started on our planet, it would have had to emerge anaerobically.

L-forms are not just engineered in the lab. They have been isolated from humans and other animals, and can cause disease. Where do these naturally occurring L-forms come from? It is possible that modern medicine has facilitated their emergence. β-lactam and glycopeptide antibiotics have been extensively administered in a wide variety of scenarios to both treat and prevent bacterial growth. These antibiotics target peptidoglycan synthesis. L-forms lack this target molecule, making them naturally resistant. Furthermore, the lack of peptidoglycan also allows L-forms to more easily evade detection from immune cells, since peptidoglycan is a major activator of the innate immune response [15,16].

The findings from Kawai *et al.* [1] reveal another possible selective advantage for L-form proliferation in the human host. The authors show that L-form formation is associated with mutations that downregulate endogenous ROS production and increase the synthesis of proteins dedicated to combating oxidative stress (Figure 1). Bacterial pathogens are often challenged by host-derived ROS. For instance, pathogens must combat the oxidative burst of activated neutrophils and, if encapsulated by phagosomes, they must resist being bombarded by various forms of ROS. L-form bacteria are naturally poised to avoid these challenges. Their low endogenous ROS production and their heightened oxidative stress response prime them to combat ROS-mediated killing by the host cells. Thus, stripping the peptidoglycan wall is associated with benefits that L-forms can exploit to survive in the stressful environment of the host. Perhaps evolution teaches us that sometimes the best approach forward is taking a step backward.

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Neuroecology: Tuning Foraging Strategies to Environmental Variability

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http://dx.doi.org/10.1016/j.cub.2015.04.042

Caenorhabditis elegans **has been shown to measure variability in environmental food density, using the information to fine-tune foraging strategies; a compact neural circuit has been identified that responds to large fluctuations in food-related cues and uses dopamine to encode the amount of recently encountered variability.**

The world is unpredictable. For animals, this means that no strategy is optimal under all circumstances, and behaviour must be tuned to environmental fluctuations that occur over multiple time scales. This need is reflected in plasticity mechanisms that also occur across a range of time scales, from short-term habituation to life-long

habits to evolutionary specification of innate behaviours. The nematode worm *Caenorhabditis elegans* is a workhorse of anatomical and genetic reprdoducibility — its nervous system consists of 302 neurons of known and invariant identity across clonally reproducing individuals. Furthermore, the synaptic connections among these neurons have been completely mapped by serial electron microscopy [1]. Despite the determinate structure of its nervous system, *C. elegans* exhibits individual variability and diverse forms of behavioural plasticity throughout life. The anatomical reproducibility across individuals creates an excellent opportunity to study genetic, epigenetic and neuromodulatory pathways that produce behavioural plasticity in response to experience. Calhoun *et al.* [2] recently took advantage of this opportunity by examining how experience-dependent modulation of the worm's navigation circuit modifies the spatial extent of foraging.

Much of *C. elegans* locomotion can be described in terms of simple behavioural motifs: forward crawling, reversals, and turns. The motifs themselves can vary: forward crawling can be straight or curve toward an attractive stimulus; reversals can be long or short; turns can be singular or occur in clusters of reversal-turn combinations called 'pirouettes'. Navigation strategies and behavioural states can be described by changes in the detailed features and frequency distributions of these motifs over time [3,4].

In the lab, a *C. elegans* worm typically feeds on a patch of bacteria on an agar plate. Upon forced removal from food, they engage in 'local search' behaviour, which consists of frequent reorientations (reversals and turns, often in bouts), before transitioning to a 'dispersal' mode characterized by extended forward crawling and few reorientations [4]. Calhoun *et al.* [2] asked whether prior experience — in particular, the characteristics of a recently-experienced food patch — altered off-food search behaviour. They found that animals reared on smaller patches reorient less, and thus disperse more, during the initial 'local search' phase of foraging. A key insight is that it is not the size of the patch *per se* that matters, but rather the frequency of animals' encounters with patch boundaries. Bacterial food patches are much thicker at the borders, creating a narrow circumferential environment that is both richer in food and food-related cues and differs in O_2 and CO_2 levels [5]. Because of the greater circumference:area ratio of small patches, animals encounter the border much more frequently and thus experience more environmental fluctuation compared to animals raised on large patches.

By retrospectively analysing the relationship between the timing of boundary encounters prior to off-food foraging across many individual animals, Calhoun *et al.* [2] were able to fit a behavioural filter showing that boundary encounters within 5–25 minutes prior to the foraging assay were predictive of off-food behaviour. How is this information collected and represented in the foraging circuit? Previous work using systematic laser ablation of specific neurons identified a sensorimotor network involved in regulating off-food reorientation behaviours [4]. Genetically dissecting this network, Calhoun *et al.* [2] found that glutamate signaling from two foraging circuit sensory neurons, ASK and ASI, was essential for experience-dependent patterning of local search. Additionally, dopamine release — but not sensory function — from a third sensory neuron, CEP, and neurotransmitter release from a shared set of interneurons postsynaptic to ASK and ASI were required. Calcium imaging experiments revealed that ASK and ASI are specifically tuned to large fluctuations in food-associated cues, with ASK responding to food removal and ASI to food presentation.

