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A nano-reference-system based on two orthogonal (molecular) micro-goniometers: the centrosome of animal cells.

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ABSTRACT
The centrosome, because of 9-fold-symmetry of its orthogonalcentrioles and their circumferential polarity (non-equivalence of the nine centriolarblades,each one molecularly distinguishable), constitutes a biological discrete interface, composed of two orthogonal macromolecular protractors, capable of recognizing and decoding morphogenetic instructions, translating them and delivering targeted molecular complexes into their expected 3D real location in the cell: like an interface or a wiring device, the centrosome recognizes each targeting sequence, matches it with the corresponding receptor, soconnectingit with the correctly-oriented microtubule, directed and targeted towards the desired definite cortical compartment.Morphogenetic geometric instructions (DNA coded) are translated by the centrosome into actual locations in cells, and, as a consequence, macromolecules, labeled by DNA geometric signals, can be correctly delivered into their programmed cell locations. In addition, the centrosome (the most chiral and enantiomorphous cell structure) plays a geometric key role in left-right patterning: axial centriole circumferential polarity, if reversely oriented, constitutes a likely molecular base for bilateral symmetry.

Keywords–Centriole, centrosome, microtubules, γ-Turc.

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I. INTRODUCTION

Cells are not bags of disordered molecules: in a cell there are approximately ten billionsof protein molecules (Earth population: ~7 billions), subdivided into about ten thousand different types; a cell contains also millions of ribosomes, thousands of mitochondria, thousands and thousands of surface receptors… Even more complex is the extracellular matrix that surrounds cells, with dozens of different proteins and glycans (each type having many different isoforms) showing astonishing precise dispositions and orientations (the corneais made up oforthogonal layers of parallel fibres). "A living cell is not an aggregate of molecules but an organized pattern, structured in space and in time. Some conceptual issues in the genesis of spatial architecture: how molecules find their proper location in cell space, the origins of supramolecular order, the role of the genes, cell morphology, the continuity of cells, and the inheritance of order. The discussion is framed around a hierarchy of physiological processes that bridge the gap between nanometer-sized molecules and cells three to six orders of magnitude larger. Stepping stones include molecular self-organization, directional physiology, spatial markers, gradients, fields, and physical forces. The knowledge at hand leads to an unconventional interpretation of biological order. I have come to think of cells as self-organized systems composed of genetically specified elements plus heritable structures. The smallest self that can be fairly said to organize itself is the whole cell. If structure, form, and function are ever to be computed from data at a lower level, the starting point will be not the genome, but a spatially organized system of molecules. This conclusion invites us to reconsider our understanding of what genes do, what organisms are, and how living systems could have arisen on the early Earth" (Harold, 2005, in "Molecules into cells: specifying spatial architecture" [3]).Cells must avoid chaos: in living beings the goal of development is to perform complex large organs, planned to accomplish sophisticated functions, like balance, hearing and sight,assembled in organisms capable of running, flying or swimming [1]. Huge numbers of small dividing and replicating units (the cells) are put and held together, orderly arranged in order to realize high quality architecture. What is the key to success in development and growth?Developmental mechanisms are highly directional: orientations of cell division planes, cell movements and intercellular adhesions follow precise directions; internal and external forces (osmotic pressure, tension of extra-cellular fibers) stretch and bend cylindrical structures according to the angle between cell axes and extra-cellular fiber directions [2]. A single fertilized oocyte (the zygote) develops into an adult organism (composed of billions of cells) which shows the stereotypical shape characteristic of its species: how is the correct species specific shape achieved? How are cells guided to occupy their forecast position in the complex architectural plan of

each organ? How cells know the real physical location of "up", "down", "front", "rear" (points of reference that must be common and shared with all the cells belonging to the same organism)?To better explain this concept, let's think about a dividing cell: the respective position of the new arising daughter cells can be dictated by the orientation of the division plane (which is a geometrical process) or the topological disposition of adhesion factors on the cell membrane (which is a geometrical process too: polarity and adhesion factors must be located on a controlled 3D grid line); both processes require that the cell has been previously mapped and that a tool exists, able to manage a cell reference system [3].

