

Does Hydra have an associated microbiome? Yes, it does. Like the human gut, *Hydra* is home to an array of bacterial residents. The composition of the microbiome for a particular strain of *Hydra* seems to be quite stable. How the microbiome is maintained and what it contributes to the host are important questions that are starting to be addressed. *Hydra* is a much simpler model for studying host/microbe interaction than vertebrate models such as humans and mice.

I've heard that Hydra is immortal; is that true? It appears so. Daniel Martinez followed 100 adult *Hydra* for four years, discarding the buds as they were produced. The parental animals did not undergo age-related senescence. Individual cells die in *Hydra*, but the organism as a whole does not have a fixed life-span. There is, however, evidence that some species of *Hydra* undergo senescence following sexual reproduction. Genes associated with the aging process in other animals have not yet been examined in *Hydra*, but clearly one would like to know more in this regard.

Where can I find out more?

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Primer

The natural history of *Caenorhabditis elegans*

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In the laboratory, the nematode *Caenorhabditis elegans* lives on the surface of nutrient agar in Petri dishes, feeding on a lawn of the uracil auxotroph strain OP50, an *Escherichia coli* mutant strain. This sentence sums up the fundamentals of *C. elegans* ecology, as most of us know it. While over 15,000 articles on diverse biological aspects of *C. elegans* attest to the worm's undisputable virtues as a major model organism, its biology in the wild remains mysterious. To properly interpret and fully understand the available wealth of genetic, molecular and other biological observations made in the laboratory, it will be important to know its natural history and to place the species in its ecological and evolutionary context. With the aim of connecting the discoveries that have been made about *C. elegans* biology to its 'real life', we shall discuss recent studies on the worm's natural habitat and population biology, and outline key issues in attaining a modern natural history of *C. elegans*.

Natural habitat

Where does *C. elegans* live? Efforts to systematically sample *C. elegans* in nature were initially hampered by the absence of precise ecological information on the whereabouts of this tiny roundworm, which reaches a length of only 1–2 mm as an adult. The first description of *C. elegans* and its site of isolation by the French zoologist Emile Maupas did not simplify this task: "J'ai rencontré à deux reprises cette espèce dans les environs d'Alger: une première fois en mai, la seconde en novembre 1897. Elle vit dans l'humus gras" ("I came twice across this species in the surroundings of Algiers: a first time in May, a second time in November 1897. It lives in rich humus", Maupas wrote in 1900). From then on, *C. elegans* was referred to as a soil nematode in the literature. Yet, as

one of us (M.A.F.) has experienced, long years of skimming through soil samples from all corners of the world have been frustratingly fruitless.

Human-made compost heaps are a relatively reliable source of *C. elegans*, allowing the first 'semi-natural' studies on the extent and spatial structure of its genetic diversity, population dynamics and outcrossing rate. Several more years had to elapse before *C. elegans* was regularly sampled from more undisturbed habitats. Thanks to repeated scouring of various microbe-rich samples in diverse habitats, we and others have found *C. elegans* and other *Caenorhabditis* species in different types of rotting plant material, such as fruits, stems and flowers (Figure 1).

Current data thus indicate that *C. elegans* is not principally a soil nematode, but rather a colonizer of various microbe-rich habitats, in particular decaying plant matter. Improbable as it may seem, rotting fruit/plant material thus unites three major lab model organisms in the same ecological context: *Saccharomyces cerevisiae*, *Drosophila melanogaster* and *C. elegans*. What the three species share is a rapid lifecycle, a likely legacy from their boom-and-bust lifestyle exploiting ephemeral resources.

Phylogenetic context and biogeography

The genus *Caenorhabditis* presently comprises around 25 described species, of which only seven have been maintained as live or frozen lab stocks. Their natural habitat and ecological specificities are very poorly understood, mainly because many species have been isolated only once or twice. The exception is *C. drosophilae*, which seems to be ecologically specialized: this species has been found on rotten Saguaro cactus in Arizona, in a phoretic (transport) association with the fly *Drosophila nigrospiracula*, allowing dispersal between cactus plants. Although the *Caenorhabditis* species forming the 'Elegans-group' are morphologically similar, they are highly divergent at the genetic level. To what degree this divergence is linked to alternative ecological specialization of different species remains so far largely unexplored.

