Abstract
This is the last 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. This review serves as a base for a physical approach to Life developed elsewhere attempting to provide the missing physical understanding. We apply here that new understanding through hypotheses about findings dug out of the literature to give a feel for the thrust of the approach.

Introduction
We have placed here interpretations that use the view from the relevant part of the Origin of Space thesis (Gouin, 2004a, b, c, d) to separate facts from speculation.

The centrosome and mitosis + role of kinetochores (Parts A and B)
The phenomenon of mitosis is central to the Life part (phase 2) of the study. The texts reviewed on that subject were behind the development of the theory. A key figure used during this development is in Vandré and Borisy (1989), reproduced below for reference (Fig. 1).
Fig. 1 –
A diagram of the centrosome containing an orthogonally orientated pair of centrioles (a) in interphase, (with primary cilium), and (b) during mitosis (cilium, dense sheath and feet are lost).

PC, parent centriole;
DC, daughter centriole;
C, primary cilium;
MS, cilium membrane sheath;
DS, dense sheath around parent centriole;
CF, centriolar feet;
S, centriolar satellite;
FM, (PCM) fibrous pericentriolar material;
MT, microtubule.

PCM is primarily associated with the parent centriole.
Of course, a lot of additional data have been found about centrioles since Vandré and Borisy, but the profound mysteries of their inertia and geometrical duplication remain; and so the physical theory we advance gets more sustained with time going by, especially when considering the impossible facts now known about their cousins, the “basal bodies” of cilia and flagella.

Gratton (2004): “Virtually all eukaryotic cilia and flagella have the same basic organization, based on the 9+2 arrangement of microtubules illustrated in the diagram (Fig. 2). The two inner microtubules are singlet structures, but the outer ring consists of 9 doublet microtubules, each bearing hundreds [thousands] of dynein molecules distributed along their length. The individual doublet microtubules are cross-linked by nexin and connected to the central structure by radial spokes. Consequently, when the dynein molecules in one doublet exert a force on the neighbouring doublet, the whole structure bends instead of the microtubules sliding against each other. This also requires that the activity of individual dynein molecules is regulated in some way.”

Wargo and Smith (2003) advanced (with arguments against by others) that this regulation was provided by the central rotating doublet structure sending a tempo signal to the outer doublets. Yet “the molecular mechanism of this signal transduction pathway is not well understood,” which is a key understatement since the required speed of propagation is beyond chemical diffusion. We have here again a problem of physically impossible forces. The answer from our theory is a leptonic space modulated photon pulse from the center doublet evolution going through the spokes keying the outer doublets evolutionary patterns directing the dynein appendages, themselves located via specific stationary patterns on these doublets.

Gratton (2004) goes on: “Dynein molecules towards the outside of the cilium have three functional head groups, but those on the inside have only two. [unexplained spatial pattern] In addition to the bending motility of the axonemes, there are separate anterograde and retrograde transport systems inside each cilium/flagellum to assemble and replace the protein components, and a third system responsible for surface motility on the plasmalemma surrounding the organelle. One of the dynein light chains is essential for the retrograde transport system.”
So, not only do we have a large-scale \textit{spatial (not chemical)} “regulation,” but many independent specialized “sub-regulations” as well. Now we can no longer be surprised about the large-scale holistic behavior found in mitosis. Here in fact recent texts address the impossible aspect of textbook mechanistic explanations for this mitotic function. Bloom (2002): “The current models, based on a balance of antagonistically acting mitotic ‘motors,’ kinetochores that can sense their position and direction of ‘force,’ dynamic microtubules, and ‘polar winds,’ \textbf{have the daunting task of explaining how forces are generated on slippery tracks}. [Furthermore] None of the extant models are completely satisfactory in explaining the diversity of mitotic ‘mechanisms’ in nature. An alternative hypothesis invokes the existence of a [unseen] matrix within or around the mitotic spindle.”