Taking all this together, Calhoun *et al.* [2] suggest that frequent activation of both ASK and ASI in high-variability (small patch) environments increases CEP dopamine release, which encodes the amount of recently-encountered variability (Figure 1). While ASK is presynaptic to CEP, ASI is not, and here the authors encounter the sometimes hazy correspondence between the *C. elegans* wiring diagram and the molecularly identified senders and receivers of signals at the cellular level. Whereas both ASK and ASI activity is required, there is no straightforward synaptic route from ASI to CEP, and some layers of signaling may be missing here. Dopamine, on the other

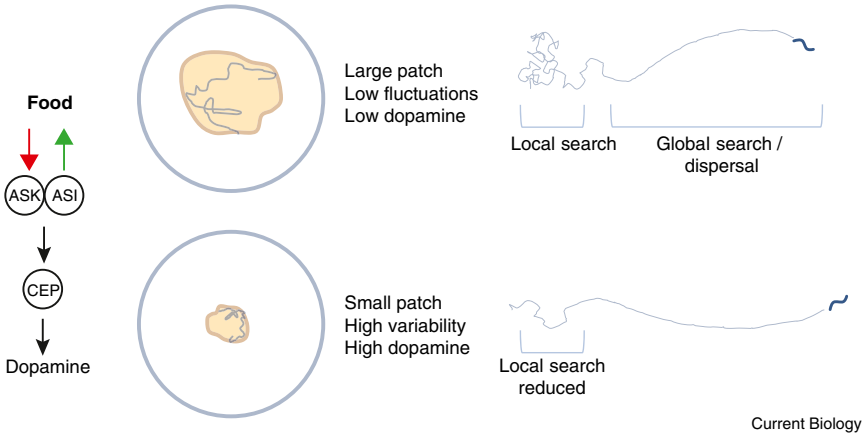

Figure 1. Tuning of *C. elegans* foraging strategy to environmental variability.
Animals on large patches encounter less environmental variability, while those on small patches encounter frequent fluctuations in food levels due to encounters with the thicker bacterial patch borders. Sensory neurons ASK and ASI respond to food fluctuations and regulate dopamine levels through CEP. Upon food removal, animals that encountered high variability exhibit attenuated 'local search' and adopt a more dispersal-oriented foraging pattern.

hand, is known to act as an extrasynaptic neurohormone [6], and here acts through D1-type receptors at both the sensory and interneuron level to modulate off-food behaviour. Exogenous dopamine while on-food, but not after removal from food, alters off-food foraging and sensitizes ASI responses to food presentation, consistent with the model that dopamine accumulates as a measurement of recent fluctuation prior to off-food foraging.

An interesting observation left unexplored is that measuring environmental variability seemed to require actually eating food, in addition to the experience of sensory variability. Calhoun *et al.* [2] noted that animals eat faster when at patch borders and showed that feeding-defective *eat-2* mutants, which have defects in pharyngeal pumping, did not exhibit patch-size dependent plasticity in foraging. One possibility is that directly sensing food intake or an internal measurement of satiety is independently required for modulating future foraging. Previously, mechanosensory responses to feeding on bacteria were shown to elicit dopamine release from CEP, which sensitizes escape responses [7,8]. However, this specific mechanism is unlikely here given that CEP sensory cilia are dispensable for experience-dependent foraging [2]. Alternatively, feeding may contribute to food chemosensation — it would be interesting to measure ASI and ASK responses to bacteria in an *eat-2* background.

Calhoun *et al.* [2] suggest that the 'default state' — as represented by loss of ASI and ASK inputs into the circuit — is that represented by a low-variability (large patch) environment. In other words, animals assume a fairly uniform environment. A recent resurgence of interest in the ecology of *C. elegans* suggests that they primarily forage in rotting fruit and live in fluctuating, patchy environments [9,10], but the detailed statistical features of their natural environment(s) are not well characterized. In contrast, the strain used here (N2) was raised under standardized laboratory conditions for many years before cryopreservation. Other foraging-related traits, including edge-occupancy and frequency of patch leaving, vary among strains, with N2 occupying one extreme end of the spectrum [11,12]. These behaviours are modified by both naturally-varying and lab-derived alleles [13–15]. We might expect to find different 'default' states in isolates from environments with different features.

This new work is notable for a number of reasons. First, the experiments and analysis are contextualized in the ecologically-relevant need to measure the environment and use this information to modify behaviour in the near term. Second, Calhoun *et al.* [2] take an interesting information theoretic approach to mapping the relationship between behavioural dynamics and prior experience based on maximum noise entropy [16]. While they do not explicitly compare this approach to others, they note it makes fewer assumptions compared to standard correlative methods. Finally, while functional conservation is well-established between nematodes and other animals at the molecular level, it is less clear the extent to which the functional logic of the *C. elegans* nervous system can generalize. This work's demonstration of humoral dopamine signaling acting to modulate risk/reward behaviours [17,18] adds to a growing body of evidence that, remarkably, the mechanisms of many of these higher-order neuromodulatory systems are shared from worms to humans.

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