The recent burst of world-wide sampling from rotting plant material has yielded many new *Caenorhabditis*

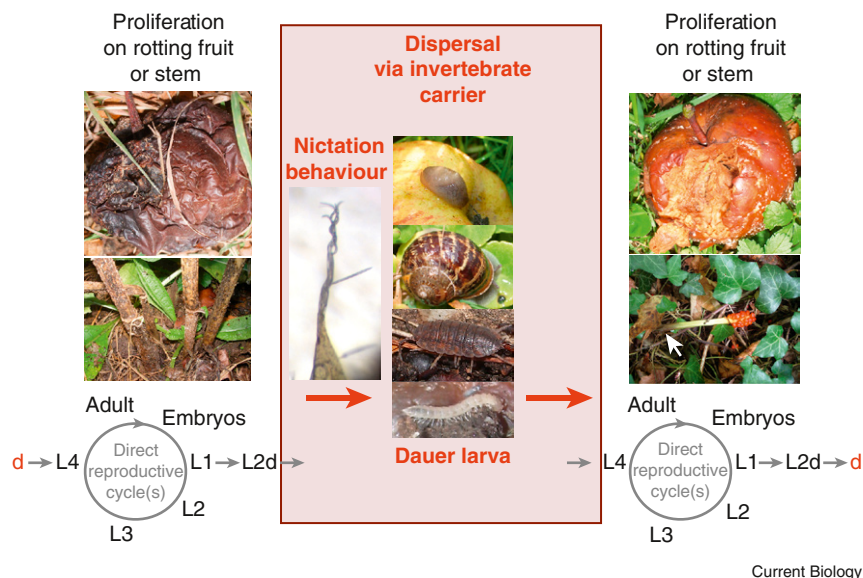


Figure 1. The life cycle of *C. elegans* in its natural habitat. *C. elegans* proliferates in various types of rotting plant material, such as fruits. Dauer larvae are the stress-resistant, alternative L3 stage, induced by crowding, food depletion and high temperature. Dauer larvae may actively disperse to colonize new food sources. Alternatively, their nictation behaviour — standing on their tail on pointy surfaces such as moss leaves and waving — may allow them to attach to disperse via carriers, such as slugs, snails, isopods or myriapods, until a new food source is encountered, where development resumes. L1–L4, larval stages; d, dauer larva; L2d, pre-dauer larva in the L2 stage.

species and given a clearer picture of the distribution of *C. elegans* and relatives. There are, however, still important geographical sampling biases — often coinciding with past holiday or congress locations of zealous *C. elegans* naturalists. *C. elegans* is cosmopolitan, being found on most continents and many isolated islands. It shares the temperate regions with two relatives of the ‘*Elegans* group’, *C. briggsae* (also a facultative self-fertilizing species) and *C. remanei* (a male–female species). Sampling in the tropics has yielded *C. briggsae*, *C. brenneri*, and many as yet undescribed *Caenorhabditis* species, but *C. elegans* relatively rarely.

The recent discovery of these novel *Caenorhabditis* species has considerably enhanced the phylogenetic context of *C. elegans* and provided a tool for novel genomic and phenotypic studies, such as genetic analysis of species hybrids. For example, *C. briggsae* has several close relatives, including its present sister, *C. sp. 9*, a male–female species with which it can form fertile hybrids. Unfortunately, the search for a sister species of *C. elegans* has so far been without result — this despite a tantalizing cash-and-naming prize offered to anyone who finds one (for

details, see <http://blog.wormbase.org/?s=sister+prize>).

Development, diapause and dispersal

When well-fed in the laboratory, at 20°C, *C. elegans* passes in about 3.5 to 4 days through a short embryonic developmental period, followed by four juvenile stages (named L1 to L4), separated by a phase of lethargus and moulting. *C. elegans*, or rather the reference lab strain N2, can develop and reproduce at a wide range of temperatures, but development halts below 8°C and the animals become sterile above 27°C.

