Mechanisms for macroscopic chirality in organisms

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Preface: why this topic for Landau?

Biological physics ... necessarily "pathological"?

In my other work – frustrated spins, toy fermionson lattices, quasicrystals – I try to explicitly connect microscopic Hamiltonian to coarse-grained parameters, opposite to Landau's spirit.

But this topic deduces **physical** consequences from a priori, **fundamental symmetry principles.**

Outline

Need **physical** mechanism to get chirality from micro to macro scale.

1. Introduction:
   Examples
   Assumptions/facts
   Classifying mechanism: cell/collective level)

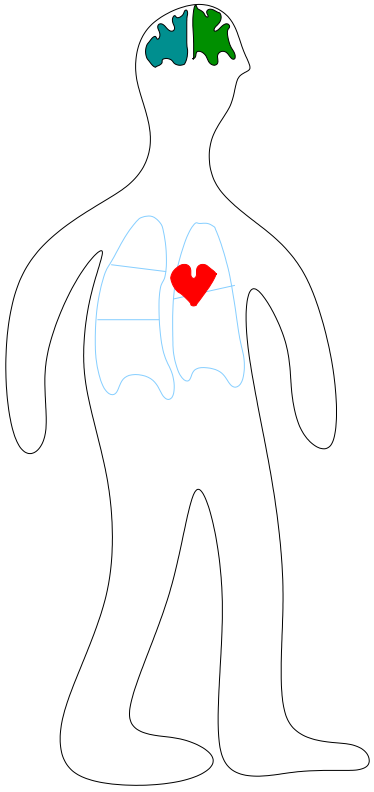
2. Review of vertebrate case: cilia-driven flow
3. LR asymmetric transport of chemicals?
4. Twist in cell division
5. Conclusions

1. INTRODUCTION

1.1 Examples

a) Vertebrates: heart, lungs, etc.
(fraction reversed: $\sim 10^{-4}$)
Model species: chick, Xenopus frog,
zebrafish, mouse

b) Human brain: left-hemisphere dominant /
= "right-handed"
(fraction reversed: $\sim 10^{-1}$)



c) *C. elegans* (nematode "worm") and flies: twisting of gut

(sorry, no image)

d) molluscs: shell twists right-handed
Image: mating is awkward for R snail and (rare) L snail

No universal answer expected! (This is biology!).
Different mechanisms (likely) apply to different cases.

1.2 Question and starting assumptions/fact:

An embryo develops 2 axes: **head/tail**=x, and **front/back**=z,
by **spont. symmetry breaking**.
How to ensure 3rd axis (y) fulfills "right-hand rule" (**y= z**× **x**)?
Symmetry ⇒ need all 3: **x** and **z** axes, also (fibers') **chirality**)

Take as given:

1. From genetic control + chirality of molecules
   (**not** shape of mother's womb/egg)
2. L/R, too, is **spontaneous** symmetry breaking (usually);
   systematic bias amplified from **small** symm. breaking field.
   ⇒ a small L/R ($O(10^{-2}?)$ effect will suffice
3. Seek the **earliest** L/R asymmetry ⇒ whatever makes the
   asymmetry, preceded it and was (**functionally**) symmetrical

1.3 Claim: it's not a "biological" mechanism

Usual "biological" mechanism:

transport/diffusion of signaling molecules + reactions

$\otimes$ diffusion doesn't distinguish handedness

Requires a **physical** mechanism:

semi-macroscopic elements: long fibers

(yes! in each cell's cytoskeleton)

forces and torques (molecular motors that run on the fibers)

1.4 Review of the cytoskeleton

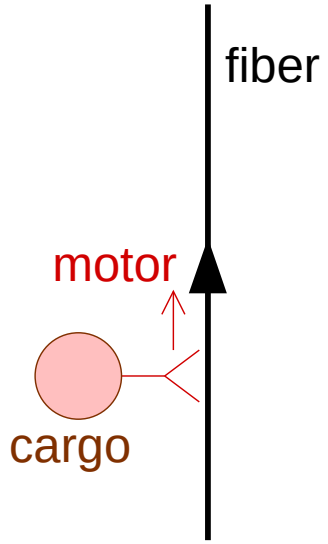
Cytoskeleton: Framework in each cell (of higher organisms), built from long, stiff, **directed, helical** macro-molecules ("fibers")

