Using Intelligent Design Theory to Guide Scientific Research

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Intelligent Design theory (ID) can contribute to science on at least two levels. On one level, ID is concerned with inferring from the evidence whether a given feature of the world is designed. This is the level on which William Dembski's explanatory filter and Michael Behe's concept of irreducible complexity operate. It is also the level that has received the most attention in recent years, largely because the existence of even one intelligently designed feature in living things (at least prior to human beings) would overturn the Darwinian theory of evolution that currently dominates Western biology.

On another level, ID could function as a "metatheory," providing a conceptual framework for scientific research. By suggesting testable hypotheses about features of the world that have been systematically neglected by older metatheories (such as Darwin's), and by leading to the discovery of new features, ID could indirectly demonstrate its scientific fruitfulness.

In November 2002, Bill Dembski, Paul Nelson and I visited the Detroit headquarters of Ideation, Inc. Ideation is a thriving business based on TRIZ, an acronym for the Russian words meaning "Theory of Inventive Problem Solving." Based on a survey of successful patents, TRIZ provides guidelines for finding solutions to specific engineering or manufacturing problems. When Ideation's president took us out to lunch, he told us that before ID could be taken seriously it would have to solve some real problems.

TOPS

I was inspired by this to sketch out something I called a Theory of Organismal Problem-Solving (TOPS). Strictly speaking, I suppose the biological equivalent of TRIZ would survey successful experiments for guidelines to solve research problems posed by existing hypotheses. I chose to try a different approach, however: As I formulated it, TOPS suggests how ID could lead to new hypotheses and scientific discoveries.

TOPS begins with the observation that the evidence is sufficient to warrant at least provisional acceptance of two propositions: (1) Darwinian evolution (the theory that new features of living things originate through natural

selection acting on random variations) is false, and (2) ID (the theory that many features of living things could only have originated through intelligent agency) is true.

TOPS then explicitly rejects several implications of Darwinian evolution. These include: (1a) The implication that living things are best understood from the bottom up, in terms of their molecular constituents. (1b) The implications that DNA mutations are the raw materials of macroevolution, that embryo development is controlled by a genetic program, that cancer is a genetic disease, etc. (1c) The implication that many features of living things are useless vestiges of random processes, so it is a waste of time to inquire into their functions.

Finally, TOPS assumes as a working hypothesis that various implications of ID are true. These include: (2a) The implication that living things are best understood from the top down, as irreducibly complex organic wholes. (2b) The implications that DNA mutations do not lead to macroevolution, that the developmental program of an embryo is not reducible to its DNA, that cancer originates in higher structural features of the cell rather than in its DNA, etc. (2c) The implication that all features of living things should be presumed to have a function until proven otherwise, and that reverse engineering is the best way to understand them.

It is important to note that "implication" is not the same as "logical deduction." Darwinian evolution does not logically exclude the ID implications listed here, nor does ID logically exclude every implication of Darwinian evolution. A Darwinian may entertain the idea that other features of an embryo besides DNA influence its development, and Darwinians can (and do) use reverse engineering to understand the functions of features in living things. Furthermore, an ID viewpoint does not logically rule out genetic programs or the idea that some features of living things may be useless vestiges of evolution. The differences between Darwinian evolution and ID that form the starting-point for TOPS are not mutually exclusive logical entailments, but differences in emphasis. The goal of TOPS is not to show that Darwinian evolution leads logically to false conclusions, but to explore what happens when ID rather than evolutionary theory is used as a framework to ask research questions.

Take, for example, research on the vast regions of vertebrate genomes that do not code for proteins. From a neo-Darwinian perspective, DNA mutations can provide the raw materials for evolution because DNA encodes proteins that determine the essential features of organisms. Since non-coding regions do not produce proteins, Darwinian biologists have been dismissing them for decades as random evolutionary noise or "junk DNA." From an ID perspective, however, it is extremely unlikely that an organism would expend its resources on preserving and transmitting so much "junk." It is much more likely that non-coding regions have functions that we simply haven't discovered yet.

Recent research shows that "junk DNA" does, indeed, have previously unsuspected functions. Although that research was done in a Darwinian

framework, its results came as a complete surprise to people trying to ask Darwinian research questions. The fact that "junk DNA" is *not* junk has emerged not because of evolutionary theory but in spite of it. On the other hand, people asking research questions in an ID framework would presumably have been looking for the functions of non-coding regions of DNA all along, and we might now know considerably more about them.

