Nano Molecular Machines

Nanobots **have** certainly captured the public imagination:

comicvine.com

thehottestgadgets.com

retinareality.com

zeitgeistaustralia.com

singularityhub.com

But popular concepts don't hold up well under critical analysis

You may already have picked up their many flaws in movies or books

But for a more detailed analysis you can also take a look at

my dissection of one best-selling Sci-Fi novel:

"The Fictions (?) of Nano Science Fiction"

Which concludes that fictional nanobots often **cannot** work as described

based on their disconnects with fundamental scientific laws!

But what is wrong with "classic" nanobots?

Classic concept = Extreme miniaturization of life-sized technologies

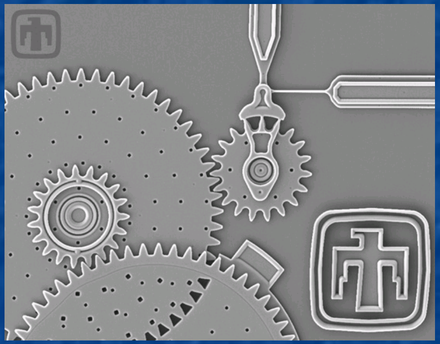
That is, a **Nano-transformer** like mechanical robot

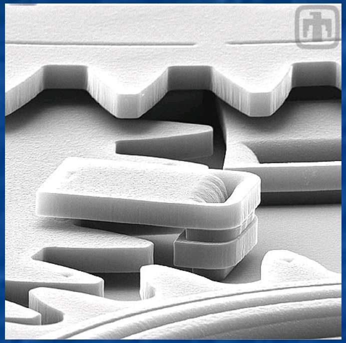
Let's analyze such an imagined nanobot step by step:

- How could we make the pieces of such a Nanobot?
- How would we get those pieces to assemble?
- Would they work even if we could get them assembled?
- How would their programming/direction be provided?

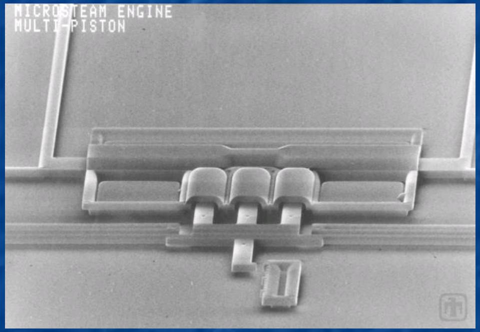
Closest we've come to this is MEMS

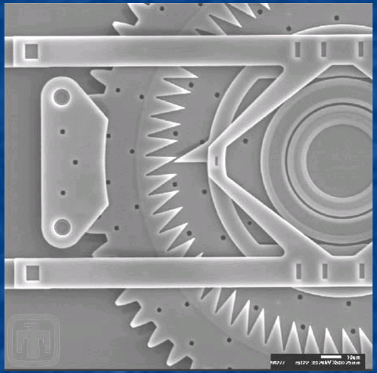
Remember (lecture 4)? MEMS = Micro Electro Mechanical Systems





"Courtesy of Sandia National Laboratories, SUMMiTTM Technologies, www.mems.sandia.gov"





Microns wide, tenths of microns thick, made via optical microfabrication

Extrapolating MEMS Technology:

Could we thereby make the pieces of a nanobot?

MEMS uses light-based lithography: Not quite nano (and never will be)

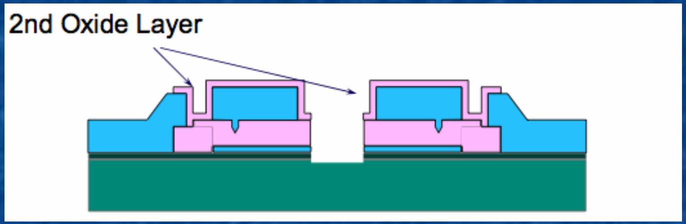
But we could use electron beam lithography - If we didn't care about time and cost

Could we thereby assemble the pieces of a nanobot?

MEMS elegantly side-stepped the assembly challenge:

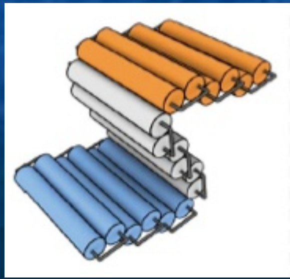
Pieces were never fully separate

Were carved from connected layers:



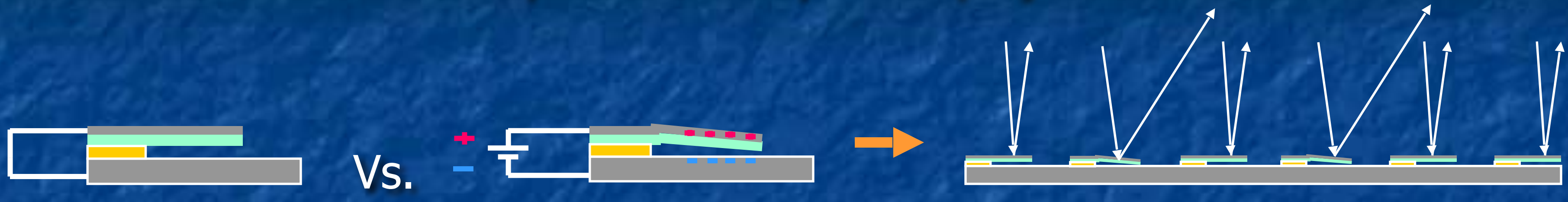
Resulting structures essentially flat ≠ Classic 3D Nanobot

But we might then fold them as with DNA rafts:

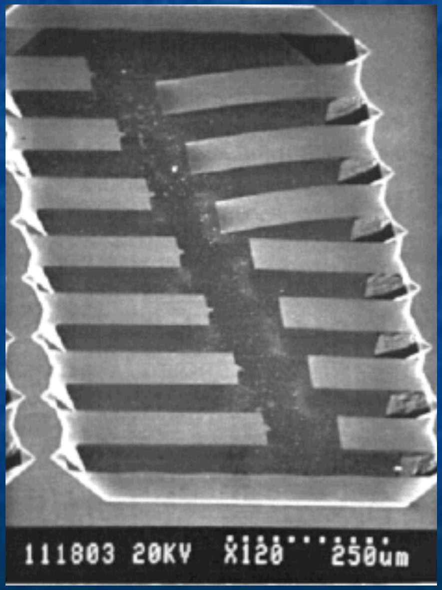


But would an extrapolation of MEMS-like technology work?

The cantilever beams that produce today's DLP projection TV's:



That's the goal, but early cantilever beams ended up looking like this:



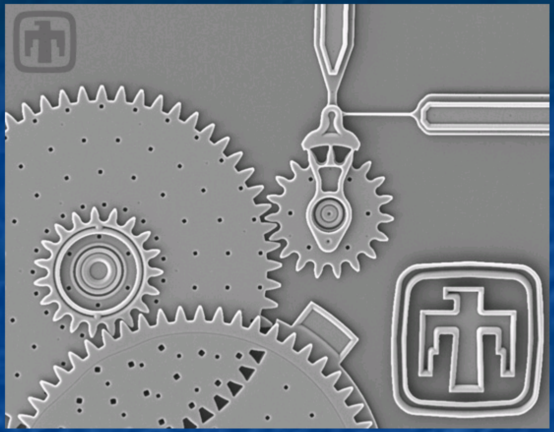
← Longer cantilevers drooped down and "welded" themselves to substrate

Cause? Moisture!

More specifically: Surface tension of minute amount of residual water trapped between beam and substrate

T. Abe and M.L. Reed, J. Micromech & Microeng 6, 213 (1996)

And even bigger problems surfaced for rotary / sliding motions:



Sandia's micro-transmission worked:

Small (30 μm) gear spun at 300,000 RPM

BUT seized up after 477,000 rotations:

477,000 / 300,000 → 95 second lifetime!!