Another geometrical question is mirror symmetry: in Metazoa(the animals) bilateral symmetry is a fundamental basic property of their locomotive apparatus and sensorineuralsystem: bilateral symmetry is the simplest and the most efficient way to drive and control the direction of movements and to localize the perceived signals (differential stimulation of two equal bilateral effectors or receptors); indeed without bilateral symmetry, the control of balance would be a difficult problemfor animals; this seems to be the reason of the extraordinary evolutionary success of bilateral symmetry in mobile organisms. In mathematics [4] bilateral symmetry of two dimensional objects consists in the opposite sign +/- of only one of the three coordinates: when a plane of symmetry is chosen (the "zy"plane, as an instance), any point P of coordinates "x, y, z" is symmetrical to the point P' which has coordinates "-x, y, z"; in a spherical reference system, only the sign of the coordinate φ changes. Assemblingtheonly goniometer responsible for the angle φ with inverted polarity (counter-clockwise / clockwise sequence of marks), each instruction relating to coordinate φ iscarried out symmetrically. Bilateral symmetry has strictly but simply geometrical bases: the astonishing symmetry of our ears (pinna, middle ear and its little bones, semicircular canals, cochlea and their inner structures) is incredible, but its symmetry consists in nothing but the sign of only one coordinate of each point [5][6].What, how and where is the geometrical interface capable of recognizing, understanding and translating (symmetrically)DNA-coded genetic geometrical instructions?

II. DEVELOPMENT AND MOLECULAR MORPHOGENS

Gradient of morphogens (signaling molecules that control and regulate gene activity) are thought to be capable of organizing developmental processes and generate the shape of organs and organisms, but there are fundamental theoretical difficulties and criticalities: chemical gradients, based on diffusible molecules, are subject to thermal fluctuations and the ability of receptors to discriminate small differences in their concentration changes the sensitivity to concentration in different parts of the gradient; then 3D spatial resolution is limited: thermal fluctuations impede precise positional information [3] [7] [8]. A striking demonstration that organ geometry is controlled by "discrete" precise geometric instructions comes from hair tilting in animals: millions of hairs,covering more than three square meters of skin of the familiar cow, show the same precise local inclination (bilaterally symmetric) in respect to the body-axes (anterior-posterior, dorsal-ventral, proximal-distal): if such an orientation (constant precision oflocal angles) were built under the control of chemical gradients, a clear Gaussian distribution of tilting angles would appear; on the contrary the inclination is the same in millions of structures. Similarly the feathers of birds have a common precise invariable orientation in order to fly [9]. In any case, if each new dermal *papilla* of a hair or a feather were able to produce a correctly oriented 3D gradient, its cells should know the position and orientationof body axes: the necessity of a geometric tool emerges again. Moreover: how can chemical gradients organize the (bilaterally symmetric) semicircular canals, each one correctly disposed on a Cartesian axis in respect to the body-axes? How can chemical gradients organize the (bilaterally symmetric) rotation of our opposable thumbs?Shaping a 3D chemical gradient (composed of billions and billions of very fast mobile molecules) appears much more difficult (if not impossible) than shaping organs composed of thousands of immobile cells (migration is restricted to few cell types).Size and dimension of organs and organisms can vary (Gaussian distribution of height or weight), but not angles, whose values are strictly controlled and chosen in a limited discrete set of values: homotehty (or isotropic Euclidean scaling) is the fundamental developmental law in multicellular organisms [10]. Leaf disposition follows a well-known geometrical rule (phyllotaxis): each new leaf bud arises in a point rotated of a precise angle in respect to the last leaf, generating a typical Fibonacci's spiral disposition [11]. Plant hormones, auxin above all, through their finely-tuned concentrations, control the expression of many genes and molecular pathways [12]; some of these genes necessarily code "geometric" positional information: plant cells divide showing a limited number of orientation of division planes (periclinal i.e. the division plane is parallel to the plane tangent to the external surface, and anticlinal, orthogonal to the periclinal plane and oriented parallel to the longitudinal axis or transverse to it): how can plants build cylindrical structures (stems, roots, trunks) if they use only three orthogonal axes apparently able