a) microtubules → motors dynein or kinesin

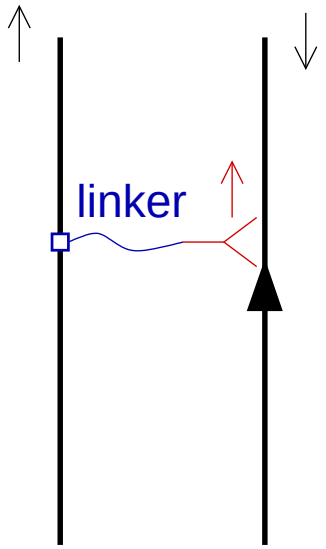
b) actin → motor myosin

Each motor (literally) walks in a fixed sense (dissipating energy) carrying cargoes
(chemicals in vesicles = little membrane bags)

Rarely (by thermal fluctuation)
motor falls off its fiber;
→ diffuses till it reattaches to some fiber



In place of a cargo, motor can be attached to another fiber, so one moves relative to other. (e.g. muscles).



There are many flavors within each kind of motor (used for specialized purposes)

1.5 Classifying mechanisms

(1) Two levels in any mechanism

a) intracellular

b) collective (intercellular): plan of the body's tissues

(2) Two styles in development (for different groups of animal):

a) **early: (many) invertebrates**
as cells first divide, each gets a determining label
$\Rightarrow$ primarily cell-level mechanism suffices for L/R

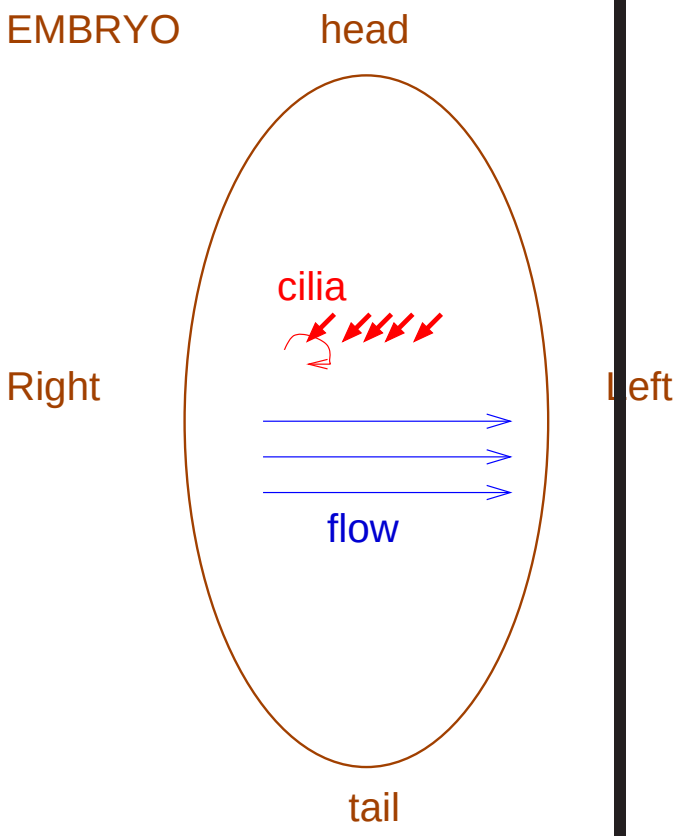
b) **late: vertebrates**
cells' fate isn't fixed early but pattern formation later
$\Rightarrow$ need an inter-cellular mechanism

2. NODAL FLOW MECHANISM

Review: a **late-stage** mechanism in **vertebrates**

2.1 Cell-level story

Special cells on **front** of node (a key place on the embryo) have cilia:
(moving tails that stick out from surface)
tilted towards embryo's **tail** end.
Cilia move **circularly** (CW looking down).
Check: **all 3 ingredients** were mentioned.



