On the Origin of Space

Part 20A: Non-Local (Holistic) Life
- A Survey - Basic Cell Data

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Abstract
This is the first part of a 4-part survey taking a look from a physics standpoint at selected biological texts, identifying the widespread need there to consider holistic aspects in order for key observations to make physical sense. We point out the tendency of that literature to instead ignore these holistic aspects, as no physical theory appears to be available to cover them. This review serves as a base for a physical approach to Life developed elsewhere attempting to provide the missing physical understanding.

Introduction
In a review task as wide as this one, the basics must be dug out of the details. The texts covered here and in the other parts provide a good base in that regard, identifying key physical features and relations among cells, but we don’t pretend to cover everything. The biological cell design is evaluated here and in the next part of this article. The third part deals with cell inter-relations, while the last advances physical hypotheses about the features found. Outside a few cases, we will not discuss the cell eukaryotic nucleus system and its design, and this from both lack of space and enlightening literature on the matter.
The centrosome and mitosis

1. Vandré and Borisy (1989) - called VB here - concentrate on the centrosome appearing in mitosis, and mention many variations on the “typical” behavior and form of this “organelle.”

Nothing is mentioned however about how microtubules (MTs), simple cylindrical polymers of α- and β-tubulin proteins, find themselves during mitosis in a spindle shape between the centrosomes containing the centrioles. They ignore the obvious coordination with the system of kinetochores. I shall see in the next part of this article that the neighborhood of the kinetochores may induce the MT polymerization also, but then straight out in a barrel pattern.

A network of thin filaments (later found to be “pericentrin”) called the pericentriolar material (PCM) was then reported surrounding the centrioles in a spheroid centered around the parent centriole, with no physical reason why. The organization of a focused region of microtubule growth may precede the accumulation of PCM at that site. A quadripartition experiment is reported to have been done using a chemical that stopped the centriole replication. Then two spindles formed from 4 mono-centriolar poles, followed by the cell splitting as a cloverleaf fashion into 4 cells. From then on mitosis occurred with single poles. Separately, the PCM association with the child centriole was found to occur only after the splitting of the pair. We can only conclude that centriole-centrosome replication and DNA-nucleus replication are events coordinated in time, but are otherwise independent holistic processes.

A few years after this text, a new tubulin protein called γ-tubulin was found to be forming “lockwasher” rings in the PCM, nucleating MTs (Urbani & Stearns, 1999). This was besides the known α- and β-tubulin in MTs and centrioles.

The physical origin of the generation of a child centriole (especially at a perpendicular location from the parent) and the “focused region” of MT generation by the PCM are still unknown after 25 years of research, and this in spite of the exquisitely detailed chemical knowledge we have now of that area of the cell.

There is a trend today toward finding chemicals that would “regulate” these functions, but such knowledge would not answer the physical question on WHY such spatially “focused” events happen with their observed non-local geometry. The MT nucleating capacity of the centrosome is tied to the mitotic cycle, not the centriole cycle, so there must be agents communicating signals between the
two apparently holistic systems, but how they are communicated between them is the key unknown. In fact, a few years after VB, the CDK2-E complex was found to be produced by the nucleus to synchronize the centrosome cycle from the DNA process cycle side, but the physical reason for that complex to leave the nucleus and to find itself in the centrosome area of the cell is still unknown.

There is material (later found to contain ε-tubulin) that deposits on the parent centriole slats as a dense “sheath,” with growths in fin-like shapes called “centriolar feet” by VB at the distal end of the parent centriole (away from the child), from where a short cilium grows. As Margulis identified (see later below), this identifies the centriole to be originally a flagellum “basal body,” but this very localized happening is unexplained to this day. The PCM expands during mitosis with concomitant loss of these centriolar feet and cilium while there is a ten-fold increase in MTs nucleating capacity within an astral array. This manifestly holistic process has no physical explanation.

Besides the mystery of the perpendicular location of the child centriole vs. the parent, a series of questions are left without answers still to this day:

1. How is the PCM maintained (spatially) as a spheroidal entity?
2. Why does it find itself around the centrioles?
3. What is the physical relationship of the centrioles with the PCM?
4. How is the spatially directed initiation of MTs physically controlled?
5. Is the centrosome controlling the length of MTs, and if yes, how?