TOPS and Cancer

In November 2002, I decided to apply TOPS to a specific biomedical problem. Not being one to proceed timidly, I chose to tackle cancer.

I quickly learned from reviewing the recent scientific literature that cancer is not correlated with any consistent pattern of DNA mutations, but it *is* correlated with abnormalities at the chromosomal level -- a phenomenon called "chromosomal instability" (Lengauer et al., 1998). Chromosomal instability, in turn, is correlated with centrosome abnormalities -- particularly the presence of extra or enlarged centrosomes. A growing number of researchers regard cancer not as a DNA disease, but as a "centrosomal disease" (Brinkley and Goepfert, 1998; Pihan et al., 1998; Lingle and Salisbury, 2000).

In 1985, I had published a hypothesis about how centrosomes might produce a force in dividing cells that pushes chromosomes away from the spindle poles (Wells, 1985). Cell biologists have long been aware of this "polar ejection force" or "polar wind" (Rieder et al., 1986; Rieder and Salmon, 1994), but its mechanism remains unknown. The force has been attributed to microtubule elongation and/or microtubule-associated motor proteins, but neither of these explanations fits all the facts (Wells, 2004).

In the hypothesis I proposed in 1985, magnetic interactions in the centrosome would cause spindle microtubules to "wobble" like a laboratory vortexer, though at a much higher frequency and much smaller amplitude, producing a centrifugal-like force directed away from spindle poles. I subsequently realized (with help from physicist David Snoke) that the magnetic interactions I had proposed in 1985 would not work. In 2002 it occurred to me, however, that the still-viable vortexer concept might help to explain the link between centrosomes and cancer: Centrosomes that are too numerous or too large would produce too strong a polar ejection force, damaging chromosomes and leading to chromosomal instability.

If the polar ejection force were really the link between centrosomes and cancer, however, and the polar ejection force were due to a vortexer-like motion of spindle microtubules, what could be the mechanism producing this motion? My attention quickly turned to centrioles.

Centrosomes in animal cells contain centrioles, tiny organelles less than a millionth of a meter long. Except for their role in nucleating eukaryotic cilia and flagella, their precise functions remain mysterious (Preble et al., 2000). They

have never been a favorite object of study within the framework of Darwinian theory, because even though they replicate every time a cell divides they contain no DNA (Marshall and Rosenbaum, 2000), and they have no evolutionary intermediates from which to reconstruct phylogenies (Fulton, 1971).

The cells of higher plants do not contain centrioles (Luykx, 1970; Pickett-Heaps, 1971); nor do they produce a polar ejection force like the one observed in animal cells (Khodjakov et al., 1996). It occurred to me that the correlation might not be accidental. Centrioles might be the source of the polar ejection force, and they might hold the clue to understanding cancer.

In the electron microscope, centrioles look like tiny turbines. Using TOPS as my guide, I concluded that if centrioles *look* like turbines they might actually *be* turbines. I then used reverse engineering to formulate a testable, quantitative hypothesis linking centrioles, polar ejection forces, and cancer. That hypothesis is summarized below, and the detailed technical version (Wells, 2004) has been submitted for publication in a biology journal.

Centrioles as tiny turbines

Centrioles are roughly cylindrical in shape, and when mature they typically have a diameter of about 0.2 μm and a length of about 0.4 μm. The end of a centriole closest to the center of the cell is called "proximal," and the other end is called "distal." The organelle is composed of nine clusters of microtubules. These are organized as triplets in the proximal half, but the outermost microtubule in each triplet terminates about halfway toward the distal end, which consists of doublet microtubules (Stubblefield and Brinkley, 1967; De Harven, 1968; Wheatley, 1982; Bornens, et al., 1987).

The triplet microtubules making up the proximal half of a centriole form blades that are tilted about 45 degrees relative to the circumference. Various authors have noted that the triplet microtubules have a turbine-like disposition. If the centriole were actually a tiny turbine, fluid exiting through the blades would cause the organelle to rotate clockwise when viewed from the proximal end.

In order for the centriolar turbine to turn, there must be a mechanism to pump fluid through the blades. Helical structures have been observed in the lumens of centrioles (Stubblefield and Brinkley, 1967; Paintrand et al., 1992). Helical structures have also been observed associated with the central pair apparatus that rotates inside a ciliary or flagellar axoneme (Goodenough and Heuser, 1985; Mitchell, 2003), and axonemes are nucleated by basal bodies that are interconvertible with centrioles (Preble et al., 2000). If the helix inside a centriole rotates like the central apparatus of an axoneme, it could function as an "Archimedes' screw," a corkscrew-action pump that would draw fluid in through the proximal end and force it out through the triplet-microtubule turbine blades.