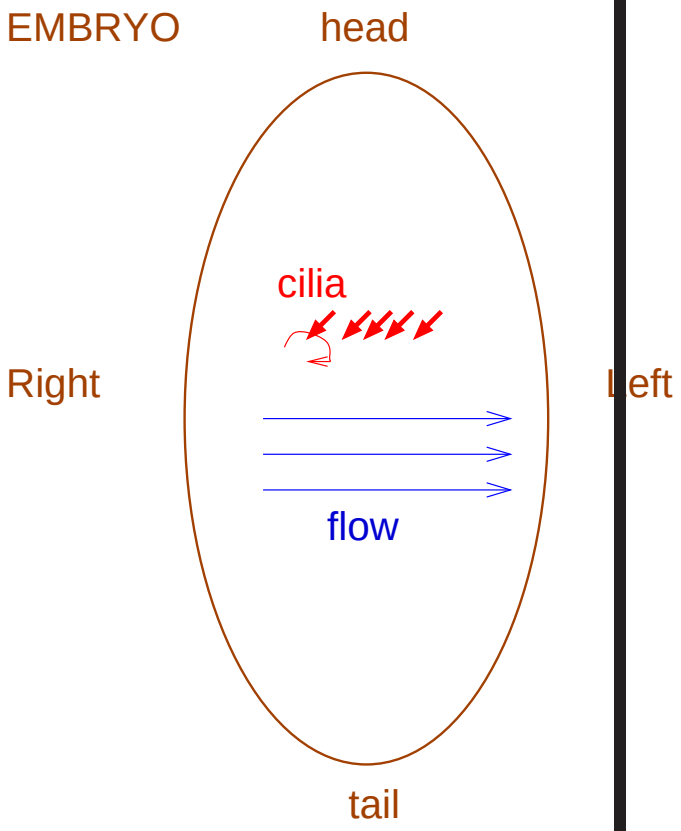
Why node-cilia move circularly? Plausible from structure:

cilium has 9 pairs of microtubules that run its length
each pair is linked by dynein molecules oriented clockwise
(assembles from a microscopic template in the cell membrane)

The interesting physics would be:
how this structure leads to circularly polarized motion
(usual cilia move back and forth, not in circles)
Would need elastic theory + fluid dynamics.

2.2 Collective-level story

Sufficient to break symmetry:
fluid flow gets driven **R to L**
if a signaling chemical (still unidentified)
is released, flow carries it to L side.
Exp't: **force flow** the wrong way
$\Rightarrow$ **reversed** embryos come out (in **mice**).



On the other hand, **earlier** L/R asymmetries are seen (in **frogs**)
(Maybe early symmetry breaking has no functional importance?)

3. ASYMMETRIC TRANSPORT?

A "biological" mechanism uses **transport** of signaling molecules.
Can we have a **late**-stage, transport-based mechanism?

- Use: fiber molecules with motors (active transport works thus))
- Consider for simplicity a planar geometry (front and back sides) (indeed embryos are flattish at an intermediate stage)

Aim for: a "Hall effect" analog:
head-tail transport direction gets rotated by small angle.

Cell level is the nontrivial level for this mechanism.

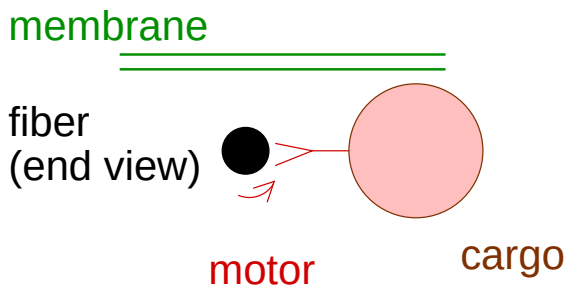
3.1 Single cell level

Assume (as common) array of fibers **just under** cell's membrane.
(There's the **front/back asymmetry**)

Assume fibers oriented exactly along $\pm z$.
(**not** (yet) the head/tail asymm.)

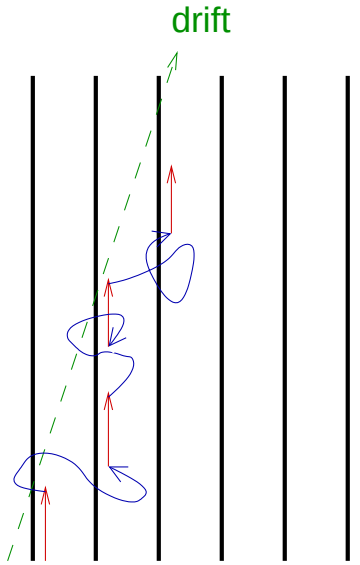
Active transport depending on motor motion
$\Rightarrow$ L/R **must** be due to the **generic helical component**
of any motor's motion down any (microscopically) helical fiber.
(There's the **chirality**.)