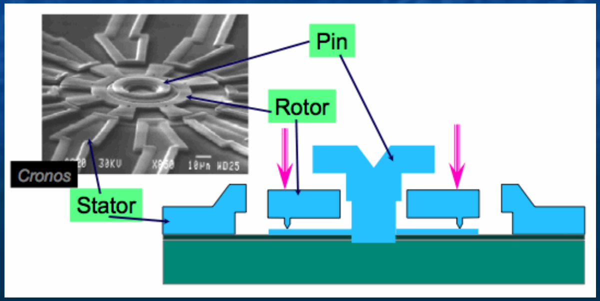
Problem = "Stiction" = Sticking + Friction

- Sticking due to surface tension of captured water

  Solution = Encapsulate in ultra dry environment

- Sticking due to Van der Waals bonding

  Minimize contact area by adding bumps:



Scorecard on MEMS inspired Nanobots:

- To fabricate at nanoscale would require excessive time + $ (via e-beam)

- 3D Geometries might be very limited (e.g. folded sheets)

- To work at all might require moisture-free environment

- Rotating pieces might operate for only seconds before seizing up

=> Why many discount possibility of mechanical (transformer) nanobots:

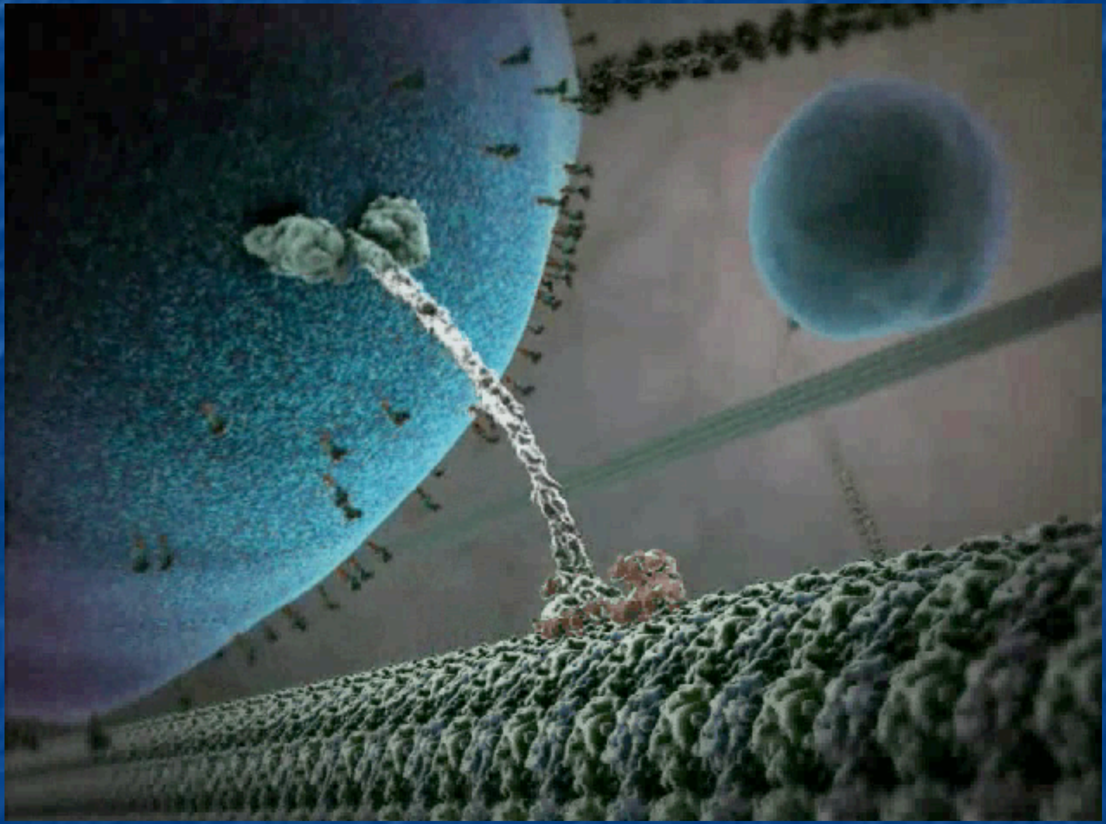
Essays such as "Rupturing the Nanotech Rapture"

Books such as Richard Jones' "Soft Machines"

Have we indeed run into a wall? Time for a reality check:

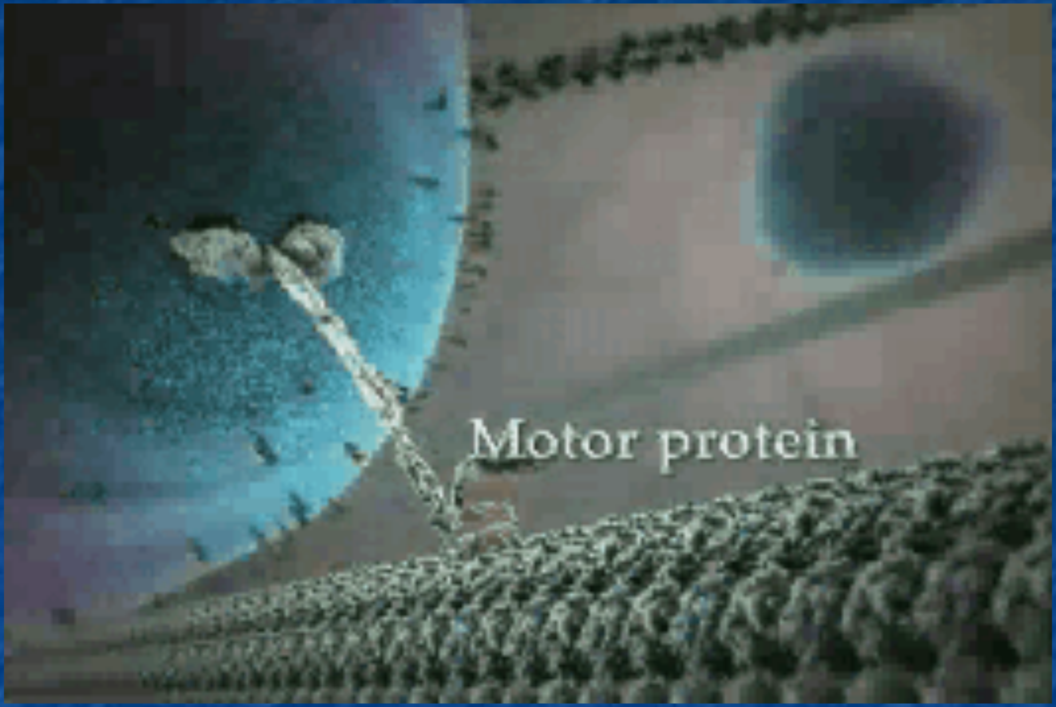
Has mother nature come up with anything resembling a mechanical nanobot?

She sure has!



Harvard University's "The Inner Life of the Cell" animation:
[Nano Molecular Machines - Supporting Materials – Cellular Visions 1]

Or version with full technical narration:



Harvard University's "The Inner Life of the Cell" animation:

[Nano Molecular Machines - Supporting Materials – Cellular Visions 2]

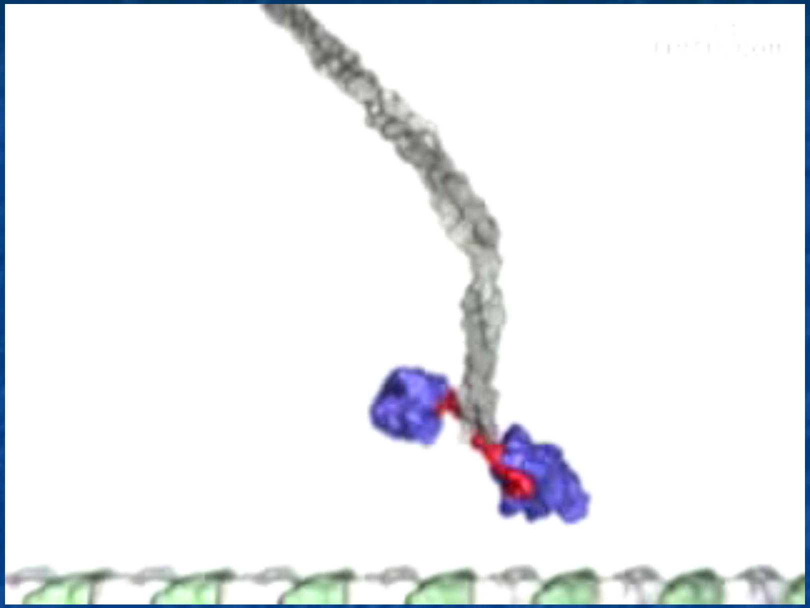
But is this only a computer animator's fantasy?

No, it's for real (as shown in this high-speed AFM movie):

Supporting webpage with embedded "Molecular Biology of the Cell" animation:

[Nano Molecular Machines - Supporting Materials – Organelle Movement]

But HOW does it walk?



