The Mind of a Worm

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Prologue

Ihr habt den Weg vom Wurm zum Mensch gemacht
aber vieles ist in Euch noch Wurm.

(You have made your way from worm to man,
and much within you is still worm.)

**Friedrich Nietzsche, Also sprach Zarathustra,
Vorrede 3**

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(about 40%...)

Nematodes = Roundworms

- Length varying from 50μm to 1m
  - C. elegans: 1mm length, 30μm diameter
  - Ascaris l.: 30cm length, 0.5cm diameter
  - Ascaris equus: 1m length
- Last common ancestors with humans: 0.6 - 1.2 billion years ago

Nematodes are extremely successful

- Known nematode species: 20,000
- Estimated total species: 40,000 - 10 million!
- Numerically extremely abundant: millions of individuals per square meter
- Four out of five animals on this planet are nematodes!

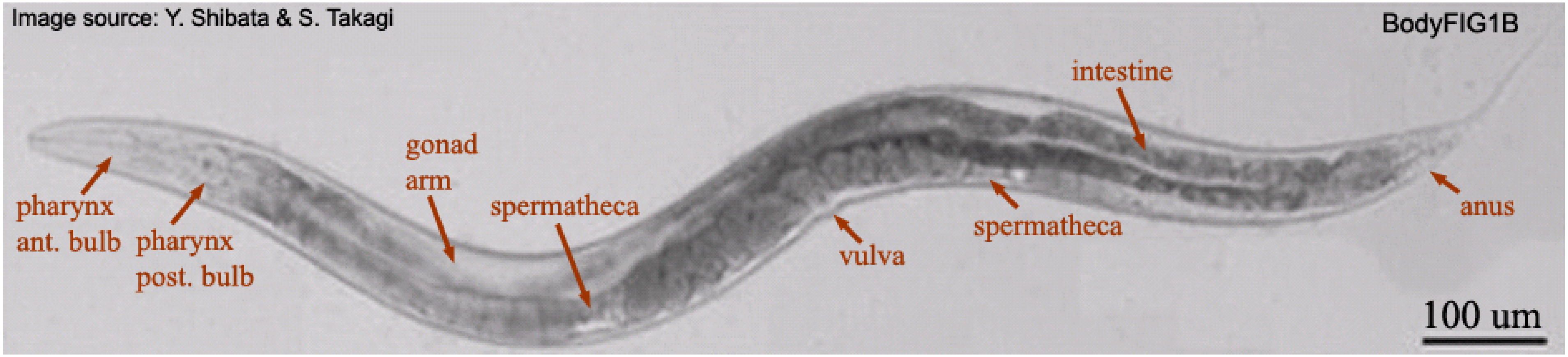
Nematodes are commercially important

- 25% of all humans are infected by **50%** oscopic parasitic nematodes: *Ascaris lumbricoides* (1 billion people), hookworm (600 million), trichinella, ...
- Essentially every animal and every plant is infected (domestic and wild) '***the ghostlike appearance...***'
- Plant parasites: root nematode *Meloidogyne s*. alone: 100BS loss/year

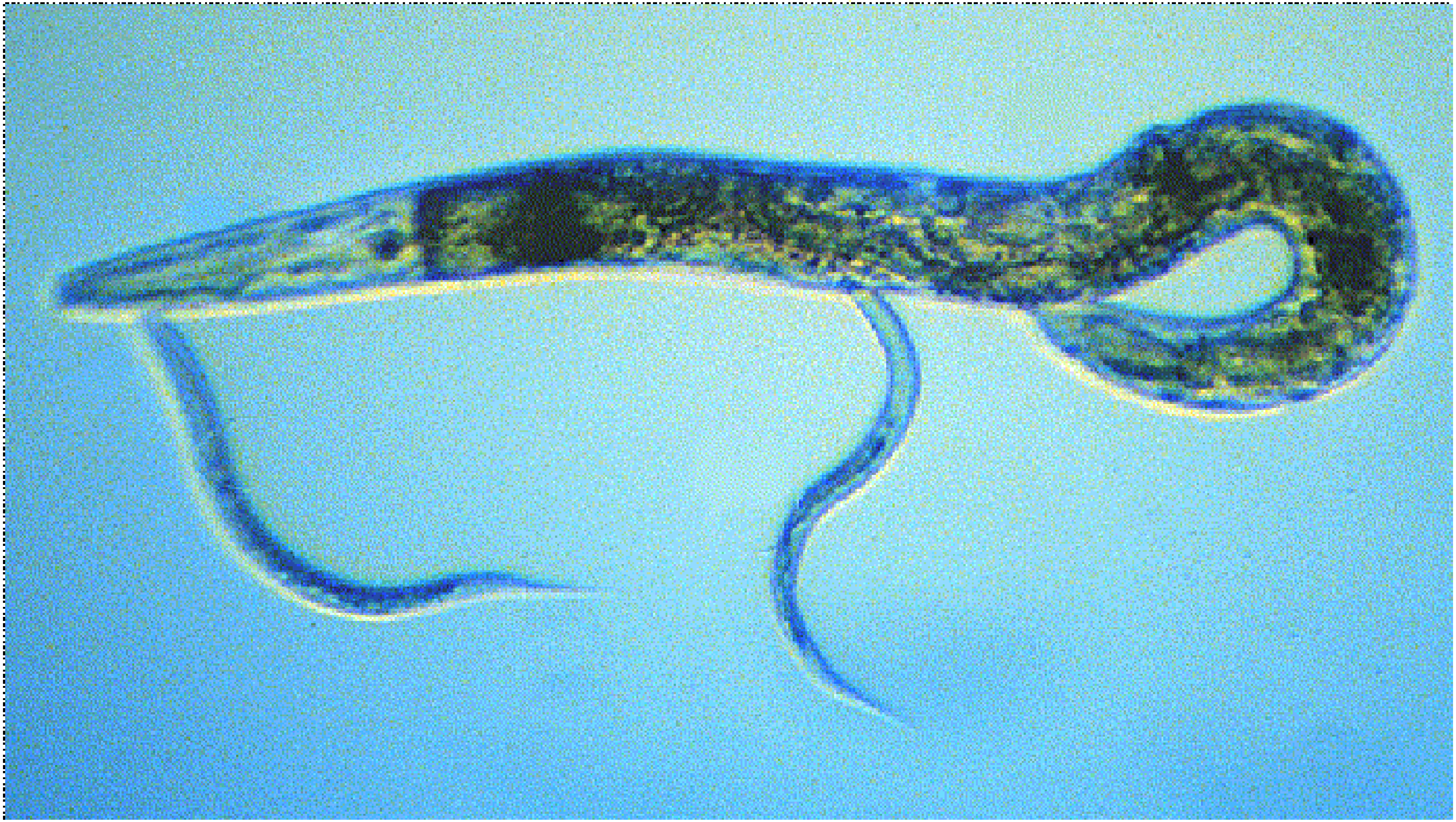
OTOH: Very successful for biological pest control!