Say motor spirals **counter-clockwise**; $\Rightarrow$
pulls cargo till jammed against membrane.
i.e. travels on **right** side of road



If cargo reattaches to a neighboring fiber, it's more likely to attach to the fiber on left side. Result: sideways drift: transport current at angle θ from z, where

$$\theta \sim r_{\text{cargo}}/\ell \qquad (1)$$



Here $\ell \sim 1\ \mu m$ is typical distance that motor goes before falling off, and $r_{\text{cargo}} \sim 25\ nm$ is an effective distance of the cargo from the fiber axis (defined so r_{cargo}/d is probability of reattaching to the next fiber at a separation d)

So $\theta \sim 2.5 \times 10^{-3}$? **Might** suffice as a biasing field...

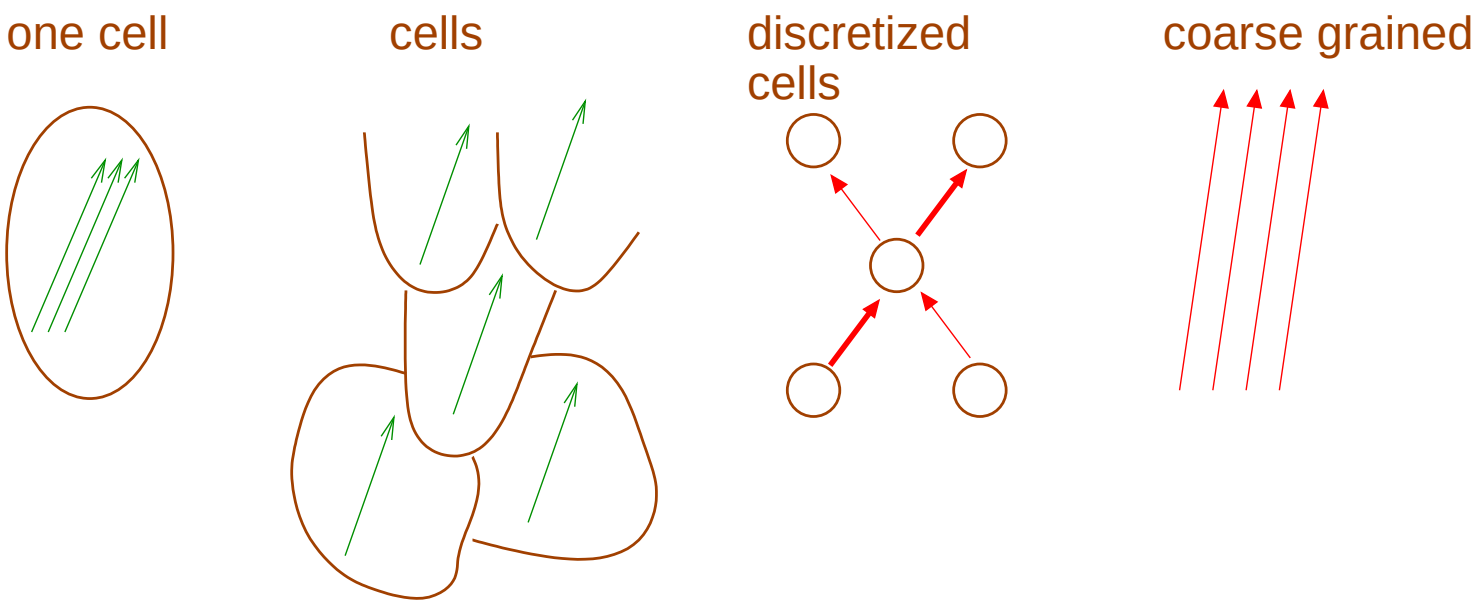
3.2 Collective level

Now this array is only on the **front** side of the **front** layer of cells
(Check: using front/back asymm. on organism level.)

