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Special Issue:
Where is Science Going? Scenarios and Perspectives of Contemporary Technoscience

Guest editors:

D. Altobelli, J. Parravicini & N. Schiavone

Anatskaya, Aroldi, Baker, Bardi, Bicocchi, Carati, Chiavenuto, Cragg, De Francesco, De Vitis, Erenpreisa, Galgani, Gambacorti-Passerini, Gravina, Lavacchi, Marzella, Parravicini, Perissi, Ricci, Salmina, Silvestrini, Strumia, Vinogradov

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Botanic Garden of Tomsk, Siberia.
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Editorial

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A Century of Empty Promises?

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It is a sort of tradition. At the end of each year, prominent biomedical journals express their concern about the alleged successes and patent failures in explaining carcinogenesis and treating cancer. The half-full or half-empty glass metaphor applies to the usual way of perceiving success and failure. The bad news for both researchers and cancer patients here, though, is that a more realistic metaphor should indicate a 10% full and 90% empty glass. Indeed, the bold introductory sentences of reviews and papers about rare, expensive, and minimal yet unexplained successes of immunotherapy stand for 10% of such a metaphoric glass. A litany of failures in chemotherapy, alone or combined with other approaches, follows.

Reports of unforeseen incompatibilities with the dogma of Somatic Mutation Theory (SMT) also appear when dealing with carcinogenesis. A Nature commentator recently posed a rather provocative yet naive question: "If having multiple driver mutations does not make a cancer, what does?" (Naxerova 2021). This and further similar comments represent the tip of the iceberg of dissent, which has been building up in the sea of scientific and public opinion over the past two decades. More specifically, considering, "the low value of many oncological treatments that do not contribute significantly to cancer mortality reduction, but lead to unrealistic patient expectations and push even affluent societies to unsustainable health care costs," a Dutch group compellingly argued for "an urgent call to raise the bar in oncology" (Schnog *et al.* 2021). The authors critically list multiple examples of unfulfilled claims of cancer "cures" based on preliminary reports of dubious factual nature. Intriguingly, those critical comments do not offer a plausible alternative rationale to explain carcinogenesis nor propose therapeutic options. Regarding the latter, killing cancer cells has not significantly altered the bad outcomes that have been familiar to oncologists for decades.

The dominant view on carcinogenesis has relied on SMT for over a century. Its theoretical premises are the following: (1) cancer derives from a single somatic cell that has accumulated multiple DNA mutations; (2) the default state of cell proliferation in metazoa is quiescence, and (3) cancer is a cell proliferation disease caused by mutations in genes that control cell cycle and proliferation. All along, most experimental and clinical researchers have remained loyal to SMT despite the compelling evidence of its shortcomings, as noted by credible commentators. Recently, technological advances made massive DNA sequencing possible. This allowed for revealing that cells in certain cancers carry no driver mutations, while normal cells do. Some well-known researchers have reacted to such a blatant incompatibility with SMT by minimizing its relevance and refusing any correction of its course. Their *ad hoc* justifications involve proposing new epicycles to the old paradigm (Colom *et al.* 2021; Shiu & Lander 2021; McNeal *et al.* 2021).

Have we reached the tipping point? In Popper's terms, SMT has been reliably "falsified," while in Thomas Kuhn's terms, it has suffered multiple anomalies. Nevertheless, mainstream oncology stands impermeable to the emerging plausible alternative theories. It rather proposes to rely on more technology under the umbrella of the old paradigm, which means larger and more costly projects for the same failure.

When searching for explanations of this stasis, it might be timely to ask whether the salaries of those who benefit from the U.S. Government's "War on Cancer" extravagant investment, and that of their international counterparts, may have a role in it. As stated by Upton Sinclair "It is difficult to get a man to understand something, when his salary depends upon his not understanding it!"

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Experimental Studies

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Upper Limb Structural Anatomic Mechanisms of Protection (SAMPs)

Luciana Marzella[a], Rocco De Vitis[b], Pasquale Gravina[c], Giulia Ricci[d], & Francesco De Francesco[c]*

[a] *Istituto Ortopedico Galeazzi, Milan, Italy*

[b] *Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Del Sacro Cuore, Istituto di Clinica Ortopedica, Rome, Italy*

[c] *Department of Plastic Reconstructive Surgery and Hand Surgery, Azienda Ospedaliero Universitaria Ospedali Riuniti, 60126 Ancona, Italy.*

[d] *Department of Experimental Medicine, Università degli Studi della Campania "Luigi Vanvitelli", 80138 Naples, Italy.*

***Corresponding author:** Giulia Ricci, Email: giulia.ricci@unicampania.it

Abstract

Introduction Nature has provided living bodies with extraordinarily effective reparative mechanisms. Furthermore, the biological processes involved in anatomical structures are built-up to protect life against external injuries. A series of these protective systems in the upper limb are herein described. *Material and Methods* From 2009 to 2017, 864 fresh frozen cadaveric upper limbs were dissected from the axilla to the fingers during the Italian Hand Society surgical anatomy dissection course. *Results* Arrangement of anatomical structures in the upper limb is able to protect major life supporting organs. *Conclusions* External injuries affecting the upper limb may cause damage to many important structures resulting in severe functional impairments. The layout of the structures and the relationship between them are organized to preserve arteries integrity first, more than muscles and nerves. This means, in our opinion, that these structures are organized to preserve life even if this has functional cost.

Keywords: protection mechanisms, upper limb, anatomy, injury

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Introduction

The human body is capable of spontaneous repair and wear resistance more than any other existing system. Indeed, regenerative mechanisms are continuously active on our DNA and tissues (Talaoui *et al.* 2016). The preservation of our organism is pursued not only by regeneration but also by preservation of the most important anatomical structures. Collateral circles and the presence of different structures performing the same function are examples of this concept.

A trauma is defined "complex" when at least three main anatomical structures are involved (muscle, bone, nerve, vessel). The goal of surgery is to guarantee appropriate vascularization to preserve vitality of the upper limbs (De Francesco 2020). Upper limb trauma is a frequent injury especially for manual workers who are commonly prone to accidents involving specific working tools i.e. saws that produce deep wounds with a cut-laceration trauma mechanism. On arrival in the emergency room, the patient will present with damage to the musculocutaneous and neurovascular structure and occasional cases of intactness of the vascular bundle albeit laceration of the nerve.

In the last eight years, an accurate study of the upper limb anatomy has revealed the presence of structural anatomical protection mechanisms, intrinsic to the disposition of anatomical structures. We defined them Structural Anatomic Mechanisms of Protection (SAMPs). The existence of these mechanisms provides important educational implications for biomedical studies as well as crucial clinical and surgical perspectives.

1. Background

From 2009 to 2017, during the Anatomic Dissection Course of the Italian Society for Surgery of the Hand (SICM, Società Italiana Chirurgia della Mano), 864 upper limbs were dissected. During the courses, anatomy lessons were associated to clinical evaluations and surgical technical demonstrations. The accurate study of the upper limb showed peculiar disposition features, which may be described as intrinsic protection systems of the upper limb due to their specific exposure to trauma compared to other systems. Self-protection of the head and thorax using the upper limbs is an instinctive reaction to unexpected incidents, which renders specific limbs vulnerable and mostly exposed to trauma. The specific disposition of nerves, vessels, and tendons, thus plays an important role to ensure vitality of these limbs.

Upper limb anatomical structures were examined from the axilla to the hand and accurate dissection was performed in compliance with objectives of the anatomic dissection course and reciprocal relations.

1.1. Anatomical description of upper limb's components: the anatomical basis of SAMPs

We were able to expose several SAMPs, which we hereby describe as progressing from proximal to distal.

1) The Brachial Plexus – This is a network of nerves beginning in the upper limb, generally represented in textbooks as a flat "M" shaped structure but is substantially cylindrical (Zhong 2017). Primary trunks, which are the proximal components of the plexus, occupy the supraclavicular fossa between the anterior and middle scalene muscles, lying posteriorly to the subclavian artery. These muscles run between the inferior border of the clavicle and superior border of the first rib towards the axilla, sending forth the anterior and posterior divisions, which anastomose to form the Cords (or secondary trunks). These Cords are known as Posterior, Lateral and Medial, in relation to the axillary artery location and represent the distal components of the plexus. The posterior cord arises from the union of the three posterior divisions; the lateral cord emerges from the union of the anterior divisions of the superior and middle trunks; the medial cord is basically the continuation of the anterior divisions of the inferior trunk. Bulky muscles surround and envelop the cords: the Pectoralis Minor muscle and the corresponding clavipectoral fascia enclose the cords anteriorly, the Subscapularis muscle posteriorly, the Teres Major proximally, and Latissimus Dorsi tendons distally. This disposition allows for protection of the Axillary artery, which is surrounded by the plexus and a thick resistant fibrous structure or fibrous tissue called Brachialis Plexus Fascia (Franco 2008) and represents a supplementary protective barrier for the principal vascular structure of the upper limb (Figure 1). In case of direct trauma to the arm, the artery is protected by specific structures, first and foremost by the brachial bulky muscles and subsequently by the brachial plexus sheath which are both considered important but not essential for life. The expendability of nervous structures to protect vascular structures is found throughout the upper limb, on condition that an artery is more superficial and exposed to external events.

2) The Median Nerve – This nerve is found at the antecubital fossa, in juxtaposition and acts as a shield for the Brachial artery, in the most superficial area (Figure 2). Moreover, to guarantee the blood supply to the forearm in case of trauma or throughout the range of motion of the elbow, the Brachial artery gives off collateral branches, which constitute, together with the recurrent branches of the Ulnar and Radial artery, an anastomotic circle. Since the antecubital fossa is an exposed area, with only skin coverage containing major vascular bundles for forearm vascularization on the upper limb, we are able to understand the quantity of anatomical variations involved in this area (Shyamala 2013; Kusztal 2014; Cherukupalli 2007; Klimek-Piotrowska 2013)

3) At the wrist level, the ulnar artery is medial to the ulnar nerve and both represent an alternative anatomical protective mechanism, running under

the flexor carpi ulnaris muscle. To reinforce the importance of the ulnar artery and nerve, flexor carpi ulnaris possesses a long muscle ending in the hand that covers and protects both structures (Figure 3).

4) Deep Palmar Arch – The presence of a complete Superficial Palmar Arch was reported by different authors, with a percentage varying from 78,5% to 84,4% (Gellman 2001). The existence of a Deep Palmar Arch, less exposed to traumatic events, represents a SAMP. The superficial palmar arch is based mainly on the contribution of the ulnar artery in 66% of cases (Joshi 2014). These data justify the presence of multiple protection mechanisms for this artery (Figure 4).

5) Digital Collateral Nerves – A similar disposition previously described is also encountered distally in the fingers. Indeed, the digital collateral nerves run more externally and superficially than the digital collateral arteries. On examination of the radial digital bundle, we observed that the digital nerve is more radially positioned compared to the artery. Conversely, the ulnar digital pedicle nerve has a greater ulnar deviation compared to the artery (Figure 5).

6) Collateral Digital Arteries – A common observation during surgery is the difference in calibre of the ulnar and radial collateral digital arteries of the finger. As demonstrated by Leslie (1987) in both arteriograms and cadaver specimens, the dominant vessel in the index and long finger is the ulnar digital artery, differing mainly in the long finger, while in the ring and small finger, it is the radial digital artery. A SAMP is thereby indicated by the main blood supplying vessel of the finger which is protected by the other fingers from traumatic events. The external side of the fingers is, undoubtedly exposed to injury.

7) Flexor Tendons – The hand is the most traumatised part of the upper limb. The two flexor tendons in each long finger represent functionality but also play a role in protecting and preserving flexion in case of tendon injury. The two tendons run into a complex structure of pulleys that not only favour the flexion, but also contribute to envelop and protect the tendons. Moreover, the specific relationship between the superficialis and profundus flexor tendons represents a SAMP in itself. The deep flexor tendon passes through the fibers of the superficialis in the Camper's Chiasm, which is located in the area where the forces are stronger due to the strength grip, between the metacarpal head and the PIP. Accordingly, the deep flexor tendon, an integral part of finger flexion, is enveloped and protected by the superficialis where the risk of injury is higher. Camper's Chiasm may be considered not only as a mechanism pumping synovial fluid through the flexor tendons sheath but also as a protective system.

8) Extensor Digiti Indicis (EDI) and Digiti Minimi (EDM) – In the dorsal part of the fingers, the extensor tendons are extremely superficial. The presence of an appropriate extensor tendon for the second and fifth finger, along with the Extensor Digitorum Comunis (EDC) tendons for all the long fingers, represents a SAMP preventing the loss of the pincer grip, even in cases of EDC lesions.

9) Extensor Pollicis Brevis (EPB) – A SAMP in the thumb was observed by the concomitance of the Extensor Pollicis Longus (EPL) tendon running into its own third compartment in the extensor retinaculum, separately from the more expendable EPB, running in the first canal together with the Abductor Pollicis Longus (APL). In this canal, an inconstant septum may be in a seen in a variable percentage. (Lee, 2017).

1.2. Classification of SAMPs

The anatomical structures in the upper limb follow a specific scheme with the purpose to protect the most important elements for viability and function of the limb. Herein, a teleological interpretation of anatomy is not intended. The matter is rather the findings of the consequence of natural selection, which is the key of the evolutionary process. As Monod (1998) clearly states in his essay *Chance and Necessity*, a fortuitous and useful evolutionary event may be attributed to a specific structural change in the body.

We can divide the SAMPs into two categories:

1) Protection of limb viability: the axillary artery is protected by the brachial plexus, the brachial artery is protected by the median nerve, the ulnar artery is protected by the ulnar nerve. Moreover the superficial and deep palmar arches are evident, and the collateral digital arteries are protected by the collateral nerve and with a larger calibre and a high frequency of

trauma occurrences concerning the lateral aspect of the finger.

2) Protection of limb function: two flexor tendons are evident for each finger and two extensor tendons for the thumb, index, and small fingers.

In the axilla, consistent connective tissue was observed, forming the bundle sheath, providing protection to the nerves and artery. These findings are consistent with Franco's analysis (2008), which described the fibrous structure as an expansion of the prevertebral fascia. On the contrary, Cornish (2008) suggested that such fibrous structured sheath may be the result of connective tissue coalescence in cadavers. The protective role of muscle and tendon tissue from nervous damage has been recently studied by Lee and colleagues (2016) who evaluated the protective role of Flexor Radialis Carpi (FCR), Palmaris Longus (PL) and Flexor Carpi Ulnaris (FCU) in wrist lesions, where the neurovascular bundles are most superficial, and which present a higher exposure to injury. The authors showed how FCR is protective to the radial artery in radial side lesions, PL in the median nerve in median side lesions and FCU for the ulnar nerve in ulnar side lesions. From the anatomical dissections, it is clear that the neurovascular bundle is positioned externally to the corresponding vessel, suggesting a non-incidental arrangement which provides protection to the vascular bundle.

It is noteworthy that we do not yet fully understood how specific nerves are guided to supply specific muscles (Al Qattan *et al.* 2009). In particular, blood vessels and nerve fibers are often closely arranged in parallel throughout the body. Therefore, neurovascular interactions may be important for the development of vascular networks. In view of these considerations, investigations have demonstrated that JunB is induced in endothelial cells by neuro-vascular interactions and regulates neurovascular juxta-positional alignments during embryonic vascular development (Yoshitomi *et al.* 2017). It is also worth mentioning that mesenchymal signals and mesenchymal extracellular matrix deposition represent fundamental cues that drive nerve and blood vessel elongation. Concomitantly, the mesenchyme provides differentiating information for myoblasts and connective cells. In the light of these observations, reciprocal induction of upper limb cellular players may occur during embryonic development, and that this molecular dialogue is accountable for the acquisition of their anatomical localization (Deries & Thorsteinsdottir 2016). Moreover, the protective roles of tendons or nerves in vascular injuries is an important aspect of upper limb traumatology with the brachial plexus exerting a significant protective barrier effect for the axillary artery in the axilla (Figures 6 and 7) while at the middle third of upper limb, the brachioradialis muscle and the flexor carpi ulnaris muscles provided a significant protective barrier respectively for the radial artery and ulnar artery (Figure 8). Finally, the digital collateral nerves offered a protective barrier for digital collateral arteries in the finger (Figure 9).

1.3. Consequences and Discussion

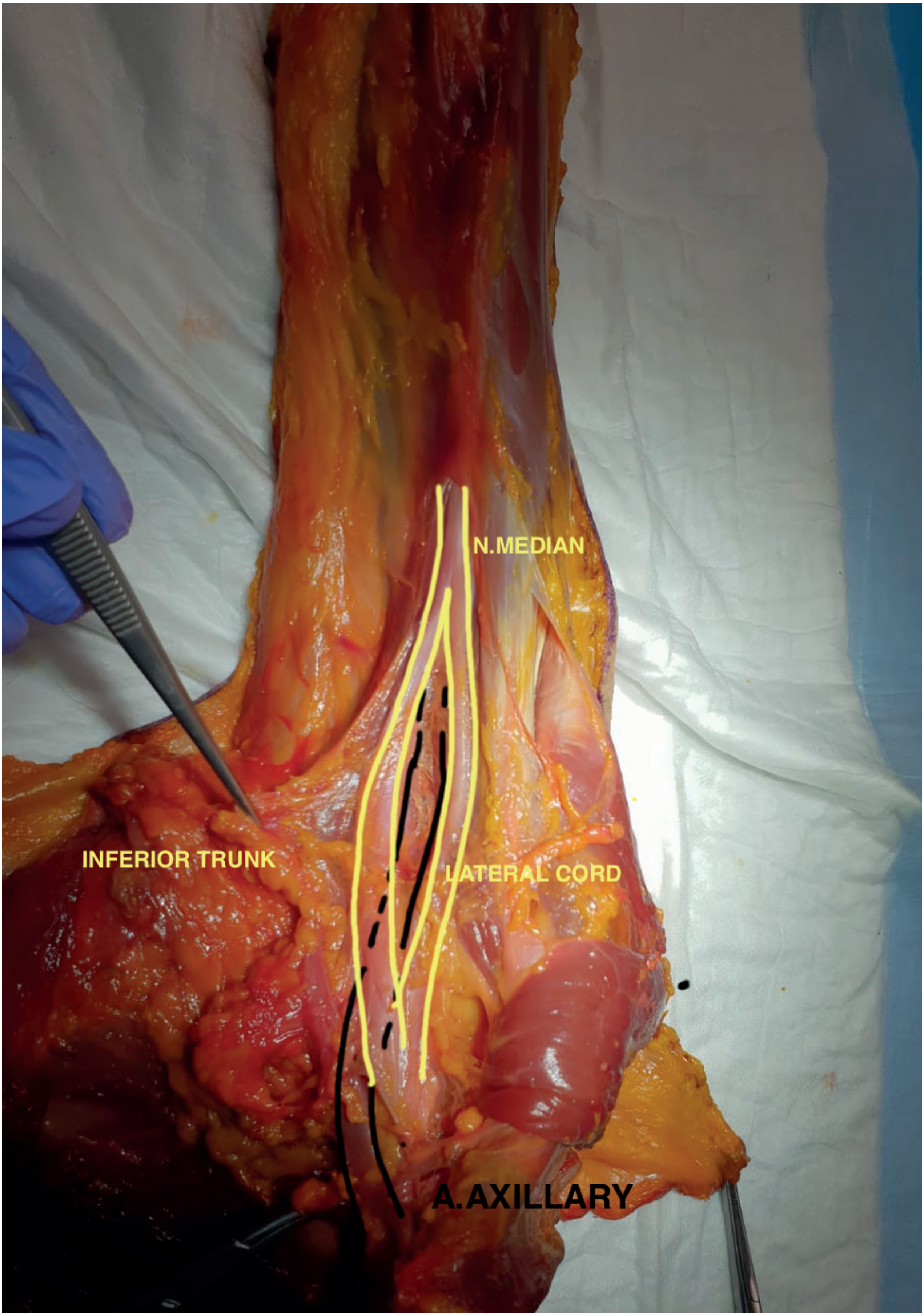
Adequate knowledge of anatomy is crucial to diagnosis and treatment. It is imperative for a surgeon to be well- trained in the dissection of normal anatomical structures to avoid the most common complications and to prevent errors, in consideration of the potential anatomical variations.