Supporting webpage with embedded
"Molecular Biology of the Cell" animation:
Nano Molecular Machines - Supporting Materials – Kinesin

OK, but what exactly are ADP and ATP?

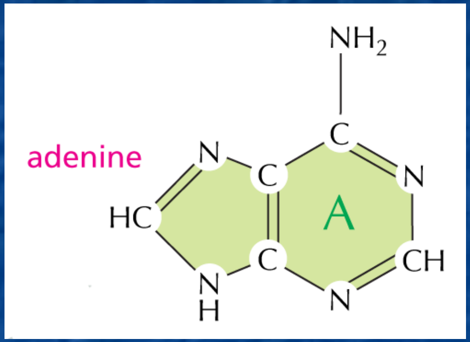
And how would their "hydrolysis" produce all of these effects?

Specifically, how/why is shape of feet being changed? Answer:

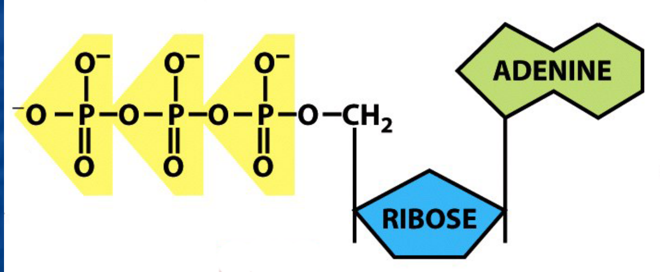
Energy transfer and shape-shifting as protein wraps itself around ATP:

Energy is supplied by ATP to ADP conversion:

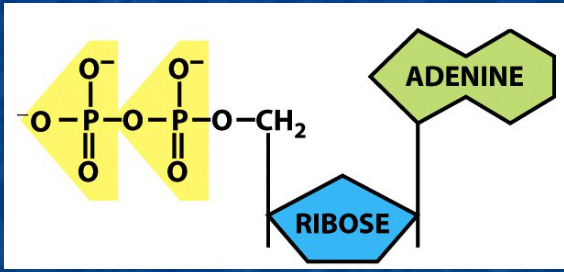
Adenosine **T**ri and **D**i **P**hosphate are based on Adenine (one of the four DNA bases):



ATP (3 PO_4 + Ribose + A) **ADP** (2 PO_4)+ Ribose + A)



+ H_2O =>



*

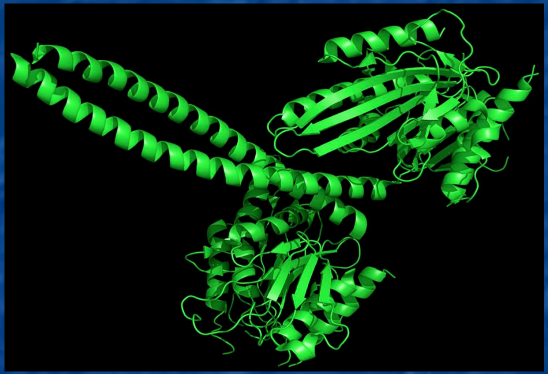
"Molecular Biology of the Cell" panel 2.6 and figure 2-27

*(= 7.3 kcal / mol)

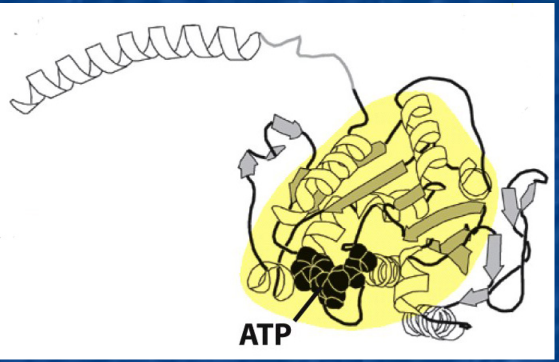
Which also drives the shape-shifting:

Detailed structure of kinesin protein (the feet) as determined by X-ray diffraction:

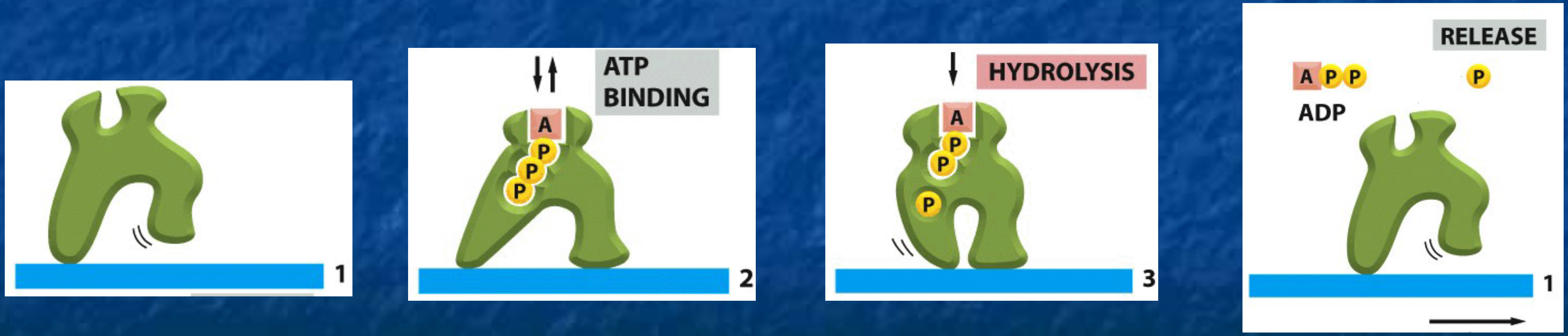
Full two-footed kinesin protein:



One foot with **bound ATP**:



Reshaping the feet/legs via ATP absorption, conversion to ADP, and its liberation:

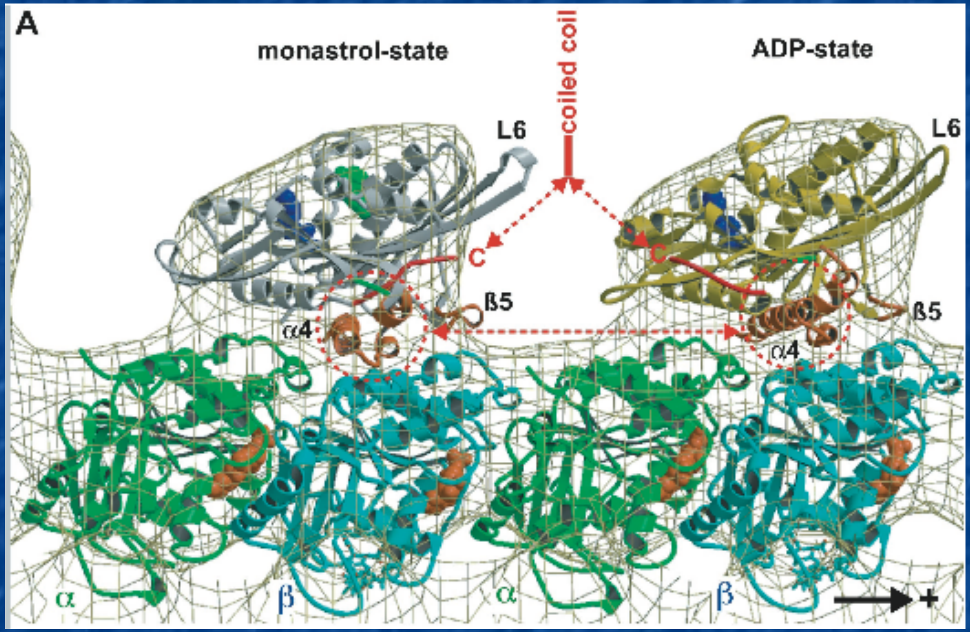


"Molecular Biology of the Cell" figures 11-60 and 3-77

But are "they" sure that this is how kinesin works?

Details are still being worked out

An example from the Andreas Hoenger modeling group at U. Colorado, Boulder:



Microtubule at bottom (mesh, with embedded blue and green protein domains)

First kinesin protein foot wrapped around LEFT microtubule bump

Second kinesin protein foot, with embedded ADP, wrapped around RIGHT microtubule bump

Comparison with our classic mechanical nanobot:

Our "mechanical" way of building things:

Fixed frameworks / trusses / girders

Joined by pivot points / hinges

Determining single well-defined types and ranges of motion

Moved by gears

Driven by transmissions / pulleys / chains

Delivering and translating motion of discrete motor units

To which fuel is supplied via pipes or wires

Many **DIFFERENT** components each with a **single/unique** role

Nature's approach is VERY different:

MUCH greater use of folding

- Natural because biology's structures are **based** upon protein folding!