to realize just cuboid parallelepipeds?To drive cell movements, DNA (the operator) needs a "steering wheel", a rudder that transforms (translates) its genetic coded orders into correctly oriented actions. This implies the existence of a tool able to organize a 3D reference system, made up of real molecular cellular structures; a classical Cartesian reference system with three axes crossing the cell does not exist (this assertion is true for Metazoa, whereas in Plants parallel microtubule rings under the cell wall design a real grid line, like a globe with parallels but without meridians, something similar to a "cylindrical reference system"); on the contrary a spherical reference system organizer does exist in animal cells, which requires a structure, as small as is desired, composed of two molecular nano-"protractors/goniometers",orthogonal to each other and capable of generating oriented rays (Fig.1): this is the centrosome, with its two orthogonal centrioles, built with 9-fold symmetry and capable of assembling robust microtubules in oriented directions to wire, compartmentalize and map the cell membrane and its cortex (Fig.2).

III. THE CENTROSOME

The centrosome (on the Internet many clear images are freely available) is the only organelle, unique with the nucleus, which exists in single copy in the cells of animals [13] [14] [15]; it is made up of two orthogonal centrioles, disposed like the capital letter "L" (Fig.3): an axial "Mother" Centriole (MC) and an eccentric "Daughter" Centriole (DC) embedded in a protein matrix named PeriCentriolar Material (PCM), responsible for nucleation of microtubules (MTs); microtubules are long, hollow and robust tubes, made up of polymerized α- and β-tubulin dimers: the tubulin dimers polymerize in thirteen filaments which associate laterally to form a microtubule. An "aster" of non-intersecting MTs irradiates radially from the centrosome to the cell cortex. MTs are nucleated by γ-Tubulin Ring Complexes (γ-TuRCs) displaced on the centrosome surface and supported by protein scaffolds; the centrifugal direction and orientation of each MT is the consequence of the orientation and inclination of the γ-TuRC from which the MT arises: the PCM is a well ordered frame of proteins able to orientate γ-TuRCs and their scaffolds. Centrioles are roughly cylindrical structures composed of nine blades ("triplets", each one made of three parallel MTs) arranged in a cylindrical or, rather, prismatic barrel. In transvers sections centrioles resemble a "cartwheel" with a central hub connected by nine spokes to the nine triplets [16]. The orthogonal arrangement of the centrioles in the centrosome suggests that this organelle, in addition to its role in separating chromosomes (which is an exquisite mathematic/geometric task) is the nano-organizer of the cell "reference system" [8]: a spherical-reference-system builder, discrete and resistant to thermal fluctuations, based on two orthogonal protractors/goniometers, one (the axial centriole, said "mother") to manage geometry in the "xy" plane, the second (the eccentric transverse "daughter" centriole) to manage geometry in an orthogonal plane containing the "z" axis.Centrosome geometry and architecture must necessarily imply its function [17]: as a technical designer firstly squares a sheet, similarly, during the last period of each cell division, through the centrosome, DNA firstly maps and wires the non-polarized and homogeneous cell cortex/membrane of the newly formed cell [18] reproducing the orientation of the axes as in the mother cell: so, DNA can build the intrinsic (tissue-shared) 3D map of the cell, transforming a (DNA-coded) "virtual" grid line in a real "actual" cellular (shared) grid with intrinsic points of reference which dictate and orientate the position of membrane polarity factors [19]; DNA uses the centrosome to polarize the whole cellular cortex and membrane in order to assume the control and the mastery of the cellular and extracellular (tissutal) environment. Fixed in the ground, plants control their anisotropic growth by extrinsic reference systems (gravitropism and phototropism); animals, on the other hand, need an intrinsic self-made reference system to manage their (shared) geometry: plants do not have orthogonal centrioles, animals do.Plants, centrosome-free, have developed an own characteristic tool, a system of parallel microtubule rings under the cell wall to control cellulose fibril disposition, sensible to light and gravity and able to fix only few reference points, correlated to the intrinsic proximal-distal and interior-exterior axesand to external cues (mechanical forces, gravity, light) [20] [21] [22]: they build simple anatomical and histological 2D structures, with cylindrical or laminar arrangement: beautiful but anatomically simple, repeated a large number of times. In contrast animals, centrosome equipped, have developed anatomical forms that are particularly varied and complex (really 3D) whose architecture implies the existence of a right and proper geometric tool: the peacock's livery or the shells of crustaceans; animals show a high architectural accuracy and precision also at the tissue level: kidney cortex and medulla or spongy bone osteons and trabeculae; the same holds true for organs: skeleton or heart. In Vertebrates the shape of structures that perform complex functions is astonishing: the curvature of cornea, lens and retina strictly meets the need for projecting and focusing images; the inner ear -labyrinth and cochlea- in Mammals and Birds has a shape perfectly suited to measure the different vector-components of acceleration and analyze the frequency of acoustical signals (the basilar