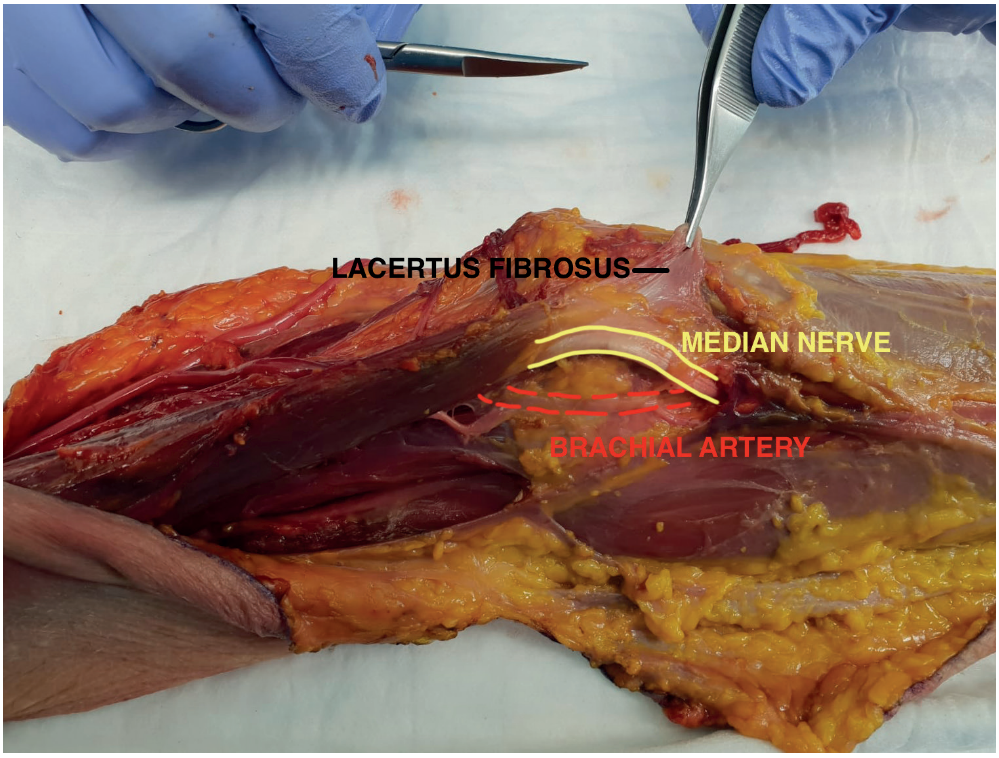
SAMPs are to be acknowledged for their importance in the diagnosis and surgical management of upper limb conditions. Every structure plays a role in the function of the entire limb and should be preserved or restored after surgery. The knowledge of the molecular dialogue among blood vessel, nerves, and muscles during limb patterning is still poor, but represents a theoretical foundation in the identification of mechanisms that assess the embryological origin of SAMPs.

"The only sure foundations of medicine are an intimate knowledge of the human body, and observation on the effects of medicinal substances on that." (Thomas Jefferson 1829).

3. Figures

Figure 1 (next page): The anatomical specimen showed that the Axillary artery was protected by the plexus (lateral cord and inferior trunk, which join to form the median nerve) and a thick resistant fibrous structure.


N.MEDIAN
INFERIOR TRUNK
LATERAL CORD
A.AXILLARY



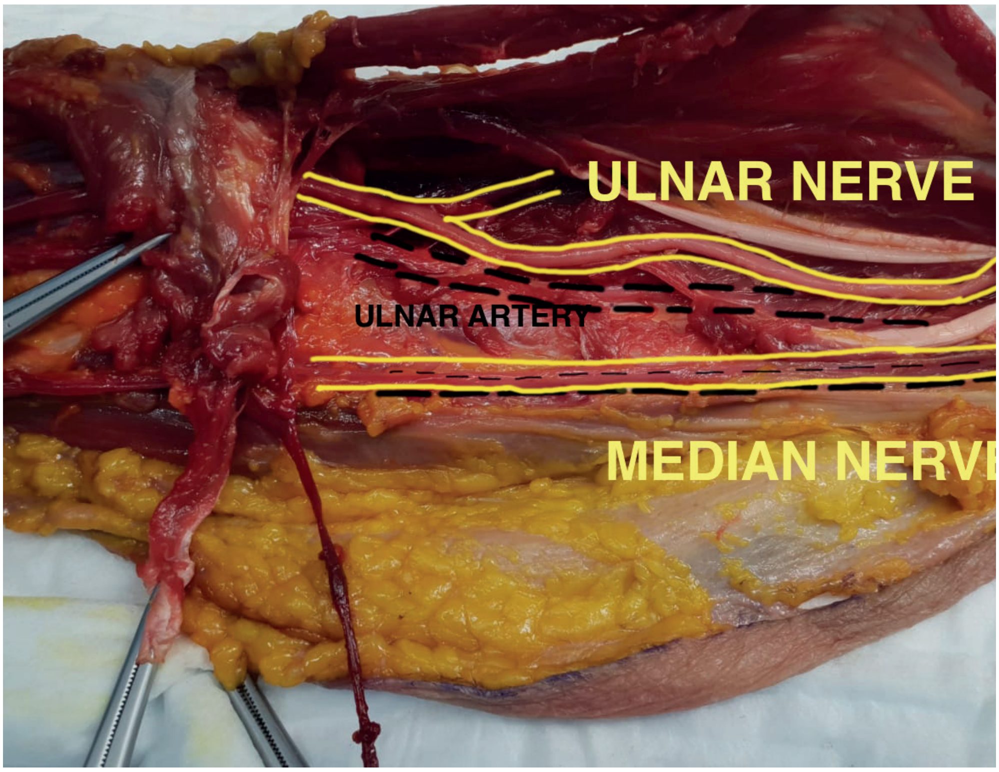


Figure 2 (above): The anatomical specimen showed that the brachial artery, in the forearm, was protected by the median nerve, which is located superiorly to it, the entire nervous vascular bundle is then covered by the fibrous lacer.

Figure 3 (below): The anatomical specimen showed that the ulnar artery, in the wrist, was protected by the ulnar nerve which is located superiorly to it, the entire nervous vascular bundle is then covered by the flexor carpi ulnaris.

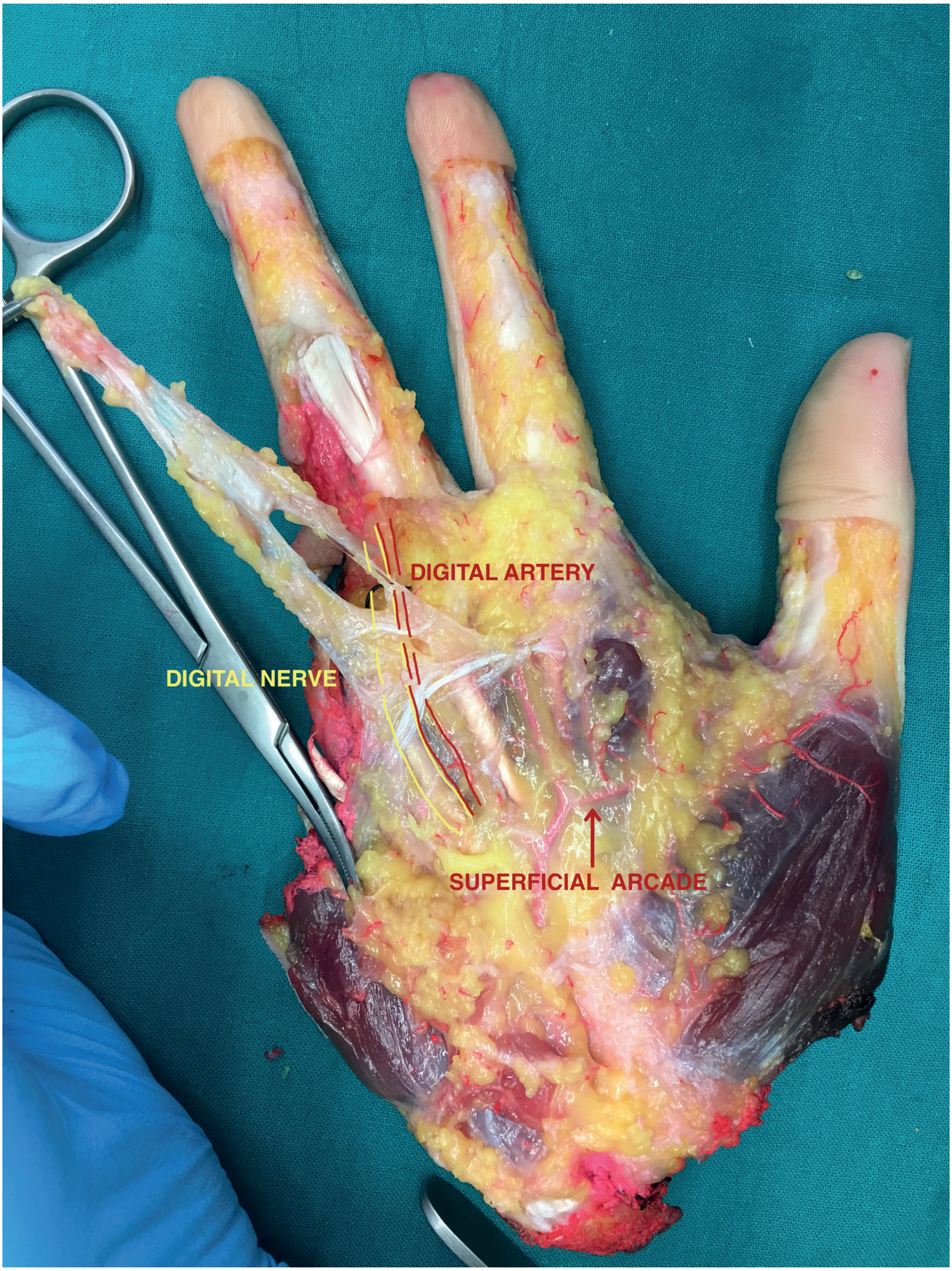


Figure 4: The anatomical specimen showed the superficial arch, in the palm, which protected the deep arch, and the digital collateral artery was protected by the digital collateral nerve.

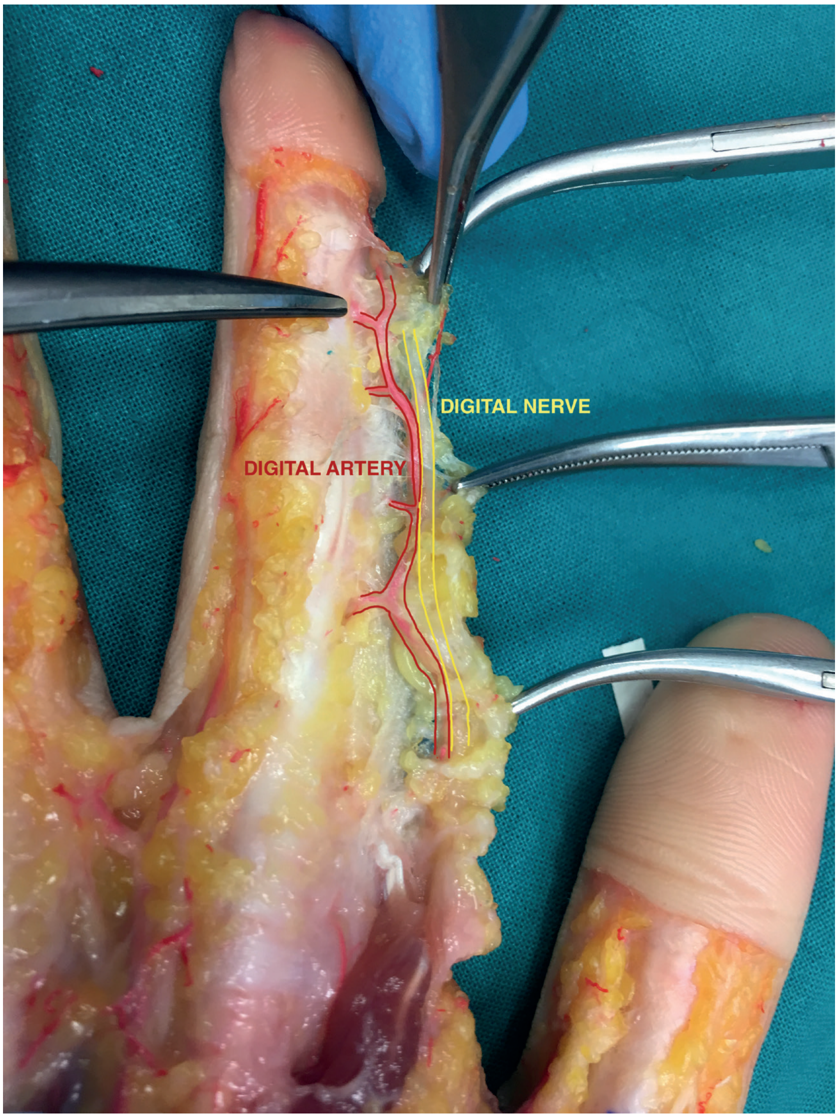
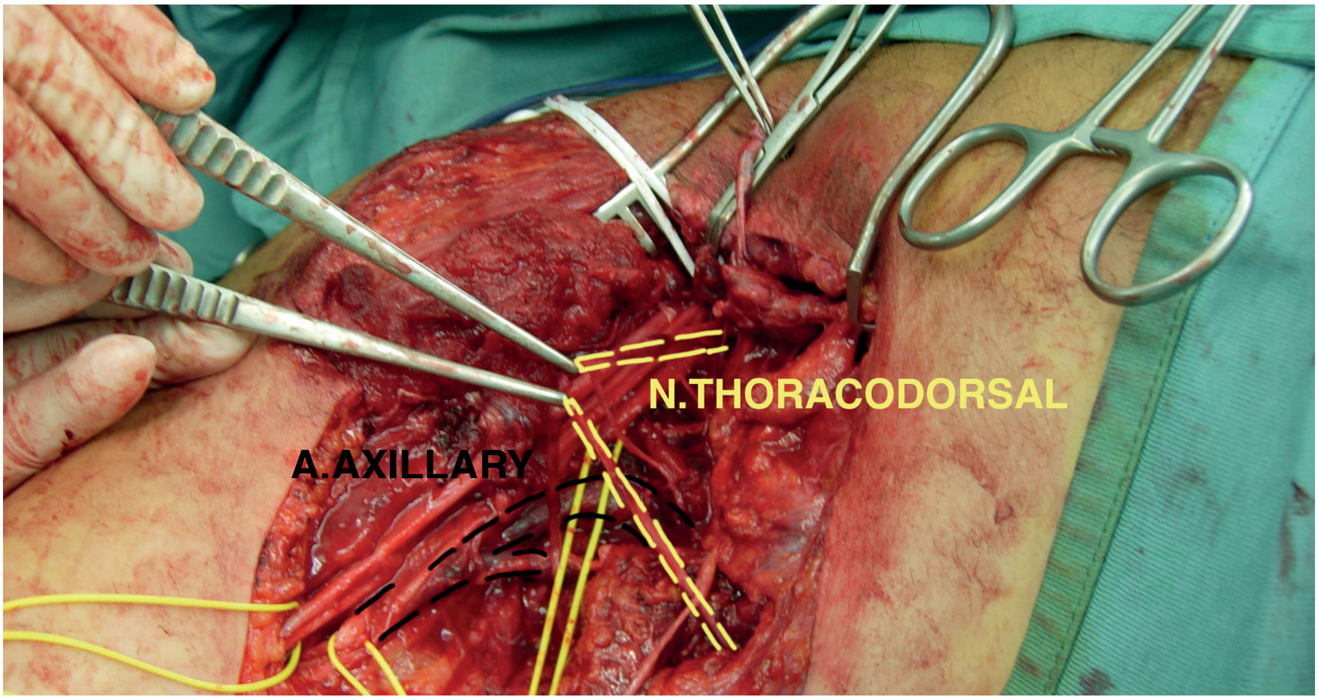


Figure 5 (right): The anatomical specimen showed the system of connections between the two digital collateral arteries through the interphalangeal arches and the digital collateral nerve, which is located above the corresponding digital collateral artery.

Figure 6 (below): Intraoperative image showing the position of the plexus above the axillary artery with injury to a branch of the brachial plexus (thoracodorsal nerve) and fibrous fascia.



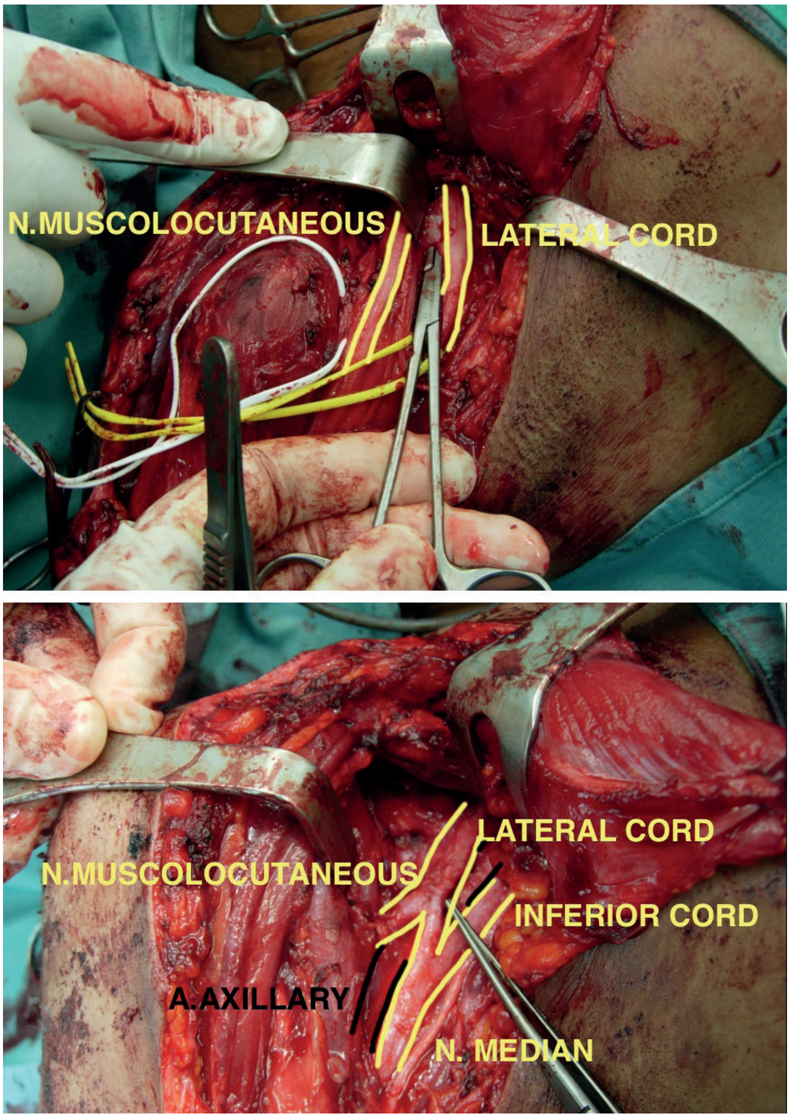
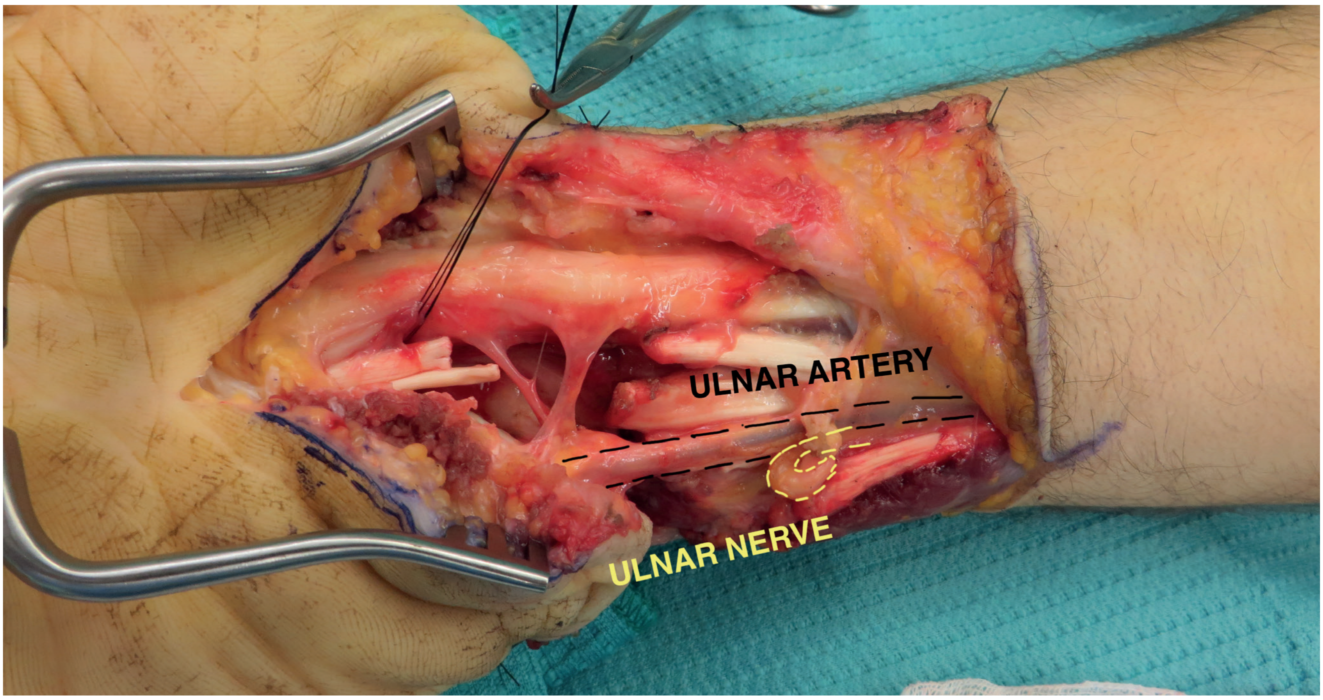


Figure 7 (left): Two intraoperative images showing the position of the plexus above the axillary artery with injury of a branch of the brachial plexus (lateral cord) and fibrous fascia.