2. Margulis (1993) gives a wide view of where the centrosome organelle belongs to in microbiology at large and in the evolution of Life, adding to the previous VB text the background needed to understand and follow the meaning of the events observed.

As Margulis shows, from earlier Cleveland’s work, the shape of the spindle (its width at the equator) depends on the chromosomes presence by holding the kinetochores. So the spindle bulge must come from the spatial requirement created by the presence of the chromosomes (their bulk dimension).

“Mitosis is then a chimeric [composite of several systems] process, the establishment of which involved symbiosis as well as direct filiation through the new nuclear membrane.” The symbiosis of the DNA system with MTs was the one that led to multicellularity, while prokaryotes (bacteria) remained as “dust” in the long history of Life.
Margulis argues here that the nucleus with its “double membrane enigma” is the basic organism (containing the DNA) which had to create a membrane to protect itself against attacks by surface spirochetes (microtubular or MT organisms?) that ended in eukaryotes as being the MT system and mitotic apparatus.

In the ciliate mating process, “the cytoplasmic parent, not the nuclear parent, determines the transmission of certain cortical traits.”

The question is asked: "What kind of selection pressures gave rise to mitosis?" A hypothesis is given as answer: "In the absence of efficient mechanisms for ensuring the equal distribution of newly synthesized DNA to progeny, the genetic complexity of the earliest eukaryotes must have been limited." Then “the interactions of populations of the surface spirochetes that became undulipodia underlie the species-specific patterns and the autonomous genetic behavior of the ciliate cortex.” This leads to the hypothesis that the nuclear membrane evolved also from spirochete genes, and that “the precise distribution of genes led to the final refinement of mitosis,” all derived from spirochetes.

Also: “An incomplete distribution of genes exerted continuing pressure for improved mechanisms of chromatin segregation.” Then Margulis goes over her set of steps that led to present mitosis, showing that the present centrioles are the descendants of spirochetes that superposed their division system with the host system where the spindle starts from the centrosome instead of the nuclear material, presumably giving a much more reliable segregation knowing the rigors of natural selection. This leads to the hypotheses that “the failure to solve the problem of reproduction and motility led to the origin of multicellularity” and that “the genome from spirochetes provided cell differentiation in metazoa.”

*Synchronism* is a big theme in the motion of spirochetes. This has been explained (or explained away) through hydrodynamics. Yet the reproduction part (mitosis) being an internal process, hydrodynamics can’t explain that phenomenon, leading to a **holistic phenomenon** of unknown physical origin to this day.

Margulis gives a good reason for the existence of centrioles: The improvement of mitosis reliability in chromosomes separation, allowing the development of large gene banks. She portrays centrioles as exclusively supporting the MT spindle in mitosis. No mention is made of mitosis without centrioles in metazoa (multicellulars) early in embryo development. She takes the synchronization between centrioles “emitting” MTs as granted even though it is an unexplained
while immediately observable phenomenon. This theme of synchronism is brought clearly in the description of spirochetes motion. What kind of phenomenon are we looking at in mitosis, if not a non-local holistic process of unknown origin?

Cell medium and motion

Even though an older text, Hameroff (1987, Chap. 5) has a number of insights as to the kind of medium Life has constructed for itself. This is very important because the a priori idea of using statistical mechanics in that area of science becomes irrelevant when the description of the very “tight” medium of the cell is considered.

Hameroff quotes Albrecht-Buehler: “Cell movement appears to be determined by some kind of chemical computer, the nature of which is beyond our present understanding.” Then he adds: “Internal movement such as streaming of the cytoplasm, secretion of cell product vesicles, engulfment of matter, and the separation of paired chromosomes in cell division are routine functions whose complexity, organization, and precision generally boggle biologists.” It certainly would be so if such a system was only an assemblage of separated entities acting only from knowledge of their nearest neighbor. So let's see the details of this medium to find the kind of physics we really need.

1. The cytoskeleton

   a. Microtubules (MT) - “When MTs are required by a cell for a particular function, MTs assemble in the appropriate part of the cell, with the necessary orientation, and, as MTs are no longer needed, they depolymerize.” Hameroff sees MTs as “real time executives of dynamic spatial activities within living cells.” He fails however to mention that MTs themselves appear to be “organized” around a centrosome, but it is true that MTs assemble not only from the centrosome but also by themselves “like viruses” in neurons where there is no centrosome or centriole. They are stable in cilia and flagella, and unstable in mitotic spindles, with no physical reason given, except that they are tied to “basal bodies,” which are centrioles.