Also, see today's NYT: hookworm as allergy cure???

C. elegans:
A regular guy



Caenorhabditis elegans



Aging worm, and some dauers

C. elegans: A real animal!

- Hatches from egg
- Moves around, searches comfy environment, searches for food, eats, mates (*), lays eggs, ages, dies...
- Reacts to (at least) chemical, thermal and mechanical stimuli
- Learns!

Reacts to predation

C. elegans as a model organism

- Complete development: Sulston 1983
- Complete wiring diagram: White et al, 1985
- Complete Genome: Sulston, Waterston et al, 1999

All cells are transparent

Proposed as a model organism by
Sydney Brenner, MCR Cambridge (1960s?)

The Compleat Development

- Complete Lineage from fertilized egg to adult animal (**956** cells)
- Few unifying principles
- Allows laser ablation

Genome for nervous system: Most channels similar to vertebrates

- 90 neurotransmitter gated channels: glu (AMPA AND NMDA), GABA, ACh, G-proteins, second messengers,...
- 50 peptide receptor channels
- 80 K+ channels, Ca++
- BUT: No Na+ (predicted 1988, Niebur and Erdos), no rhodopsin (vision)

The Compleat Nervous System Anatomy

- 302 neurons (of 956 cells total)
- Connectivity mapped at EM level: 5000 chem. synapses, 2000 gap j.s
- Largely conserved betw. individuals
- Some functional anatomy: laser ablation, neurotransmitters, ...
- Compare with *Ascaris l.*: approx. 250 neurons (50,000 cells!)

The (not-quite Compleat) Nervous System

- Not known:
  - 'Strengths' of synapses
  - 'Signs' of synapses (excitatory/inhibitory)
  - synaptic kinetics
  - membrane properties, passive and active
  - etc...
- Some hints in all cases, e.g. Neurotransmitters and data from other nematodes ('conservativeness' of nematode phylum)

Computational Neuroscience Approach

- Detailed model of whole animal may not be impossible but would certainly benefit from understanding of parts
- Two candidates, with clear interface to rest of nervous system:
  - esophagal pumping control (approx. 15 neurons)
  - somatic motor control (approx. 60 neurons)
- Selected: motor control

Undulatory locomotion

- Undulatory (snake-like) propulsion is the most obvious behavior of C. elegans
- We want to understand how the nervous and motor system of C. elegans can generate the force patterns necessary for propulsion

Biomechanics of crawling

- First need to understand the forces involved
- Known in snakes (Gray, 1964)
- More complicated in C. elegans because of the lack of a rigid skeleton: 'hydrostatic skeleton'
- Worm moves along groove created by surface tension