Figure 8 (below): Intraoperative image of the wrist showing retrieval of the ulnar artery deeper than the injured ulnar nerve and the injured flexor carpi ulnaris and injured flexors digitorum profundus of the fourth and fifth finger.



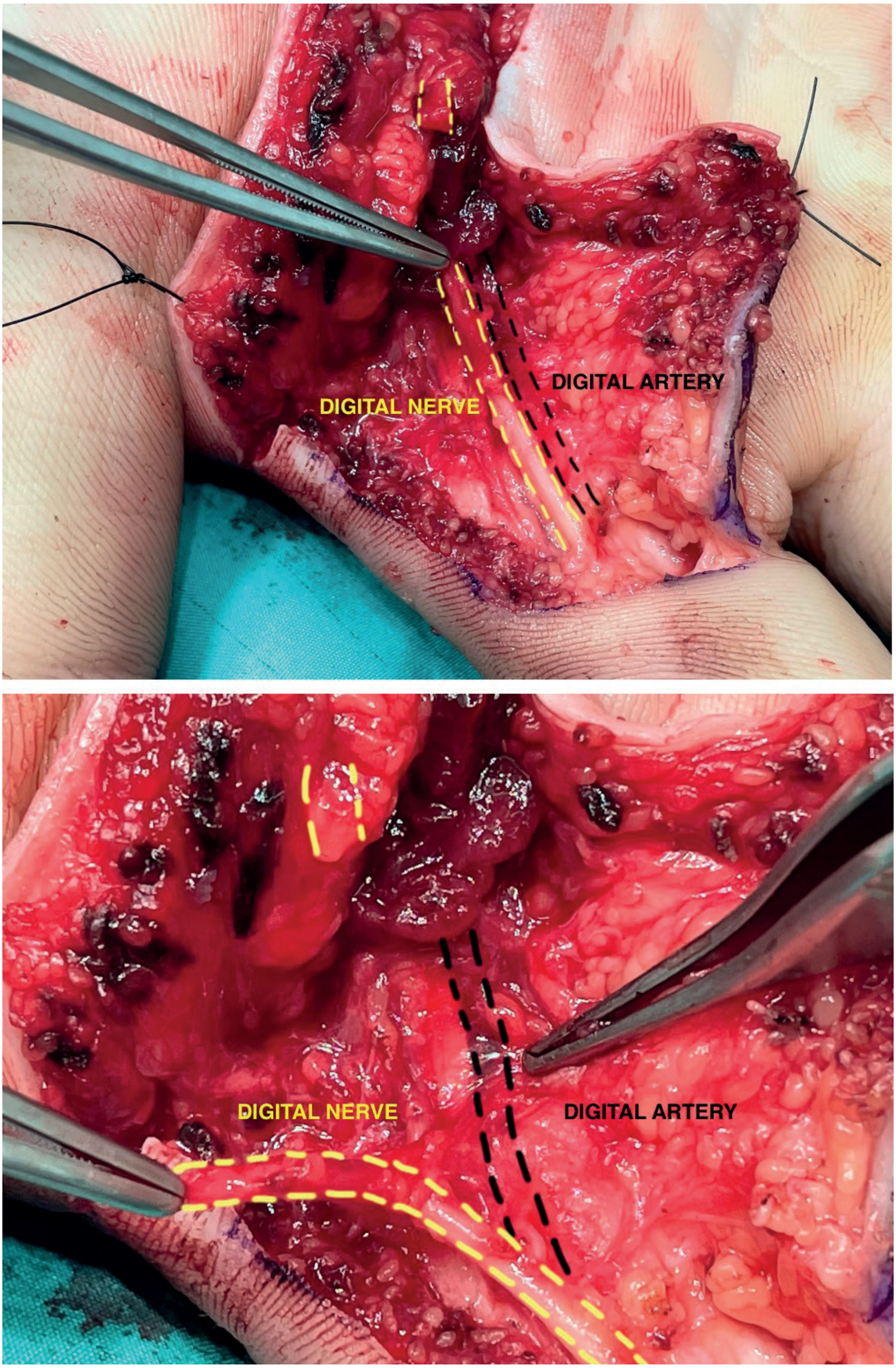


Figure 9: Intraoperative images of the finger showing the retrieval of the collateral digital artery deeper than the injured collateral digital nerve.

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Conflict of Interest

The authors declare no conflict of interest.

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Special Issue: Where is Science Going?

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Where is Science Going? The Main Road Overlaps Disciplines and Crosses Reductionism

Dario Altobelli, Jacopo Parravicini & Nicola Schiavone

Guest editors

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The special issue *Where is Science Going? Scenarios and Perspectives of Contemporary Technoscience* features a specific multidisciplinary approach. The call's topic was developed according to the modern tripartite pattern of knowledge: humanities/social sciences, life-sciences, and physical-sciences. In fact, the papers in this issue display a large overlap and interplay between scientific branches while highlighting several problems that were suggested in the call. Such an original and fruitful path toward a future, sound knowledge addresses both the practice and the debate of technosciences.

The problem of scientific truth and reliability of research are faced by Baker and Bardi *et al.* Both these papers quote the same statement by H. Poincaré, "An accumulation of facts is no more science than a pile of bricks is a house."

Starting from the perspective of biological sciences, Baker's commentary, inspired by a recent opinion piece by renowned biologist Paul Nurse, highlights the problem of the giant amount of data currently available, and still growing, in contemporary scientific enterprises. This theme is developed, with suitable examples, underlining that true knowledge is not just a matter of collecting data. Rather, it is about understanding and predicting—an articulated process where data, theories, and errors play a key role. In this sense, epistemological and methodological questions belong to a broader panorama where they should be understood and resolved, calling into question the role of scientists as subjects aware of the implications of their work. These, for example, directly affect research programs funded by states and enterprises, sometimes generating perverse results such as the "Machiavelli effect".

The perspective of Bardi *et al.* refers to scientific communications, i.e. the domain of knowledge and public debate on technoscience, for which the scientific discourse and its applications become valuable if clearly understandable by the general public. In this vein, scientific communication should become a duty of scientists; but this requires, *inter alia*, the scientific community to undergo suitable changes. To this end, the authors propose a tool inspired by Seymour Papert's book *Mindstorms* expanding his concept of "mind-size learning" to match the current scientific enterprise. Employing the metaphor of science as one of the dragons of Western mythology, described as sitting on their hoard of gold but not using it for any useful purpose, Bardi *et al.* note that a broad paradigm shift is also needed from a social and cultural point of view. We should thus encourage scientific communication and the redistribution of the scientific treasure of knowledge in the form of "mind-sized" memes.

This theme refers, clearly, also to the problem of the "social structure" of contemporary democratic societies in relations with science, a crucial question already addressed by Robert Merton around the first half of the 20th century. Here, Parravicini stresses how the current conditions and role of the scientific community in democratic societies are embodying a sinister social scenario, predicted by K. Popper decades ago: the joining of relativism in knowledge and authoritarianism in research, which leads to a compression of political and intellectual freedoms.

On the other hand, Bicocchi focuses on issues relating to the sphere of law. She recalls the need for still-lacking efficient legal regulations concerning technoscience in neurology and underlies the potential misuses of scientific discoveries. Bicocchi warns that, in this regulatory vacuum, new and potentially dangerous market niches have been created for invasive devices dedicated to our mental activities. The possible negative consequences are attested by the growth of neurotechnological means of social control and surveillance. This calls for establishing independent ethics committees about "neurorights."

On the epistemological level, the contributors focus on the inadequacy of reductionism and on the correlated topic of complexity.

Strumia gives a comprehensive review of several issues correlated to complexity in natural sciences. He emphasizes how information plays a determinant role in generating order and organization in complex systems, recalling the ancient Aristotelian-Thomistic logic/ontology and *form*. The holistic approach is shown to be mandatory in the field of fractal geometry, whose implications in many branches of nature, spanning from the shape of galaxies to the anatomy of biological organ in a living system, like a human heart, are given.

The same topic consideration of the natural universe as a whole, the so-called *holistic approach*, is also dealt with in three physical science works, facing the foundations of quantum mechanical theory. Interestingly, the two papers by Silvestrini and the contribution by Carati & Galgani propose almost opposite interpretations of this charming topic.

Silvestrini starts with the concepts correlated to the "local realism," on which A. Einstein based his criticisms of quantum mechanics. After recalling the experiments on Bell's inequality violation, which demonstrate that Einstein's assumptions are not satisfied, Silvestrini proposes an interpretation, entirely based on quantum mechanics, where all physical systems in the universe should be considered as synchronically correlated.

On the contrary, the work by Carati & Galgani aims at explicitly recovering Einstein's program to explain microscopic systems within a classical mechanical framework. The authors note that this can be done if and only if in classical electrodynamic equations both temporal retarded and anticipated terms are considered. This requirement introduces the innovative concept that also classical mechanics can predict a sort of general correlation among physical systems in the universe.

Finally, the investigation of biological systems can be seen as a field where all the previous issues come together. This is the topic of the works by Erenpreisa *et al.* and Gambacorti-Passerini & Aroldi. The first considers some features of cancer cells, where complexity and chaotic behavior play a key evolutionary role, which is relevant for treatment resistance. Here, paradoxically, the potential mechanism of "explorative adaptation" is initiated in cancer cells only, "on the brink" of catastrophic damage. The paper eschews a reductionist framework and proposes, in this specific field, an application of the epistemology deriving from the thermodynamics of unstable open systems discovered by Ilya Prigogine. Erenpreisa and colleagues stress that the described regulation does not conform to the expected linearity between the severity of an applied drug and the final effect on cancer.

Gambacorti-Passerini & Aroldi shed light on the unknown side-effects of vaccines based on nucleic acids, particularly in the mid and long term. Their production was expedited based on urgency, and authors warn that such an approach risks becoming an excuse to omit a much needed surveillance activity. They conclude referring to the wider problem of the relationship between science and society and claiming, on one hand, that genuine knowledge is possible only by protecting scientific work from extra-scientific interests and pressures; and on the other, that transparency, reliability, and science-based opinions win people's trust much more than coercion.

All the papers, according to their specific disciplinary approaches, but with an interdisciplinary and conscious vision of the social role of science, demonstrate that global society is questioning the boundary between an internal and an external domain of the technoscientific "machine." This is reflected at every level of scientific enterprise: theoretical, imaginary, discursive, operational, applicative, and technological. The immeasurable expansion of the skills and effects of technoscience extends from the level of representation to that of practice, seamlessly and with no obstacles, to reach social totality. Therefore, a sort of redefinition or rather a re-foundation of society emerges from a technoscientific lexicon, which is still heavily mortgaged by a reductionist and neo-positivistic epistemology. Moreover, further and more serious problems emerge, including, not least, that of politics and financen that arrogantly use the scientific practice for their own purposes.

Such an open issue has serious implications for democratic societies. The scientific community must face and solve it even through a though, critical, but always open and democratically oriented dialogue and discussion.

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Popper's Nightmare

Jacopo Parravicini[a*]

[a] *Università di Firenze, Dipartimento di Fisica e Astronomia & LENS, Florence, Italy*

***Corresponding author:** Jacopo Parravicini, Email: jacopo.parravicini@unifi.it

Abstract

Epistemological relativism and authoritarianism are compressing political and intellectual freedoms by replacing facts with interpretations, as Karl Popper predicted several decades ago. Some suggestions to cope with this situation in science are provided.

Keywords: Karl Popper, post-academic science, epistemological relativism, epistemological authoritarianism, CUDOS, PLACE

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1. "Ideas Are Dangerous and Powerful Things" (Popper 1967)

"Science" is an ambiguous word. It can have several meanings. Among them, it indicates a method, a set of known facts, a community of persons, or a set of explanations. However, all of these meanings share knowledge as a general objective. The issue of determining what we exactly mean with "knowledge" is the long-standing branch of epistemology, which, in the Modern era, is inextricably intertwined with the so-called philosophy of science. Most scientists do not like to think about scientific knowledge itself; they like to think about the natural phenomena they are investigating. This is why the theoretical reflections about the scientific method and the scientific community are generally carried out by philosophers and sociologists. During the 20th century, the most famous epistemologist was Karl Popper, whose work provided a conceptual framework, albeit ideal, to the pattern of the modern scientific method of knowledge. The work of Popper faces the issue of determining whether a theory, a scientific explanation, can be considered true or false. Popper is also seen as a strong supporter of freedom, democracy and open society, a position that is commonly considered a consequence of his epistemological pattern. Instead, the concern about freedom is not the end, but the starting point of his thought (Popper 1962). In the core of his epistemological framework we find the problem about what can be called "truth" and how it can be determined. In the introduction of his "Conjectures and Refutations" he writes

> "I believe that Russell is right when he attributes to epistemology practical consequences for science, for ethics, and even for politics." (Ibid.)

Popper recognised that this issue was correlated both to experiences of fascist and communist dictatorships and to ordering of democratic western societies that emerged after the World War II. While Popper was building up his model of scientific method, from the 40s to the 70s, the actual structuring of communities of scientists was studied and systematized by the sociologist R. K. Merton (Merton 1942, Kellogg 2006). He identified the guiding principles of the scientific community, the so-called *academic science* policy, which he summarized in five terms, i.e. *Mertonian norms*. These, in the formulation of J.M. Ziman, state that scientific research should be: *communalist, universal, disinterested, original, skeptical* (for a specific description of their meaning see Ziman 2000); their acronym reads CUDOS, a word correlated to Ancient Greek κῦδος, meaning "glory", "honour", "good name". As pointed out by the title of his original essay, the first concern of Merton was the issue of democracy, just like his contemporary Popper (Merton 1942). Therefore, Popper and Merton, maybe the most important academics on scientific knowledge and principles, share the vision of a scientific structure as entangled in, rather foundational of, our democratic societies. Since the time of Popper and Merton, many changes have occurred both in science and society. Nowadays, our civil societies are challenged by issues where the scientific community plays a key role. Never as now, interplay between science and society has become important: actually, it affects difficult choices on present and future of people. So, it is worth trying to briefly examine the current historical circumstances from the point of view of Popper and Merton.

2. Truth and Freedom

Affirming the existence of a reality whose truth can be perfectly known through human means, as positivists did, is a viewpoint that can become dangerous. This was the opinion of Popper after the experience of the World War II and with the Cold War still in progress. Of course, such a viewpoint had opened the door to authorities claiming to possess the Truth, as he had said in fascisms and Marxism. Notably, Popper also recognized a danger in the opposite claim, i.e. that a knowable truth does not exist; actually, if so, what is socially considered "true" has no correlations with objective data, so it can be arbitrarily established by the temporary rulers.

> "epistemological relativism, or the idea that there is no such thing as objective truth, and epistemological pragmatism, or the idea that truth is the same as usefulness, are closely linked with authoritarian and totalitarian ideas." (Popper, 1962)

Given that the risks correlated with the absolutism of dictatorships were evident, Popper recognised in relativism a subtler risk for the future of our democratic societies.

> "The belief of a liberal—the belief in the possibility of a rule of law, of equal justice, of fundamental rights, and a free society—can easily survive the recognition that judges are not omniscient and may make mistakes about facts [...]. But this belief [...] can hardly survive the acceptance of an epistemology which teaches that there are no objective facts; not merely in this particular case, but in any other case; and that the judge cannot have made a factual mistake because he can no more be wrong about the facts than he can be right." (Ibid.)

Everyone recognizes that during past decades, especially since the beginning of 21st century, in western societies the relativistic approach has spread both among general public and among academics, namely scientists and researchers. In the current historical moment, we are at a turning point: what about Popper's concerns? In the last 30 years the development of scientific knowledge has suffered from several diseases (Kellogg 2006). Namely, some researchers demonstrated the possibility of publishing gibberish papers. Even worse, some authors pointed out that the most part of research findings are not trustworthy because they are strongly biased by previous interpretations, scientific community, competing interests, financial interests, public expectations, so demonstrating that such claimed discoveries can be considered false (Ioannidis 2005). In the same period, the issue of scientific frauds arose in all fields of scientific research: among others, Schoen's scandal erupted as a warning signal at the begin of this century (Reich 2009). A journalistic inquiry of Science subsequent to this event revealed that 10% of the interviewed researchers were aware of major scientific misconducts in their fields, while just 0.01% were misconduct documented cases, with the largest portion in medical and life-sciences (Marshall 2000). All this made effective the idea that evidences, phenomena, trustworthy facts, namely the truth, do not exist everywhere, even in science. Scientific truth would coincide with agreement among experts (framework of T. Kuhn) or, even worse, by those who are able to prevail (framework of P. Feyerabend). One of Popper's fears came true: the dominance of epistemological relativism, and it can be seen as the triumph of Popper's above-mentioned foes. But, as he said, the problem of truth is not just a matter of academics: what we know and what we do not strongly involve decisions for citizenry. If scientific methods and scientific community do not seem to be able to provide feasible knowledges, somebody will assume power to arbitrarily decide which results should be considered. This power is assumed by backers, by stakeholders, by corporations, and by politics, especially when personal interests are involved. Actually, in these conditions, when politics and decision makers (such as managers and executives) establish to embrace a given scientific interpretation, they operate a "misleading oversimplification": we know that scientific method requires that no theory be embraced and, for today's scientific major issues, the work of the -scientific community is almost always still in progress (Abbasi 2020). Nonetheless, rules of politic and economic powers walk into the careful scientific research process with their strong not scientific interests, so that one speaks about "suppression of science" (Ibid.). Actually, scientists expressing scientific doubts about political choices on hottest topics, say e.g. global warming or COVID-19 pandemic, are most often delegitimized, even though they raise reasonable and valid issues:

> "The same tools used to discredit disingenuous expressions of doubt can be used against those who express well-supported doubt. Those with particular political views may declare some doubt to be unreasonable, even if it is actually quite reasonable." (Allison *et al.* 2018)

In this situation, the usual scientific debate becomes biased, so intellectual and research freedom among academics is heavily restricted. The arising of the COVID-19 emergency found this situation causing, as a catalyst, a strong "politicisation" of science.

