating off-food. These animals are urged to explore their environment in order to find food and are eager to take a certain degree of risk through incursions in hot environment while exploring. Actual worm behavioral parameters are likely to reflect a balanced selection between the energy expenditure due to movement, the need to find food, and the detrimental impact of heat on growth and fertility.

One striking implication of these observations is that maximally efficient avoidance and escape mechanisms cannot co-exist. Indeed, animals simply cannot simultaneously go fast in straight line and slow in curved trajectories. This is the *raison d'être* of using distinct behavioral regimes and selecting them according to immediate requirements.

Integrating Motile Forces and Kinetics

Thermal hysteresis and dynamic tuning effects have a profound impact on the way a worm population will disperse in temperature gradients. Notably, these effects differentially influence two key parameters: (1) the mean temperature reached at equilibrium (T_{eq}) and (2) the time needed to reach T_{eq} when starting away from this target temperature. **Figure 2** shows the results of navigation simulations over 2 h with worms initially starting at 30 °C in a linear temperature gradient. Interestingly, only the thermal hysteresis effects constitute a motile force able to significantly lower T_{eq} . This is illustrated in **Figure 2A**, which compares the simulation of wild-type worms with that of worms for which the thermal hysteresis effects are artificially disabled. Conversely, the dynamic tuning effects have no significant impact on T_{eq} ; instead, they influence the time needed to reach T_{eq} (compare the kinetics in **Fig. 2B**). Ultimately, both parameters are important because they will impact the time spent by worms at suboptimal/

damaging temperatures that may reduce fertility, growth, and/or survival.

Figure 3 presents a schematic view of the different behavioral mechanisms into play when *C. elegans* navigates in a temperature gradient covering innocuous and noxious temperatures. It indicates at what temperature each mechanism is engaged and how each contributes to avoidance and escape behaviors.

Continuous Behavioral Transitions Require Well-Coordinated Changes

In order to navigate efficiently in temperature gradients covering innocuous and noxious heat, worms need to coordinate changes over several behavioral parameters, both as a function of temperature and as a function of temperature changes. We don't know yet exactly how this is operated. Interestingly, these bidirectional transitions between avoidance and escape regimes are reminiscent of the behavioral transitions produced during switches in foraging strategies and exploratory behaviors.²⁸⁻³¹ Actually, at least one regulatory signaling pathway, involving the neuropeptide receptor NPR-1, is shared between the coordinated control of foraging strategies and thermogradient navigation.^{21,24,29,32} Due to the small size of the worm nervous system, it is quite likely that the regulation of these behaviors has more in common; for example, the involved neural circuits could overlap.

While a clear conceptual gap is made here between avoidance and escape regimes, actual transitions seem to be quite progressive. This is very similar to the emerging view on worm locomotion in foraging and feeding behaviors, which was proposed by Gallagher and collaborators.³³ Their work shows that the very distinctive features classically used to describe behavioral states represent extreme cases along a continuum, rather than discrete states.

Escaper and Avoider Mutants

Based on the strengths of the *C. elegans* model, the molecular and neural mechanisms controlling these behavioral transitions can now be addressed. As a first step, we analyzed the contribution of two

signaling pathways: the signaling through the neuropeptide receptor NPR-1 and through the TRPV channels OSM-9 and OCR-2, both of which had been previously shown to regulate noxious heat-evoked behaviors.²¹ When comparing *npr-1* mutants and *osm-9 ocr-2* double mutants to wild-type, we found that disrupting either pathway had a very pleiotropic impact on the multiple behavioral components involved.²⁴ However, the impact of mutations in the TRPV genes and in *npr-1* profoundly diverged. Disruption of the TRPV channels led to a constellation of effects, including decreased speed and withdrawals at high temperature and increased steering at lower temperature, that all converged to decrease worm escape efficiency. Conversely, disruption of NPR-1 led to increased speed and decreased steering at low temperature that markedly reduces avoidance efficiency. To summarize, *npr-1* mutants are like stuck in the escape regime, whereas *osm-9 ocr-2* mutants are stuck in the avoidance regime. Based on these observations, we propose that TRPV channels and NPR-1 receptor might be components of two pathways controlling the multiple behavioral changes along the innocuous-noxious temperature continuum that are required in wild-type animals to operate coordinated transitions between escape and avoidance regimes.

Future Directions

As already mentioned, the study reported in Schild and Glauser²⁴ was performed in starved worms. Our conclusions are therefore clearly limited to this physiological state. However, now that the strategies of heat avoidance and escape are better defined in starved animals, it would be interesting to study how they integrate with other thermotactic responses in fed worms. Another important consideration is that the benefits of transitions between escape and avoidance behavioral regimes have no reason to be limited to temperature signals. Many environmental parameters can cover innocuous/noxious or non-toxic/toxic continua and worm navigation is likely to be affected by the same constraints as for temperature. Thus, we could speculate that worms might use

similar behavioral regime transitions to improve goal-directed navigation in spatial gradients of other environmental stimuli, like for example dioxygen, pH, or various chemicals. Furthermore, it is conceivable that these strategies have also been adopted by other organisms.

In conclusion, our recent work has shed a new light on the behavioral mechanisms used by worms to reduce their exposure to noxious heat. Our findings include some largely unrecognized mechanisms, which will deserve to be considered in future analyses of the behavioral responses to other environmental stimuli and in other organisms. In the future, we also hope to be able to further dissect the molecular and neural bases of these mechanisms, thanks to the useful experimental tools available in the *C. elegans* model.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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