Forces involved in crawling

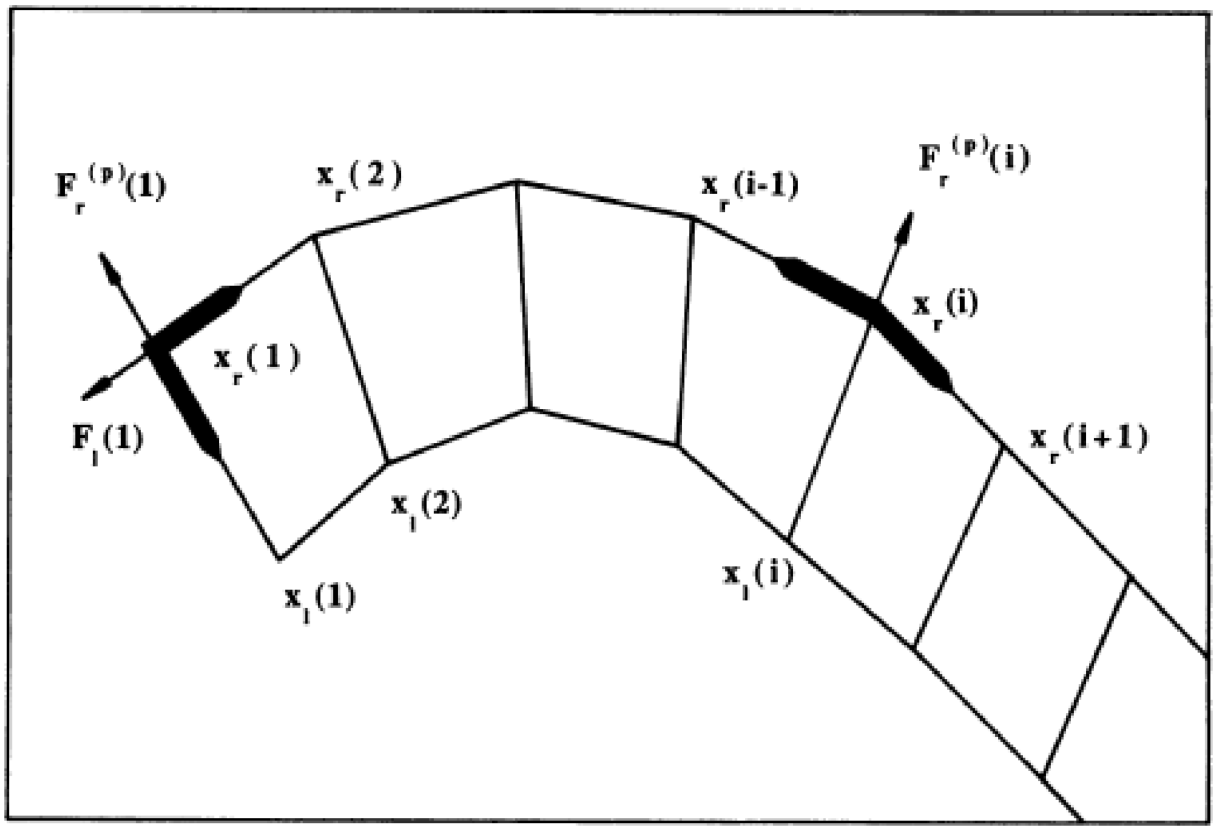


FIGURE 2 The interior pressure exerts forces on the body wall which are directed outwards. The figure shows a part of a vermiform body, whose body wall and the limits between segments are shown by thin lines. The pressure forces acting on two points, $x_r(5)$ and $x_r(1)$, are shown. The former is an interior point on which the force $F_r^{(p)}(5)$ acts, cf Eqs. 12 and 13. The latter is a boundary point, on which the forces $F_r^{(p)}(1)$ and $F_l(1)$ act, cf Eqs. 14, 15, and 18. The parts of the body wall on which these pressure forces act are represented in the figure by thick lines.

Niebur & Erdos, 1991

Summary of Forces

- Elastic forces of cuticle
  (Much higher contralateral than ipsilateral)
- Contractile muscle forces
- Friction in groove and orthogonal to it
- Internal pressure, keeps volume constant
- Trajectory control (only at end segments)

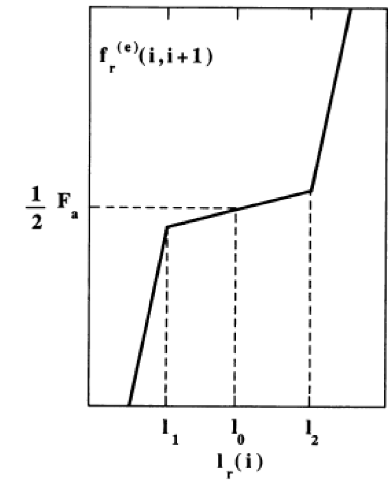


FIGURE 3 Elastic force assumed to act between two ipsilateral points, i.e., end points on the same side of a given segment, as a function of the distance between them. $f_r^{(e)}(i, i+1)$, defined in Eq. 25, is plotted as a function of $l_r(i)$, defined in Eq. 24. The ordinate is proportional to the force acting along the two endpoints of the segment; the abscissa is the distance between these points. The slope has the value k_2 for $l(i) < l_1$, k_1 for $l_1 < l(i) < l_2$, and k_3 for $l(i) > l_2$. This ensures that the force is small when the cuticle is only slightly stretched or compressed, but is large when the cuticle is overstretched or overcompressed.

Equilibrium without muscle activity

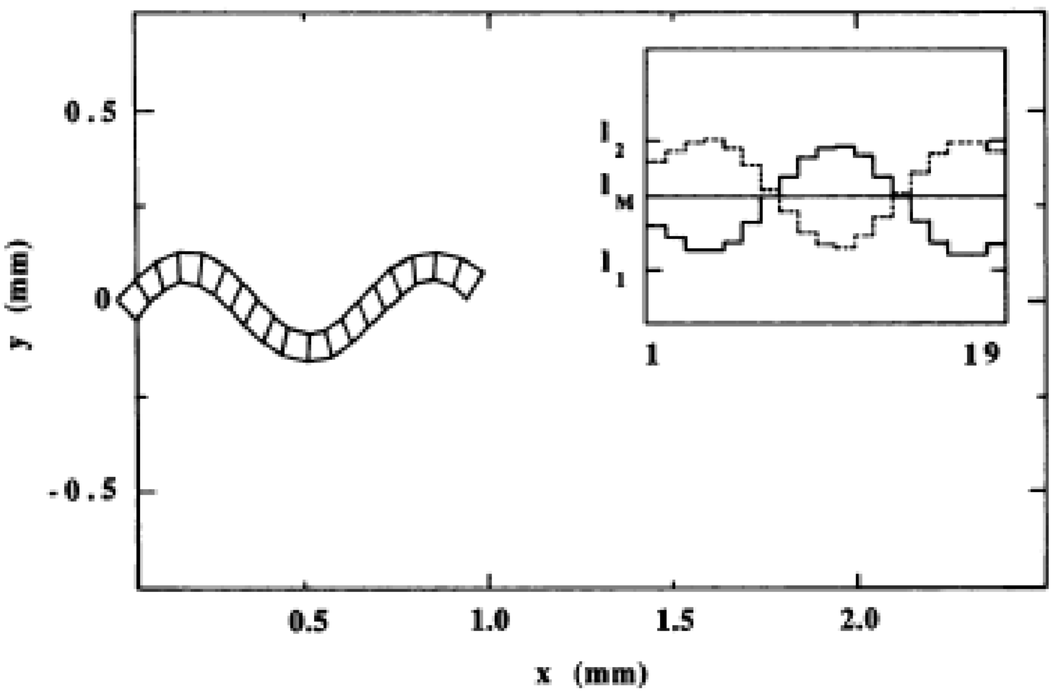


FIGURE 5 Computer simulation with vanishing muscle forces. The figure shows the shape of the worm after $t = 2$s, the shape at $t = 0$ being described in Fig. 1. The resting state has been attained and the worm has not moved forward. Its position is the same as at $t = 0$ (Fig. 1) (cf Section titled Initialization and numerical solution procedure). For the meaning of the inset, see the caption of Fig. 1.