> "Science [...] rarely applies to every setting or every population. It doesn't make sense to slavishly follow science or evidence. A better approach is for politicians, the publicly appointed decision makers, to be informed and guided by science when they decide policy for their public. But even that approach retains public and professional trust only if science is available for scrutiny and free of political interference, and if the system is transparent and not compromised by conflicts of interest." (Abbasi 2020)

This intrusiveness of power is the second fear expressed by Popper come true: a central authority that rules, by its own force, what is the "scientific truth" to be followed, that delegitimizes doubts and suppresses scientific debate. This means that, in our present times, the epistemological relativism has resulted in epistemological absolutism: joining of these two opposites has contributed to compress (sometimes even suppress) political and intellectual freedom. Let us remember the political concerns behind Popper's thinking: *Popper's nightmare* has become true.

3. Scientists Exist, "Science" Does Not

How has this occurred? In the above-mentioned distorted mechanism of intellectual and political control, decision makers usually say "Science states that..." to substantiate their decisions, but we know that "Science is rarely absolute" (Ibid.), especially when facing new and complex issues. Politics and decision makers want certainties, they need parading certainties; genuine scientific research does not claim to provide certainties, it provides correct results within an estimated confidence level. As a matter of fact, science is an abstract idea, that actually does not exist; phenomena, data, methods, theories, and scientists exist. Scientists make up a community of people that uses methods, observes phenomena, records data, builds theories to increase knowledge. Scientists are the pivot of the entire process, so their correct conduct in their investigation is the only guarantee for achieving a real increase in knowledge. Actually, ideal principles to be followed in practical scientific activities were identified by R. Merton as specific features of democratic societies (Merton 1942). Nevertheless, for several decades numerous people have talked about "Collapse of Mertonian norms", by which the scientific community has passed from the principles of CUDOS to the principles of PLACE, i.e. scientific activity has become *proprietary, local, authoritarian, commissioned, and expert* (Kellogg 2006, Ziman 2000). Again, the meaning of this new acronym is not accidental, indicating the usual goal of several scientists within the scientific community. PLACE can be seen as the *post-academic science* policy (for a specific description of their meaning see Kellogg 2006 and Ziman 2000). Of course, both CUDOS and PLACE are just models, real things are much more complex, though these models well highlight the passage from the old to the new paradigm reflecting the passage from the *academic* to the *industrial* (*post-academic*) science (Kellogg 2006). As all structural changes, this transformation entails both opportunities and risks. The paradigm of industrial science, e.g., increases number of researchers, total amount of knowledge, overall resources, collaborations, interdisciplinarity. Nevertheless, PLACE is a system with many drawbacks which contribute to science degradation. Among them, over-proliferation of publications (summarized in "Publish or perish" motto) and the spreading of frauds have decreased reliability and trust in scientific knowledge, feeding *epistemological relativism* (Marshall 2000, Karachalios 2008). On the other hand, the vast majority of research funding has passed to be provided through grants on specific calls: this has exposed researchers to a strong centralized control. Which topic will be supported it's decided by private and public funding holders, almost always without following scientific criteria. Both public and private controls have meant that, within this paradigm, investigations are no more moved by curiosity and aimed at knowledge, but they are commissioned tasks to solve specific issues. Put simply, science has become authoritarian (*epistemological absolutism*). We are then distinguishing that the structural change to PLACE has paved the way to the realization of *Popper's nightmare*. Following this line of reasoning, the shift from CUDOS to PLACE seems to have been an effective instrument allowing the reduction of political and intellectual freedom we are experiencing. Is the PLACE pattern inherently unsuitable to give support to free democratic societies? If the interpretation of Merton is correct (Merton 1942), we should also ask: do free democratic societies generate Mertonian principles or do Mertonian principles belong to fundamental pillars of free democratic societies? Of course, answers to these questions would be long, need large, specific analyses and most likely would not be univocal. We can here just stress some factual evidences.

1. Merton's original analysis demonstrated that CUDOS principles are found in the scientific practice within free democratic countries; conversely, Nazi and Soviet sciences (in his days) were following almost the opposite principles, being commissioned, authoritarian, centralized, highly controlled. These features are analogous to features of PLACE paradigm.

2. However, the CUDOS paradigm is merely an ideal paradigm, which has never, also in the past, exactly matched the real situation of scientific practise; on the other hand, the arising of PLACE paradigm is a consolidated phenomenon, whose rejection by some nostalgic would be meaningless (and not viable).

3. No paradigm can be separated from proper behaviour of scientists: if they do not refer to phenomena, data, methods, theories and to tried and tested good practices, the increase of knowledge, i.e., the final objective of scientific research, will be missed. Scientists should communicate through the standard instruments of scientific community (e.g. peer-reviewed publications); if they do not, they open the way to be exploited for non-scientific goals. Summarizing, scientists bear a major responsibility both as regards to the advancement of knowledge and towards the general public, and they cannot exclude themselves.

Conclusions: Bringing Truth Back

Summarizing, *Popper's nightmare* is the joining of relativism in knowledge and authoritarianism in research, bringing to a compression of political and intellectual freedoms. We come to the conclusion that when politics walks with arrogance into a scientific practice weakened by relativism, the strong interference from non-scientific criteria makes facts "cease to exist"; they are "replaced" by (political) interpretations. These interpretations are then imposed as facts: scientific practice is crushed by a form of authoritarianism. In agreement with Popper and Merton, we are seeing that this dynamic is a great threat to knowledge and to the general public. We can sketch some suggestions for trying to respond to this cul-de-sac.

From a practical point of view, the CUDOS principles should be explicitly known and taught by all academics, provided they are an ideal reference model and not a rule list. Activity spaces where CUDOS norms can be easily followed, reasonably and explicitly free from the constraints of PLACE, should be provided and maintained for present day and future science. Put simply, in every country a hard core of "academic science", of scientific activities free from non-scientific interests, should be carefully maintained. In this, the role played by states in funding without profit is crucial.

From an epistemological point of view, impacts on societal freedom pointed out by Popper require the concept of truth to be brought back. Not trusting an existing truth of things, a truth of phenomena which can be (approximatively) achieved by mankind, all this stuns. Trusting that mankind has power to decide on the truth, to establish and arbitrarily manipulate natural phenomena, all this stuns. Stunning makes us fall asleep; Popper and Merton showed that in this sleep, political and intellectual independence risks to be curtailed. We have to wake up soon. If we want to exit from *Popper's nightmare*.

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Non-locality in the Science of the Millennium

Paolo Silvestrini[a*]

[a] *Università della Campania Luigi Vanvitelli, Dipartimento di Matematica e Fisica, Caserta, Italy*

***Corresponding author:** Paolo Silvestrini, Email: *paolo.silvestrini@unicampania.it*

Abstract

The most recent experimental evidences of Quantum Physics and the new theoretical considerations connected to them have paradoxically questioned the basic founding principle of the scientific method, called the local realism principle. The main consequence of this cultural revolution is the need for a different approach to complexity in the world view through a phenomenon that I have called quantum synchronicity.

Quantum synchronicity is a phenomenon that is associated with the principle of cause-effect and tells us that in the quantum world there is an intrinsic correlation between systems, not attributable to a recognizable and expressible physical interaction, which means that a quantum system, and in general the entire universe, cannot be traced back even in principle to a set of separable parts, which can be defined locally and interacting only according to causality. The non-local quantum vision has its laws, potentials and limits, which we are learning to know and use for our evolution. The possibilities are largely yet to be explored, and range from technological applications, such as the quantum computer that is almost ready to be commercialized with immense implications in information management, to a revolution in looking at our essence and the world that contains us as inseparable elements.

Keywords: Local realism principle, quantum synchronicity

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Introduction

The first attempts of commercializing prototypes of quantum computer have started (Arute 2019). Quantum computer is a complex macroscopic object capable of functioning according to the laws of quantum mechanics (Feynman 1982; Devoret 2013; Leggett 2004; Nielsen 2000). The realization of quantum computer (CQ) first of all demonstrates that quantum mechanics laws also work in everyday life, although they are not normally directly visible to the way of seeing limited by our usual mental capacities (Bohm 1980). The possible use of CQ normally advertised is to process quantum information to make classically inconceivable calculations, but then the emphasis falls on the classical information that can be extracted from this colossal ability to process information. This classical information, while important, is very little when compared to the worldview revolution entailed by quantum computers. In this text, I invite the reader to become aware of the all-round awareness revolution that follows the new discoveries of quantum physics, and to use the new, emerging "intelligence" to address the challenges of such an evolution. The phenomenon of quantum coherence in macroscopic systems and entanglement has been supported by a large amount of experiments (see for instance Arute 2019; Chiorescu 2003; Emary 2014; Gerlich 2011; Hackermuller 2004;

Nakamura 1997; Wan 2016), opening the door to large-scale scientific speculations, both from an applicative point of view and from a philosophical and ethical point of view. It is important that the whole humanity, and not just a narrow scientific oligarchy, becomes aware of the possibilities that are opening up with these new discoveries and the related worldview.

Among other things, the recent developments in Quantum Physics undermine one of the most radical founding principles of the classical scientific method, called the local realism principle, and therefore require a profound revision of the scientific method by extending it to phenomena not directly measurable at the local level. Locality is a way of conceiving physics that attributes reality only to physical systems that can be defined through the measurable characteristics in the immediate surroundings of the system itself. Any other distant object cannot contribute to the reality of the local system. The interactions are also local, the presence of which can be measured in the immediate vicinity of the systems under consideration. In a local and mechanistic vision, reality is always separable into elementary parts, possibly interacting more or less intensely. This is the basis of classical scientific reductionism.

Non-locality, on the other hand, indicates that distant physical systems can be related in an inseparable way, to form a single quantum system. This correlation is not measurable at the local level, but means that the overall system cannot be separated into simple elements without losing its essential feature. As an intuitive, evocative example of what I mean, we know that a living organism cannot be separated into parts without losing its essential feature, which is life. We can then say that "vitality" is a non-local phenomenon, and as such it cannot be defined in classical physics. Similarly, quantum entanglement and synchronicity are non-local phenomena.

As opposed to classical reductionism, I would like to call the principle of non-locality at the basis of a new method of scientific investigation a "synchronic principle". The current scientific paradigm based on reductionism has been dominant since the Enlightenment, and places knowledge at the service of the immediate needs of humanity (real or presumed as such), neglecting or underestimating the effects that the use of new technologies have on the rest of the nature. As an undesirable side effect, technological development has thus contributed significantly to the recent global social and environmental crises. The main reason for this long supremacy is that this worldview allows for immediate material gains and economically profitable knowledge production, with a minority class of investors holding the controlling power. However, the awareness of having to verify how, in the face of short-term profits, reductionist technologies influence the ecosystems and complex systems with which they interfere, is increasingly spreading, first at the level of the cultural avant-garde and now in an increasingly widespread form. This type of approach to the interconnections of complex systems must be multidisciplinary and not local in nature, and I hope that academic institutions will soon open up to the holistic approach, as required by our new understanding. Science naturally realizes that most natural phenomena are of a complex type, meaning by this a system consisting of a very large number of elementary components interacting in a non-linear way, and therefore not deterministically predictable, whose collective properties are not simply attributable to the sum of the properties of the individual constituents. All biological systems, atmospheric phenomena, and in general all mechanical systems whose evolution is determined by non-linear equations that can lead to chaotic solutions are complex systems. Famous is Edward Lorenz statement: "The flapping of the wings of a butterfly in Canada is enough to cause a typhoon in Brazil the next day", indicating with this that it is enough to change the conditions by a trifle boundary to arrive at completely different solutions in mathematical models subject to non-linear equations.

The classical and deterministic scientific method is not applicable to these systems subject to chaotic solutions, as it cannot produce reliable predictions. Alternative mathematical methods are therefore being sought to be able to determine, at least in probabilistic terms, the possible evolutions of the system. This has created a new discipline in the scientific field that we can call the science of complexity, which has recently undergone great development. However, even for the study of complexity science starts from an approach based on the principle of local realism and of cause-effect, albeit trying to consider a complex circularity of causality relationships: it is hypothesized that in complex systems the simple elements influence each other through cause-effect relationships inextricable in their circularity characteristics, making the overall system inseparable into simple elements without losing some of its essential characteristics.

The synchronic principle introduces a new, I would say revolutionary, element in the approach to complexity, linked to the possibility of "non-mechanistic choice" that complex systems can have in their evolution. This possibility, which with anthropomorphic terms we could venture to call "conscious choice", is present in correlated systems through quantum synchronicity, and could be much more generally widespread than we can hypothesize in a reductionist paradigm.

Orthodox science is still tied to the reductionist approach that most scientists follow, consciously or not, as a widely accepted general theoretical paradigm to determine the design of research and even what is an acceptable research topic. An ideology of scientific progress is followed as a cumulative system of knowledge that grows steadily, drop by drop, in a single direction. The history of science teaches us that when anomalies are discovered that do not fit the dominant model, at first one tries to underestimate their revolutionary significance, then the tension grows as the evidence of new effects increases until one is forced to accept the revolutionary consequences of new discoveries. The dogmatic aspect of previous knowledge then falters and shatters. Thus a great leap forward in awareness is produced in the service of truth. In this way, modern science was born, and in particular quantum physics, as a quantum leap in stark contrast to the dominant paradigms at the time in which it was born.

The revolution that is approaching in the transition from the hegemony of the reductionist to the holistic approach envisages this type of discontinuity and offers us the opportunity for another great leap forward in human awareness. Scientific reductionism has brought us this far, and we must be grateful to it for the great progress achieved that have produced an abundance of material resources that cannot be compared with any previous historical era. But now the time has come to renounce the hegemony of reductionism, not to renounce the tools of the scientific method that work on a material level, but to integrate them in the service of a broader vision based on the synchronic principle. The question now is: what will be the new organization of science based on a synchronic principle? How can reductionist knowledge be integrated into a holistic hegemony?

In the first part of this article, I propose a synthesis of quantum synchronicity and the emergence of the classical worldview from the quantum model. In this synthesis, told without using any mathematical formula, I have no claim to be complete or original, but rather to be as clear and simple as possible without trivializing the concepts. In the second part I mention through some simple examples how quantum synchronicity can intuitively manifest itself in daily life, and I invite an integration between art and science in a new vision of the world that values the holistic principle towards the millennium community.

Of course, the field of investigation is very new, and we do not yet know the revolutionary consequences that a different approach to scientific knowledge can bring to everyday life, but in my opinion, an opening to new possibilities is already necessary right away.

Considering quantum mechanics as a theory adhering to physical reality simply means accepting that our possibility of knowing the world from a local point of view is severely limited. From a broader point of view, what appears to a local view as "very small quantum effects", often paradoxical, instead have dramatic consequences on the non-local conception of the world, and the phenomena that we are currently capable of considering in the classical scientific method are only the tip of an iceberg, the submerged part of which is immensely larger than that observable at first glance.

But there is no need to fear this submerged part whose effects begin to emerge in our most sophisticated experiments. These effects of Quantum Physics, if reported in our daily life, can be the guideline for a change in human awareness towards a different way of conceiving individual and collective happiness, to produce a change of direction in our personal choices towards a real development, globally sustainable, and to live life individually in a fulfilling way. Each individual can make her contribution, and each individual contribution has consequences on the collective global system that can be very relevant. Individuals can fully regain confidence in the power of their choices, without necessarily feeling like a small insignificant part of a huge system, whose inertia seems to be completely beyond the control.

In this regard, I like to conclude this introduction by making my own the statement of Richard Buckminster Fuller, the great American architect and stylist, pioneering advocate of sustainable development:

> "Think of the Queen Elisabeth: the whole ship and its helm. And then to the fact that there is a little contraption, called the trim-tab, correction flap. It is a miniature rudder, and it is the movement of that small fin

that creates the pressure that causes the rudder to rotate. It requires almost no effort."

So I told myself that the little individual can be a trim-tab in the big ship that is the global eco-system of life on earth!

1. Entanglement and Synchronicity

Entanglement is a mathematical consequence of the expression of quantum states in terms of vectors in Hilbert's complex space: it can be seen mathematically that if we have two or more particles, alongside particular cases in which the collective state can be separated into independent states concerning the single parts, in the vast majority of cases there are collective, tangled states that do not allow the individual parts to be separated even if they do not physically interact with each other. The quantum universe is interconnected through a classically inexplicable mechanism and not directly detectable or attributable to interactions between objects, to which Schrödinger has given the name of "entanglement".

The entanglement state is the mathematical representation of a phenomenon in which the quantum state of two or more physical systems depends on the quantum states of each of the systems that make up the whole, in a way that an action on one of the components causes an effect immediate on the state of the overall system, regardless of their space-time distance.

Albert Einstein branded the oddities predicted by quantum mechanics relating to entanglement phenomena as "spooky actions at a distance".

Albert Einstein himself, together with two co-authors, Boris Podolsky and Nathan Rosen, demonstrated in 1935 that quantum mechanics violates the principle of local realism through the mechanism of entanglement.

Rather than giving up this principle underlying all classical scientific thought, deeming it absolutely indubitable, Einstein stated that quantum mechanics is an incomplete theory and that it should be supplemented with hidden variables. These hidden variables should take into account the information necessary for the local realism principle to continue to apply, but are not contained in the quantum theory which would therefore be incomplete. The apparent non-locality of nature predicted by quantum theory would therefore be due to the impossibility of acquiring all the information necessary to describe a microscopic system. The argument is known as the EPR paradox (acronym for Einstein Podolsky Rosen 1935).

In quantum physics entanglement is a very general phenomenon, which affects every complex system up to and including the universe itself, as will be discussed later. However, its break with classical thought by now deeply rooted in our belief system, which imagines reality made up of separable parts, is so disruptive that it is difficult to visualize its scope, if not at an intuitive level. In fact, this whole text is an introduction to trying to figure the effects of entanglement (which I will later call quantum synchronicity) in our view of the universe. From a communicative point of view, entanglement can be described in the simplest possible case, i.e. the case of only two elementary particles distant from each other, albeit correlated to form a single system described by a single wave function not separable into parts. This is also the example that led Einstein and the other pioneers of quantum physics to introduce (and often critically consider) the concept of entanglement. So let's try to understand in the simple case of two particles what the difference between a classical and a quantum correlation consists of.

Suppose we have two classic particles of different color, say two marbles, one white and one black. We place the two marbles in a closed box, extract them one at a time and, without looking at the color, give them to two observers who then move away from each other. Later, when the two observers are very far away, we ask them to observe the color of the marbles. It is clear that the two measures are related: if one observes the black marble, at the same time it can be assumed with certainty that the other has a white marble, and vice versa, even without carrying out the measurement directly or communicating in any way with the other. Obviously we do not find anything strange in this, since the correlation of the measures is linked to their past history, which is precisely traceable: the different marbles were delivered to the two observers from the beginning, and from that moment the result of the future measure was set, even when the measure had not yet been carried out. We only lacked the information that came later with the observation, but the "reality" of the two marbles can never be questioned: one of the two has always had the white marble and the other the black; there is no need for the measure to fix the two marbles in a defined color.

The situation is completely different in quantum physics. The two marbles in the black box are indistinguishable and quantistically related: both may manifest as a white or black marble at the time of measurement, but their quantum state before measurement is a coherent superposition of the two states, where the choice has not yet been carried out. Both quantum marbles coexist in the two states. There is also a correlation between the two marbles, which in turn form a unique quantum system described by a single state consisting of a superposition of "entangled" states of the two particles. We know with certainty that if one of the two manifests itself as white at the moment of measurement, the other must necessarily manifest itself as black, or vice versa, but the "reality" of the marbles is not determined except at the moment of measurement through the collapse of the wave function. If you measure one of the two, its quantum state instantly "collapses" to a given value, and the state of the entangled particle also instantly collapses, whatever its distance from the first. In that case, it is as if information on the quantum state of one particle has been communicated to the other with a speed greater than that of light (instantaneously, to be precise).