The helical pump could be powered by dynein. Dynein produces microtubule-mediated movements in the axonemes of cilia and flagella, though its mode of action in centrioles would have to be different from the former. Cilia and flagella move because of dynein-based sliding between doublet microtubules (Brokaw, 1994; Porter and Sale, 2000). In centrioles, however, the only dynein-like structures appear to be associated with internal columns in the lumen. (Paintrand et al., 1992) Dynein molecules in those columns could drive an internal Archimedes' screw pump by interacting with its helical blades. By analogy with the central pair apparatus in axonemes, the helix inside a centriole would presumably rotate at about 100 Hz.

Dynamics of a centriole pair

Most centrosomes contain a pair of centrioles connected near their proximal ends and oriented at right angles to each other (Bornens, et al., 1987; Paintrand et al., 1992; Bornens, 2002). The older member ("mother") of a centriole pair is distinguished from the younger ("daughter") by various structures, including "distal appendages" that project at an angle from the distal-most edges of the doublet microtubules, and "subdistal appendages" that form a thick collar around most of the distal half of the mother centriole and serve as an anchor for microtubules that extend into the spindle (Paintrand et al., 1992; Piel et al., 2000). When centrioles are isolated under low calcium conditions, the subdistal appendages dissociate from the wall of the mother centriole while the distal appendages remain connected to it (Paintrand et al., 1992). These characteristics are consistent with a model in which the subdistal appendages form a bearing connected to the cell's cytoskeleton, and the distal appendages form a flange holding the mother centriole in its bearing. (**Figure 1**)