Result:
Motor pattern suitable for locomotion

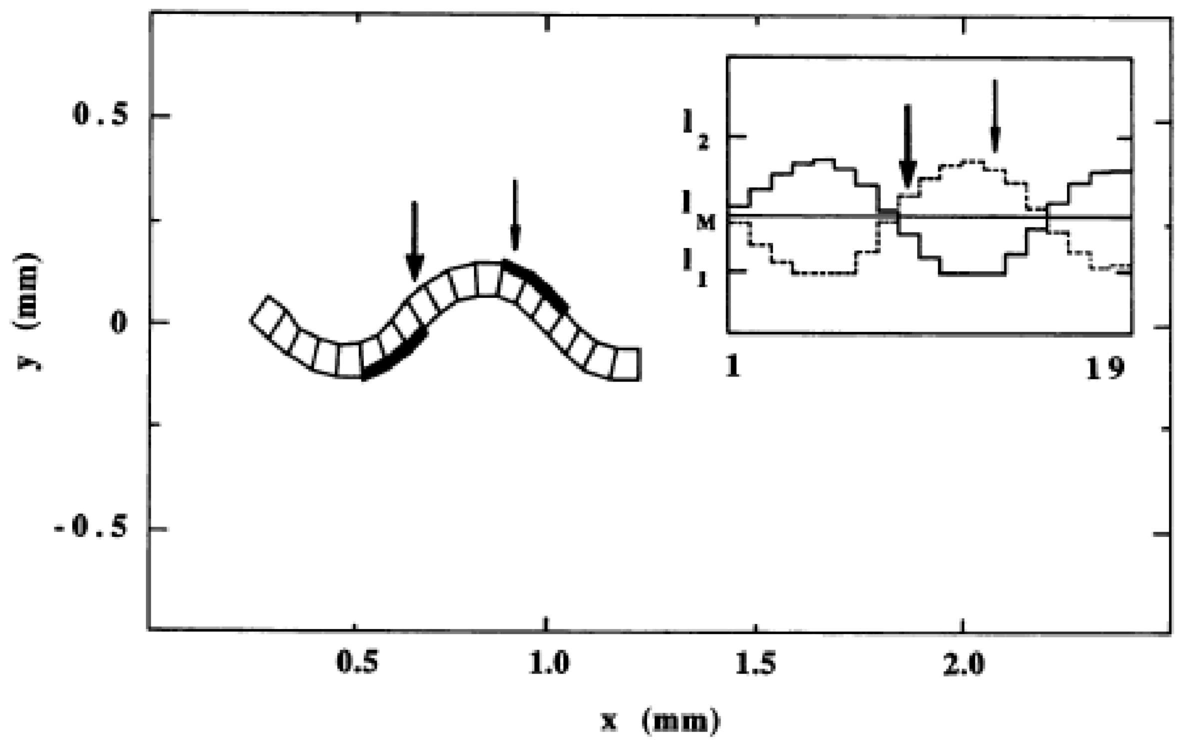


FIGURE 6 Muscle control by stretch receptors. To illustrate the stretch receptor control, one segment (the ninth) is marked by a thick arrow, both in the figure and in the inset. It is seen that the length of this segment on the right side of the body is greater than l_M (*dotted line in inset*), and it is smaller than l_M on the left side of the body (*full line in inset*). Following Eq. 54 and using $\Delta = 1$, the muscles of the right side of segment 13 are excited, but not those of the left side. In the figure, excited muscles are represented by thick lines. Segment 13 is marked by a thin arrow, both in the figure and in the inset. Note that the stretch receptor is located behind the muscle it controls because the worm moves in $(+x)$ direction.

Neural control of propulsion: To explain (partial list)

- C. elegans can move forward and backward
- Speed is variable (apparently continuously), from zero (stop!) to a max of about 1mm/s
- The animal can remain at rest for (apparently) arbitrary periods of time
- It resumes moving 'voluntarily' forwards or backwards
- Wavelength varies little during crawling (but not swimming!), ca. 1 body length
- Not limited to homogeneous environment; the natural environment of C. elegans is interstitial spaces in soil!