In reality there is only one state of the particle system, and this is not separable into the states of individual particles. Quantum mechanics is a non-local theory, and the quantum universe cannot be separated into individual constituents.

Rather than accepting this state of affairs that quantum theory suggests, Einstein preferred to hypothesize that the two entangled particles were correlated from the beginning through hidden variables, for the moment unknown to us, so that if one of the two manifested a state l the other should manifest the complementary state even without exchanging information: similarly to how it happens in a classical correlation of the type described above, only through a more complex and yet to be determined mechanism. For Einstein, therefore, the correlation is formed at the moment in which the particles interact and, when they move apart, each of the two already exists in a defined state that we cannot know unless we carry out the measurement. In this way, the local realism principle can be saved: the description of the system given by quantum states would be correct but incomplete, and the apparent violation of the locality principle would arise from our ignorance of the variables necessary for a complete description of quantum systems.

The EPR paradox generated a debate on the interpretation of quantum mechanics, initially between Niels Bohr, a keen supporter of the "orthodox" quantum vision, and Einstein, a supporter of the incompleteness of quantum mechanics and the principle of local realism. The dispute continued even after the death of the two great scientists, between the promoters of the two interpretations. The debate could last so long because it is very complex to think and carry out an experiment that establishes the fall of locality principle. This type of experiments became possible only many years later, starting from the 1970s (Freedman 1972; Aspect 1981; Weihs 1998), but unambiguous evidence of the need to renounce local realism could only be found very recently with various experiments (Giustina 2015; Hansen 2015; Kneee 2016).

It should be clear from what has been said so far that the quantum nexus that connects two distant systems (which are often called Alice and Bob) is of a-causal type, i.e. there is no cause and effect relationship between the two systems.

Without a causal link, the result of the measurements that Bob takes is not affected in any way by the measurements made at the same time by Alice: Bob cannot know if Alice has actually carried out the measurement, or vice versa.

In the EPR paradox it is not possible to think that the result obtained by Alice is the cause of the result obtained by Bob: there is no cause and effect mechanism that causes the correlation. It is impossible even to establish whether the event concerning Alice's measure or the one concerning Bob's measure happened before.

We are assuming that Alice and Bob are far away at the time of the measurement, far enough that nothing traveling with the speed of light or less can depart from Alice when she takes the measurement and arrive at Bob when he does the same thing, or vice versa. In such a situation, it does not make any physical sense to ask which event happened first. According to the theory of relativity, I can find reference systems in which Alice is described making the measurement before Bob, but I can find reference systems where the opposite happens, and also I can find a frame of reference where events happen simultaneously. Whatever Alice does cannot be the cause of something happening to Bob.

In reality, Alice and Bob are not two separate systems connected through some "exotic" mechanism, but are the same inseparable, non-localized quantum system.

The a-causal quantum link does not contradict the cause-effect principle, but is complementary to it: through entanglement it is hypothesized that, alongside causality that acts in the direction of the progression of time and connects phenomena that occur at different times through a cause-effect relationship, there is a principle that "merges" the phenomena that occur at the same "time" but in different "spaces", between which no type of causal communication is possible.

Without causality, the word "time" must be in quotes, because the principle of cause and effect is fundamental to distinguish time in the usual way as past and future. This "time" instead describes a concept of synchronicity, through which the quantum system as a whole manifests itself in evolution without a specific cause and effect relationship between the parts, without a necessary consequentiality between past and future. It is clear that these concepts of "time" and "space" I am referring to here are very different from Einstein's concept of space-time.

The reality of quantum entanglement can be verified with particular experiments, through a statistical comparison of measurements made in several distant laboratories.

In 1964, John Stewart Bell, a British physicist who worked at CERN, demonstrated that local realism was expressed in mathematical terms by a series of inequalities, which have gone down in history as Bell's inequalities (Bell 1964). These inequalities link together, in statistical terms, the preparation of the experimental apparatus and the measurements obtained by two or more experimenters in different places, in the context of a correlation based on a causal principle. Now, according to Bell's proof illustrated in his theorem, inequalities are violated in processes based on quantum entanglement, and in general in any non-local theory.

Bell's theorem is an elegant and viable way to experimentally test local realism. Since then, dozens of experiments that refer to Bell's theorem, able to measure in the laboratory–or rather, in pairs of laboratories–have been carried out, experimentally demonstrating the violation of inequalities and highlighting the existence of a non-local quantum correlation (Ansmann 2009; Aspect 1981; Freedman 1972; Giustina 2015; Groeblaker 2007; Hansen 2015; Weihs 1998; just to cite some of the them).

The violation of the local realism principle manifests itself in the EPR-Bell experiments in which we are able to relate coincidences of measurements that occur in separate spaces without there being a cause-effect correlation between the parts. In this case, synchronicity manifests itself as a deviation from the law of chance that we would expect in the classical case. To understand this, we can give a very simple example taken from everyday life: it is as if we rolled many times two "entangled quantum dice" and we find that, despite each of the dice has taken every number between 1 and 6 with equal probability, the sum of the two numbers are always the same, say 7. Therefore, although observing each dice individually (local observation) we would not find anything strange, the correlation between the two measures (non-local synchronicity) cannot be the result of chance but indicates that there is an "invisible" and classically unexplainable relationship between the two events.

These are the simplest cases of entanglement between two quantum systems.

In more complex cases, the correlation can lead to situations that cannot be exemplified in a classical representation. Of course the level of entanglement between quantum systems can vary: in some cases it may be extremely high, or even the maximum possible, and involve a large number of particles, in other cases less strong, but in any case it always implies that the events that occur are significant of a certain correlation that cannot be traced back to any observable interaction between the parties. The experiments relating to Bell inequalities carried out so far refer to simple systems, such as pairs of electrons or "entangled" photons, or qu-bits, which we can call EPR-Bell experiments, but the proof of the non-locality it is indirectly verified even for more complex systems, so that entanglement is now an accepted and used phenomenon, especially in quantum information. In the quantum computer the level of correlation between quantum bits is the basic principle of its functioning. In reality we will see later that entanglement must conceptually extend to the whole universe.

As paradoxical as it may seem to the rational mind, quantum physics envisages an inextricable interconnection between events in space and time, which includes observers, through a single quantum state, the manifestation of which takes on a specific form only at the moment of observation. This implies that every local action has an impact on the whole related system, which however does not have a directly visible effect at the local level.

2. The Emergence of the Classical World from Quantum Theory

The paradoxical aspects of reality which the experiments conducted on microscopic objects oblige us to accept, have often been considered as belonging exclusively to a vision of the world valid only on very small scales, that is to say in the atomic or sub-atomic world, or in very particular conditions. According to this idea, there is a substantial difference between how the classical world that we commonly experience behaves and the described reality of quantum theory. In other words, there are two distinct models of reality, one classical and one quantum, which function in radically different ways, described by completely different physical laws. For the proponents of this hypothesis, there must be a physical process that allows the two worlds to be clearly separated. The collapse of the wave function due to the measurement has often been interpreted in this sense: as a physical process of a fundamental nature that necessarily transforms a quantum state, described by a coherent superposition of classically incompatible states, into a single classical state, the one that we experience in everyday life. Whatever way the measurement is made, the result will inevitably be a classical state anyway, obeying the logic of the classical world.

According to the statistical view of the theory, the mathematical formalism of quantum mechanics does not describe "physical reality". What it does is to provide an algorithm for calculating the probabilities for events as consequences of our experimental interventions. However, the world may be such that it cannot always identify a reality independent of our experimental activity. Consequently a vision of "objective" reality, that is, which exists independently of our subjective perception, would be impossible.

In other words, in the statistical interpretation of Quantum Mechanics (Ballantine 1970) the possible existence of an objective reality independent of what the observers perceive is not denied; this "objective reality" is simply not directly accessible to our experience since each of our observations substantially modifies the natural course of events.

I believe that most exponents of statistical interpretation would argue that since "collapse" is not a physical process for them, no "dynamic description" of it is needed. Collapse is something that happens in our description of the system, not in the system itself. Likewise, the time dependence of the wave function does not represent the evolution of a physical system. It only describes the evolution of probabilities for the results of our potential experiments on that system. This is the only sense of the wave function in the extreme statistical interpretation.

What to say now about the evolution of a macroscopic object: can it be described by a quantum state? In reality, nothing prevents it, as long as the forecasts we get are consistent with the results of the observations.

Let us examine the famous Schrödinger's cat paradox seen from this perspective (Schrödinger 1935). Here is the "paradox": a cat is in a closed box, where a photon is sent through a polarization filter. If the photon passes through the filter, then an ampoule containing a deadly poison opens. If, on the other hand, the photon is absorbed by the filter, then the bulb remains closed. The presence of the deadly poison in the box is therefore linked to a properly quantum process, described by a superposition of states, and therefore the "classic" state of the cat must be in a logically inconceivable superposition of "alive cat" and "dead cat" at the same time. However, if we do not attribute a measurement independent reality to the wave function, the paradox disappears. A quantum physicist stays outside the lab and calculates the cat's wave function. According to him, the cat is in a coherent superposition of states, simultaneously alive and dead in equal measure. But there is nothing paradoxical about this wave function; it represents only the greatest possible knowledge of the state of the cat obtainable outside the closed box. Reality cannot be known until one looks inside the black box containing the cat and the ampoule. If we open the box and observe we will always find the cat either dead or alive. Looking from inside the box, as soon as a detector was activated, the cat's status changed. Some time later, the physicist peeks into the box: thereby he gains new knowledge, and thus changes the wave function he uses to describe the cat.

From this example, it is clear that in this interpretation a wave function is only a mathematical expression for the calculation of probabilities and depends on the information of whoever is doing the evaluation of the various possibilities. In this way there is no paradox. Instead, attributing an objective reality to quantum states leads instead to a series of "quantum paradoxes" (for a review see Ballentine 1970).

This interpretation appears completely consistent, as long as it is integrated by a premise that constitutes the fundamental aspect that underlies the hypothesis of the collapse of the wave function as a non-physical process and is taken for granted in the statistical interpretation of quantum mechanics. We can formulate this premise by stating that for macroscopically distinguishable quantum states there can be no interference effects. If this is always true, then the quantum superposition between macroscopic states must be absolutely indistinguishable in every possible experiment from a classical statistical superposition. Only with this premise when we observe Schrödinger's cat we will always find it either alive or dead (with relative probabilities that can be calculated through the knowledge of the wave function), but never in a state of interference between the two possibilities. In the statistical interpretation, interference phenomena between macroscopic quantum states are not admissible, as the wave functions do not have a corresponding element of reality associated in the physical world, but serve only to calculate the probability that an observation produces one or the other possible result.

Until the late 1970s it seemed that no experiment could ever have the resolution needed to detect macroscopic quantum interference effects, even if it existed. From the beginning of the eighties until today, however, the possibility of macroscopic quantum effects has been highlighted in a series of increasingly convincing experiments (it is impossible to mention all the experiments: see for instance Chiorescu 2003; Friedman 2000; Martinis 1987; Mooji 1999; Nakamura 1997; Rouse 1995; Silvestrini 1997). Faced with the possibility of the superposition of macroscopically distinguishable quantum states, a theoretical investigation began at the same time to investigate this aspect (Caldeira 1981; Zurek 1981). Some theoretical physicists have tried to hypothesize models to describe the transition from the quantum world to the classical world, using exclusively the formalism of quantum mechanics. Quantum de-coherence theory (Zurek 2003) is one such model, considered valid today by most physicists and widely used to describe quantum mechanical experiments at the macroscopic level (Devoret 2013; Leggett 2004; Myatt 2000).

3. Quantum De-Coherence

Let us now try to mention the guidelines that underlie the theory of quantum de-coherence, in order to understand its scope and limits. Since macroscopic objects are made up of microscopic particles, all of which obey quantum mechanics, there should be a way to connect the classical world and the quantum world, macro and micro reality. We have seen that the traditional interpretation of quantum mechanics answers the questions regarding the definition of the state that manifests itself in the observed reality through the measurement process, a special process that cannot be traced back to the other rules of quantum mechanics.

The theory of de-coherence develops completely within the orthodox quantum formalism, and therefore uses the concept of measurement. In the theory of de-coherence privileged observers are not allowed, but every system can be considered both as an object to be observed and as an observer (Fields 2016).

Complex systems, made up of an incredibly large number of elementary components, can therefore be observed from parts of the system itself: in a sense, macroscopic systems can measure themselves, causing the collapse of the wave function and the emergence of the classical world, giving up a part of the information of the complex system as a whole. The information obtained in this process defines classical reality.

The mathematical theory of classical de-coherence, pioneered by Caldeira and Leggett (1981) and by Zurek (1981) independently, is a quantitative model of how this transition from quantum physics to classical mechanics occurs, and involves systems that make local measurements on themselves. The basic consideration is that every macroscopic object can never be completely separated from the environment. The degrees of freedom related to the environment are seen as a system of observation of the macroscopic object on which attention is being drawn (Zurek 2003). Our universe is therefore divided into two parts: the system we are considering, which is treated with quantum mechanics, and an environmental component, which is treated statistically. When the environment is coupled to the system, a part of the quantum information that the system transfers to the environment is lost, while the considered system loses its quantum coherence and over time becomes a statistical mixture, justifying the success of the statistical interpretation of Quantum Mechanics .

Now I try to visualize how the de-coherence occurs with a simple example that uses the phenomenon of interference through a double slit. So let's imagine conducting an experiment through a double slit using complex quantum objects, consisting of a large number of elementary components; this macroscopic object is inevitably interacting with the environment. One can imagine using large molecules made up of a large number of atoms (Gerlich 2011; Hackermuller 2004), or even more macroscopic objects. In the case of simple systems, such as electrons or photons, an interference pattern will appear on the screen, which is a consequence of the coherent superposition of quantum states in which electrons (or photons) pass through both slits simultaneously. This figure, however, disappears if we add to the experiment a measuring apparatus capable of identifying the trajectory followed by each electron, to become a classical statistical mixture in which there is an equal probability that each particle passes through a slit or through the other. In the case of complex molecules (and macroscopic objects in general) it happens that the particles interacting with the environment leave a "trace" of their passage in the environment. This trace provides information on the trajectory followed by the molecules even without the presence of a specific measurement apparatus, destroying the interference figure and collapsing the wave function in a classic mixture. This information is dispersed into the environment and may not be accessible to the experimental physicist, but it still exists and produces the phenomenon of de-coherence.

It is important to keep in mind that de-coherence is inherently a local phenomenon. That is, if we consider our entire universe, the system plus the environment, from the point of view of quantum mechanics, the classical effects do not emerge. Rather, for the emergence of "classicality" we need to focus attention on a particular component, and neglect the quantum information that has to do with the environment.

A great advantage in formulating the theory of de-coherence is that the mathematical apparatus allows to calculate the time in which the coherent quantum effects disappear, called the de-coherence time. This time turns out to be extraordinarily short in the vast majority of cases, thus justifying the fact that the superposition of macroscopically distinct states is not observed in everyday life. In some particular systems, however, paying particular attention to separating the system from the external environment, the de-coherence time can be long enough to allow laboratory measurements that highlight the superposition of states in macroscopic systems. These measurements, although confined to rather particular systems, nevertheless have an extraordinarily important significance, both from an applicative and a conceptual point of view. From an application point of view, they have opened up the possibility of a new discipline, called quantum information, which includes the phenomenon of quantum computing with the possibility of building quantum computers in the coming years, based on elementary bits of a quantum nature. Such a computer will have the potential to process quantum information with absolutely unthinkable perspectives for classical information, many of which are yet to be discovered but certainly extraordinary (Arute 2019; Feynman 1982; Nielsen 2000; Preskill 2018).

From a conceptual point of view, macroscopic systems showing quantum coherence effects indicate that there is no classical world and one quantum world described by different laws, but there is only one quantum universe in which the logical paradoxes we have discussed are real (Bohm 1980).

Since the theory of de-coherence predicts that the observable states of any system interacting with a surrounding environment will appear in a very short time classic to the observers who are present in that environment, it is considered by many to be an explanation of the apparent "classicality" of the observable states.

From a mathematical point of view, de-coherence theory is simply an application of quantum theory to the system-environment interaction. When we carefully examine the calculations of de-coherence, it is immediately clear that the mathematical methods provided by the theory of de-coherence are applicable in practice only if supplemented by classical assumptions. In particular, we must assume that during the interaction with the environment the system considered can be defined separately. A hypothesis of this type can only be an approximation in quantum mechanics, since the phenomenon of entanglement dynamically and inseparably binds all interacting degrees of freedom. The calculations of the de-coherence also involve the hypothesis that the observer does not obtain any information from the environment; this assumption is often rendered mathematical by assuming that the dynamic variables of the environment can be treated using classical statistical mechanics.

If we omit the classical assumptions and instead assume that quantum mechanics is a theory of general validity, the mathematics of de-coherence simply describes how the phenomenon of entanglement spreads in the environment.

In a quantum view, entanglement with the surrounding environment does not remove quantum coherence from a system; rather it couples the system and the environment in a way that quantum coherence expands to their joint state, also including the observer. The phenomenon described by de-coherence therefore does not cancel quantum coherence, but diffuses it into the environment, demonstrating that in quantum mechanics separate systems are only an approximation.

This is an inconceivable concept for our classical belief system that underlies our usual way of interpreting reality, but it is what recent experiments seem to confirm.

4. A Quantum World

Now I want to try to describe how we should interpret the quantum world in case we attribute a physical correspondence with reality to the mathematical formalism of the theory. This is the position that for me best suits the most modern and sophisticated experimental evidence.

The fundamental concept that introduces quantum theory is quantum connection, entanglement. The quantum world is an inextricably interconnected world. It is not separable into limited, temporary and re-identifiable entities that can be considered independently of each other. Our idea of separate independent systems that persist over time is, from a quantum point of view, only an approximation (Fields 2016). It is often a good approximation, good enough to allow for daily experimental testing in the laboratory, with uncertainties better than one part in a billion. This only means, however, that it is a good approximation for us, in our way of seeing things: we define the systems that we believe to be separate in space and time, and these are the systems for which the approximation is good. How does it work? What allows us to define the systems that appear to us to be separate? (Wheeler 2014). The phenomenon of entanglement shows us that any separation between observer and world (i.e. all the rest of the universe that is not an observer) is somehow arbitrary: the world itself can be considered as the observer (and therefore in this subdivision the observer becomes the world), and in general can contain infinite other observers, since any subset of the universe can be considered as an observer. The only entity that has an absolute existence, persistent over time albeit with changing forms, is the universe in its totality.

What we call "observer" is therefore a subset of the universe, arbitrarily chosen, which exchanges information with the rest of the universe. As a limited system it can exchange and store a limited amount of information. As we know from computer science, information is contained in the fundamental elements, which are called bits, two-state elements that can only take on two possible values, 0 or 1. Any type of information that a classical observer shares can be expressed as a string finished with "classic" bits. A computer in fact operates completely in a binary language through the creation and/or destruction and storage of a limited number of "classical" bits. Even the text I am writing right now is nothing more than an ordered string of bits that can later be decoded and interpreted by the reader, who in this way gives it meaning. With the evidence of the possibility of superposition of macroscopic states, we must assume that in fact information is coded by qu-bits. A qu-bit is a two-state system that can exist in an arbitrary coherent superposition state of classical states zero and 1. It has now been seen that a qu-bit cannot be duplicated (Zurek 1982) and that a single quantum bit in an unknown state cannot be described by a countable sequence of classical bits (for a review see for instance Nielsen 2000). In a quantum world, any limited subset of the universe cannot therefore receive, store, and exchange information through quantum bits. Therefore, our way of representing the world through classical information, be it a text, a thought, a mathematical formula, a complex theoretical system or any other shareable classical representation, cannot be a complete representation of the quantum reality. Hence the paradox of measurement in quantum theory, and all the other paradoxes we have mentioned in previous chapters. It can also be assumed that quantum theory is the most efficient logical system for managing shareable information that comes from a wonderfully complex and interconnected world, in which any subdivision into limited and independent subsets is completely arbitrary. The extraordinary agreement that quantum theory shows with an enormous amount of experiments conducted with great accuracy seems at the moment to support this hypothesis.