Signal chemical is released from (say) tail end.
(**Now** using **head/tail** asymmetry.)

Then we argued signaling chemical has a **sideways bias**
relative to the array in each cell

$\Rightarrow$ **macroscopic** transport has a similar bias



Summary: it's not easy to generate late-stage asymmetry with a transport mechanism!

4. CELL DIVISION

Early-stage, **cell-level** mechanism.

4.1 Experimental facts:

For **Molluscs** (snails).

1) 1st 4 cells in a square

2nd 4 cells form on top with twist

(normally in the sense shown).

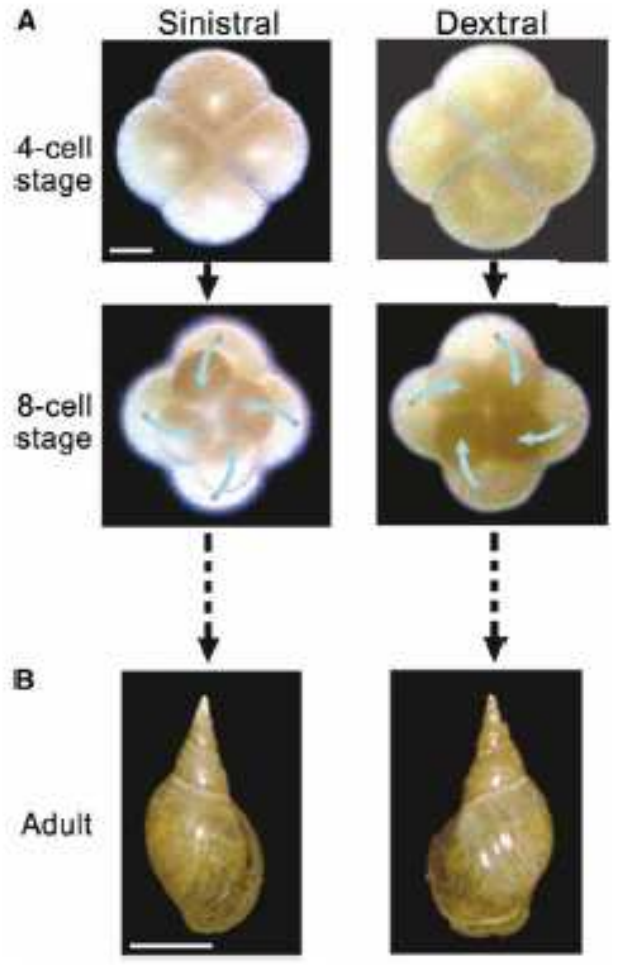
2) Twist depends on **actin**

but **not** on microtubules,

of the 2 kinds of fiber.

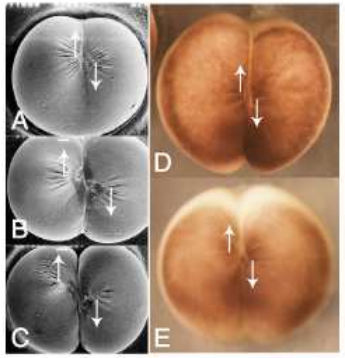
(?! cell division is driven by

an array of **microtubules**)

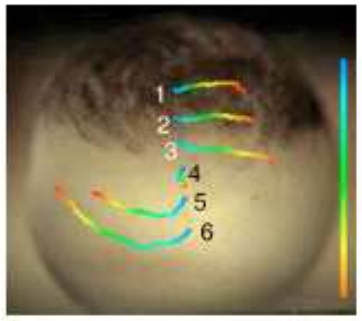


3) in frog eggs, same twist is observed and is due to actin;
the parallel actin molecules shear past each other
always in a clockwise sense; the motor mysin I-D is responsible

Actin forms a band pointing around the cell, in the plane where the split will occur;



Time lapse shows fluorescently labeled points along several fibers: uniform shear.