Pickett-Heaps et al. (1997): “A UV-microbeam cut several kinetochore fibers (k-fibers) in newt epithelial cells at metaphase and the half-spindle immediately shortened: In several cells, the remaining intact spindle fibers bowed outwards as they came under increased compression. Thus, severing of k-MTs can lead to increased tension between chromosomes and poles. This observation \textit{cannot be explained by models in which force is produced by motor molecules at the kinetochore} actively disassembling k-MTs.”

The above reference then attempts to bring the notion of \textit{tensegrity} as Ingber advances (see Part A) assuming an \textit{unseen} matrix - called a “cytoplast” - that would be under tension (is this another form of cosmological dark matter?).

Scholey et al. (2001): “Based on the effects of severing spindles using glass microneedles instead of UV irradiation, the motor for anaphase A is likely to be located at or near the kinetochore, rather than being distributed all along the kinetochore fiber. Therefore, at the present time \textit{no definitive evidence for the existence or molecular identity of the presumed microtrabecular matrix exists}.”

In effect, by admitting they can’t see the “matrix” they postulate behind the spindle, Pickett-Heaps et al. and Scholey et al. experimentally demonstrate in an independent manner that \textit{the collective motion of chromosomes can only come from spatial manifolds evolution considerations}, as Gouin (2004d) describes.

“When you have excluded the impossible, whatever remains, however improbable, must be the truth.”


\textbf{Monopolar mitotic spindle (Part A)}

The chemical obtained is replacing the neatly separated set of leptonic manifolds created by DNA kinetochores and centrioles programming with a single
manifold by statistically spreading out the leptonic manifolds dimensions. The split in two sets of dimensions for leptonic manifolds is no longer possible, and chromosomes can no longer be separated through the inflation of these manifolds as the thesis describes. The chromosomes are seen having oscillatory movements to and from the centrioles by MTs simply polymerizing and depolymerizing in a collective fashion at the edge of the single spheroidal leptonic manifold.

The disruption of the MT network through infection by a virus (Fig. 3) is a telltale of both the interaction of the virus with the cell leptonic space manifolds and the holistic quality of the MT network itself. Actin shows the intersection of ordinary space with the leptonic manifold sustained by the MTs and actin.

Kinesin and Dynein – organelle transport (Part B)

The “motor” molecules follow the dynamics of the quantum conformation waves of patterns along the surface of the MTs, patterns themselves selected by the centriole or the cell receptors. The fact these molecules are needed for transport is not an indication that they direct the transport on their own – they can’t provide that in such a unison manner! See earlier about cilia: The directions for the motion must come from the MTs quantum dynamics.
The molecules that effect the body circadian rhythm (Part B)

Motion in and out of the nucleus of molecules as cargo of “importin” must be controlled through the overall “feel” of the cell generated by the quantum program of its membrane receptors. Heat shock has demonstrated the influence of these receptors on the nuclear trafficking of specific molecules.

The wonder of unattended chemical “signaling cascades” (Part B)

In order to maintain the holistic entity, these series of chemical reactions cannot by magic decide on their own trigger and thus on spatial events (a misplaced mysticism if ever!). They have to be controlled/triggered by the cell receptors (quantum) program, probably translating their messages through lipid rafts to effect the needed chemistry. The chemist’s literature of course forgets to mention that physical fact. Haglund et al. (2004), as an exception, identify lipid rafts and receptors on the membrane as the (spatial) “integrators” of such cascades, in turn triggering growth cones in neurons. This function is to be connected to the similar centrosome function “as functional [spatial] integrator of the pathways contributing to the triggering of mitosis” (Dutertre et al., 2004). Physical relocation of molecules is a key, essentially non-chemical, unexplained fact of Life, and is usually not addressed by the chemical literature.

Cell form - Cell medium and motion – Chemotaxis (Parts A, B, C)

The unobservable topography of leptonic space manifolds looks to be defining the tracks being spoken in texts about motion of “signaling” molecules, helped by the “tune” of the dynamics of the molecules at the start and end of the voyage.