Critical life-history choices likely reflect adaptations to the fluctuating and ephemeral natural habitat of *C. elegans*. At several specific points of development, the animals may undergo a developmental arrest, known as diapause, characterized by reduced metabolism and increased stress resistance. In young larvae, various types of stress induce the formation of dauer larvae as an alternative L3 stage, evolutionarily related to the infective stage of parasitic nematodes (Figure 1; see below). Dauer larvae are resistant to many stressors and can survive without food for several months, whilst adults usually live about two weeks. When L4 larvae are starved, they may

develop into adult hermaphrodites that enter reproductive diapause. In addition, in the adult stage, individuals may promptly stop laying embryos upon food depletion, while the embryos remaining in the uterus continue to mature, hatch internally and feed on the decaying mother during the initial larval instars — perhaps a strategy guaranteeing that a small number of internally developing larvae reach the dauer stage. Finally, if starved, *C. elegans* may also diapause in the L1 stage — the only stage that survives freezing over years. Whether this freezing resistance is ecologically relevant, for example for survival during cold winters in temperate zones, is not known.

Many developmental genetic studies have investigated dauer formation — a prime example of apparently adaptive phenotypic plasticity. In the lab, dauer entry is induced during the L1–L2 stages by synergistic effects of low food concentration, pheromone sensation at high population densities, and high temperature. This developmental choice involves sensory regulation through the TGF- β , insulin and steroid pathways. Among natural isolates of *C. elegans*, substantial genetic variation is found in the sensitivity to entering the dauer stage in response to given amount of dauer pheromone or temperature. Exit from the dauer stage is a key, irreversible decision made at the individual level. Lab studies indicate that high food concentration and low temperature are cues favouring dauer exit, but natural cues may differ and are not necessarily symmetric with those for dauer entry. In a given substrate sample, *C. elegans* and other *Caenorhabditis* species, such as *C. briggsae*, may often be found primarily in the dauer stage, whereas other rhabditid species are actively proliferating. Understanding the cues that regulate dauer entry and exit in the wild, and how these responses evolve in different environmental contexts, are thus highly relevant, but unresolved issues of *C. elegans* ecology.

C. elegans dauer larvae can be isolated either from rotten plant material after peaks of population expansion, or from invertebrate carriers, such as isopods (Figure 1). In contrast to other nematode species, *C. elegans* does not seem to have highly specific associations: carriers include various species of slugs, snails, isopods, myriapods and perhaps

some insects and mites. Crucial experiments to decode *C. elegans* ecology will include quantitative, unbiased sampling of a wide range of invertebrates to identify carrier specificity (also in relation to worm genotype) and the study of ecological associations between nematode and carrier. Such associations may be phoretic (transport), necromenic (once the host has died, worms feed off the host corpse and associated microbes) and possibly commensal or parasitic. While dauer larvae may actively disperse at a small scale between food patches, long-range dispersal likely occurs through these carrier arthropods and gastropods, or even frugivore vertebrates (birds and mammals, including humans). *C. elegans* dauer larvae are behaviourally active and their sensory perception and behaviour are elaborate. They are able to move rapidly, or erect themselves to adopt an intriguing waving behaviour (known as nictation; Figure 1), which may facilitate finding a passing carrier. Relatively little is known about dauer mechanoreception and olfaction, which are potentially involved in seeking out carriers and sensing cues for dauer exit.

Reproduction: how many sperm?

C. elegans reproduces through self-fertile hermaphrodites and facultative males. In XX animals, the soma is female, but the germ cells initially develop as sperm during the late L4 stage, before irreversibly switching to develop into oocytes. The resulting adult hermaphrodite is self-fertile but not capable of inseminating other animals. About 0.1% of animals in the lab develop as XO males, after spontaneous non-disjunction of X chromosomes at meiosis. Exposing L4 animals to various environmental stressors, such as high temperature or ethanol, can increase the proportion of males. Males reproduce through mating with hermaphrodites.

This unusual reproductive mode appears to have evolved repeatedly in rhabditid nematodes. Most *Caenorhabditis* species reproduce through XX females and XO males — the absence of the Y chromosome is an obvious facilitator for the evolution of selfing in the lineages leading to *C. elegans*, *C. briggsae* and *C. sp. 11*. Particular ecological parameters, most prominently an ephemeral habitat and extreme population bottlenecks upon

recolonization (see below), may also have favoured the evolution of selfing, which assures reproduction of an isolated individual.

The hermaphrodite reproductive system has another peculiar feature in that the number of sperm, rather than oocytes, limits offspring production (in benign lab conditions). Most *C. elegans* isolates produce a maximum of about 200–350 sperm, the range of observed offspring production in the laboratory. The irreversible sperm-to-oocyte switch generates a trade-off between two key life history parameters: offspring number (sperm number) versus maturation time (the time point when the first oocyte can be fertilized). Genetic variation for self-brood size can be found among natural isolates of *C. elegans*, which is presumably generated by regulatory changes of germline sex switching. How ecological components correlate with such variation in reproductive capacity remains uninvestigated.