4.2 Model: asymmetric detachment

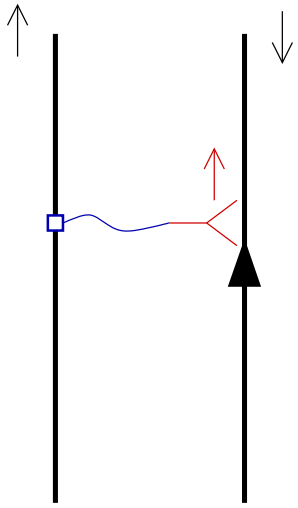
Start with array of parallel/antiparellel actin fibers.

Actin array's shear **must** be driven by the actin motor, myosin. Each myosin walks on one actin fiber; it **must** be connected and bonded (directly or indirectly) to another fiber, in order to make any shear. I'll assume these connections are permanent bonds.

To drive clockwise (CW) shear, dominant
bridging bonds **must** be placed as shown:
(connect to R or to L, according to polarity of walked-on fiber).

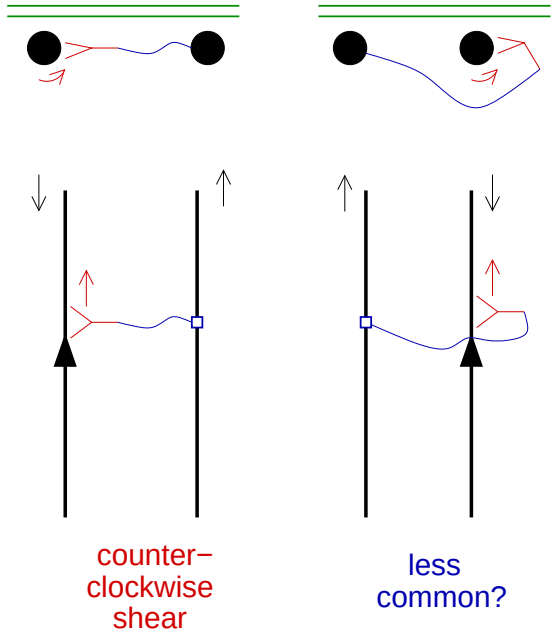
[both ideas as in previous mechanism].
(1)How to get directed? **Must** depend
on **helicity** of fiber, namely:
myosin walks on actin with left-handed screw.

(2) Also, **must** depend on
front/back difference; (probably)
means interaction with **membrane**



clockwise
shear

Consider myosin motor bonded
to fiber 1 and walking on fiber 2.
Motor spirals around fiber 2
till it comes against membrane
When motor is on **far** side of fiber 2,
linker strained ⇒ myosin falls off easier
⇒ near-side case dominates.
(Quantitative? depends on elasticity.)



Con: Predicts CCW! (wrong sense of shear)

5. CONCLUSIONS

Symmetry is key!

Any of the mechanisms to produce L/R asymmetry
must explicitly use 3 ingredients:
front/back asymmetry, **head/tail** asymmetry,
and **helicity** coming from the microscopic chirality of molecules.

Helicity generally comes by **screw mechanism**:
convert translation of **molecular motor** along **long fiber**
$\rightarrow$ rotation around it

Universality of mechanism ?

Physics modeling allows less trivial universality:
may have same mechanism using different motors and fibers
(myosin on actin $\rightarrow$ dynein on microtubules).
Biologists would tend to treat these as totally unrelated.

Future experiments: suggestions

Study how motors carry cargo near a membrane

Study mutant forms of motor known to affect L/R:
do they have changed screw motions around the fiber?

(Near) future theory

Quantitative estimates for the various mechanisms
(to test plausibility).

L/R in **plants** (no time in this talk!).