   Random assembly prevails instead of organized assembly in energy depleted cells. The energy from phosphate bond hydrolysis used by MT polymerization is unaccounted for (i.e. unexplained). Our conclusion here is that if local inertias are developed in the cell, as Bornens (1979) reported, energy has to be used to pro-
duce such a physical effect.

Drawings show the various cell components located along MTs coming from the centrosome. Without MTs the cell becomes totally disorganized.

Then Hameroff asks: How can a peripheral clue lead to reorganization deep in the cell? He hypothesizes that either a signal is relayed through the MTs to the centrioles, leading somehow to a change in the nucleation orientation out of the centrosome, or that a local signal acts like a domino effect to affect the entire cell, maybe both, resulting in a particular overall functional role for the cell.

He adds that the delicate array of the two centriole pairs, with their connected MT spindles, and the projections to the cell cortex have suggested to many observers some type of electromagnetic field pattern. But since e-m fields can't be possible in such a medium, what physical effect are we looking at?

b. Intermediate filaments (IF) - Neurofilaments are seen as providing axons structural strength. However their existence is unexplained in neurons in general.

c. Microtrabecular lattice (MTL) - The MTL is the lowest level of the cell cytoskeleton, with actin mixed with various types of myosin filaments. It is a filler between the other cytoskeleton components, forming a sort of cytomuscle creating patterns dividing the cell into domains. Upon trigger by calcium ions waves the MTL switch domains between their “gel” and “sol” state. This switching is part of amoeboid movements as a result of MT relocations.

Diffusion in the cell cytoplasm is much slower than expected, knowing the cytoplasm aqueous phase occupies 4/5 of its volume. Such a discrepancy is explained by molecules like RNA being dynamically bound to the cell MTL “solid state.” This feature would also account in general for the efficiency of various enzymatic processes. The MTL vast surface being lined up with “ordered” and “vicinal” water would account for the lack of Brownian motion observed in cells, a sign that stochastic diffusion can only have a very short span there.

2. Cell development and collective motion

a. Amoeboid feelers - Moves of an amoeba using “feelers” are described. These protrusions made of actin are sensory elements responding to lack of stickiness or presence of obstacles. So there is a chemical regulatory system at work realizing the motion process. But every few hours the cell changes direction for no reason. Why? Only a random thing? Indeed, 2% of a fibroblast can be
torn out of the cell body and then moves on its own protrusions, so each cell compartment is a physico-chemical system by itself capable of autonomous (random) motion.

However, the cell motion has a front-rear axis, an overall motion coordination, and rules for changing direction. Therefore, as part of the cell, there is need for coordination of many MTL domains and navigation commands which involve assessment of the overall environment. It appears that the MTs in the area provide this coordination, and the MTs in turn receive orders from the centrosome (centrioles). But how?

b. Neural axon “growth cones” - This activity is similar to the feeler movements above, using actin also. They continually probe their surroundings by sending out and then retracting delicate ruffles known as lamellipodia, and finger-like projections called filopodia. These dynamic appendages are a meshwork of actin filaments. MTs and neurofilaments splay into the growth cones, but generally stop short of the actin-rich areas. MTs are necessary for the growth of neurites, while actin filaments are essential for growth cone protrusions. A complex interplay between actin and MTs is then required there. Hameroff hypothesizes that the MT cytoskeleton is in charge of such process. But how could it know what to do? The same question would be asked from an outside “scent” the cytoplasm would receive. This is a fundamental problem for present microbiology. This subject will be discussed further in the other parts of this article.

c. Axoplasmic transport along MTs – Contrary to how they are portrayed, being mere localized elements, kinesin and dynein “motor” molecules are not the physical agent that decide on molecular transport in cells. Since microtubules are the physical common entities supporting them, it is much more physical to assume that these “motors” are controlled by the internal evolution of their support, and merely help the precision of the operation. This evolution can only be an unobservable physical phenomenon acting behind the scenes.