Male insemination of hermaphrodites may increase offspring production beyond 1000, and the larger and more active male sperm has precedence over hermaphrodite sperm. The complex mating behaviour of males is, however, partially degenerated in selfing *Caenorhabditis* species. For example, because of a retrotransposon insertion in the corresponding muscin structural gene, males of many wild *C. elegans* isolates are unable to synthesize the copulatory plug, a sticky gelatinous structure that partially hinders insemination by other males.

Life cycle and population structure

How much does *C. elegans* mate and outcross in the wild? The vast majority of individuals isolated from natural populations are hermaphrodites. Moreover, the frequency of heterozygous individuals is very low, indicating an estimate of the short-term outcrossing rate of approximately 1%. The long-term outcrossing rate, estimated from the level of linkage disequilibrium between loci, is 100-fold lower. This discrepancy among outcrossing rate estimates may be explained by the presence of outbreeding depression. Predominantly selfing species, such as *C. elegans*, seem to have overcome inbreeding depression in the past, and genetic incompatibilities may occur

between genetically distinct, isolated clonal populations, thus causing outbreeding depression. A particular case is the widespread incompatibility between two haplotypes on the left arm of chromosome I, functioning as a poison-antidote (*peel-1-zeel-1*) system, present in some *C. elegans* isolates but absent in others. Both allelic combinations co-occur in some locations and the maintenance of both presently requires an explanation.

The population genetic structure of *C. elegans* is a consequence of specific organismal characteristics, especially selfing, dauer persistence and migration, and use of ephemeral resources. The colonization of a new food source by one or a few genetically identical dauer larvae can result in locally clonal populations at a small spatial scale (a few cm³). At a larger spatial scale, migration appears sufficient for a substantial portion of the (known) genetic diversity of the species to be present in areas of less than a km², perhaps due to the transport of dauers by other animals. The role of colonization hazard in structuring *C. elegans* spatial distribution is unknown.

The estimated overall molecular diversity in *C. elegans* is on the order of 10⁻³ per base-pair — around 30-fold lower than in the male–female species *C. remanei*. This low overall genetic diversity in *C. elegans* is likely the result of the combined effects of selfing, strong population bottlenecks and selective sweeps, reducing the long-term effective population size. In comparison to *C. elegans*, *C. briggsae* has a slightly higher genetic diversity and shows stronger spatial structuring around the globe.

C. elegans population bottlenecks are followed by rapid population re-expansions. Bottlenecks increase the probability of fixation of deleterious mutations. Subsequent compensatory evolution to suppress such negative mutational effects has been observed in the lab through study of mutation accumulation lines where, upon population re-expansion, extragenic suppressors alleviate the effects of deleterious mutations. The metapopulation structure of *C. elegans* with frequent bottlenecks and expansions, further influenced by probable source-sink dynamics, are thus critical elements to account for when studying the evolution of its genetic and phenotypic properties.