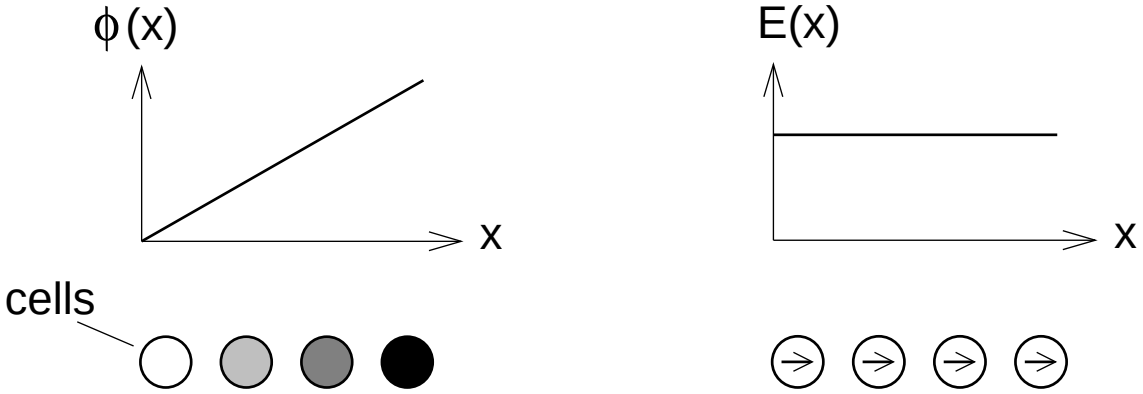
L/R in cell locomotion (nerve cells migrate far).

[skip slide] 1.5(3)

note too (3) Two ways to represent L and R

"positional information": chemical conc. $\phi(x, y, z) \propto x$.

a polarization: $\vec{E}(\mathbf{r})$.



Of course $\vec{E}(\mathbf{r}) = \nabla\phi(\mathbf{r})$. Nontrivial to convert:

- $\phi(\mathbf{r}) \to \vec{E}(\mathbf{r})$: OK
  (Animal cells are big enough to sense
  conc. gradients between one side and the other)
- $\vec{E}(\mathbf{r}) \to \phi(\mathbf{r})$: HARD
  (To get imbalance in conc. $\phi(\mathbf{r})$ of a chemical,

it must be actively transported with a bias along $\vec{E}(\mathbf{r})$)

[skip slide] 3.3 Alternate: array itself is twisted

How could an array get aligned with systematic twist θ? By collective behavior:
A fiber is nucleated at a random orientation at a certain rate per unit area; then it grows till it runs into some other fiber.
that favors roughly parallel axes (in either sense).

Assume the fiber has a **right-hand** screw.

Say fiber 2 is growing and its end hits fiber 1. If it hits from the **right** [looking in the sense of the growing fiber 2], then fiber 2 gets carried **down** (by the screw thread of fiber 1); carried **up** if it hits from the **left**.
(here we used **helical** asymmetry!)

[skip slide]

Imagine next that if fiber 2 gets carried **up** (hitting the membrane) it is more likely to **stop** growing; but if carried **down**, it's more likely to get carried under and beyond fiber 1, and **continue** growing. (Write difference as a small dimensionless factor f) (here we used up/down asymmetry!)

Hence: new fibers at an orientation where they hit old fibers from the right grow longer; the new fibers' orientation will be rotated **counter-clockwise** by an angle of order f. (I'm glossing over possible logarithmic factors.) So, if the array started out aligned in the z direction, its later orientation is rotated by an angle θ of order f times the number of generations of fiber growth since the start.

[skip slide] 4.1

[skip slide] 4.3 Alternate Model: reshuffling of fibers

Cartoon: actin array is a mix of "new" fibers which are free, and "old" fibers which are crosslinked to each other (or otherwise attached to the cell), and **also** have more links bonded to them.

Myosin motor bonded to "old"fiber 1 walks along "new" fiber 2. When fiber 2 is on far side, elasticity of linker tends to pull fiber 2 around fiber 1 (which doesn't move since it is attached to the cell). Thus, the only stable arrangement is when motor is on the near side, giving clockwise shear. is on near side.

Pro: A more collective mechanism: with enough time, most fiber-fiber links are shearing in the same sense.

Con: Assumptions about formation of network.

Pro or con? Above version also predicts CCW shear; but may predict CW – depends on elastic assumptions?

[skip slide] 4.4 Mutations can reverse the twist

Experimentally, in snails (or flies)

Note: reverse-twist behavior is **not** an exact mirror image: less strong?

Conjectures

1) mutant myosin motor twists around actin fiber in opposite sense, relative to its walking direction? (Note: some myosins walk in different senses.)

2) There are naturally two flavors of motor which twist in opposing senses. The mutation inactivates the dominant flavor, allowing the second flavor to win.

3) We had completely different mechanisms opposing each other. Mutation inactivates the myosin mechanism, allowing the

other] mechanism to control L/R.