The randomization of the cell motion under certain conditions reminds one of the randomization occurring in mitotic spindle formation seen earlier. Could the protein involved in the mutation be an leptonic space manifold carrier?

What physically implements the holistic character (“wholeness”) of the system, the living entity? The study proposes that leptonic space (outside our 3 dimensions) lining up ordinary space, originating from the quantum, and created through hydrophobic pockets in specific molecular arrangements forms the binding physical support of an extended whole system invisible to direct observation, but with indirect consequences, such as multi-cellularity.

Chemical gradients do produce chemotaxis, but such would then merely act as a complement to the fundamental subjacent leptonic space topography. The
biologist would only see the shadow of such a physical entity through the various proteins types and spatial motion behaviors. Such a limitation in vista would explain the present difficulties in narrowing down the origin of the physiological effects observed, from cancer to developmental problems.

**Morphogens**

Since each of the two mitotic spindle poles have their leptonic space manifold in different dimensions, we could envision molecular complexes, “morphogens,” that carry submanifolds in a specific direction (as I have described for kinetochores in mitosis), except that such complexes are spread outside cells using various physical devices (they do not “diffuse”). Then their submanifolds will connect to the corresponding dimensionality manifolds held by the mitotic spindle poles within each cell.

How such leptonic space manifolds carriers can affect cell fate? While they localize the mitotic spindles, they have to split in other complexes at that point being then part of a much larger manifold, and must follow the leptonic space manifolds tracks to the nucleus (carried by the MT cytoskeleton) that exist in their own dimensionality. Once there, they identify the genes to express. (Here the study of the nuclear holistic system is required to say anything further.)

As described with the mitosis cleavage furrow, actin senses the connections with such manifolds, and thus is induced to produce hair, axons, etc., at a specific location in ordinary space. The genes define the topography of leptonic space, and centrioles coordinate its real-time non-local existence via MTs quantum evolution. Such an evolution in turn defines the location, orientation and cell fate of other cells. The morphogens are the carriers of the required leptonic space topography, which features depends on the existing genes, and WHEN they were produced. They do NOT regulate anything. They are mere “stakes” for the invisible physical spatial process that defines a whole organism.

**Development: Cytonemes and morphogens (Part C)**

Fig. 4 gives a hint on the kind of phenomenon happening close to the molecular level. Does that look to be a classical statistical effect?
Endocytosis (Parts A and B)

This key phenomenon for the survival of the cell (for energy and component material) has to be triggered through the lipid rafts on the membrane. Since rafts trigger endocytosis, they must be the physical origin of vesicular budding through generation of local leptonic manifolds attracting the “bending” molecules.

Receptors are most likely the distributed data processors that are orchestrating the various localizations of chemicals inside the cytoplasm, and this by creating dynamic fields attracting or repulsing specific kinds of molecules. Such “fields” are, as described in Gouin (2004b, c, d), local spatial warps akin to gravitation, except they are due to the quantum dynamics of the supramolecules, and thereby undetectable except by the correct types of molecular bond assemblies contained in the molecules mentioned in the reviewed texts.

Development: Lipid rafts (Part C)

Here is the conclusion of a Nature Timeline article (Edidin, 2003) on cell membranes: “The first missing element is dynamics. We’ve noted that lipids ‘dance to many tempos’; the problem is therefore to keep track of all the dancers and to see how they change their dance from one tempo to another (for example, from disordered and closely apposed to diffusing among other lipids, and then to diffusion in and out of a lipid domain that persists for a few seconds).”

“A third missing element is the association of the cytoskeleton with the bilayer. There is a large amount of literature on this topic, but it has not been integrated into a new membrane model.”
The large amount of literature may reflect the waffling on the matter as the physics of the connection with the cytoskeleton is unobservable, at least from chemistry, except for the connection via caveolae (Fig. 5) receiving-sending material through MT transport. The symphony of Life is there though, but in a different form.