EVERYTHING is flexible

Where motion is required, just program flexing via chemical reaction

- Built right **into** the part (no separate motor/transmission/hinge...)!

IMMERSE in SEA of fuel (i.e. no piping/wiring to only certain points)

Do minimum work necessary, leaving rest to Brownian vibrations

- Kinesin "machine" provides **only** the latching and unlatching
- Brownian motion does the rest: Swing of foot to new position

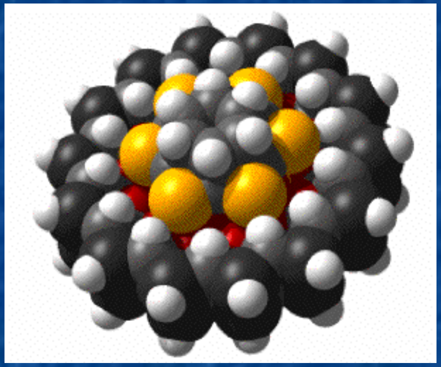
Returning to mechanical approach, but enlightened by nature:

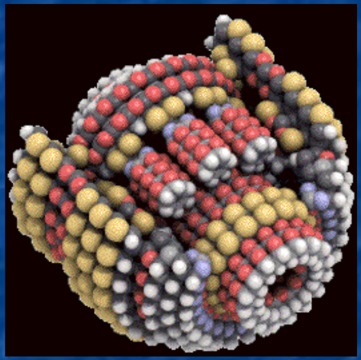
Start by taking vibration and flexibility into account:

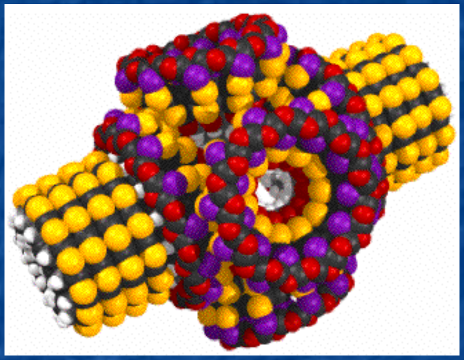
One group tackling this is led by futurist K. Eric Drexler

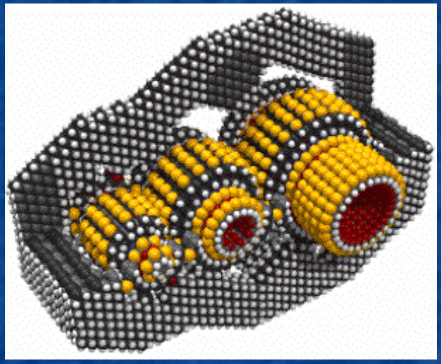
Working with computer modeling firm Nanorex

Which has proposed and modeled these nano-mechanical components:


Small Bearing

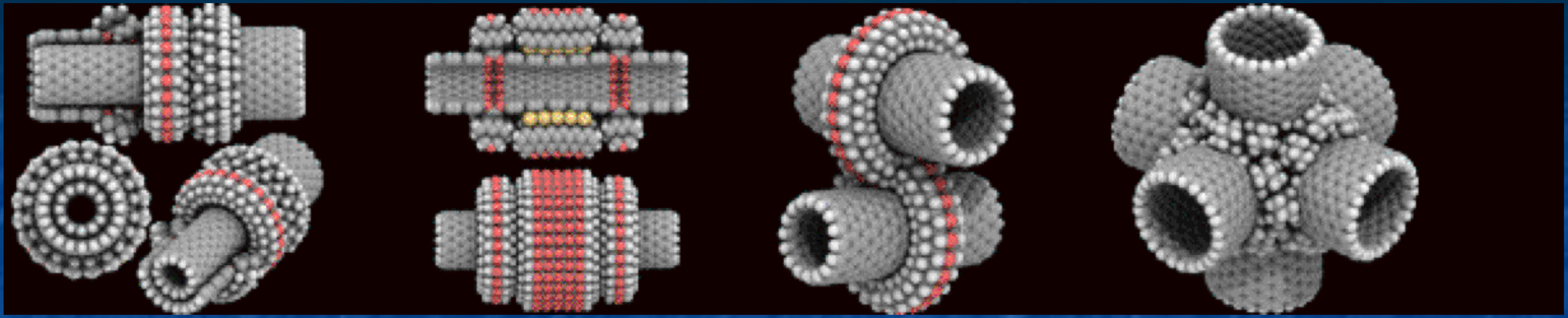

Planetary Gear


Differential


Transmission

To see fully animated action of these gifs go to: Nano Molecular Machines - Supporting Materials - Nanorex

Or even more complex nanotube proposals:



But these ARE only computer modeled proposals

Which, some argue, underestimate vibrations and/or Van der Waals bonding

That is: Would they instantly vibrate apart, or seize together?

More importantly: HOW COULD YOU POSSIBLY ASSEMBLE SUCH THINGS?

In Nature: By attraction and fit, protein is layered upon protein

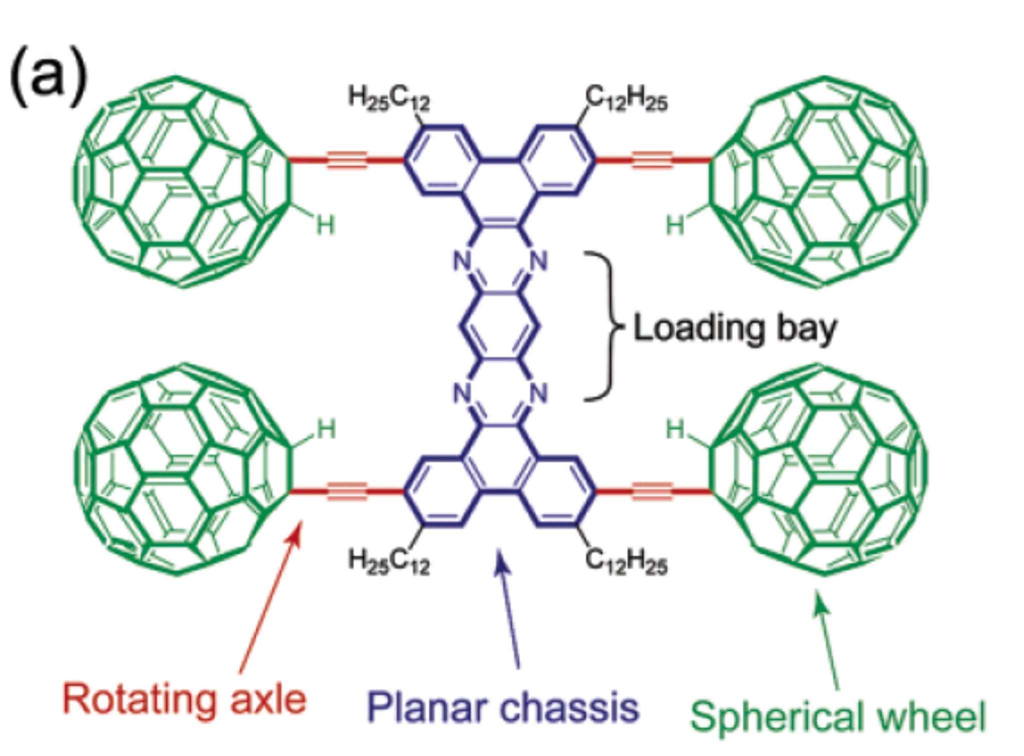
But in these models: One molecule is tightly wrapped around another molecule

How would we get larger molecule to bond around inner molecule?

Or squeeze inner molecule inside already complete outer molecule?