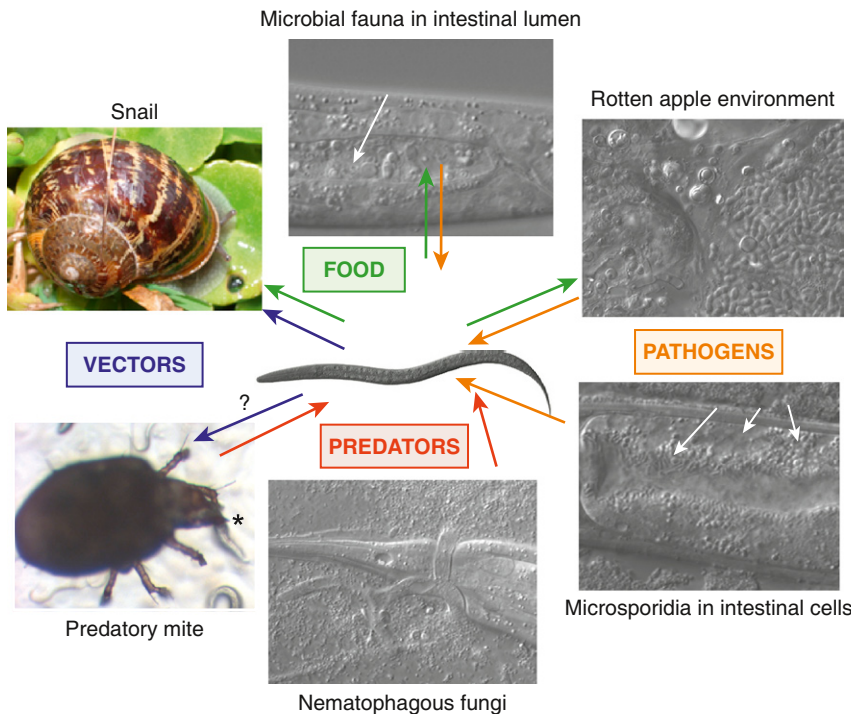


Figure 2. Biotic interactions of *C. elegans*. Schematic overview of possible interactions between *C. elegans* and its food sources, pathogens, predators and carriers. Pictures from wild sampling of *C. elegans*. **C. elegans* being slurped up in a spaghetti-like fashion by a predatory mite (*Sancassania* sp.).

Environmental interactions

C. elegans has a broad repertoire of features for sensing and coping with environmental complexity in its natural habitat. Out of the 302 neurons in the hermaphrodite, 60 ciliated neurons build the primary sensory system mediating chemical, thermal, or mechanic stimuli. Sensory processing guides various behaviours, including feeding, mating and egg-laying, as well as developmental decisions, such as dauer formation. Recent studies have characterized pheromone cocktails that drive mating behaviour and dauer formation. Information on chemosensory preferences may provide clues about relevant ecological parameters linked to foraging and habitat choice in the wild. *In silico* analysis of the *C. elegans* genome indicates that chemosensation of gustatory and olfactory cues involves close to a thousand G protein-coupled receptors, evolving at fast rates through gene duplications and pseudogenization, with signatures of positive selection. Such genes functioning in environmental interactions are therefore prime candidates for involvement in

adaptation to novel and heterogeneous environments; however, we lack any insights into the relationship between chemoreceptor diversity and their ecological significance.

The flexibility that allows *C. elegans* to endure environmental fluctuations is further reinforced by a complex molecular stress response machinery, apt to counter potentially harmful agents, including hypoxia, osmotic stress, heat, cold, toxins, acids or diverse pathogens. The intestine is a major organ involved in detoxification of chemicals as well as pathogen resistance (see below). While many stress responses are rapidly triggered, such responses can also amplify across generations. For example, animals exposed to high salt concentrations for several generations show a transgenerational increase in osmotic stress resistance, apparently due to elevated parental provisioning of glycerol and sugars to developing embryos. Worms further accommodate experience and environment in their foraging behaviour through sensory adaptation or associative learning. How established lab responses differ from natural ones, where conditions are

highly heterogeneous across space and time, is still unclear.

Microbes: the good and the bad

Microbial communities undoubtedly play a crucial part in *C. elegans* ecology and have shaped many features of its biology. Bacteria and small eukaryotes serve as food source and also encompass potential pathogens (Figure 2). Given that food quality and quantity have dramatic influences on overall life history, a rather worrisome problem is that we still have a very limited idea of the main natural food sources of *C. elegans*. In the lab, *C. elegans* readily feeds on a wide range of bacteria and yeasts. Cholesterol uptake — essential for steroid synthesis — may occur in the wild through ingestion of small eukaryotes.

How *C. elegans* navigates through diverse microbial patches, and to what extent it can discriminate between alternative food sources, is difficult to evaluate, but its pharyngeal pumping does not appear to be very selective. *C. elegans* N2 is able to disrupt *E. coli* OP50 cells in its pharyngeal grinder, and its fast defecation cycle only allows for a short food residence time in the intestine. Live OP50 cells may survive grinding, enter and proliferate in the intestinal lumen of old N2 animals. Such a phenotype is considered abnormal by *C. elegans* lab biologists, yet is the norm in freshly isolated wild animals, which often show intestinal colonization by live bacteria and possibly fungi, leading to ‘constipation’ phenotypes (Figure 2, top). Characterizing the natural interactions between *C. elegans* and its microbial community will clearly be important in constructing the natural history of this organism.