membrane of the organ of Cortiperforms, in a sense, a "biological Fast Fourier Transform").

3.1How must a molecular nano-goniometer be organized? Basic characteristic of the 9-marks-goniometers.

Goniometers must be oriented (Fig.1): in a globe, one goniometer is "horizontal" (equatorial) the other, "vertical", passes through the North and South poles. The first goniometer, arranged on the equatorial plane, lies on the "xy" plane of the spherical reference system and its axis coincides with the "z" axis of the system: it is responsible to indicate the longitude (φ coordinate). A "0°" mark is used to orient the goniometer: on the globe it coincides with the meridian passing through Greenwich; on the "x y" plane it coincides with the "x" axis. Its nine marks indicate nine meridian (or vertical) spherical wedges.Orientation of the second goniometer: the second goniometer, responsible for the latitude (θ coordinate) is vertical, orthogonal to the first (Fig. 1); it is possible to define its "top" and its "bottom", like in a clock on a wall the mark "12" lies on the vertical axis and is always at the top; in the centrosome thisgoniometer showsits "0°" mark at the top and aligned with the "0°" mark of the first goniometer. In a classic spherical reference system, θ takes values from 0° to 180°, then it is convenient to consider the second goniometer divided, by the "vertical" diameter crossing its "0°" mark, into two halves (two facing symmetric hemi-goniometers) the "right" one showing on its round external border four marks (+40°; +80°; +120°; +160°) clockwise ordered starting from the "0°" mark, the "left" one showing the same four marks, but counterclockwise ordered (-40°; -80°; -120°; -160°).So, these eight marks (four "right" and four corresponding "left") are symmetrically positioned relatively to the "0°": they divide the space into five parallel "horizontal" sectors (two polar caps and three rings): each sector is subdivided in nine parts by the first goniometer(Fig.4). It is not necessary that goniometer centers coincide.This "two-goniometers-instrument" (9 meridian wedges and 5 parallel sectors -2 polar caps and 3 parallel disks-) is sufficient to subdivide the cell into 45 pyramids (or cones) with the apex at the center (at the end of cell division, the centrosome is positioned near the center of the cell), each one "labeled" by its own longitude and latitude (φ and θ coordinates, corresponding to the goniometers' marks): each base faces and subtends a vertex solid angle of $4\pi/45$ steradians, then its extension ($4\pi r^2/45$), in a cell with a diameter of 10 µm (radius: 5 µm; surface: approximately 314 μm^2) corresponds to about 7 μm^2 (a circle with a radius of 1.5 µm, or a square with a side of 2.6 µm) (Fig.2). These dimensions together with the physical properties of the MTs (bending-resistance and rigidity) give an idea about the interesting order of magnitude of the noise-resistance of this discrete system and of its precision, possibly better than that of chemical gradients.What are the fundamental requirements of abiological protractor? The marks of a protractor/goniometer are different each other. Non-equivalence of the triplets, their molecular-structural individuality capable of distinguishing each other, is then the main question to face. Then we must look for a plausible molecular "hardware" (geometrical PCM structure) and a corresponding molecular "software" (targeting sequences and centrosomal γ-TuRCs receptors) able to perform such functions.Indeed, from many study on Protists, centrioles appear really like cylindrical/prismatic goniometers with nine different molecular marks ("triplets") capable of arranging other self-assembling macromolecules and able to transmit their structural chemical non-equivalence (Protists are unicellular organisms: Ciliates are Protistspossessing cilia that are organized by a "basal body" which is a centriole).These studies have demonstrated that the nine triplets of their centrioles are different (not-equivalent) [23] [24], distinguishable and recognizable each other, arranged in an ordered sequence: circumferential polarity of basal body triplets is accorded with the disposition of the diverse fibers of the cytoskeleton. Geimer and Melkonian[25] have described an "acorn-like" structure in the inner distal part of the basal body, adhering in a highly asymmetric manner to the triplets 2-1-9-8-7, and another structure, shaped like the capital letter "V" in contact with the triplets 9, 5 and 4: "Whereas the cartwheel is thought to nucleate the nine fold rotational symmetry of the microtubular triplets the acorn might play an equally important role imposing rotational asymmetry on the microtubular triplets, perhaps leading to the asymmetric assembly of basal-body-associated fibers and hence cellular asymmetry in general".Beisson and Jerka-Dziadosz in "Polarities of the centriolar structure: morphogenetic consequences" [26]: "Among flagellates, the appendages are also varied, biochemically and morphologically; even microtubule appendages may have highly complex shapes as, for example, in *Physarum* or in *Ochromonas*"… In *Drosophila* the movements of nuclei to the embryo cortex are mediated by forces acting on the centrosomes rather than on the nucleus itself. Asters are presumably the main target of such forces. It is then conceivable that MTs, nucleated on either side of the centrosome or which display different characteristics, are nucleated under the influence of opposite sides of the centriolar shaft, just as different appendages arise from basal bodies. The situation in *S. cerevisiae* gives some support to the idea: the spindle pole body, functional equivalent of the centrosome,