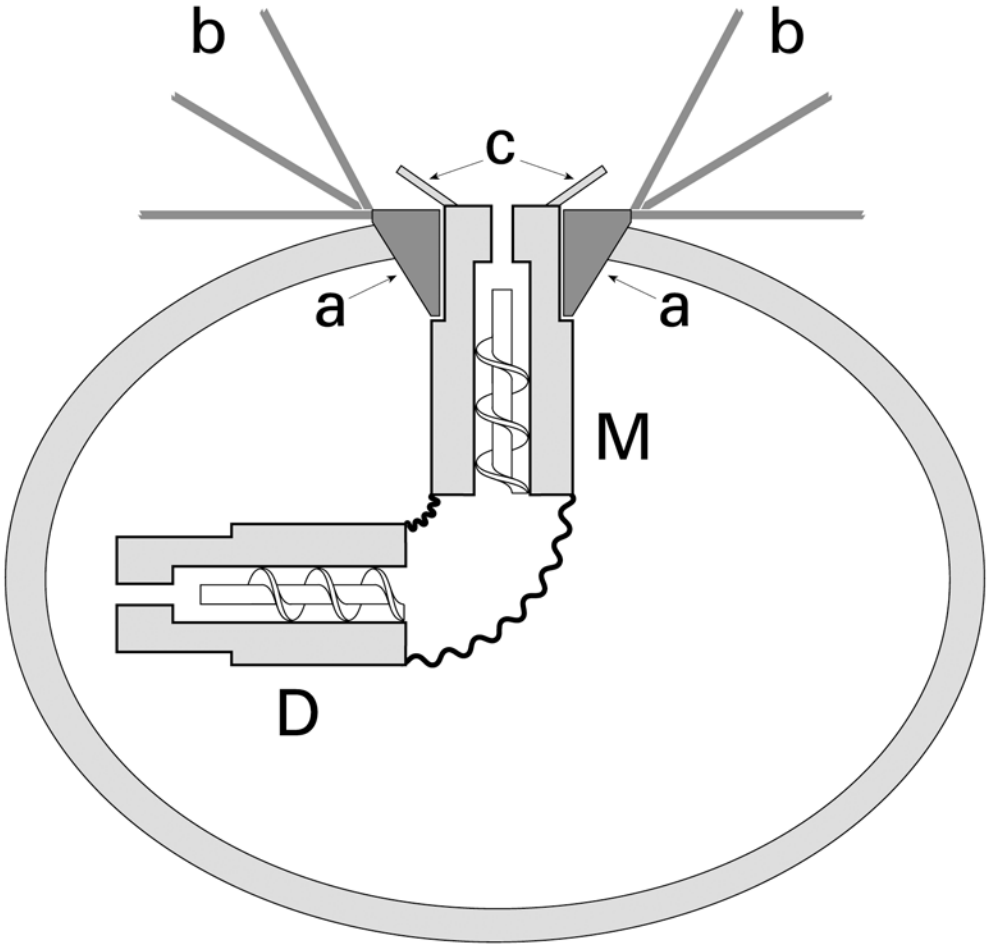

Figure 1. Cross-section of a centriole pair. (M) Mother centriole. (D) Daughter centriole. Note the internal helices in each. (a) Subdistal appendages. (b) Spindle microtubules (which are anchored to the subdistal appendages). (c) Distal appendages. In the hypothesis presented here, the subdistal appendages function as a bearing and the distal appendages function as a flange. The large ellipse is the centromatrix capsule enclosing the centriole pair.

The daughter centriole, constrained by its proximal connection to the mother, would not rotate on its own axis; instead, it would swing bodily around the long axis of the mother centriole. Nevertheless, the daughter would still function as a turbine, producing a torque that would press the mother centriole laterally against the inner wall of its bearing. The daughter's torque would thereby cause the centriole pair to revolve eccentrically, producing a wobble resembling the motion of a laboratory vortexer.

The centriole pair is surrounded by a structural network of 12- to 15-nm diameter filaments called the "centromatrix" (Schnackenberg et al., 1998). The fluid inside the centromatrix capsule would not remain stationary, but would be stirred in a circle by the revolving daughter centriole. It might seem that friction against the inner wall of the centromatrix would offer enormous resistance to such movement; surprisingly, however, the resistance could be quite low because of ""nanobubbles" (Tyrrell and Attard, 2001; Steitz et al., 2003; Ball, 2003). Nanobubbles 200 nm in diameter and 20 nm thick could render a surface composed of hydrophobic 12-15 nm filaments almost frictionless. With power being continually supplied by the helical pump inside the mother centriole, calculations show that the centriole pair could reach an angular velocity of more than 10 kHz midway through cell division (see Mathematical Appendix, below).

Centrioles and the polar ejection force

The subdistal appendages that form the bearing for the revolving centriole pair also anchor microtubules that extend into the spindle (Paintrand et al., 1992; Piel et al., 2000). Other microtubules are anchored in the pericentriolar material surrounding the centromatrix. Just as a vortexer imparts its wobble to a test tube placed in it, so the centrosome would impart its wobble to the microtubules emanating from it. Spindle microtubules would presumably not transmit this motion as uniformly as the rigid glass walls of a test tube, but they may be rigid enough to induce objects within the spindle to undergo movements not unlike the contents of a test tube in a vortexer. It is worth noting in this regard that microtubules in ordered arrays exhibit more stiffness than would be expected from non-interacting rigid rods (Sato et al., 1988). Objects within the spindle would then undergo high frequency, small amplitude circular movements perpendicular to polar microtubules, as originally proposed by Wells (1985). Objects in the middle of a bipolar spindle would thus experience a centrifugal force laterally outward from the long axis of the spindle. Calculations (see Mathematical Appendix, below) show that this force could be more than five times as strong as the force of gravity. The conical arrangement of the microtubules would convert part of this to a component parallel to the spindle axis, producing a smaller force tending to move objects radially away from the pole. The wobble produced by a revolving centriole pair could thereby generate a polar ejection force.

Implications for cancer

If centrioles generate a polar ejection force, the presence of too many centriole pairs at either pole could result in an excessive polar ejection force that subjects chromosomes to unusual stresses that cause breaks and translocations. Even more serious than the presence of extra centrioles would be a failure of the control mechanisms that normally shut down centriolar turbines at the beginning of anaphase, since centriole pairs would then continue to accelerate and generate polar ejection forces far greater than normal.

A centriole-generated polar ejection force could be regulated in part by intracellular calcium levels. In dividing animal cells, the onset of anaphase is normally accompanied by a transient rise in intracellular Ca^{2+} concentration (Poenie et al., 1986). Elevated Ca^{2+} concentrations can lead to asymmetrical bending or quiescence in sea urchin sperm flagella axonemes (Brokaw, 1987). This may be due to a Ca^{2+}-induced change in the direction of the power stroke of dynein arms (Ishijima et al., 1996), or to an effect on the central pair apparatus (Bannai, et al., 2000). If the helical pump inside a centriole is driven by dynein, then a rise in intracellular calcium concentration could shut it down.