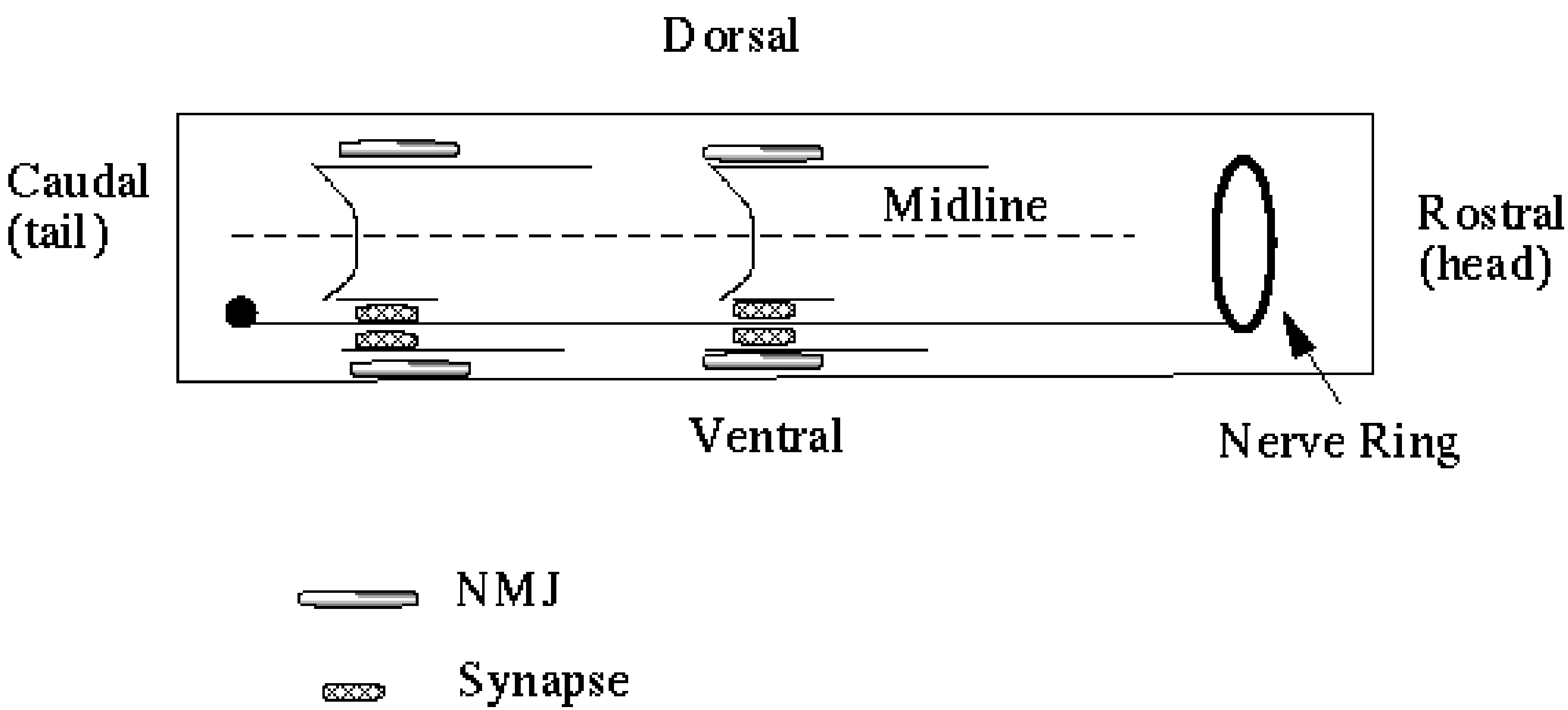
Neural control of propulsion: What is known

From laser ablation, mutants etc:

- Undulatory locomotion is controlled by 5 sequential excitatory classes (ca. 10 ea.) of motor neurons (all with cell bodies in the ventral cord):
  - VB, DB for forward movement
  - VA, DA and AS for backward movement
- These are postsynaptic to 4 classes (2 each) of interneurons that run the entire ventral cord:
  - AVB, PVC for forward movement
  - AVA, AVD for backward movement