displays a marked structural and functional bipolarity with an intranuclear spindle and an aster of cytoplasmic microtubules. Like in Metazoa, defective astral microtubules lead to defective nuclear positioning and defective budding. The biochemical and physiological differences between the two microtubule arrays are already well documented. Different γ-tubulin binding complexes interacting with the inner or outer plate respectively, are involved in the nucleation of the two microtubule arrays. Is it possible to confirm this idea that the circumferential, morphological, structural and molecular asymmetry of centrioles can be inferred from Mammals ciliated epithelia?While the circumferential anisotropy of centrioles cannot be ascertained within the centrosome, its existence can be inferred from the properties they express during ciliogenesis, be it the formation of a primary cilium or of bona fide 9+2 cilia in ciliated epithelia, some of which at least derive directly from the centrioles. As in Ciliates and flagellates, these basal bodies nucleate appendages of various molecular compositions (basal foot, striated rootlets, alarm sheets, etc. which anchor the basal body to the membrane and to the cytoskeleton) and these nucleations arise at specific sites of the basal body cylinder; in particular, the basal foot is located on triplets 5 and 6 corresponding to the side of the effective stroke of the cilium. What is remarkable is that basal feet develop before the basal bodies reach their membrane site and before they acquire their functional orientation".Recent works on the PCM structure in Mammals [27] [28] show that its organization is highly geometrical, arranged in nine compartments corresponding to the nine blade of the mother centriole (Fig.4): "By using SIM and STORM subdiffraction-resolution microscopies to visualize proteins critical for centrosome maturation, we demonstrate that the PCM is organized into two main structural domains: a layer juxtaposed to the centriole wall, and proteins extending later away from the centriole organized in a matrix. Analysis of Pericentrin-like protein reveals that its carboxy terminus is positioned at the centriole wall, it radiates outwards into the matrix and is organized in clusters having quasi-nine-fold symmetry. By RNA-mediated interference, we show that Pericentrin-like protein fibrils are required for interphase recruitment and proper mitotic assembly of the PCM matrix" (Mennella, [27]). "To understand cell organization, it will be critical to understand how the different triplets of the centriole come to have distinct molecular identities" (Marshall in "Centriole asymmetry determines algal cell geometry" [29])."Several principles of construction of a microscopically small device for locating the directions of signal sources in microscopic dimensions: it appears that the simplest and smallest device that is compatible with the scrambling influence of thermal fluctuations as are demonstrated by Brownian motion is a pair of cylinders oriented at right angles to each other." (Albrecht-Buehler in "Does the geometric design of centrioles imply their function?" [8]). So it appears that the PCM structure reproduces the structure of the centrioles, their 9-fol symmetry and non-equivalence of triplets.