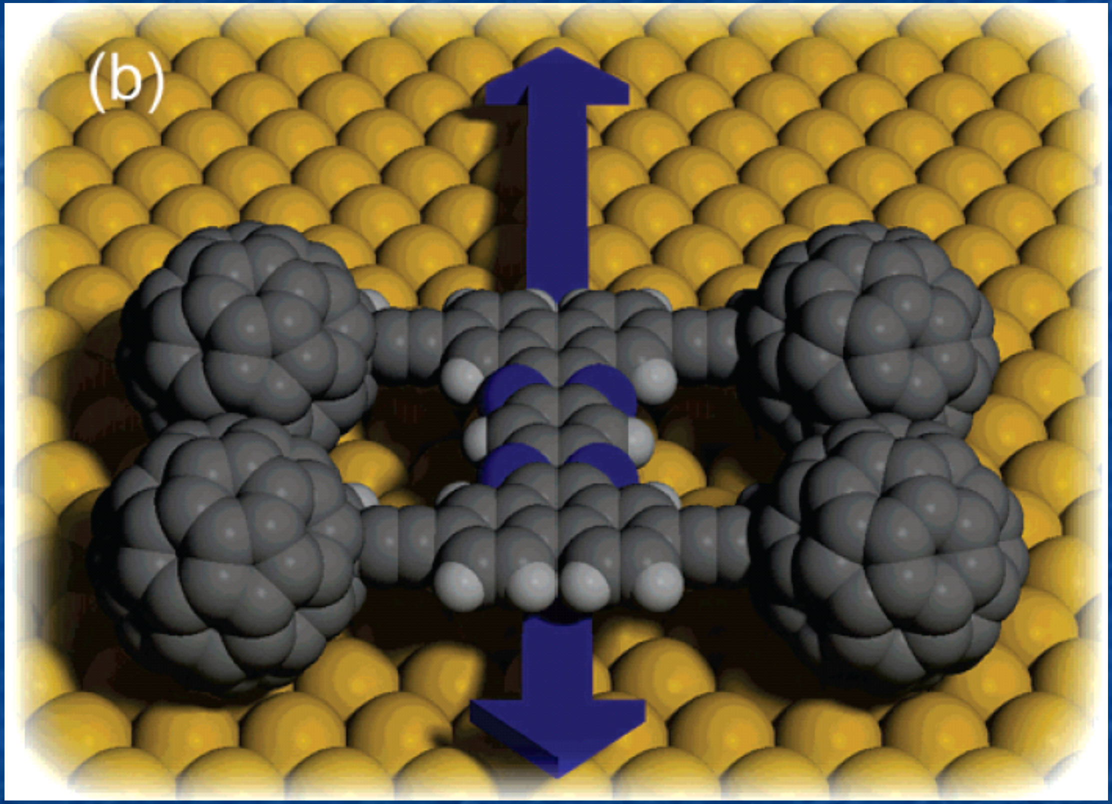
So time to again return to cold hard reality

Where my former collaborator Jim Tour is synthesizing NANOVEHICLES



Can't visualize it yet?

How about this: "NanoTruck #1"



Shirai et al., JACS 128, 4854-64 (2006)

[link to copy of paper]

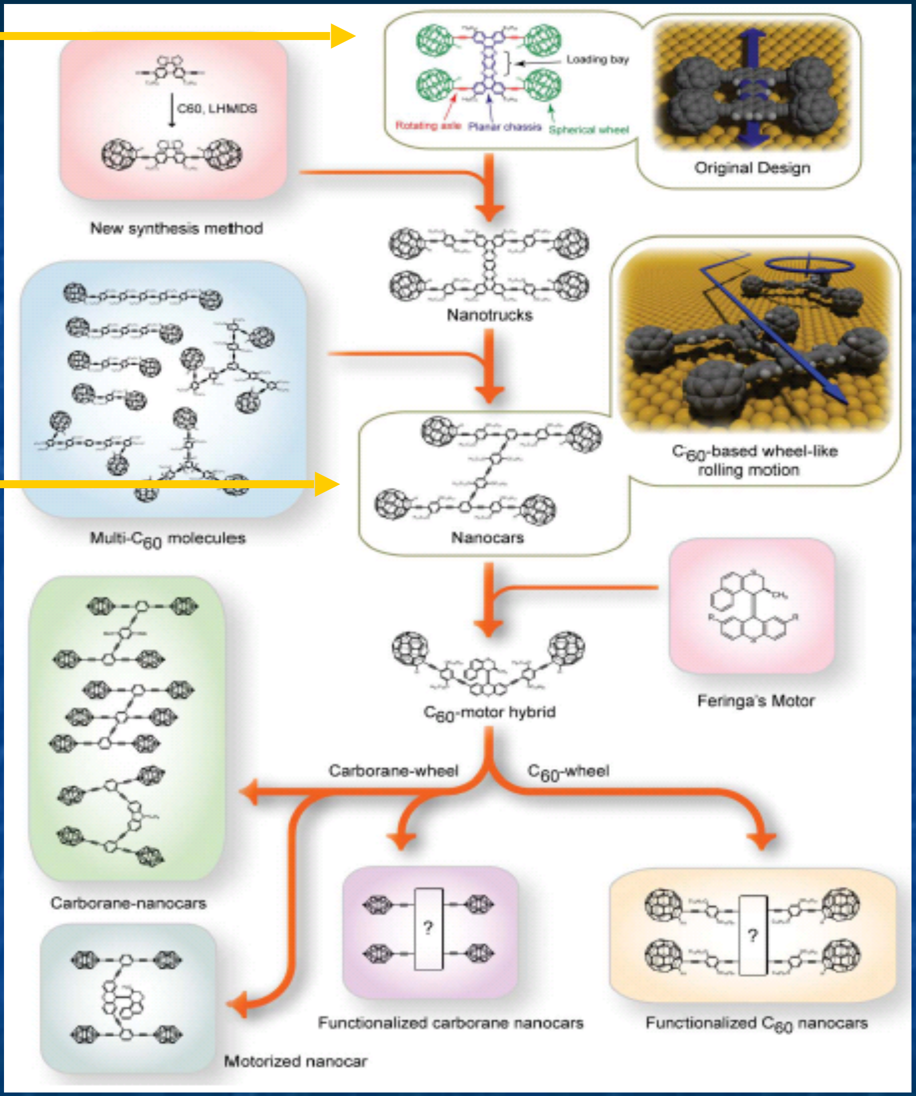
Leading to:

NanoTruck #1

NanoCar #5

Semis? (!$!@!)

NanoCar #9



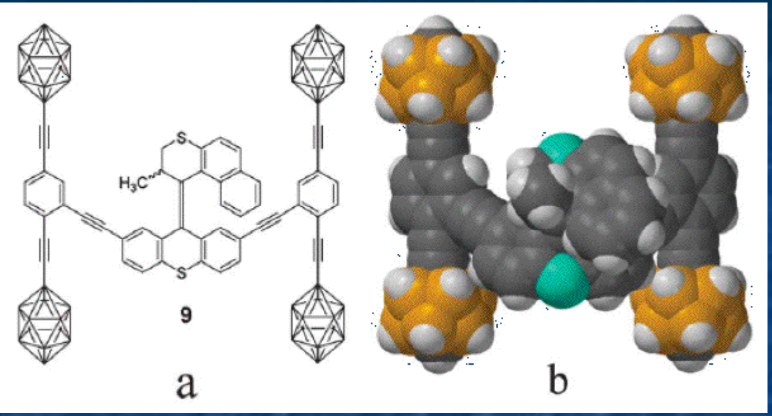
Motors (!!@#!!)

Vehicles with a (chemical) agenda

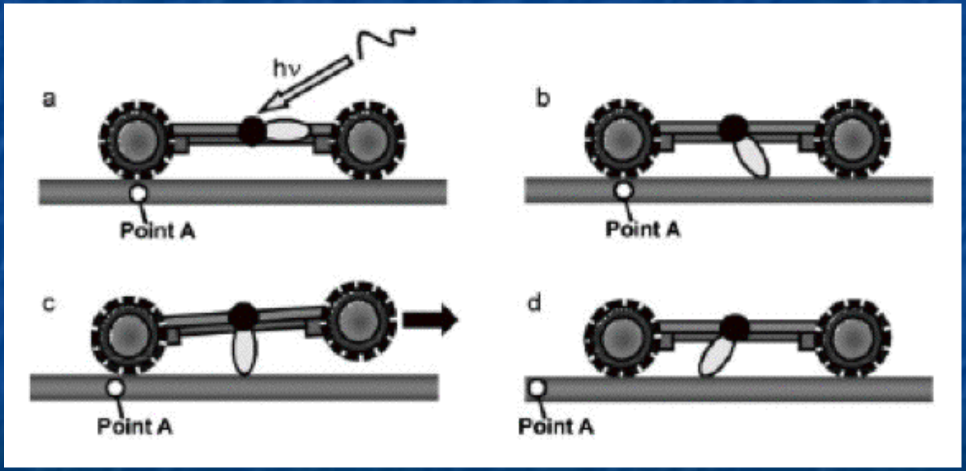
Shirai et al., Chem. Soc. Reviews, 35, 1043-55 (2006)   [link to copy of paper]