From another point of view, however, we now know that the information that we are capable of processing according to a classical and shareable logic is a very small part of the quantum information that describes the totality of the universe. The reason why we can scientifically agree on the occurrence of objective and shareable phenomena is simply that in the scientific method we consciously decide to focus our attention on a very limited part of phenomena.

This may perhaps be useful according to the classic logical view of interpreting the world, but in reality we must be fully aware that what cannot be understood according to this logic is immeasurably greater than what is shareable. Perhaps the time has come for the human mentality to become fully aware of this reality by opening ourselves to new forms of research. The scientific method can then continue to constitute the support for the resolution of practical problems, but the excessive emphasis that our culture gives to materialism and to the scientifically demonstrable aspects of reality, sometimes denying the existence of what is not scientifically demonstrable, it is not justifiable even within our current scientific knowledge.

I am convinced that a new world can emerge from the new quantum awareness that is forming in the process of global evolution, with humanity more responsible for its choices.

5. Quantum Complexity, Evolution, and Synchronicity

The reality that is the object of scientific research, and in general of all human knowledge, is characterized by a remarkable complexity which in the classical scientific vision appears to us as due to the complex interaction of an extremely large number of simple elements. This was the guiding principle of the scientific method, which schematizes reality through the interaction of a few simple microscopic elements such as quarks and leptons—which then combine in various form. Then, gradually increasing the complexity, they form simple molecules and then more and more complex systems until reaching chains such as the DNA that underlies every living process. The molecules in turn interact through chemical-physical phenomena related to energy and thermodynamic exchanges until they manifest the complexity of the entire universe starting from very few simple elements (37 are known, including leptons, quark, bosons, and gluons, with a symmetry between matter and anti-matter elementary particles) and four fundamental interactions.

Entanglement does not deny causality, but associates with it a different a-causal correlation not observable at the local level, which we have called "synchronicity". Another term that we could use to indicate entanglement is "organicity", that is, something that makes a related system organic, that is, not attributable to the simple sum of its parts and the interactions between them, as we can guess to happen in biological organisms in which the whole acquires a unique and unrepeatable identity.

In our observation of complex phenomena we can intuit that causality and synchronicity coexist, even if one of the two phenomena may appear to us more or less predominant. In general, causal relationships are more easily identifiable and measurable because they can be described in terms of cause-effect, to which our rational mind is more adapted. However, it is easy to recognize that the principle of cause and effect alone is not sufficient to explain many complex phenomena, and in particular organic phenomena. For example, in biology we can explain how the chemical-physical processes sustain life in an organism, but the beginning of life remains shrouded in mystery. To put it in a phrase attributed to the Nobel Prize in Chemistry, Ilya Prigogine that I made mine:

> "The probability that a macroscopic number of molecules will be assembled by chance to give rise to the highly ordered structures and coordinated functions that characterize living organisms is practically zero. The idea of the spontaneous genesis of life in its present form is therefore highly improbable, even on the scale of the billions of years during which prebiotic evolution took place."

On the other hand, we now know that entanglement (whose experimental evidence did not yet exist at the time of the quoted sentence by Prigogine) plays a fundamental role in the collective behavior of complex macroscopic systems.

Here I want to give an example taken from everyday life to express my thoughts about how a collective trend of a complex system can be associated with local relationships, and how synchronicity can be indicated in an evolutionary key, in the sense of probabilistic process indicated by Prigogine.

I think many have observed the collective figures that flocks of hundreds (or even thousands) of black birds called starlings sometimes perform in the skies of our cities. The movements of this set of separate individuals appear to us so harmonious and synchronized that it leads us to think that there is an "intelligence" guiding the group, a leader from whom the synchronized movement originates. There have been many scientific studies to try to understand how these collective movements can be explained in physico-mathematical terms (see for instance Attanasi 2014). The study of this type of collective dynamics is an interesting example because it is a moderately complex system (a few hundreds or thousands of elements can appear a lot, but it is nothing compared to the complexity of billions of billions of elements that synchronize in biological systems) and allows to find solutions that are currently unapproachable in more complex systems. The result of these studies is in some ways surprising, because it shows that there is no need for any leader to perform these complex synchronized figures, but it is enough to hypothesize local relationships between the elements. Each individual has no awareness or vision of the overall flight of the system, but is aware only of the motion of the first neighbors (generally 6 or 7) and starting from these is following some simple rules to move accordingly: first of all, they avoid colliding in flight with the neighboring birds, but at the same time they try to maintain cohesion with the group so as not to find himself isolated. Finally each individual tries to align with the first neighbors. With just these three elements of "local interaction" we can explain the synchronized collective motions that we observe as a whole. Furthermore, it can be seen from the mathematical models how the system, while apparently moving in a chaotic way, can maintain a high degree of global coherence. This coherence can be described in analogy with the phase transitions at low temperatures of superfluid helium or superconductivity. These latter phenomena, which require elements of quantum physics to be described, derive from the combination of a purely local phenomenon and synchronicity.

Cooper coupling in a standard BCS superconductor is indeed the result of "local" interactions (range ~ 1-2 angstroms), but the resulting correlations extend to several thousand angstroms and are manifestly entangled at least as regards the degree of freedom of spin. The behavior of superfluid 4-He helium can instead be explained on the basis of the Bose-Einstein condensation. Both phenomena constitute a quantum phase transition associated with a collective quantum state.

To understand how the combination of a local phenomenon and synchronicity could intervene in the probabilistic terms indicated by Prigogine we must understand the evolutionary function of these collective motions: in the event that the group is threatened by a predator, a movement must originate to decide in which direction to escape. The information spreads quickly to the whole system through a particularly effective and reliable mechanism that makes predation rather difficult. The hidden purpose of this collective behavior is therefore linked to the evolution and survival process of the species which individuals are not directly aware of, but which they instinctively follow. This species intelligence linked to evolution is specific to the group, and is the result of natural selection.

Now Prigogine's statement comes into play: if the process of natural selection were to act completely at random, the probability that such a finalized collective behavior would be generated would be nil even in billions of years of evolution (what about biological systems that we have seen to be exponentially more complex). In this sense we can understand what the effect of synchronicity is, which would be to determine choices that are not completely random, but with significantly higher probabilities towards the "intelligent" evolutionary purpose, using an adjective of anthropomorphic connotation. In fact, in all the experiments on the so-called Bell inequalities in quantum physics that highlight entanglement, we always have to do with probabilities that cannot be considered completely determined by chance as would be expected according to the local realism principle. Synchronicity could therefore take the place of the pseudo-scientific principle, called "anthropic principle". Such a term was coined in 1973 by Brandon Carter in his speech "Large Number Coincidences and the Anthropic Principle in Cosmology" during a symposium held in Krakow as part of the celebrations for the 500th anniversary of the birth of Copernicus. In fact I think it can be said very plausibly that the idea of the anthropic principle (although obviously not under this name) was actually introduced by Boltzmann about 100 years earlier, pointing out that it is only in an "atypical" region of the Universe that human life has been able to develop. The anthropic principle has been used to explain with ad hoc hypotheses the perceived meaning of a "guided" evolution for the exponentially improbable phenomenon that is the appearance of life on the earth (and in the universe in general). I think that it will soon be possible to formalize in rigorous terms through a more current conception of the scientific method the influence of quantum synchronicity on the evolutionary process, probably precisely with the advent and diffusion of quantum computers, which are the only tools to be able to study exponentially complex phenomena with some chance of success.

6. Harmony and Synchronicity

To me, synchronicity also plays a very important role in determining what we can call a feeling of "harmony", both in natural manifestations and in the artistic creation produced by man. I want to express my feeling in this regard, which is not rigorous but can be evocative for individual reflection. Let's start with a simple example. Suppose we listen to a symphony by Beethoven or Mozart, or a Bach sonata: I imagine that first of all we will notice a harmony linked to a local relationship of the notes, that is to say the neighboring notes form sequences that appear harmonic to us, pleasant to the listener. Following a more trained ear, a more global harmony will appear, in which even groups of more distant notes are harmoniously connected throughout the composition: we could identify for example the general tonality, the symmetries and appropriate symmetry breaking, for which the complex will appear more and more organic. Finally, we may perhaps notice single and apparently insignificant details, but which on the whole make the work a masterpiece of perfection, beyond the perfect structure of the mathematical relationships that express the various wavelengths of the notes. This "something unpredictable", this invisible thread that binds the whole work is inextricably linked to the genius of the artist, just as it is linked to the sensitivity of the execution, to the non-mechanical intelligence of those who perform the work at the moment. This invisible element, not detectable by measurements or arguments of any kind, is the "synchronicity" that makes a complex whole a unique and irreplaceable work of art. Not only this, the intuition of the irreplaceable majesty of the work also requires the listener's capacity for synchronicity, non-mechanical intelligence, in no way attributable to mathematical equations, and the mysterious empathy that is generated between author, performer and listener. This is why each performance is unique, and belongs to the magic of the moment and here lies the charm of live concerts. To put it again with a phrase of Prigogine: "Whatever we call reality, it is revealed to us only through the active construction in which we participate."

For me, Art is a work characterized by a great component of synchronicity, while mastery is mechanically perfect but has a low content of synchronicity. In the same way, intelligence for me is not a local but rather an organic phenomenon of synchronicity, where the entire universe participates, whose mechanical expression is manifested by harmonic local relations.

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The Synchronic Principle for a New Scientific Method

Paolo Silvestrini[a*]

[a] *Università della Campania Luigi Vanvitelli, Dipartimento di Matematica e Fisica, Caserta, Italy*

***Corresponding author:** Paolo Silvestrini, Email: *paolo.silvestrini@unicampania.it*

Abstract

Local realism has been superseded by recent theoretical and experimental developments in quantum physics, which show a synchronic connection between the parts. In contrast to the principle of local realism, which is the basis of classical reductionism, I have called the principle of non-locality, "synchronic principle". In a synchronic paradigm, evolution is characterized by a certain intrinsic freedom of choice that we associate with awareness. Considerations based on the evolution of the universe towards the emergence of life lead us to think that this "awareness" also exists in the vacuum state. In the model, I proposed a definition of the agents of consciousness in terms of arrays of correlated qu-bit, from the simplest one, which consists of 6 qu-bits of the quantum vacuum (a superposition of 64 base states), up to the most complex organisms consisting of a very large number of correlated quantum bits. Some of the fundamental vacuum states of consciousness can be related to known elementary particles (leptons and quarks) and to fundamental interactions. The rest constitutes purely non-local elements of consciousness with no counterpart in terms of wave or particle within the local observation limit. In this model, consciousness processes quantum information through logic gates and collapses as a result of observations, like a quantum computer does. Synchronicity does not deny the conclusions reached by traditional science. It can work at the local level, but opens scientific knowledge to new possibilities, and invites us to look at the world through a different, non-local awareness.

Keywords: Synchronic principle, non-local awareness, consciousness

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Introduction

The phenomenon of quantum coherence and entanglement in macroscopic systems is supported by both theoretical considerations (Caldeira 1981; Zurek 1981; Zurek 2003) and a large amount of experiments (among them, see Arute 2019; Chiorescu 2003; Emary 2014; Knee 2016; Martinis 1987; Nakamura 1997; Rouse 1995; Silvestrini 1997, and Wan 2016). These discoveries and their implicit worldview deserve dissemination (Bohm 1980; Leggett 2004; Nielsen 2000).

Recent developments in quantum physics undermine the local realism principle, i.e. one of the founding principles of the classical scientific method (I am referring to experiments on the so called EPR-Bell inequalities: see for instance Aspect 1981; Freedman 1972; Giustina 2015; Groeblaker 2007 Hansen 2015 just to cite a few). This calls for a profound revision of the scientific method, to be extended to phenomena that are not directly measurable at the local level.

I would like to clarify what I mean by classical locality and quantum non-locality. Locality only considers physical systems whose characteristics can be measured in the immediate vicinity of the system itself. Any other distant object cannot contribute to the reality of the local system. The interactions are also local, and can be measured in the immediate vicinity of the systems under consideration. In a local and mechanistic vision, reality is always separable into elementary parts that interacts with more or less intensity. This is the basis of classical scientific reductionism.

Non-locality, on the other hand, indicates that distant physical systems can be related in an inseparable way and form a single quantum system. This correlation is not measurable at the local level, but means that the overall system cannot be separated into simple elements without losing its essential characteristics. Entanglement and quantum synchronicity are non-local phenomena. Their “mysterious” nature depends on the fact that they cannot be traced back to actions related to the cause-effect principle (Bohm 1980).

As opposed to classical reductionism, I would like to call the principle of non-locality the “synchronic principle”, and the new science that derives from it “Synchronic Science”. Quantum Physics has shown the need to introduce synchronicity in our vision of nature. However, its interpretation of the world has remained linked to classical reductionism, confining its attention to that limited subset of phenomena that are verifiable in local experiments. Not only does official science ignore the phenomena that are based on the complexity of the synchronic principle but also it tends to label them as “borderline” between science and pure philosophical speculation, or worse. An exception are the countless studies of the last two or three decades on entanglement and macroscopic quantum coherence, with enormous funding worldwide for research on quantum technologies. The motivation for this widespread interest lies in the economic and military interest for quantum computer development.

The synchronic principle is a revolutionary approach to complexity. It links to the possibility of “non-mechanistic choice” in evolving complex systems. In anthropomorphic terms, we could call this possibility a “conscious choice”. We find it in correlated systems through quantum synchronicity, and could be much more generally widespread than we can hypothesize in a reductionist paradigm. In a synchronic view, consciousness could be a fundamental ontological element, and it would therefore make no sense to ask how it emerges in reductionist terms, or why it exists. It just exists. We can only ascertain its presence and accept its indubitable factuality, and try to understand its ways of manifesting and interacting.

This is one of the fundamental research topics I envision for synchronic science. In a synchronic view, the elementary particles are also simple elements of consciousness, which self-organize to form complex organic systems endowed with an articulated and evolved consciousness. The more the simple elements integrate synchronically, the more free and responsible are the responsible to the stimuli (Hoffman 2008).

In this article I propose a synchronic model for conscious agents starting from the fundamental state of the universe (the quantum vacuum): this model could be the basis for a unified model of subject and object, materiality and awareness. As it is constructed, it allows an association of some elements of consciousness with the elementary particles interacting through the fundamental fields, so as to automatically lead back to quantum physics in the simplest cases. In the more general case, the model contains an enormous variety of overlapping possibilities. Some of them relate with the known matter, but others are peculiar states of consciousness that interact according to the modalities of quantum computation.

This article aims at envisioning a “new” scientific method that integrates rigor and imagination for a knowledge that is at once objective and subjective. I do not pretend my considerations to be in any way definitive nor valid for everyone, and I rather wish to stimulate a discussion.

1. A Conscious Evolution

The process of evolution has gone through a very large number of bifurcation points in which parameters barely different from those observed would have led to absolutely different and lifeless evolutions. This is true right from the choice of the universal constants that determine the mass and charge of elementary particles and the relationships between the known force fields, which as far as we know could have been different from those observed, up to the very delicate initial conditions that led the highly chaotic evolution of the universe to the present remarkably ordered manifestation - in terms of clusters, galaxies, stars, planets, up to and including biological organisms - in the approximately 15 billion years that we estimate have elapsed since the big bang. The development of life on earth is a "miracle" of perfect harmony of conditions so exponentially improbable that it is really difficult to think that it was determined solely by chance.

To express this extremely improbable consideration, Carter introduced the anthropic principle in 1973. He proposed two versions of the principle: first a "weak" Anthropic Principle in consideration of the fact that "our position in the universe is necessarily privileged insofar as it must be compatible with our existence as observers ". He also proposed a "strong" Anthropic Principle, which states:

> "The universe (and therefore the fundamental parameters on which it depends) must have those properties that allow conscious observers to develop within it at a certain point in its history."

The anthropic principle wants to underline that we live in a universe that allows the existence of life, as we know it. In a local view, this fact is so particular that if we tried to calculate the probability of life evolution by randomness, then this probability would be zero. The universe is a complex system and its chaotic evolution passes through different phases of "bifurcation". Here, imperceptible differences in boundary conditions determine completely different developments. The probability that many critical parameters randomly assumed the exact values necessary for the development of life is zero. So it can be assumed that the emergence of consciousness is not the result of chance.

If life cannot be just the result of chance, does this mean that there is an end in the evolution of the universe? Does an intelligence guide evolution so that life manifests itself? Do we have to admit a principle that states that the presence of a conscious life is essential for the very existence of the universe?

Such a request may seem excessive: after all, we experience only this universe, which contains the humankind and life. We cannot refer to another universe for a hypothetical probability calculation. However, the above questions are legitimate and I would like to try to prove their validity with a simple example.

Let us consider the Rubik's cube for this purpose: in its original version, it has 9 squares on each of its 6 faces. The squares differ in color, with a total of 6 different colors. When the Rubik's cube is solved, each face has all nine squares of the same color. It starts with a random configuration, with different colors on each of the faces. The aim of the game is to trace the original position of the small cubes in each face by bringing the whole cube to have a single color for each face.

The cube can take on a huge number of possible combinations but only one is correct. This number can be calculated and turns out to be N = 43 252 003 274 489 856 000.

Let us consider an evolution of a Rubik's cube by "invisible" hands. In the event that the changes occur randomly, the probability of reaching the solution is very low: with a hundred configuration changes every second, it would still take a time equal to approximately the estimated age of the universe to solve the cube.

Indeed, we realize that the game has a purpose. Although the configuration changes may initially look random, in fact they are not. Favored combinations that aggregate cubes of the same color on the same face emerge during the process. If the intelligence that moves the "invisible" hands is an expert in the game, then the solution is quickly reached. It could even be possible to solve the cube in the shortest possible time by making as few changes as possible. In this case, no movement is casual, but each one is oriented toward the final purpose. The world record for the solution time is in fact less than 5 seconds. Even an inexpert player, who move with a certain randomness, observes the result of the movements and preserves the configurations that aggregate cubes of the same color on each face, thus directing towards the solution. This takes place in a time that is not so short but still reasonable and much faster than complete randomness.

If we observe such an evolution to happen "naturally", then we could naively think that there is no intelligence guiding the movements and therefore believe that the evolution we observe is the only possible. This is because we do not move the cube ourselves. We could strive to discover the regularities in the movements of the cube configurations, and then of course we would find them. We could even summarize them in simple mathematical equations and call them "physical laws". The more expert is the intelligence that guides the cube's evolution, the more deterministic the laws. Paradoxically, once we have found those laws, we can think that we are particularly "intelligent" and rational for having discovered them.

The discovery of those physical laws indicates a certain rationality and logic in highlighting the regularities of movements. However, it also highlights a sort of blindness that prevents us from seeing the hands, the true intelligence that guides the process.

A greater capacity for understanding could instead recognize in those same laws the presence of invisible hands and a purpose in the game, thus implicitly admitting one's own blindness.

Let us go back to the universe in which we find ourselves, which is obviously an immensely more complex system than the Rubik's cube. Here, we observe an evolution that led to the appearance of life and ourselves. This configuration is so critical and so enormously unlikely that it calls for intelligence and a specific purpose in this sense.

This request contains the essence of the anthropic principle, at least in its strong formulation, which perhaps we should call the "biocentric" principle because it places consciousness as the ultimate purpose of existence.