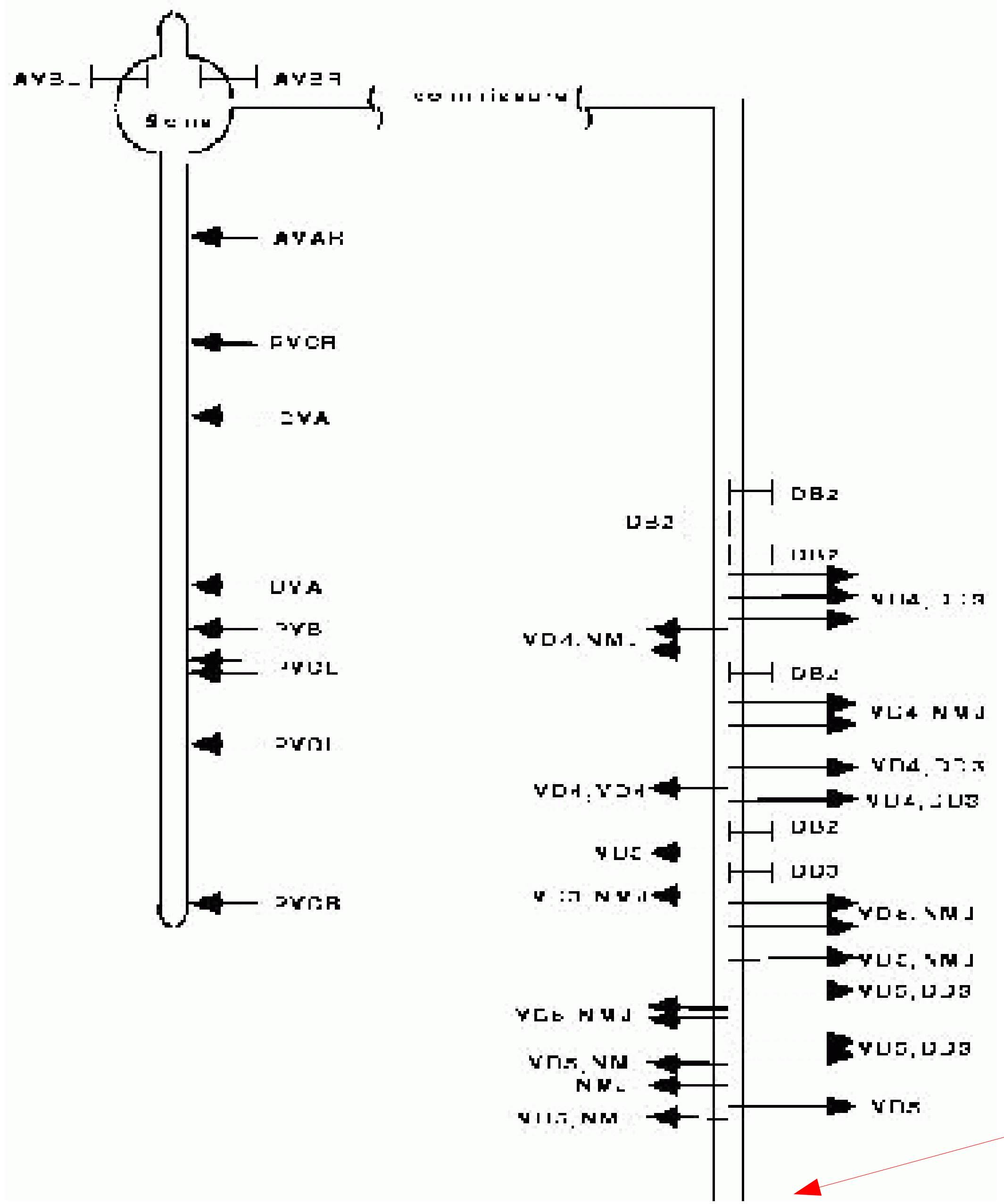
Neural Motor Control: "Gross" Anatomy

Circuit for backward motion:



Circuit for forward motion: Mirror image

Example: Motorneuron DB3



Continues with no or few synapses

A hypothesis

- R. Russell (1970s): The non-differentiated distal parts of somatic motor neurons could be stretch receptors
- A 'paradox' (for some still in 2007): why are they oriented *against* the direction of motion controlled by this neuron?

Our basic hypothesis I

- Global control of direction and speed by interneurons
- Local control by stretch receptors (excitatory when stretched --> no paradox!)
- One oscillator each in head (nerve ring) and tail (caudal ganglia) for trajectory control
- No Na^+-type action potentials

Our basic hypothesis II: *Look Ma, no oscillators!*

- No intrinsic oscillators (CPGs) in either motor neurons nor command neurons:
  - Need to vary speed, all the way to zero
  - Need to maintain memory of shape for indefinite time
  - Reverse motion at any time (e.g. due to touch)
  - In a natural environment, CPGs may be too stereotypical

Our basic hypothesis III: Proprioception to the rescue!

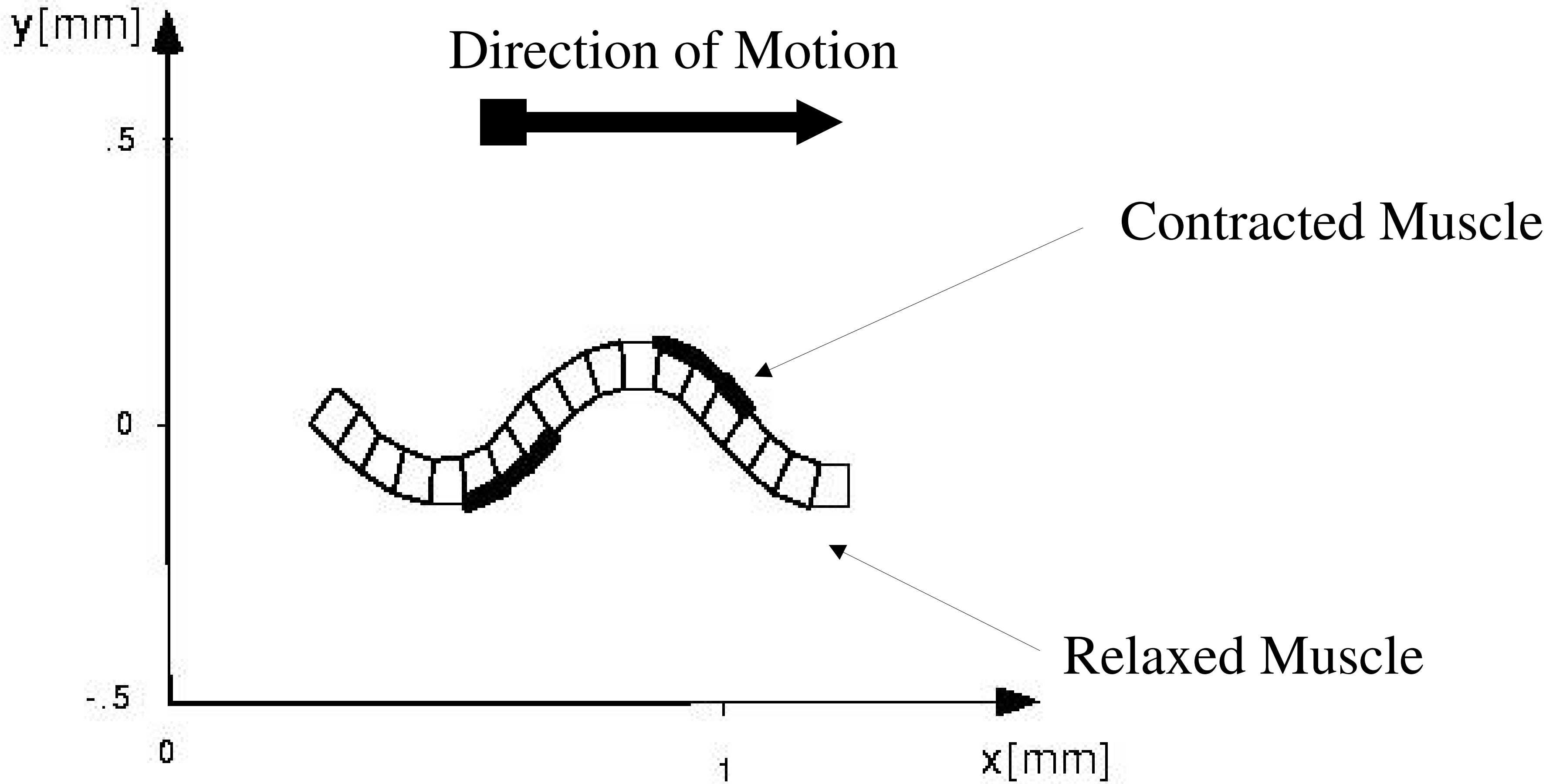
- Use information provided by the body shape itself
- 'Shape is its own representation' (a la R. Brooks)
- Phase relationships between neighboring segments are 'automatically' correct (how would the phase information of coupled oscillators be set, and maintained at all speeds including zero, during reversals etc?)