The mechanical arm process of moving vesicles along MTs is similar to muscle action processes. However, unlike for muscles which use a chemical agent, the origin of the precise directed motion is unknown. A MT removed from a cell will “glide” on a glass due to the action of its “motors,” so the collective holistic action is still there “in vitro.” It is also unclear how the energy delivered to the system is used to produce this holistic motion. Hameroff later suggested a soliton
wave process may use this energy, but being a *purposeful directed motion in cells*, this speculation has to be very unlikely. (The existence of the soliton effect remains to be proven anyway.)

*d. Collective ciliary movement* - This type of motion happens also for cilia taken out of a cell. The origin of the wave synchronization is again unknown. Hydrodynamics was thought to account for this effect in spirochetes (see Margulis), but a single “gliding” MT on a glass proved the explanation invalid, as we saw above. Even though these collective effects were identified in the early 1970s they are still not physically explained 30 years later.

**Other key holistic effects in cells**

1. Monopolar mitotic spindle

   A simple chemical has been found to prevent the cell from completing its mitosis by replacing the mitotic spindle with a point-symmetry arrangement of the chromosomes (spheroid) around the centrosome/centriole pairs, which then no longer separate. (Mayer et al., 1999) This very specifically acting chemical was discovered through long screening processes done *by observing which chemical suppresses MT motion* (a mysterious phenomenon with no theoretical explanation as we have seen above).

   Then the chromosomes have oscillatory movements to and from the centrioles by MTs simply polymerizing and depolymerizing in a collective fashion. This is a clear indication of the holistic character of the mitotic process, as the entire evolution is changed.

   Now the chemical is planned to be used as a base to identify how the spindle forms. However, this formation cannot be a chemical process, being holistic as we have seen. This product is wished to be used as part of anti-cancer drugs studies. But what would this chemical do to both centriole and DNA holistic functions throughout the body? It certainly would be a lot less hazardous if we had more than a very partial empirical knowledge here.

2. Uncomputable Life

   Inside cells, newly synthesized chains of amino acids take a short time to fold into a functional protein. But even though researchers have measured the forces between atoms in great detail and can easily predict mathematically how a handful of amino acids will interact, precisely modeling the folding of typical proteins
has been out of reach, even using the fastest computers. Even for a small protein, a simulation of just a fraction of the folding process takes months of supercomputing time. With the new IBM petaflops machine it will take about 1 year to simulate the complete folding of a typical protein. (Service, 1999)

Even then the protein-folding problem may not be solved, as the mathematical simulation method is still an approximation not taking into account all the interactions between atoms, so the result may not be correct. The complete computational problem is thus definitely intractable. How can living materials perform such foldings in very short periods of time if they do not effect a quantum many-realities parallel search at the level of the entire protein? This matter looks to be similar to the quantum formation of quasi-crystals, which is also a “hard” computational problem.

3. Endocytosis
With Marsh and McMahon (1999) we meet the key structural component participating somehow in intra-cellular transport, clathrin. Its parts, the triskelions, make a “coat” that clings on the inside of the cell membrane and curves it inward to make vesicles. The key here is that the terminals of the three branches of a triskelion attach to receptors complexes in the membrane containing “hydrophobic pockets.” This means that such pockets are then finding themselves inside the vesicle, and thus are placed in a quasi-spherical arrangement. Knowing the mitotic role of MTs in physical actions the potential for physical effects due to the hydrophobic pockets here may be in the line of the ones found with tubulin in MTs, which have such pockets, but in a cylindrical arrangement. Could this quasi-spherical characteristic be the source of key physical effects such as in the Golgi precise maintenance system and in neural synapses, where directed vesicle motions specific for their purpose are required and observed? We will revisit this matter in the next part of this article.

4. Cell form – The “tensegrity” and “mechanical integration” questions
As Hameroff (1987) described, actin filaments, with tropomyosin, support the cell nucleus in its position versus the cell membrane. They attach to the vertices of a polyhedral actin gel coat on the nuclear membrane with “integrin” involved there. How is this built? Also, when the cell is in the final stage of division, a “ring of constriction” or “cleavage furrow” encircles the equator of the cell and
constricts the cytoplasm until it is divided into two cells. What makes actin locate precisely there and act like that? Something physical must be at work. Well, we know that MTs are in the neighborhood...