Animals freshly isolated from nature frequently show other signs of infections, including bacterial films on the cuticle, fungal invasion, or intracellular microsporidial infections (Figure 2). Molecular and cellular responses of *C. elegans* to pathogen infection and pathogen-released toxins have been studied primarily with strains of medically relevant human pathogens. Several signalling pathways, including the TGF- β , insulin, p38 MAP kinase or ERK pathways, have been co-opted in various defence mechanisms, including particularly the production of antimicrobial peptides and proteins, morphological modification,

but also avoidance behaviour. The presence of an RNA silencing system (RNA interference) suggests that *C. elegans* also encounters viral pathogens in the wild. Although general response mechanisms may be activated upon pathogen infection, the *C. elegans* immune response can also be pathogen-specific. A clear future aim is to study microbial pathogens co-occurring with particular *C. elegans* genotypes or populations. Such studies may not only shed light on the co-evolution of host-pathogen interactions, but also help to understand to what extent immune responses are specific.

Community ecology

C. elegans shares its natural environment with a diverse animal community, in particular arthropods, molluscs and other nematodes, some of which also feed on microbes proliferating upon plant decomposition. Many are potential dispersal vectors as well as predators of *C. elegans*. Frequently co-occurring predators include fungi, which, depending on the species, invade the nematode through spores attaching to the cuticle or the intestine, or use trapping devices that immobilize the animal and perforate it (Figure 2). Nematophagous mites, springtails and nematodes are other potential predators often encountered in the *C. elegans* habitat.

The broader nematode community associated with *C. elegans* comprises microbivorous nematodes, often including other rhabditid nematodes, such as *Oscheius* sp., diplogastrids or panagrolaims, which likely compete with *C. elegans* for microbial food resources. Also found in rotting fruits are fungal-eating and predatory nematodes. Sometimes, *C. elegans* co-occurs with other *Caenorhabditis* species in the same location or even in the same few square millimetres of substrate. Given the rapid proliferation upon food availability, intraspecific competition for food is probably substantial.

The unnatural history of *C. elegans* research

In the 1960s, Sydney Brenner chose *C. elegans* as an easily cultivable, simple metazoan amenable for genetic dissection of development, neurobiology and behaviour. The originally used strain, N2, was isolated from mushroom farm compost in the 1950s in Bristol, UK. Nearly all of

C. elegans research has been using the N2 strain as a reference wild type, from which thousands of mutants have been derived and characterized. As for all genetic model organisms, *C. elegans* biology thus captures a very limited range of genetic variation, here essentially a single genotype. To what extent certain biological observations documented for N2 can be extrapolated to other *C. elegans* genotypes (and even more so to other species) is questionable. Recently, it has come to light that N2 indeed differs from most of its natural conspecifics for many phenotypes and that the underlying N2 alleles may have arisen in the laboratory. For example, genes involved in oxygen sensation and behaviour show a unique combination of alleles in N2 compared to its wild counterparts. These findings are not surprising, given that the N2 isolate has been undergoing adaptation to artificial lab environments and numerous bottlenecks for years before freezing.

Conclusions and perspectives

Recent research has started to examine *C. elegans* outside its cushy Petri dish, providing a basis for a revised natural history. First and foremost, a modern natural history of *C. elegans* needs to evaluate the environmental and genetic context dependence of organismal *variational* properties of genotype, environment and phenotypes and their interrelationships. A very relevant and now feasible approach to shed light on evolutionarily and ecologically relevant phenotypes is the fine-scale mapping of genetic variation underlying natural phenotypic variation by means of recombinant inbred lines or association mapping.

The most difficult challenge will be to elucidate the so-far elusive ecology of *C. elegans* through 'field studies' involving extensive and repeated monitoring of natural populations across ecologically distinct and well-defined habitats. Population samples can be easily analyzed within a few hours after placing a substrate isolate on a Petri dish and observing nematodes under a dissecting microscope. Yet, there will remain obvious limitations to meaningful observations on a one millimetre long animal in spatially and temporally highly heterogeneous environments. To test specific

ecological and evolutionary hypotheses in controlled settings, complementary approaches may include the study of individuals in lab microcosms, or experimental evolution assays to track the evolutionary process in real time, which have recently been applied for the first time in *C. elegans*. Overall, the progress to date from the integration of mechanistic and evolutionary ecological research on *C. elegans* illustrates that a more natural model organism is also a more powerful one.

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