Maybe we need to get listening devices so, instead of watching the dance, we can hear the tunes from lipid rafts attracting specific proteins, like sirens on the high seas. These sirens may themselves tune to Neptune in his centriolar form through the MTs. But then we are talking about a THIRD NEW SCIENCE, and the new kind of physical forces brought in Galileo’s late dialogues (Gouin, 2004b, d). No wonder then why we like music. (That’s what Bruno felt when he saw monads making our world.) And since the HIV-1 virus enters the cell via these lipid rafts, maybe we need to change their tune.

**Virus motion (Part C)**

Can't the geometrical arrangement of the virus capsid be a hint about where it gets its impetus for motion toward the nucleus of the cell? The study points out the geometric structure of the nuclear membrane as potentially related to the quantum leptonic space manifolds sustained by the membrane; couldn't the capsid by its geometry sustain also a set of manifolds that would connect to the ones from the nuclear membrane, thereby providing the needed impetus?

In the space generation hypothesis, the virus outer capsid via its polyhedral quantum structure generates a set of leptonic space manifolds that connect to the nucleus membrane, itself a well-known set of polygons, thereby having the impetus to go to that membrane. The microtubules also hold leptonic space manifolds according to my study, thereby providing an attractive impetus closer to the capsid. The observed stop and go motion corroborates the idea of a higher impetus.
brought by leptonic manifolds sustained by supramolecular structures along the way. We have seen earlier that a virus will affect the MT network, so there is no question that it connects with the cell manifolds.

**Glial cells and neurons - Molecules that guide axons (Part C)**

As of 1999 the literature is not looking at glial cells, while these underrated cells may form the 'Puppet Master' of the entire nervous process as identified in Gouin (2004d), relying on a space generation at the level of the quantum, very much as space generation defines the dynamics of reality at astronomical scales.

With the randomization of an axon motion, a randomization of leptonic space appears to occur, this time externally to the cells, so that axons no longer have a path to follow through the cylindrical leptonic space (as MTs have in mitosis). During the initial (developmental) growth of the axons the myelin cells arranged themselves around these cylindrical paths, but now their own residue randomizes this leptonic space. By removing their residue an axon is then free to rebuild the cylindrical leptonic space in stages with the help of new myelin cells attracted by the presence of the leptonic space. The value of the involved proteins resides then only in their ability to sense leptonic space, as actin seems to have in mitosis. In such an outlook the key to a successful research then resides in not only finding a randomizing agent during initial axonal development but also observe the glial cells in the area.

**Glial cells and neurons: Their cross-functions**

What is being thought as “memory support” in textbook neuroscience, i.e. chemicals and their releases in synapses, is merely a consequence of a change in quantum computational patterns in the glial cell centrioles. Here, as a confirming experiment, the function of vesicles should be checked after deleting the applicable centrioles (may be more than one). This function should simply cease.

**Conclusion**

The last review below will serve as a final conclusion of this survey.

“Mounting evidence suggests that glial cells, overlooked for half a century, may be nearly as critical to thinking and learning as neurons are.” This headline by Scientific American (Fields, 2004) would be an eye-opener for anybody who has not read my thesis written in 1998-1999. Back in 1999, nobody was looking
at glial cells for brain functions. The sad part of this is the very fact that still nobody has acted on my work even though it has been on the Web for 5 years now, and purely chemical considerations are still used in research on the nervous system. This article is no exception. Even though researchers say they want to “think out-of-the-box,” as obviously for them the subject is new, they have apparently no idea how to do that kind of thinking (which is part of true science). The lack of interest for my thesis is the proof of that assessment. Another proof lays in the fact this article is full of “mysterious” non-local behaviors of cells, but never raises the question of the adequacy of the tools and the line-of-thinking being used. In particular, it never wonders whether a chemical computer has any likelihood to be able to generate a thinking mind. How about that for “out-of-the-box” thinking? This is “more-of-the-same” (wishful) thinking trying to portray itself as true science, as the would-be thinkers know how limited they are in their approach on Life, having given up long ago on finding truths of Nature, as for them only “paradigms” are reachable by the limited Human mind.
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References

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