Reality (cont'd):

NanoCar #9:



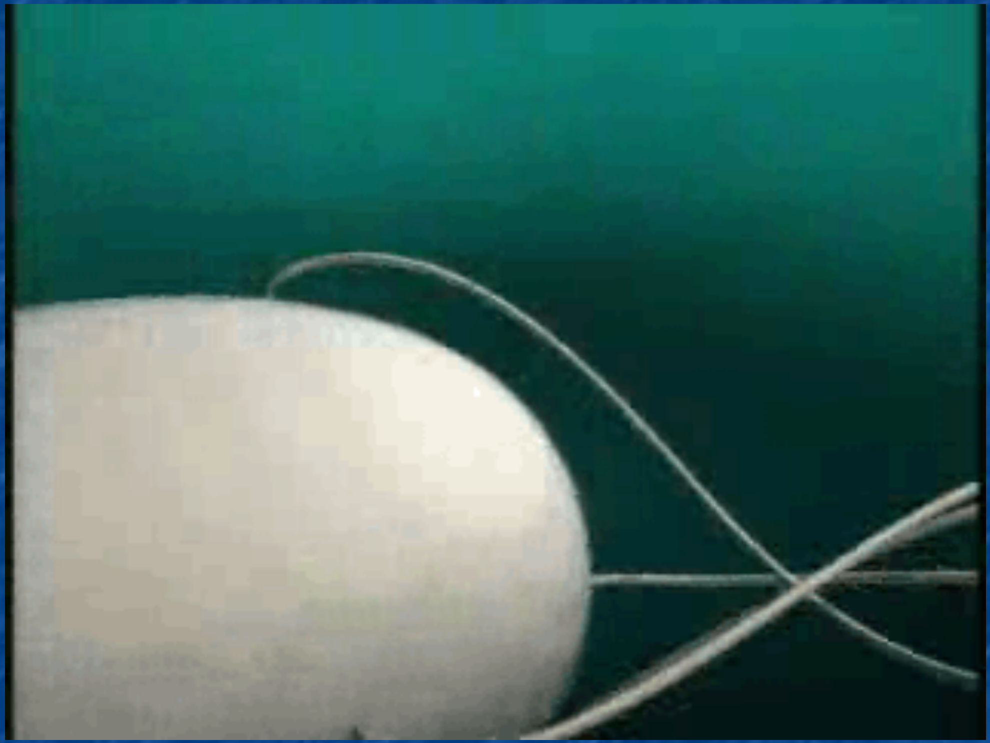
With absorption of light spinning side group and "paddling" car along surface:



(But w/ p-carborane wheels not yet proven to rotate)

Or some awfully mechanical looking biology:

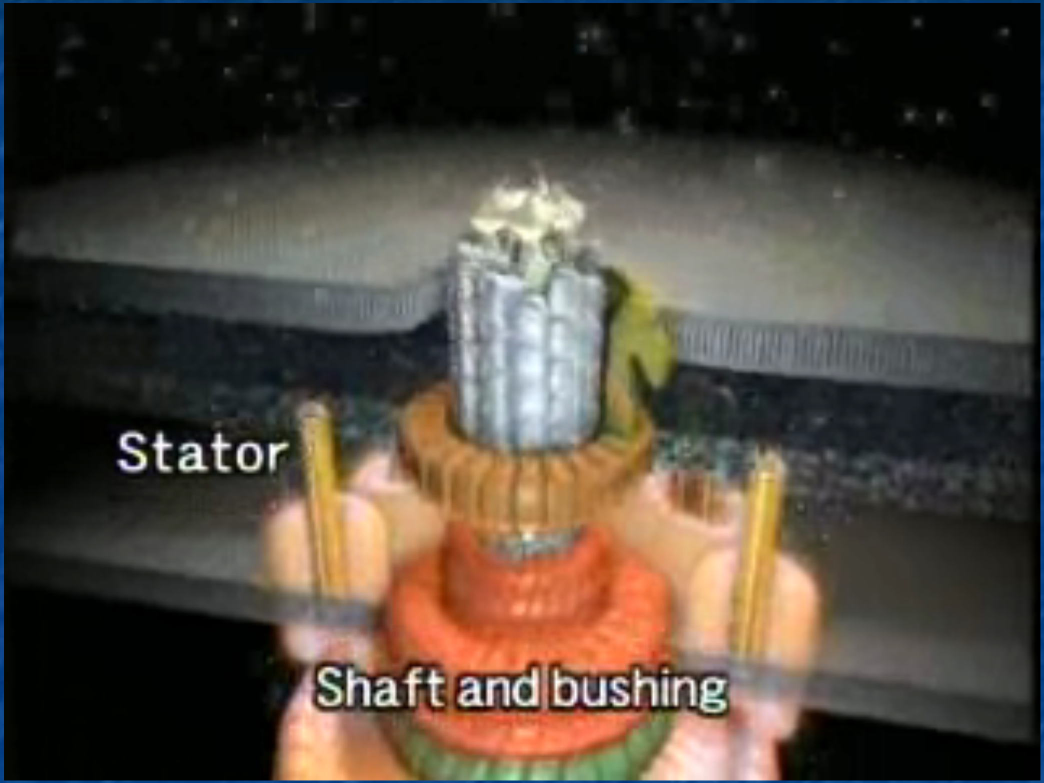
"Motor" driven propellers!



Supporting webpage with embedded Osaka U. animations:

[Nano Molecular Machines- Supporting Materials – Flagella part 1]

Which self-assemble:



Supporting webpage with embedded Osaka U. animations:

[Nano Molecular Machines - Supporting Materials – Flagella part 2]

But how exactly did that motor work?

I could not find animation on the workings of **that** motor

But I did find this animation about a very similar biological motor:

Supporting webpage with embedded
"Molecular Biology of the Cell" animation:
Nano Molecular Machines - Supporting Materials – ATP Synthase part 1

Time out for a translation:

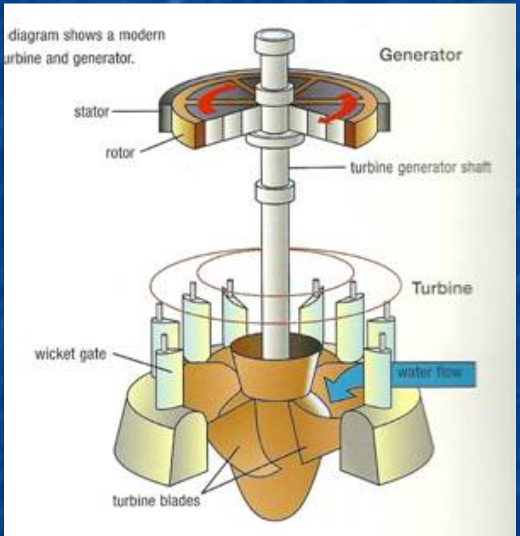
Driven by "proton gradient across membrane"

Proton = hydrogen without its electron = hydrogen ion

Higher hydrogen ion concentration above = more acidic above

So it's powered by protons above, trying to get to lower "pressure" below

Sound familiar? (it should):

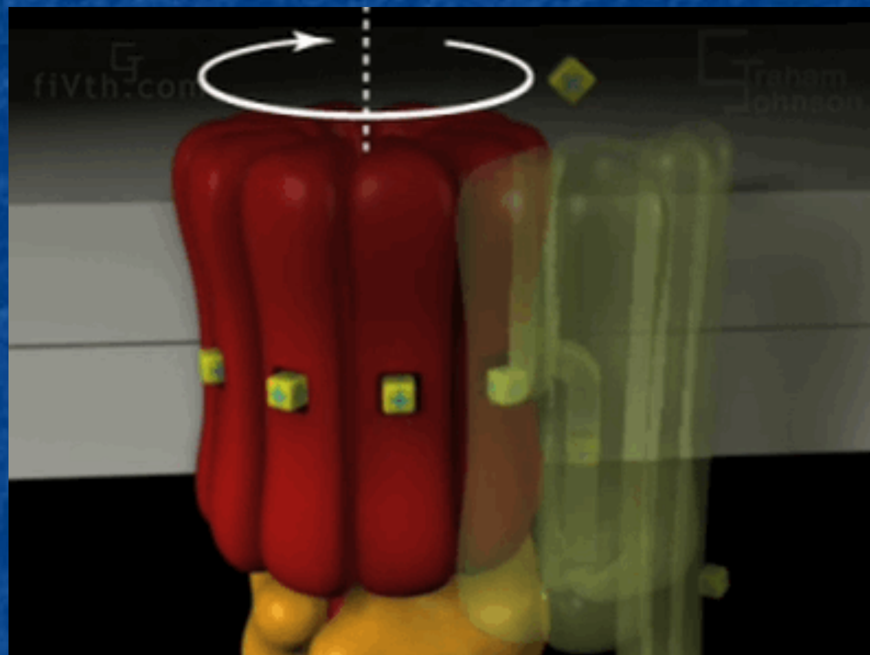


U. Indiana

It's exactly how the turbines of a hydroelectric dam work!