The synchronic principle, which has been observed in countless experiments and which is part of the formalism of Quantum Physics can replace the anthropic principle, which like all ad hoc principles leaves even the most staunch defenders of reductionism unsatisfied. In fact, synchronicity manifests itself to a local vision as significant coincidences without there being a cause-effect relationship between the events considered. Events correlated through entanglement do not occur by chance. Rather, they are part of a single quantum process that cannot be separated into distant parts. The universe that presents itself to us in the quantum model is a non-local, intrinsically connected universe. Every observer is entangled with what he observes and the universe is a single system inconceivable in any classical model (Bohm 1980).

On the basis of this synchronic principle we have hypothesized a widespread possibility of non-random choice, which we can call "consciousness" or "awareness". With this, I do not mean "human consciousness" but an all-level, universal awareness encompassing elementary particles and complex systems. Possibly, such an awareness is capable of self-organizing and include the whole universe (Fields 2016).

2. Elementary Particles of Consciousness

The main challenge of a synchronic science is to build an "observer" within the formalism of quantum mechanics. This entity's states correspond to a reasonable model of conscious awareness. What defines a conscious agent? How does it operate and how does it evolve in the universe? What is a conscious observer and a non-local observation? How can quantum information be processed without reducing it to a set of classical bits?

The new science must try to gear up to answer these questions (Fields 2018, Hoffman 2008).

Let us now try to define a "quantum observer" that can serve as a fundamental paradigm of synchronic science to build a quantum physics theory in the limit cases of local observations.

In quantum physics, any subset of the universe can be considered an observer, and therefore, by accepting the synchronic principle, a more or less complex element of consciousness. From elementary particles to systems with ever increasing complexity, consciousness must be able to expand and evolve in an increasingly inclusive way: simple elements of consciousness, which we can call elementary points of view, combining themselves must be able to form elements of consciousness that are inclusive of the sum of the original points of view, but in general also capable of a broader, non-local observation, not attributable to the simple sum of the parts. A definition of an element of consciousness must therefore satisfy the condition that the union of several elements is still an element of consciousness capable of a complexity of observation greater than or equal to the sum of the individual constituents. Furthermore, the elements of consciousness must be connected with a certain level of synchronicity, and therefore never completely separable. The separation, albeit arbitrary, can be done by defining fictitious borders between the parts of the universe. However, this leads to hypothesize an exchange of information and the possibility of the collapse of the wave function that we encountered in quantum physics.

We begin by analyzing the definition of conscious agent as proposed by Hofmann and coauthors (Hoffman 2008; Fields 2018) through the mathematical concept of a classical Markovian kernel. In this proposal, the conscious agent is in contact with the world (defined as that part of the universe other than itself) and interacts with it through a circular connection of three processes, identified as characterizing consciousness: perception, decision, and action. The conscious agent has experiences through interaction with the world. Based on these perceptions, he decides what actions to take, and because of these actions, he influences the state of the world. The process resumes in a circular connection of cause-effect relationships: the observer appreciably perturbs the characteristics and evolution of the observed system; and for its part, the observed system strongly influences the behavior of the observer, and the same rules and methods of observation. This interaction, with its characteristics of circularity, is amplified more and more when the observer's perception capacity widens. The observer is subject to unpredictable evolutions following the stresses it experiences.

Although this definition provides for a strong interaction between the observer and the observed world, the approach is still based on reductionism.

The reductionist and causal aspect of the definition of conscious agents by Hofmann and co-authors is formally recognizable in the mathematical treatment of the conditional probabilities underlying their definition of conscious agent. In fact, they are considered independent. For example, if the state of the world is w1, then the set of possible conscious experiences that could result is described by a list of independent probabilities, with the only condition that the sum is 1. If the state of the world were w2 then the mixture of probabilities would be different, but still independent, not coherently superimposed. This is the way to treat statistics in a classical view, that is, as a mixture of probabilities, with the only condition that the sum must be 1 (certainty), if all the possibilities are taken into account. In a quantum view, the possibilities are not independent, either one or the other according to a probabilistic law. Rather, the possible alternatives are coherently superimposed, with the fundamental implication of interference effects. The same classical reductionist approach is also formally recognizable in the description of the observer (conscious agent) and of the observed (the world). Despite the symmetry of the definition, whereby an observer can become the observed and vice versa in an exchange of roles that is always possible and legitimate, however the states that describe the two are considered separate and not entangled. The interaction between the two is of a cause-effect type, albeit in an inextricable and in fact inseparable circularity, given the complexity of the interaction. This type of correlation produces an evolution that needs time to manifest. We cannot detail its circular cause-effect sequence, given its complexity, but in fact, we admit that it exists in principle.

Synchronicity is a completely different type of connection of the systems involved in an a-causal, inseparable, synchronic way regardless of their cause-effect relationships and space-time distance. Synchronicity is an ever-present connection, which does not need time or causes to manifest itself: it exists and is an ontologically primary part of the universe, even if it is not visible to our objective perception.

First, I would like to try to extend Hofmann's definition by replacing his classical probability mixtures with a coherent superposition of possibilities based on quantum formalism. At the same time, I introduce the possibility of entanglement and collapse of the wave function. This too can be done within the mathematical formalism of quantum mechanics.

In a new synchronic scientific method, each element of reality must intrinsically contain the essential characteristics that we attribute to consciousness: exchange of information with one's world (perception), a certain freedom of choice (decision), freedom to act in the decided direction (non-random action). It is through these communication channels between the conscious agent and the world with which it is entangled that the evolution towards universal awareness is determined.

We should start our hypothesis from the simplest possible case, and try to understand how states of consciousness could be applied to known elementary particles. If we succeeded in this analogy, then the correspondence with quantum physics in the local and causal approximation would be automatic, while the synchronic theory could give indications of new implications.

The most elementary state possible is the fundamental state of the Universe, that is, the state of vacuum. In field theory, the quantum vacuum is not static, but a highly dynamic state. Here, virtual elementary particles, whose average life is too short to be observed, are continuously produced. The vacuum state is energetic and all virtual particles are continuously created and destroyed, compatibly with the conservation of fundamental quantum numbers. In the quantum vacuum all the fields are present, albeit in the state of minimum energy, and all the virtual particles that are the elementary excitations of these fields, in an inextricable synchronic intertwining. Let us try to build a model of synchronic elements of consciousness for the quantum vacuum that allows for the most complex conscious agents to emerge through a self-determination process, just as in a causal vision the aggregate matter emerges from the elementary particles through a causal evolution.

The three characteristics of perception, decision, and action must also be present at the fundamental level. In the elementary case, each of these intrinsic degrees of freedom can have the minimum number of possible states, that is, two. This means two possible states of perception, two possible decision states, and two possible basic actions. The combinations of all possible base states are 23, that is 8. In a synchronic view, the observer's elementary state of consciousness can exist in any combination of coherent superposition of all 8 base states. Together with the elementary observer, and symmetrical to it, the elementary observed system must exist, complementary to the first. This system constitutes the world of the observer. At the same time, it can be considered as the observer by reversing the roles: the two systems must be entangled. The basic states of the observer-observed entangled system are therefore 64, that is, all the possible combinations of the 8 states of the first with the 8 of the second, in a perfect symmetry of interchange of roles. The state of consciousness of the entangled elementary system will therefore be any coherent superposition of all 64 base states. Since the possible superposition states are infinite, the information contained in any state cannot be represented by a (finite or infinite) sequence of classical bits already at the elementary level of consciousness. However, it can be represented by an array of 6 entangled qubits, using the concepts of quantum information. In fact, I believe that the consciousness of complex conscious systems is a self-organized dynamic system capable of processing quantum information, a bit like we are trying to do with technologies related to the development of quantum computer.

According to this logical scheme, I would now like to try to associate the basic states of elementary consciousness with the elementary excitations of the vacuum state of quantum physics, that is, elementary particles. Of course, not all 64 states of elementary consciousness must necessarily associate with known elementary particles; some may be forms of consciousness that cannot be traced back to measurable objective reality, but it is worth making general assessments. This association is generic and highly speculative, but it still seems useful to show a certain

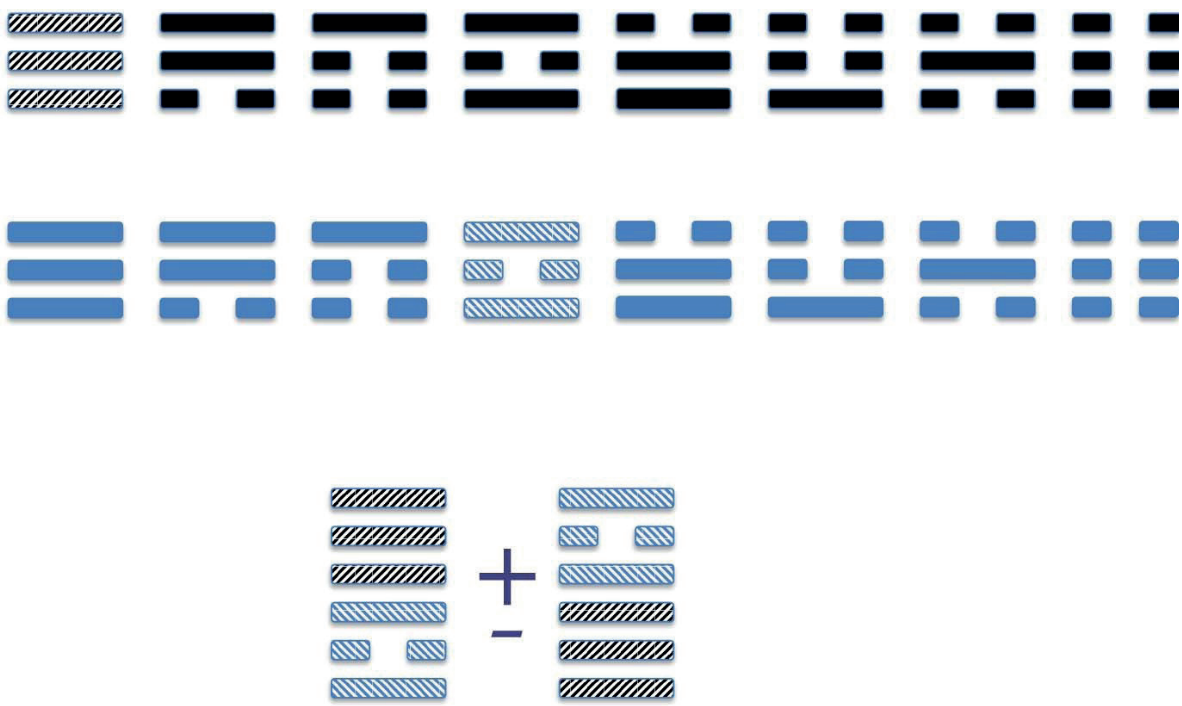

Figure 1: This 64 hexagrams represents the combinations of the entangled system.

reasonableness, since any theory that starts from the definition of the agents of consciousness must be traced back to quantum physics in the limiting case of predominance of the causality principle. First of all, let us try to take into account the perfect symmetry between observer and observed. In order to visualize my argument, let us establish to represent the 8 basic states of the observer and the observed through trigrams (ordered sequences of three superimposed lines, which can be whole or broken), in which the two states of perception, decision, and action are represented by continuous or broken lines placed one above the other. The 8 possible states of the observer are therefore those shown in the following diagram (drawn in black), and we can do the same for the observed system (in blue).

The combinations of the entangled system will be represented in this schematization by the 64 hexagrams (sequences of six whole or broken lines) which are obtained by combining the 8 upper trigrams (relative to the observer) with the lower 8 (relative to the observed). For example, the two hexagrams of Figure 1 are the combination of the first plus the fourth trigram. Due to the perfect symmetry between the observed system and the observer, the two states obtained by inverting the order of the trigrams must correspond to equivalent global situations. In quantum mechanics, in the presence of equivalent states, stationary states are coherent superpositions of the two symmetrical states that are constructed by adding and subtracting the two states (the two superpositions are called symmetrical and anti-symmetrical), as shown in Figure 1. These overlaps can be constructed only if the trigrams that form the hexagram are different (which happens for 56 hexagrams), while in the 8 hexagrams made up of identical trigrams we have only one possible combination. The symmetrical overlap is generally more stable, while the antisymmetric combination needs more energy to be activated.

Ultimately, of the 64 possible overlapping basic states to form elementary states of consciousness we have 8 hexagrams made up of two identical trigrams (which correspond to an equal state of consciousness between observer and observed), 28 symmetrical elementary superimpositions, and 28 antisymmetric superimpositions of hexagrams consisting of different trigrams with inversion between observer and observed. Therefore, using the formalism of quantum mechanics to define the elementary states of consciousness of the vacuum, we have 28 states that are obtained by breaking the symmetry, plus 8 consisting of identical trigrams, for a total of 36 states. In addition to these, we have 28 antisymmetric combinations that can be activated with greater difficulty. The vacuum state of consciousness will then be any coherent superposition of these basic states, which can be described as an array of six quantum bits entangled, in a representation proper of quantum information.

It should be noted that in a local view, introducing the collapse of the wave function, from this enormous potentiality of possible states we will always obtain only one of the 64 possible different manifestations, with different probabilities of occurrence linked to the degree of stability of the relative base states.

In a synchronic view, of course, the paradigm is completely different and evolution does not occur over time according to causal processes described by physical laws, but it is a synchronic manifestation of universal awareness, whose beauty and harmony can be represented locally by physical laws.

In this hypothesis, some of the basic states of consciousness of the vacuum can be associated in a local view to the known elementary particles (leptons and quarks, which together constitute the so-called fermions) and to the fundamental interactions, also mediated by elementary particles (called bosons). In quantum physics, at the present state of knowledge of elementary particles, we have 6 quarks and 6 leptons (these are all fermions), divided into three generations of up and down, with their antimatter counterparts; 8 gluons which are the mediators of strong interactions, the photon which is the mediator of electromagnetic interactions, and three bosons which mediate weak interactions. We also have the Higgs boson, and some hypothetical gravitons that would be the mediators of the gravitational interaction (for which, however, a satisfactory quantum theory does not exist yet). This gives 24 fermions plus 12 bosons mediators of interactions, i.e. 36 particles consisting of fermions and bosons. 36 are also the most stable basic states of consciousness, which I would associate with the fermions and interaction bosons found experimentally in large accelerators. Of the other 28 elements of consciousness that are more difficult to activate at the local level, one I would associate with the Higgs boson, another with the graviton. The remainder constitute elements of consciousness without a counterpart in terms of wave or particle in known local observation.

These elements of a purely non-local character, and as such not attributable in any way to elementary particles observable in local experiments, could be the constituents of dark matter and dark energy, whose presence is recognized by indirect cosmological measurements. In this case, the search for dark matter and dark energy in the large astrophysical experiments that are currently underway should change the investigation objective, focusing on non-local effects. These effects are verifiable in experiments conceptually different from the classical direct observation.

I prefer not to stretch further this speculation, also because I do not have a specific competence in elementary particle physics. However, the hypothesis of a primary consciousness as the fundamental substratum of the universe seem reasonable to me. Indeed, it appears perfectly consistent with the synchronic principle that manifests itself both in the recent developments of quantum physics, and indirectly through the probabilistic considerations of an unguided random evolution. Therefore, I feel to hypothesize a quantum nature of the information exchanged by the agents of consciousness, self-defined according to a criterion of free choice and non-random evolution.

In the next chapter, I will try to draw guidelines to understand how the elements of consciousness spontaneously evolve towards a broader awareness. Furthermore, I will indicate a principle verifiability methodology for the experiment of non-local predictions related to the synchronic principle in the simplest cases.

3. The Evolution of Consciousness

After our definition of the elementary agents of consciousness of the vacuum state as coherent superpositions of hexagrams consisting of arrays of 6 quantum bits, we still need to indicate how evolution takes place starting from these simple elements.

In our model, evolution occurs by not randomly determined attempts, since the elements of consciousness have a possibility of choice, limited to the minimum in the elementary case but sufficient to guide the evolution of the Universe towards the conditions necessary for the development of biological organisms. During the process of evolution, consciousness becomes more and more complex through the synchronic aggregation of elementary agents, and the possibility of choice gradually increases until it reaches the complexity of human consciousness, which we know well from direct self-referential experience, and perhaps other forms of very evolved conscience that we still do not have the possibility to perceive with our level of conscience. Our intelligence allows us many free and responsible choices, so it is now evident that our evolution does not occur by attempts determined (only) by chance but is partly guided by awareness.

The dynamics of the Universe allows us to define a time, whose arrow indicates the direction in which the evolution of consciousness naturally occurs. In our local view time is a primary concept, fundamental to define scientific laws but in a synchronic view time is a secondary concept, not intrinsic to the Universe but rather it represents the way in which our mind is able to sequentially conceive the evolutionary process. In the local paradigm, space-time is the basic substratum on which the laws of nature act through which we recognize a regularity in the dynamic process of evolution.

In the local view, scientific laws seem immutable and universal; they are part of the intrinsic nature of the Universe that moves because of these laws expressed by deterministic mathematical equations. This is the causal paradigm of evolution at the basis of the classical scientific method, in which consciousness is a random “accident”, which could or could not happen and whose emergence chance was almost zero: a true miracle of combinations starting from the first moments of the birth of the Universe. Life has come to us through an incredible combination of circumstances that a mathematical calculation would have no chance of happening synchronously.

In a synchronic model, awareness is primary and exists before the appearance of the space-time interface created by the level of consciousness of the human mind. The thrust of evolution in the synchronic manifestation of the Universe is the tendency of awareness to evolve toward increasingly inclusive forms, through attempts that are partly random and partly guided in such a way that not all possibilities are equally likely. This conscious guide has preferably selected those conditions that favor the development of life and consciousness.

This synchronicity manifests itself at the level of our local vision as a regularity and harmony. We interpret them in terms of scientific laws that operate on matter in space-time.

So in a synchronic paradigm we must admit the priority of awareness even to space-time as well as its inseparability from the state of emptiness. Evolution is determined by universal awareness, and we participate in it together with everything else that exists.

The basic consciousness agents of the quantum vacuum have the minimum possible choice, which led to the definition of the 64 hexagrams, corresponding to arrays of 6 quantum bits. In the inclusive process of consciousness evolution from the state of emptiness, we must admit multiple possibilities of choice for the most advanced forms of consciousness, some of which are not independent but conditioned. In the quantum model, conditional probabilities must also exist in coherent superposition, leading to a formidable mathematical complication. Fortunately, we have the progress made in the field of quantum information to be able to draw the guidelines.

The definition of elementary particles as conscious agents characterized by qu-bit arrays could allow us to predict interaction effects not yet seen in collisions between particles in large accelerators, through the use of quantum information processing to determine the correlation. This could be a new field of research in physics applied to elementary particles.

The field of investigation is completely new, but it could still make use of the mathematical considerations developed to treat symmetries in quantum physics and apply them to non-local effects. Quantum computer could be the system on which increasingly complex synchronic experiments are carried out, compatibly with the development of quantum technologies.

Many technologies are already here. It would be enough to shift the focus of the experiment to synchronic phenomena to make much progress in the development of synchronic science. Classical experiments let us observe the effect of a local action on the same part of the system in which the action physically occurs, with no interest in the rest of the collective system.

Synchronicity experiments will have a strong non-local component but also a locally observable relapse. We take for this purpose an entangled system. We divide it into two parts, so that there cannot be a cause-effect correlation between the two. In this way, we carry out local actions on one part and verify the changes of state of the second part on which we do not exercise any action. Although we do not interact with the part that serves as verification, the latter will show changes of state because of the synchronic link with the part we are interacting with directly. These changes of state, compared with the predictions obtainable in a synchronic theory, can constitute experimental verifications.

In the simplest cases, information can be obtained even by using simple considerations of quantum physics. For example, we can think of experiments with elementary particles, where the processing of information could be simple enough to be foreseen even without the support of a quantum computer. For example, the experiment conducted at Stanford by the "BABAR" collaboration (Lees 2012) to directly determine a temporal asymmetry (called violation of T) in the decay of neutral mesons B^0, is based on the measurement of the probability of transformation between pairs of correlated quantum states made up of matter and antimatter: since the pairs of mesons are created in a state of entanglement, the two mesons, while moving away from each other, remain intimately connected without assuming a well-defined identity. In other words, both are simultaneously both the particle and the antiparticle in a quantum superposition state. Due to entanglement, when the one of the two mesons decays spontaneously, the identity of the other meson of the pair is also determined at the same time. This property becomes a formidable scientific investigation tool: you can select the state of the second meson without having to observe it, by choosing a particular decay of the first meson. This property was used in the experiment to determine the violation of T.