Neural model

- Use anatomical wiring diagram (White et al, 1986), combined with functional data from C. elegans (and Ascaris l. if necessary)
- Passive membrane
- Conductance model for chemical and electrical synapses

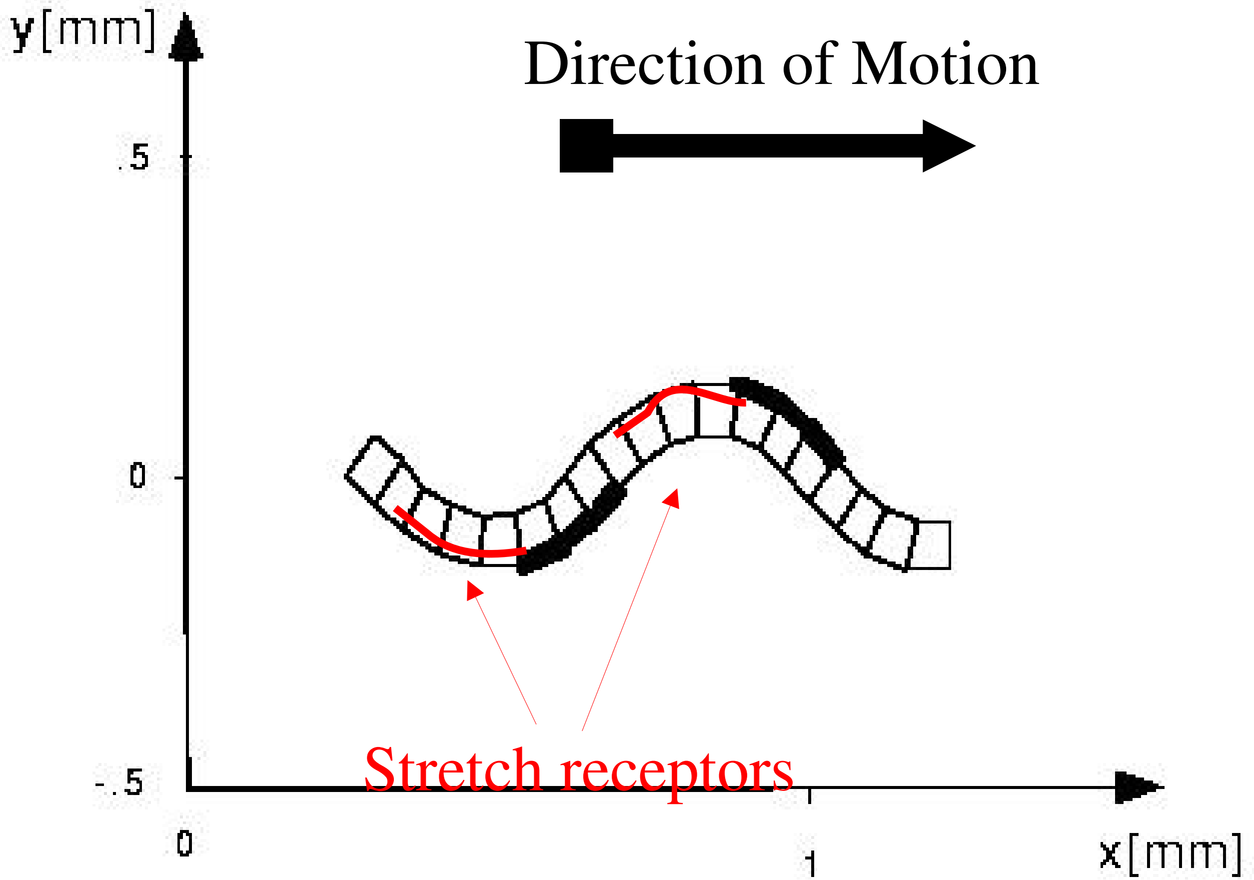
Recall: Motor pattern needed

Biomechanics: Muscle pattern to propel body
(no backbone, uses hydrostatic skeleton!)



Neural Motor Control: Modelling

- Hypothesis: Motor neurons are controlled *globally* by interneurons and *locally* by stretch receptors