But this motor powers a fuel factory rather than a propeller:

Or, more precisely, an ADP to ATP converter:



Supporting webpage with embedded
"Molecular Biology of the Cell" animation (due to M. Yoshida, Tokyo Institute of Technology):
[Nano Molecular Machines - Supporting Materials – ATP Synthase part 2]

What are "take away" lessons from Nature's nano machines?

- Nature uses designs with much less compartmentalization of functions

- **Everything** is going to be flexing and vibrating like crazy

- Nano forces and fluids are going to be unavoidable

But, surprisingly, Van der Waals + surface tension **don't** lock things up

Because, at this scale, Brownian vibrations knock them back apart!

So Nanorex style gears or transmissions might actually work!

Even though molecules WITHIN molecules may be impossible to build

More plausible would be self-assembly of molecule UPON molecule

As seen in protein self-assembly

Suggesting that micron is WORST possible scale for mechanical robots:

Macroscale robots (human down to millimeter size):

Heavy inflexible pieces, totally oblivious to Brownian vibrations

And their momentum swamps effects of friction, surface tension, charging

Micron scale robots (such as MEMS):

Pieces still big enough to be inflexible, and to ignore Brownian vibrations

But reduced momentum countered by micro binding forces => Lock-up!

Functional (?) nano scale robots:

Pieces now so tiny that they have become light and floppy HENCE

Brownian vibrations toss them around like crazy WHICH PREVENTS

Forces of friction, surface tension or charging from locking them together!

Footnote on the above hypothesis:

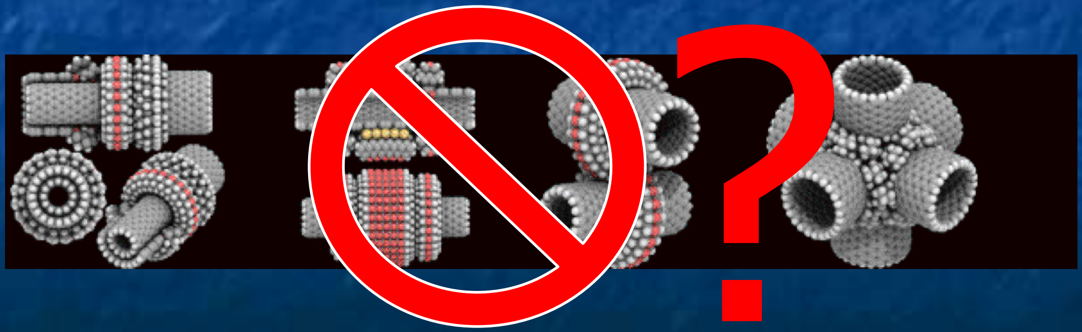
If flexibility IS the reason nanobots work well (while MEMS barely works)

We'd have to fight our inclination to try and make nanobots **stronger**!

For instance, while nanotubes and buckyballs might seem ideal components

Their exceptional STRENGTH might inhibit their flexing

Making it impossible for vibrations to un-lock them!



Leaving one untouched point: Programming / Intelligence

Overall, **construction** of mechanical nanobots now seems MORE plausible

And, in biology, we can certainly find rich examples of programming

Programming at level of recognizing when nanobot has reached target

Or its programmed response when it **does** reach that target

For instance:

Viruses or antibodies identifying and acting upon their targets

But this is a really **low level of programming**

Based on **random** encounters and two things **fitting together** properly

"Intelligence" is something quite different

Even bugs can deal with myriad stimuli and respond appropriately

Surely our classic nanobot needs to be as intelligent as an ant!

That seems to require a microprocessor's level of intelligence

Semiconductor microprocessors can contain ~ 10 billion transistor switches

Say, MAGICALLY, a single atom could replace a current day transistor

10 billion atoms in a dense cube would be ~¼ micron on a side

And that ignores need to provide routes for information flow (wiring)

Or other required "peripheral" things like:

Memory (RAM and hard disk), I/O, power supply . . .

So even with assumption of atom-scale switches, memory cells, wires . . .

Seems FAR more likely that volume of robot mind will be **microns** on a side

And even **that** would assume an external power source (e.g. ATP sea)

Would-be smart mechancial NANObot => MICRObot, cell size or larger

OK, so what if it ends up really being a MICRObot!

It could still flow through my body doing wonderful repairs!

Reality Check:

To achieve MICRObot size, I had to assume 1 atom switches/memory cells/wires

Nobody / Nothing has achieved this size/density of info / info-processing!

Let's again look to nature for what might in fact be ~ ultimate limit:

Single DNA unit is ~ 65 atoms occupying ~ pi $(1\ nm)^2$ x 0.34 nm= $1\ nm^3$

Assume that **THIS** is ~ ultimate limit for shrinking 1 switch / 1 bit of memory

1 nm^3 per switch/memory unit = 1000X my assumed single atom volume

Meaning **SMART MICRObot** => **MILLIbot: 10's -100's of microns on a side**

Inject **those** guys into your body and all you're going to get is a **stroke!**

All we seem to be left with is possibility of ***dumb*** *nanobots*

Things that could **only randomly flow and diffuse** through our bodies

And, at best, latch onto a specific target if they **just happened to bump into it**

Perhaps then delivering a drug, DNA insert . . .

FINE!

Don't discount how **important** such dumb nanobots might be!

Or how close we might be to engineering VERY USEFUL dumb nanobots!

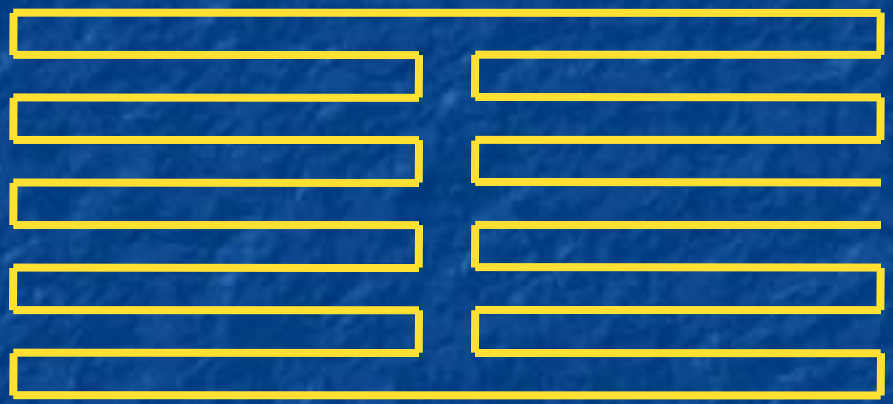
A example is provided by recent Harvard research:

Harvard's engineered nanobot:

Starts with "DNA Oragami" (as described in lecture "Bleeding Edge I: Nanomechanics"):

- An "off-the-shelf" master **single** strand of DNA is chosen

- A design is developed that lays out its 7308 nucleotide units something like this:



- "Staple" single DNA strands are then designed (196 different staples!)