3.1 Reverse or opposite rotational polarity of the MC is the base of Left-Right patterning and bilateral symmetry.

Fulfillment of bilateral symmetry can bemodeled: the MC, responsible for the angle φon the "xy" plane, built with reverse circumferential polarity of its marks (opposite or overturned or clockwise vs. counter-clockwise) is a clear chiral, enantiomorphous structure whichworks as an interface whose output is the mirror symmetric deliveryof targeted molecular complexes; one signal, two symmetric locations, same input, two symmetrical outputs.

IV. CONCLUSION

The centrosome is a geometric interface that receives geometric coded signals (input), matches each one with the corresponding γ-TuRC receptor (decoding) and nucleates oriented MTs (translation) to reach the required locations (output).

-Centrioles possess circumferential ordered asymmetry as a consequence of the biochemical difference of their triplets.
-Centrioles are platforms for a set of regulatory molecules that assist and facilitate the semi-self-assembly of the PCM.
-Centrioles transmit to the PCM their circumferential asymmetry and impress theirmolecular not-equivalence.
-Each γ-TuRC is oriented in accord to the tilt of the local tangent plane.
-Each γ-TuRC receives from both centriolesthe receptors corresponding to its own position and orientation.
-Each γ-TuRC displays its receptors to recognise the signal (a molecular ligand with a particular targeting sequence) corresponding to its own orientation and to the intended location in the cytoplasm.
-The direction of centrosomal MTs depends on the orientation and tilt of the γ-TuRCs by which they are nucleated.
-Each signal (ligand) has a 3D shape that recognises only the receptors of that γ-TuRC which is oriented in order to nucleate an MT with the desired direction: there is a precise ono-to-one correspondence between geometric signals, γ-

TuRCreceptors, γ-TuRC orientations, MT directions and cell membrane compartments.
-Aster, cytoskeleton and cell cortex, during mitosis, receive from the centrosome the same spherical asymmetry (mapping or polarization).
-Centrioles are chiral structures as a consequence of their rotational asymmetry: in the first division of the zygote the new arising cells assemble MCs with reverse rotational polarity: the embryo is already Left-Right patterned.

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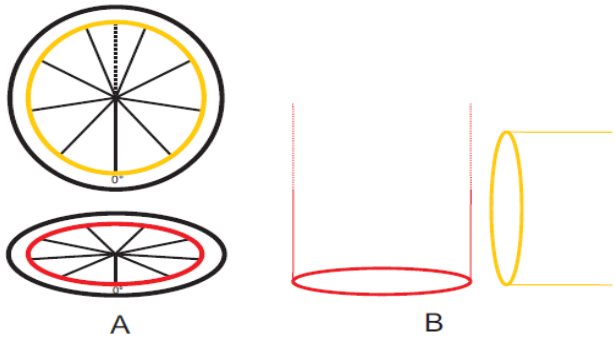

Fig.1 Centrosome theoretical geometrical model: a spherical reference system composed of two orthogonal protractors/goniometers. A: frontal view of two orthogonal protractors/goniometers, subdivided into nine sectors: the first (its base is horizontal) ison the equatorial "xy" plane; the second, (its base is vertical, orthogonal to the first), is closer to the reader.

Fig.2 Centrosome theoretical geometrical model: discrete subdivision of the centrosome and cell surface. Nine meridians and four parallels subdivide the centrosome surface into 45 small areas, each oriented in correspondence to its position: their inclination is the result of the addition of two inclinations, one imposed by the MC (longitude) and the other by the DC (latitude). As on a globe, longitude covers the entire circumference (2π; 9 different meridians or 9 different vertical 40° wedges) while latitude covers (symmetrically) only half circumference (π; 2 caps and 3 parallel discs) (see also Fig.4). Correspondently the cell cortex and membrane are similarly compartmentalized.