It is worth noting in this regard that a number of recent studies have reported a link between calcium and vitamin D deficiency and various types of cancer. Dietary calcium supplements can modestly reduce the risk of colorectal cancer (McCullough et al., 2003), and there appears to be an inverse correlation between vitamin D levels and prostate cancer (Konety et al., 1999). Analogs and metabolites of vitamin D inhibit the growth of prostate cancer cells in vitro (Krishnan et al., 2003) and in vivo (Vegesna et al., 2003), and they have similar inhibitory effects on breast cancer cells (Flanagan et al., 2003). If centrioles generate a polar ejection force, the correlation between calcium and vitamin D levels and cancer could be a consequence -- at least in part -- of the role of calcium in turning off centriolar turbines at the onset of anaphase.

Discussion

Stubblefield and Brinkley (1967) proposed that sequential movements of the centriole's triplet microtubules turn an internal helix, which they believed to be DNA, in order to facilitate microtubule assembly. It has since become clear, however, that centrioles do not contain DNA (Marshall and Rosenbaum, 2000). In the hypothesis proposed here, a centriole is a tiny turbine composed of triplet microtubule blades and powered by an internal helical pump. This is the reverse of Stubblefield and Brinkley's idea that the triplet microtubules turn the internal helix.

Bornens (1979) suggested that rapidly rotating centrioles, powered by an ATPase in cartwheel structures at their proximal ends, function like gyroscopes

to provide an inertial reference system for the cell and generate electrical oscillations that coordinate cellular processes. In the hypothesis proposed here, rapidly rotating centrioles would produce small-amplitude, high-oscillations in spindle microtubules that are mechanical, not electrical as Bornens proposed.

There are several ways to test this hypothesis. Two ways are:

It should be possible to detect oscillations in spindle microtubules early in prometaphase by immunofluorescence microscopy and high-speed camera technology.

It should be possible to regulate the polar ejection force by raising the concentration of intracellular calcium during prometaphase or blocking its rise at the beginning of anaphase.

If the hypothesis presented here withstands these and other experimental tests, then it may contribute to a better understanding not only of cell division, but also of cancer.

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Mathematical Appendix

This is only a summary; for details see Wells (2004).

A rotating helical pump would cause a fluid flow U into the proximal end of the centriole of

$$U = 4\pi\phi R_o \tan\theta (R_o^2 - R_i^2) \quad \text{(A1)}$$

in which ϕ and θ are the angular velocity and pitch of the helix, respectively; R_o is the radius of the centriolar lumen (and thus the outer radius of the helix blades); and R_i is the radius of the central column around which the blades wind. Neglecting the thickness of the blades, and using values derived from electron micrographs of centrioles and measurements of central pair rotations in cilia, the fluid flow can be calculated to be of the order of $U \approx 10^{-19}$ m^3 sec^{-1}.

The torque τ produced by the centriolar turbine would be the tangential component of the product of the velocity and the mass of fluid moving through the slits per second, multiplied by the distance of the turbine blades from the axis of rotation (approximately the outer radius of the centriole). The velocity and mass flow can be calculated from U, the approximate area of the slits between the turbine blades, and the density of the fluid being pumped through them. Since the outer radius of a centriole is approximately 0.1 μm, the resulting torque would be of the order of $\tau \approx 10^{-28}$ kg m^2 sec^{-2}.

In the rotational equivalent of Newton's force law, the angular acceleration α would be

$$\alpha = \tau / I \quad \text{(A2)}$$

in which I is the effective moment of inertia of the revolving centriole pair. This would be of the order of 10^{-29} kg m^2 (for derivation see Wells, 2004), so the angular acceleration produced by the torque of the mother centriole would be of the order of $\alpha \approx 10$ sec^{-2}. Assuming negligible friction (because of nanobubbles), this torque would cause the angular velocity of the centriole pair to increase about 10 Hz every second. One minute after start-up, the centriole pair would be revolving about 600 Hz; after twenty minutes (i.e., about halfway through cell division), the pair would be revolving about 12,000 Hz.

Orthogonally oriented centrioles would impart a wobble to the spindle microtubules and produce a centrifugal acceleration β given by

$$\beta = (\alpha t)^2 d \tan\varepsilon \quad \text{(A3)}$$

in which t is the number of seconds that have elapsed since the turbines started, d is an object's distance from the centrosome, and ε is the eccentricity of the

wobble. If the eccentricity of the wobble is 1°, then twenty minutes after start-up an object 20 μm from the spindle pole would be subjected to a centrifugal acceleration β of approximately 50 m sec^{-2}, about five times greater than the acceleration due to gravity.