With bases complementing the master strand where the staples should attach

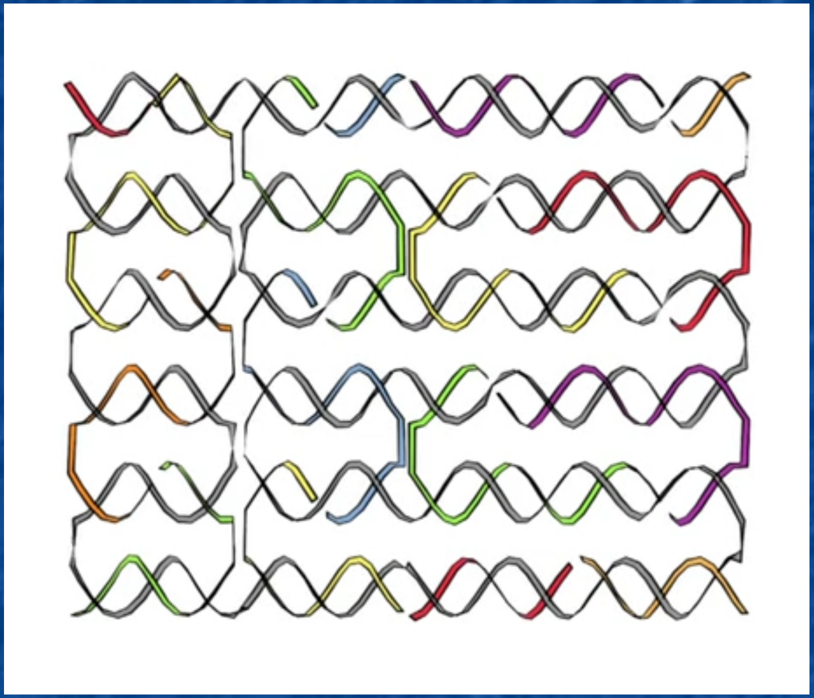
Design was facilitated by CADNANO program co-developed by this team (www.cadnano.org)

Reference: "A logic-gated nanobot for targeted transport of molecular payloads, Shawn M. Douglas et al., Science 335, pp. 831-4 (2012)

And it is then assembled:

By simply adding in the ~ 200 different DNA staple strands

And then slowly cooling, allowing complementary bases to bind together:

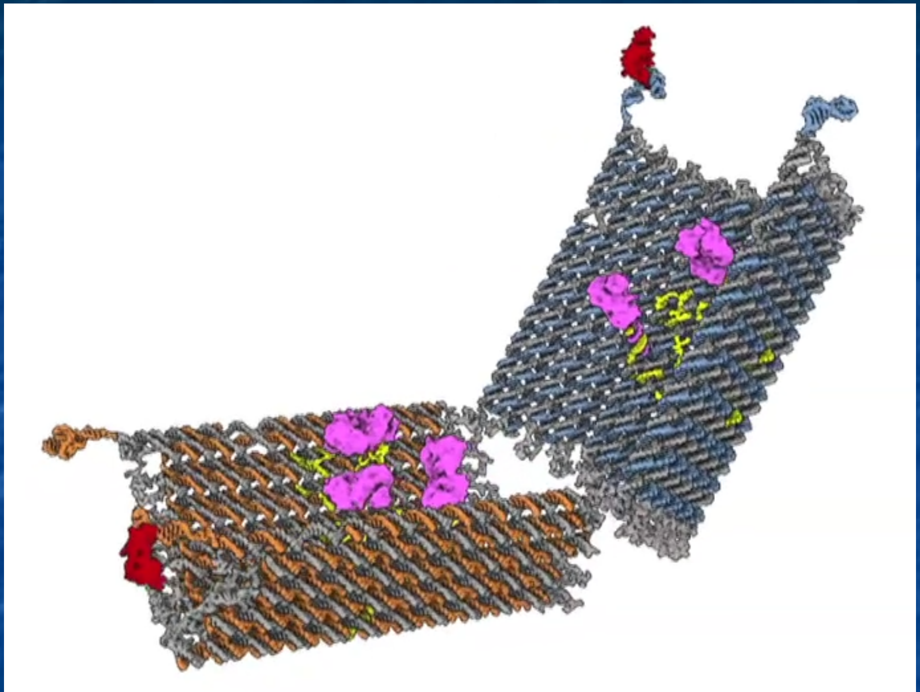


Supporting webpage with embedded Harvard animation:

Nano Molecular Machines - Supporting Materials – DNA Origami

Full animation + researcher interviews available at: http://wyss.harvard.edu/

Leading to a full structure that looks like this:



Gray = long master single DNA strand

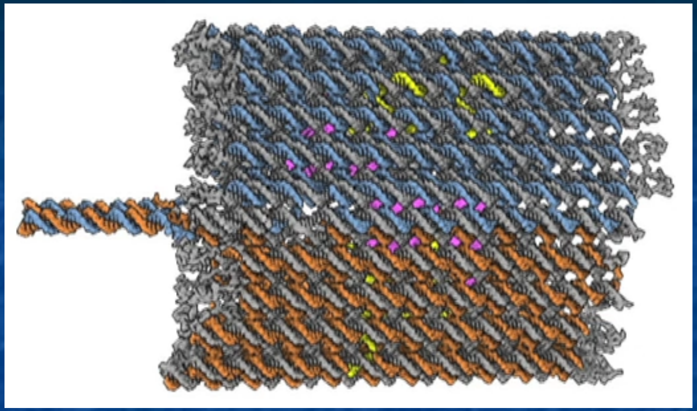
Orange + **blue** = Short DNA "staples" locking in master strand's 3D shape

Yellow = Staples with ends hanging out, attaching to **purple** "cargo"

Plus short DNA extensions at far-left / upper-right

Short DNA extensions serve as LOCKS to fold structure together

Locks (2) →



Twisted locks work because they consist of a pair of complementary single DNA strands

HOWEVER!

In each of THESE two locks, ONE of the DNA strands is very specially selected

So that, when unwound and disconnected, it curls into a complex shape

That can fit tightly around (and thus latch onto) a specific foreign molecule

THESE DNA strands were chosen to latch onto protein antigens

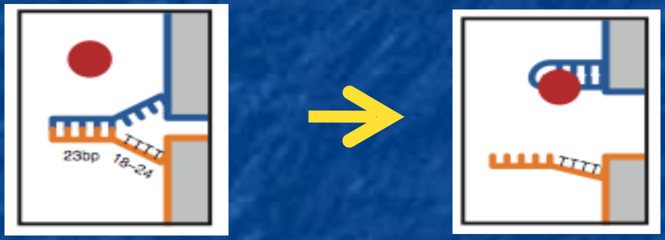
That are released by or embedded in the cell membranes of CANCER cells

Appropriate DNA recipes are **cataloged in databases** for specific antigens!

These antigen-binding single DNA strands are know as **aptamers**

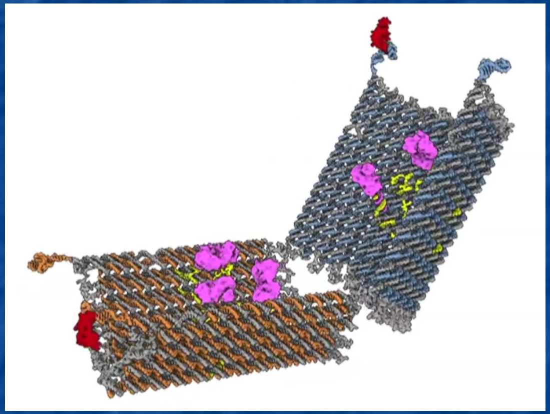
If the antigen that a lock's amptamer targets is encountered:

That aptamer/DNA strand will untwist and instead latch onto the antigen:



And this "lock" opens

If the antigens for BOTH locks are present, BOTH locks unlock, and shell springs open!



Exposing the antigen-releasing

cell to the nanobot's deadly cargo

It even works if antigen spacing on target cell does not match separation of the two locks:

1st lock springs, then nanobot wiggles around cell surface until 2nd lock springs*

*Private communication with Shawn Douglas

Conclusions about Nanobots:

The fabrication of "classic" NANObots poses MAJOR mechanical design challenges

But these might be overcome by instead using bio-inspired floppy folded designs

But killer obstacle still seems to be INTELLIGENCE often attributed to NANObots

When I invoked imaginary atom-sized switches / bits I got a MICRObot

When I invoked DNA base-pair sized switches / bits it became a MILLIbot

But that **DOES** still leave the door open for **DUMB** NANObots

From which nature DOES get HUGE mileage!

And we're surprisingly close to engineering some REALLY USEFUL DUMB nanobots!

Credits / Acknowledgements

Funding for this class was obtained from the National Science Foundation (under their Nanoscience Undergraduate Education program).

This set of notes was authored by John C. Bean who also created all figures not explicitly credited above (with the exception of lecture preview figures which are credited in their home set of lecture notes).