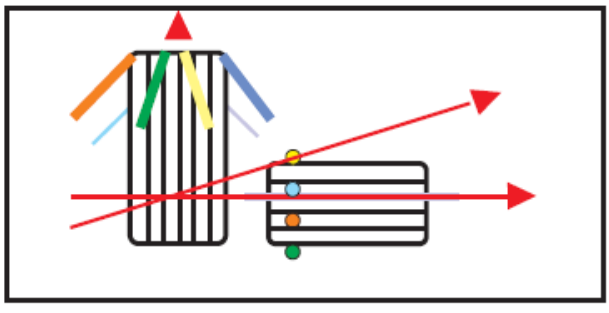

Fig. 3

Fig.3Centrosome theoretical geometrical model: orthogonality of centrioles.

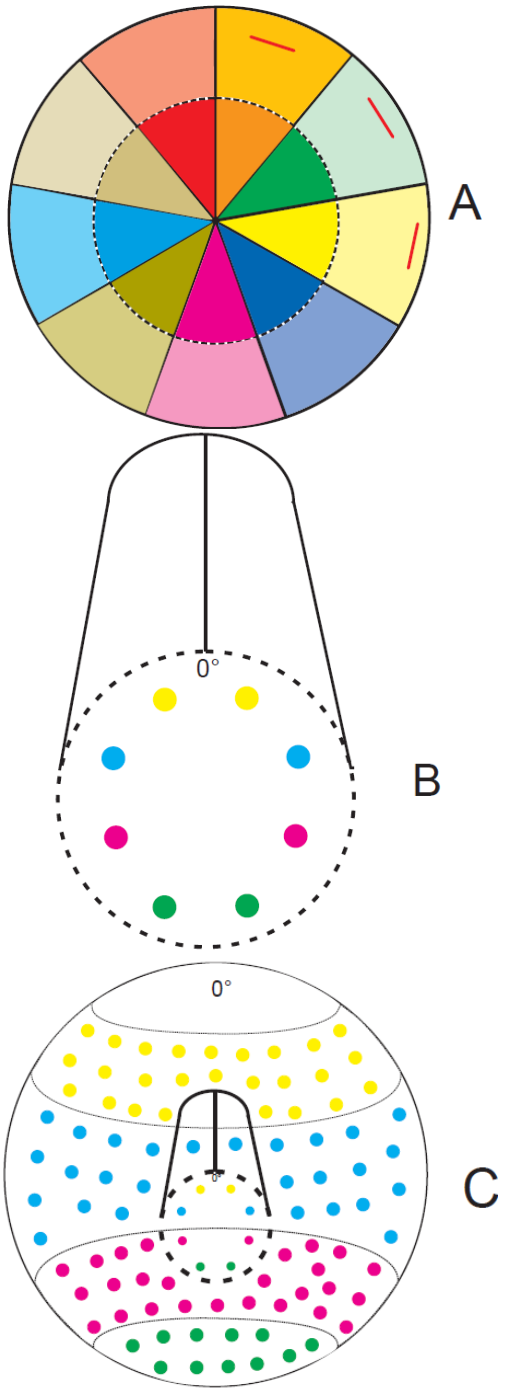

Fig.4 Centrosome theoretical geometrical model: from 2D rotational polarity to 3D spherical polarity. A: (top view): the MC (internal circle subdivided in 9 intensely coloured sectors) is responsible for "longitude", transmitted to the whole PCM (external annulus, weakly coloured), whose γ-TuRCs (small bars) acquire an inclination parallel to the corresponding centriolar blade; each MC blade faces one meridian wedge. In each wedge, all the γ-TuRCs have the same longitudinal inclination. B: after the intervention of the DC, that imposes a rotational inclination corresponding to that of its blades, each γ-TuRC acquires also the latitude inclination which is added to that of longitude. There is a double inclination: first each γ-TuRC is parallel to the corresponding blade of MC, then it acquires the inclination parallel to the corresponding DC blade; the eccentric positioned DC is responsible for "latitude" (two opposed spherical caps and three parallel spherical disks): this second centriole/protractor is composed of two symmetric hemi-protractors/goniometers. C: all the γ-TuRCs contained in the same cap or disc (coloured circles) whatever their longitudinal orientation, are rotated to acquire the same latitudinal orientation, identical in the same cap or disk. So, two 2D circumferential-rotational polarities are merged to realize 3D spherical polarity.