In that area, Ingber (1998, 2000) is another remake of “spontaneous life generation,” seen now as “mechano-chemistry.” The seriousness of the matter is that the approach is in fact an attempt at making believe it is looking for a truth about Nature, while it is a philosophical sophism, where the molecules act as if they had a mind of their own (the Intentional Stance by Dennett, 1996), and this only for the sake of putting the system into the architectural equations of tensegrity, which is a well-known mathematical formalism. Here the stance is, as first hinted by D'Arcy Thompson (1917), that, if the organism needs to have a form, it will take that form following well-known global (holistic?) geometric constraints, and will minimize the material needed to obtain it. In other words, the need generates the form. Do not ask how Nature gets to do that, molecule by molecule, as that's Nature's unknowable secret that Science cannot reach. Ingber only intends to have a mathematical model so he can make computations on it, certainly not to know truths about Nature. This reasoning, updated by Ingber, goes like this: If the energy and the amount of material needed are minimized by that shape/structure, then the organism will use that shape/structure, and the individual molecules will act in a collective ("integrated") fashion to realize it. We can see this stance in many other places in the literature when dealing with molecular self-assembly.

I will not question the fact cells do act AS IF they used that “principle,” but using such is a cover-up for the void in Science's physical understanding of what's going on. Of course, the chariot that assembled itself minimized the energy for Cinderella to go to the Ball, but this does not explain the fairy's power to produce the chariot. Further, there is no such thing as a potential for a physical field of force remotely similar to electromagnetism “to effect forms.” Molecular structures are local objects in chemistry, they follow the laws of statistical mechanics. How will such molecules, just because they are in a living environment, behave AS IF they were part of a whole, “integrating” themselves to produce a form as Ingber (2000) says? The entire article has its reasoning backwards: The ability of a molecule to bend or stiffen things does NOT direct that molecule to do so! There has to be a sensing of the whole organism need to
do so, and further that a computation needs to be going on to build a constantly changing tensegrity structure! (Bucky Fuller himself needed a computer to get to his fixed structures.)

All this is then pointing to the QUANTUM basis of Life with its propensity to self-organize holistically. There is no such capability in the non-living world, the world of entropy and “heat death.” There Ingber attempts to cover up that last fact by trying to see a similar behavior in the non-living world where there is none. We know what builds our universe outside Life, and tensegrity has no place because it is a classical world of separated elements, especially when the speed of light forbids the mechanical connections he talks about to be taken as instantaneous. The physical mystery being covered up by the sophism cannot be anything else but the mystery of the quantum, where e.g. a particle splitting in two will still be ONE particle even if its parts are light-years away (and then there are indeed instantaneous connections through the quantum via defining space itself).

Conclusion

On the matter of the role of centrioles:

In a partnership with the chromosomal kinetochores, they seem to at least bring more reliability to the mitotic process through helping the cell to split by moving the centrosomes to opposite sides of the cell, a physical event that does not occur without centrioles. The quadripartition experiment reported by VB showed that centrioles as pairs are associated more with the splitting process of the cell than with the spindle formation. So centrioles are the key component of a multicellular animal organism.

Margulis also suggested that they may allow the cell to maintain its motility during that critical phase of the cell life. However, such a function could be performed only by sensing somehow the overall cell condition as a single-cell eukaryote seems to do (and needs to do!), and influencing, somehow with a purpose, the shape and motion of that cell, including its division.

By their central location, reproduction and motion within the cell (physical actions that are by themselves unexplained), centrioles appear to provide at least some physical motion coordination. This coordination cannot be effected via chemical processes, as such processes, by their very local nature, cannot provide
a differentiated spatial action involving the entire cell. Centrioles would then have to use unknown non-local holistic physical effects.

On top of this the PCM appears to be a holistic entity by itself, as it retains the ability to generate a centriole de novo. The very fact it is a localized entity containing γ-tubulin rings that operate as a group even though not apparently connected with each other, tells a lot about the non-local origin of their function.

In the second part of this article the chromosomal kinetochores, which are related to the nucleus (DNA system), will be looked at to obtain a feel about their function in mitosis. We will get also more background information on cell transport phenomena, being extensions of the non-local effects found in mitosis.

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