Eppur si muove

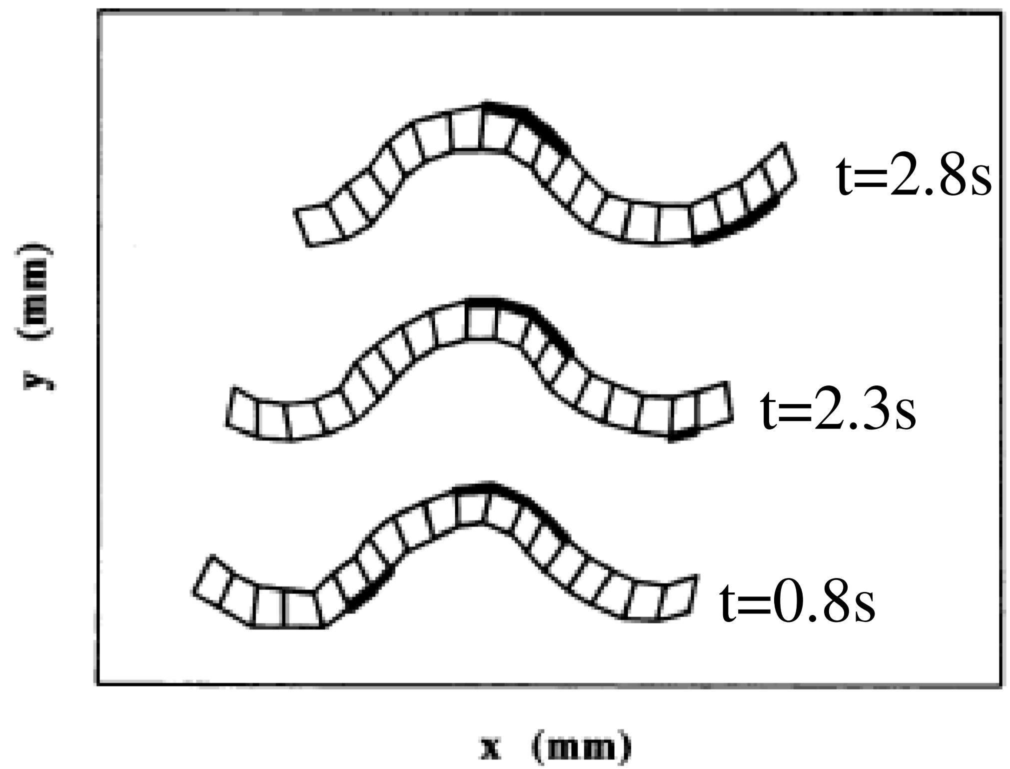
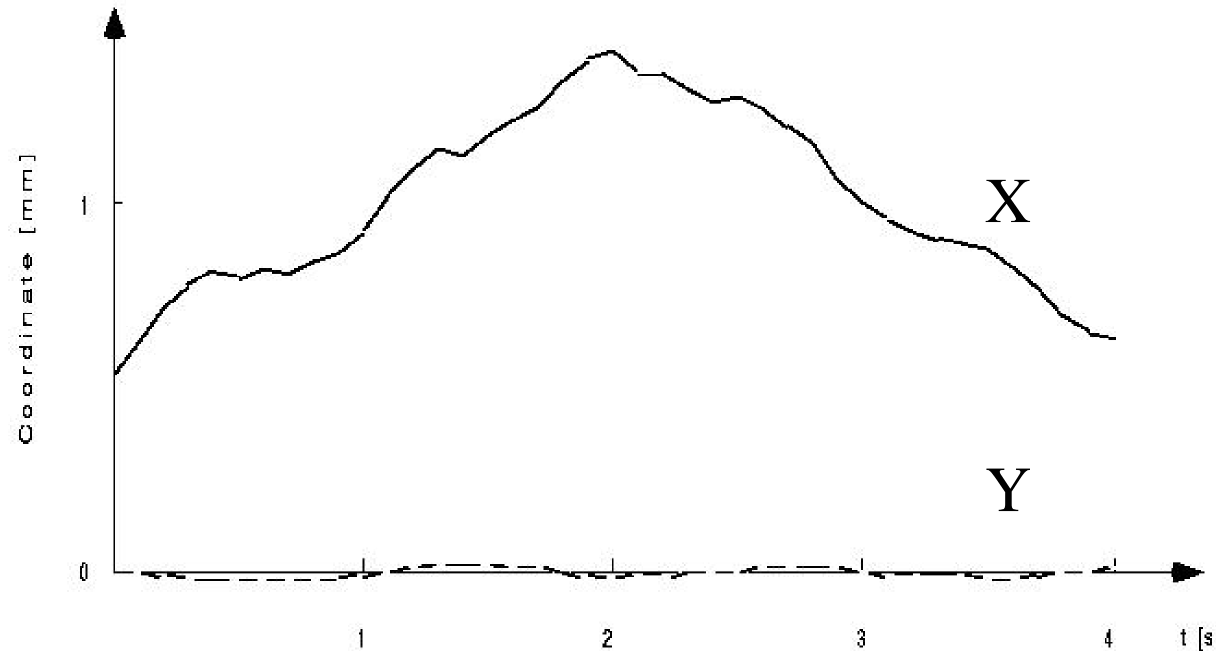


FIGURE 7 Three successive phases of the motion of the simulated worm as it is shown on the computer screen. The position of the worm is shown at $t = 0.8$ s (*bottom*), $t = 2.3$ s (*middle*), and $t = 2.8$ s (*top*). To avoid partial superposition, the lower and upper drawings have been displaced from the middle one in the y direction. The worm moves in the $(+x)$ direction.

CM velocity, with reversal

- Forward/Backward
- Controlled variable speed
- Stop
- Restart
- Inhomogeneous environment



Coordinates of center of gravity

Predictions

- *C. elegans* may not use action potentials (*Ascaris* must!)
- Local motor control by body shape (stretch receptors)
- No CPG!
- Quantitative explanation of motion patterns:
  - *Ascaris* swimming at 6cm/s
  - Continuous forward/backward crawling of *C. elegans*

Future work

- Integration with other circuits
  - Touch, tap, chemo, thermo, ...
  - Explicit inclusion inclusion of inhibitory neurons (DD,VD)
  - Simultaneous simulation of forward and backward circuits
  - Other motor patterns: Omega turn; copulation?
- Swimming
  - Complicated mechanics: Reynold's number ~1!

Summary

- We know more about C. elegans than about any other animal (at least, relative to what is there to know...)
- Surprisingly few insights outside molecular biology
- Computational principles may be very close to the physical substrate (details DO matter!)

Epilogue

- Es spricht nicht gegen die Reife eines Geistes dass er ein paar Wuermer hat
  (It says nothing against the ripeness of a spirit if it has a few worms)

  Nietzsche, "Human, All Too Human"