This is a quantum physics experiment, in which synchronicity was only a tool and not the object of the investigation. However, the procedure already contains the characteristics that the more complex synchronic experiments must have. By applying a causal action to a part of the correlated system, information is obtained and a transformation is generated in the other part of the system, which is the real object of the investigation. Since the state is one of superposition, the change that occurs in the second part cannot be predicted in a deterministic way.

This is what happens in every experiment in synchronic science: in any case we will not have the certainty of obtaining a desired effect locally, but we can try to maximize the probability of manifestation of the desired effect, and select only the cases of interest.

Conclusions

We are accustomed to considering scientific laws as immutable natural laws, valid in any place and at any time. Indeed this belief was assumed as the principle of symmetry of the universe, and associated with two fundamental conservation laws in both classical and quantum physics: that of energy-momentum.

Furthermore, the physical laws are assumed to be the same for each observer, and this belief is the basis of Einstein's theory of relativity. Another consolidated belief is that reality is unique, that is, that nature cannot manifest itself through parallel realities.

In a synchronic view we must revolutionize these beliefs that appear so natural and obvious to us. First of all we have seen that space and time are secondary concepts, created by the human mind to conceive the synchronic reality of the Universe in a sequential way; therefore there are no immutable laws in space-time except in the representation of human consciousness. We have also seen that the human representation of material reality is only an interface that simplifies the synchronic complexity of the universe; the function of this interface is not to create a true model of reality, but to create symbolic icons through which to quickly and efficiently manage interactions with "our world" for the purposes of survival and natural selection, toward an increasingly inclusive consciousness. The primary reality in the universe is awareness that self-organizes itself into elements of consciousness of ever more inclusive complexity: from the fundamental elements of emptiness and matter, up to the most advanced forms of consciousness. The most inclusive forms of conscience are aware of themselves and of the less evolved ones, while they are unable to have direct experience of the most evolved and non-local forms of consciousness.

Each level of consciousness therefore has its own reality, its world described by its laws: there are as many parallel realities as there are levels of inclusion of consciousness.

In a synchronic universe, in which consciousness and choice are primary aspects, it is not possible to establish principles or physical laws valid at every level of inclusion. Physical laws and universal principles can be recognized at the lowest level, that of vacuum and elementary particles (and in general the level of inert matter).

At the first level, the material one, the degree of freedom of choice is low and is limited to the choice of universal constants that characterize elementary particles and fundamental interactions in order to allow the conditions for the emergence of life and more inclusive consciences. This is the level that all conscious agents share and on which everyone can agree. Given the scarce freedom of choice at this level it is possible to make predictions described by exact physical laws: this is the world described by Quantum Physics, where experiments can be carried out whose results are comparable with theoretical predictions.

The emergence of synchronicity from the quantum model however warns us that this is only the initial level of consciousness, and a reductionist vision of reality is generally not possible.

The reductionist model of reality is very reassuring for the rational mind, which would like to be able to predict events with deterministic certainty and fear the unexpected. This defensive attitude has tended to relegate scientific considerations to those aspects of reality that are simple enough to be somehow tractable with the classical scientific method, considering as unscientific those phenomena that are not rationally accessible starting from simple schematizations. We dramatized, or even avoided by branding them as superstition, all those phenomena in which non-locality constitutes an inevitable structural element, exasperating the contrast between what is "scientific" and what cannot be understood in a reductionist model. This attitude has dried up our conscience, and restricted the field of priority interest to the immediate material and economic aspects. The world that is accessible to our perception is much wider, and this text is an invitation to recover the potential of the human level of consciousness also from a scientific point of view.

The level of consciousness immediately above the material one is that of quantum synchronicity. At this level we have to give up making predictions through sequential logic, and we have to think in overall holistic terms. This is the level that all biological organisms share, including ecosystems and the "living planet", our earth. Physical laws at this level cannot be deterministic and reproducible, since each organism is unique and irreplaceable.

Each agent of consciousness has its reality and its laws that describe its world, with which it is synchronously connected, inseparable from it.

If we assume that the mathematical formalism of Quantum Physics continues to apply, it can be used as a guide tool for the intuitions to be verified in direct experience: in particular, the quantum computer could process information without reducing it to the classical one and help human consciousness to make the right choices, that is, the most inclusive ones, in all situations that can be programmed through quantum algorithms. This use of the quantum computer could lead to experimentally verifiable situations, the value of which could be shared by the scientific community, despite the impossibility of absolute reproducibility.

These verifications could be the driving force for a transformation in a more inclusive sense of human consciousness as a whole.

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Einstein Classical Program Revived

Andrea Carati[a*] *& Luigi Galgani*[a]

[a] *Department of Mathematics, Università degli Studi di Milano, Via Saldini 50, 20132 Milan, Italy*

***Corresponding author:** Andrea Carati, Email: andrea.carati@unimi.it

Abstract

The Einstein Classical Program is well known: to prove that, at least in the domain of atomic physics, quantum mechanics can be recovered from a theory presenting some “realistic character”. Here we address an extreme form of the program in which the realistic theory is just classical electrodynamics of point charges, and give concrete examples in which typical “quantum phenomena” are explained. Namely, spectral lines (in the case of ionic crystals) and chemical bond (in the case of the H_2^+ ion of the Hydrogen molecule). Additionally, an explanation is given of a phenomenon (existence of polaritons in ionic crystals), for which a quantum explanation is still lacking. Concerning the general objection that a classical theory would be impossible because of radiative collapse (radiation emission by accelerated charges), we illustrate how it is removed for charges in a medium, in virtue of the Wheeler-Feynman cancellation. The impact of such results for the general reductionistic program is also commented.

Keywords: microscopic electrodynamics, Wheeler-Feynman absorber theory, IR crystal spectrum, H_2^+ bond

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Introduction

The modern reductionist approach is dominated by mechanism, i.e. by the prejudice that every phenomenon may ultimately be explained as due to the motion of ultimate components, namely, for what concerns atomic physics, by the motions of atoms and molecules. The motion of such components is governed by the laws of quantum mechanics. Thus, such theory ideally holds up the whole conceptual building of modern science. However, quantum mechanics, beyond its known interpretative paradoxes, is not without problems: in particular, nobody has yet succeeded in building up a quantum theory of fields in a self-consistent way, nor in providing a rigorous theoretical basis for statistical quantum mechanics, perhaps the most important step for carrying up a self-consistent mechanistic program. In other words, while many formulas “explain” a multitude of observed phenomena, such formulas remain, in the spirit of the familiar P.A.M. Dirac’s comment at the end of his treatise, at the level of “valid rules” of a “workable theory”. This state of things was felt by some physicists, first of all Einstein himself (Schlipp 1949), as unsatisfactory, and as a clue that, perhaps, quantum mechanics may be nothing but a “shortcut” leading to an explanation of phenomena that would require, in the still unknown ultimate theory, a long deductive work. In other words, quantum mechanics might be deduced as a theorem from a more complete theory.

In our approach, we travel an alternative route. Instead of trying to deduce the quantum theory, we aim at reproducing phenomena considered impossible to explain outside of the quantum paradigms, such as spectra and chemical bond. The theory we consider is just classical electrodynamics of point charges, as developed from the times of Planck, Abraham and Lorentz, through the works of Dirac and then of Wheeler and Feynman, up to the present days.

Now, it has always been stated that such extreme version of the program would be impossible since, according to classical electromagnetism, accelerated charges should radiate energy away, and for example electrons would fall on nuclei within 10-8 seconds (instability of the Rutherford atom). We will refer to such objection as the *radiative collapse*. However, this is proven for a single charge, or a system of few charges, while completely isolated. Instead, the charges are in fact immersed in a medium, constituted by a huge number of charges subject to mutual electromagnetic interactions, with their characteristic long-range reach. This global feature—that we inherit from the Wheeler-Feynman approach to classical electrodynamics in a medium—is indeed a key point also for our approach to the relations between quantum and classical mechanics. Now, it will be seen that, as a consequence of the Wheeler-Feynman theory, in general the medium produces a cancellation of the radiations emitted by the single charges. Thus, the radiative-collapse objection is removed, and it would rather seem as if the presence of a medium necessarily had to be taken into account, even in quantum mechanics.

So, how does it happen that the common local approach used in quantum mechanics, in which single isolated systems are considered as if the medium did not exist, in fact works? Think of the computation of the energy levels of an atom, with its implication for the spectra. Now, whereas a justification does not seem to exist in a quantum framework, it will be shown here that the situation is different in a classical setting. Indeed, a local approach for computing the electromagnetic forces was recently justified in the case of ionic crystals, through a fulfillment of the Wheeler-Feynman theory. So it is now made plausible that, within a classical framework, an analogous property may be proven to occur in general cases, for example in the case of gases.

Anyway, in the case of ionic crystals a theoretical computation of infrared spectra was performed through a completely classical treatment within statistical mechanics, according to Kubo's linear response theory. The result, illustrated in Figure 1, shows that the experimental data are reproduced in an astonishingly good way, and in fact even better than through a quantum computation. Additionally, still in the case of ionic crystals a phenomenon was proved, i.e. the existence of polaritons. This plays an essential role in explaining transparency properties of crystals, but, being due to retardation of the electromagnetic forces, could not yet be proved in a quantum framework.

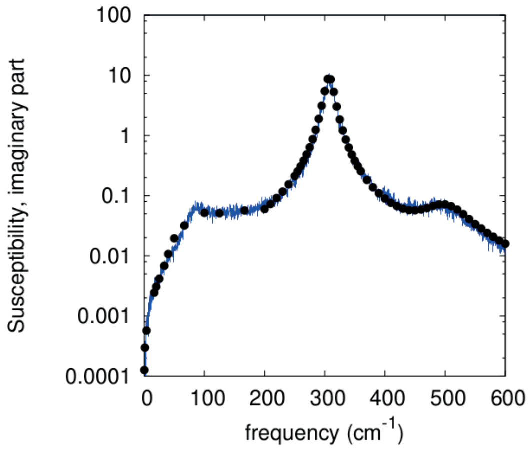

Figure 1: Infrared spectrum of the Lithium Fluoride crystal. Imaginary part of susceptibility vs. frequency, at room temperature. Comparison between calculations (solid line) and experimental data taken from Palik 1998 (points).

In Section 1, the Wheeler-Feynman theory is illustrated. In Section 2, it is described how such theory, formulated by them at a formal level, received a "rigorous" formulation in the particular case of ionic crystals. In the conclusive Section, some general comments are given. In particular, it is pointed out how the Wheeler-Feynman approach has apparently devastating consequences for the general problem of reductionism in science, since it leads to equations of motion in which the familiar deterministic Laplacian character is apparently lost.

1. The Wheeler-Feynman Theory

The Wheeler-Feynman theory can be illustrated as an invention of them to eliminate a paradoxical feature of classical electrodynamics. This shows up when a material medium is conceived as constituted by a multitude of microscopic charges (rather than as a continuum) with mutual electromagnetic interactions. The paradox is that in an infinite medium classical electrodynamics of charges could not exist, since the total electromagnetic forces on each of them apparently diverge. Wheeler and Feynman showed it through a very simple argument (Wheeler-Feynman, 1945, see also Wheeler-Feynman, 1949), with the aim of explaining the origin of the damping force acting on accelerated charges. In fact, the theory of Wheeler and Feynman is a fulfillment of the great Dirac's contribution of 1938 (Dirac, 1938). Without it, such theory would not exist.

1.1 The Paradox of Wheeler and Feynman

The paradox says that *if, contrary to what occurs in optics, the electromagnetic field would propagate in a medium with the speed of light in vacuum c, then the forces between the charges would diverge*. Thus, removing the paradox not only allows one to explain phenomena (optics), but it is even a founding fact of the microscopic theory itself, since otherwise the latter would be contradictory.

To understand this fact, consider a plane wave propagating in the medium: every charge will suffer a force, and thus an acceleration a_i proportional to it. As it is well known, an accelerating charge radiates. The point is that its radiation field decreases very slowly with distance, i.e., as $1/r$, in a much slower way than the Coulomb field, which decreases as $1/r^2$. Therefore, for the total electric field created by all the radiating particles, one obtains the expression,

$$E_{tot} = \sum_i \frac{e_i^2}{c^2} \frac{(a_i \wedge n_i) \wedge n_i}{r_i} \quad .$$

Here c is the speed of light, while e_i is the charge of i-th particle, and a_i its acceleration. Moreover r_i is the distance between the i-th charge and the point at which the field is computed, while n_i is the unit vector in the direction of the i-th charge. All quantities are to be computed at the retarded time.

One sees that every shell of radius R contains a number of charges proportional to R^2. Therefore, it contributes in absolute value with a term of order R to the sum, and so the sum diverges, in absolute value, for macroscopic bodies (i.e., when one lets R tend to infinity). How can it be possible that this field is instead rather small in ordinary circumstances? The point is that, for a generic propagating plane wave, one can show that there will be a destructive interference among all the spherical waves emitted by the charges (i.e. the series converges). One should observe however that a destructive interference could occur only if the plane waves propagate with a speed less than c, otherwise, an infinite number of terms in the sum would have equal phases, the field would diverge, and an inconsistency would appear.

1.2 The Wheeler-Feynman Identity

According to Wheeler and Feynman, such fact has a great impact on microscopic electrodynamics. Indeed, by considering the electromagnetic field produced by all charges in the medium, i.e., the field,

$$F_{\mu,\nu}^{ret} = \sum_{all\,k} F_{\mu,\nu}^{ret,k}$$

(written in relativistic notations), they arrive to the conclusion that

$$\sum_{all\,k} F_{\mu,\nu}^{ret,k} = \sum_{all\,k} F_{\mu,\nu}^{adv,k} \quad ,$$

where the advanced fields

$$F_{\mu,\nu}^{adv,k}$$

are the standard solutions of the Maxwell's equations with a given source. The difference is that, instead of involving the "retarded" time t-r/c, they involve the "advanced" one t+r/c, as if the solution would depend on the future position of the source. In fact, the difference,

$$\sum_{all\,k} \left(F_{\mu,\nu}^{ret,k} - F_{\mu,\nu}^{adv,k} \right)$$

that Dirac *calls radiation field* (the reason will be explained later), is a solution of the free Maxwell equations (i.e., without sources), so that it propagates at the speed of light c, and thus, by consistency, has to vanish. In other terms, in order to have a self-consistent microscopic electrodynamics in a medium, the *Wheeler-Feynman identity*

$$\sum_{all\ k} \left(F_{\mu,\nu}^{ret,k} - F_{\mu,\nu}^{adv,k} \right) = 0 \qquad (1)$$

has to hold. In their paper, Wheeler and Feynman, working at a formal level (i.e. neglecting convergence problems of the series defining the electromagnetic forces acting on each charge) give strong arguments indicating that their identity should hold "generically" for infinite systems of charges. Still within a formal approach, a proof was given in a paper (Carati, 2014) under a conspicuous condition. In fact, the identity is proven, for an infinite system, if the motions of the particles are assumed to satisfy a decorrelation property, analogous to those considered in the usual treatments of statistical mechanics. Instead, in the case of ionic crystals, following a method introduced by Ewald in 1917 (inspired to a work by Riemann), the series could be summed (see Lerose, 2014), and the identity was proven in a "rigorous" way.

1.3 The Wheeler-Feynman equations of motion

What impact does the Wheeler-Feynman identity produce on the dynamics of particles? An apparently devastating one indeed, since the equations of motion then turn out to take the form (see below)

$$m_i \ddot{x}_{i,\mu} = e_i \dot{x}_i^{\nu} \sum_{k \neq i} \frac{F_{\mu,\nu}^{ret,k} + F_{\mu,\nu}^{adv,k}}{2} \qquad (2)$$

Here the dot denotes derivative with respect to proper time, while m_i and e_i are mass and charge of the *i*-th particle. Now, this is a system of equations for which the usual Cauchy problem no more makes sense: indeed the retarded field

$$F_{\mu,\nu}^{ret,k}$$

depends on the whole past history of the *k*-th particle, whereas the advanced field

$$F_{\mu,\nu}^{adv,k}$$

depends on its future history, so that the force turns out to be undetermined, unless the whole trajectories of all particles are assigned (for all times). In this sense, the equations of motion are not evolution equations but compatibility equations among all histories of the single particles. In fact, one considers the set of all possible trajectories (in the configuration space of the whole system), and the good ones are those for which the compatibility conditions are satisfied. Laplacian determinism receives here a big hit, indeed.

1.3.1 From Equations of Motion to Compatibility Equations

One starts up with equations of motion of the usual form, in which the product mass times the (four) acceleration of a particle is set equal to the sum of the forces acting on it. These are on the one hand the (generalized) Lorentz force due to the electromagnetic retarded fields produced by the other particles, and on the other hand the damping force due to the radiation emission by the particle, i.e., the force acting on a charge, that takes into account the energy it radiates away due to its acceleration. This problem was first discussed by Planck in a phenomenological way and then by Abraham and Lorentz through models of the charges. A definitive answer was eventually given by Dirac, who expressed the damping force in terms of the fields, as

$$K_{i,\mu} = e_i \dot{x}_i^{\nu} \frac{F_{\mu,\nu}^{ret,i} - F_{\mu,\nu}^{adv,i}}{2} \ .$$

One has thus the equations of motion

$$m_i \ddot{x}_{i,\mu} = e_i \dot{x}_i^{\nu} \sum_{k \neq i} F_{\mu,\nu}^{ret,k} + K_{i,\mu} \ .$$

So, inserting the Dirac expression for the damping force, and expressing the retarded force as semi-sum plus semi-difference, one obtains

$$m_i \ddot{x}_{i,\mu} = e_i \dot{x}_i^{\nu} \sum_{k \neq i} \frac{F_{\mu,\nu}^{ret,k} + F_{\mu,\nu}^{adv,k}}{2} + e_i \dot{x}_i^{\nu} \sum_{all k} \frac{F_{\mu,\nu}^{ret,k} - F_{\mu,\nu}^{adv,k}}{2}$$

that reduces to the stated equation in virtue of the Wheeler-Feynman identity (1).

1.4 The Radiative Collapse Removed: Application to Plasma Physics

But the most important consequence of the Wheeler-Feynman identity for us is the failure of the fundamental objection against the use of charges' trajectories in atomic physics, i.e., the instability of the Rutherford atom or more in general the radiative collapse. In fact Dirac shows (see Dirac 1938) that

$$F^{ret,k}_{\mu,\nu} - F^{adv,k}_{\mu,\nu}$$

represents the field radiated by charge k. So, if the Wheeler-Feynman identity holds, it means that the total radiated field vanishes, i.e. that the energy of the system remains constant. The energy that a particle loses by radiation is compensated by the energy it absorbs from the fields due to the remaining particles. So persistent motions, of the type required in the Rutherford model, can exist. Examples of this type of persistent motions were exhibited in several papers (Lerose, 2014; Carati, 2003; Marino, 2007).

This fact has a relevant impact in plasma physics too, in connection with what is commonly called *the reabsorption problem*. Indeed, in fusion machines electrons are confined by strong magnetic fields that keep them gyrating about magnetic lines. But this is the same situations of electrons orbiting about nuclei. So, according to common wisdom, in fusion machines electrons should collapse, emitting an incredibly huge radiation, whereas this is not the case, and such instability in general does not occur. In our opinion, the reason is again the validity of the Wheeler-Feynman identity (see Carati, 2021). In fact, this is proven only in the case of not too large densities. An instability is indeed observed at large densities, and this fact too seems to be theoretically justified in the present approach.

2. The Infrared Spectrum of Ionic Crystals

In the previous Section it was shown how the Wheeler-Feynman identity allows one to overcome the fundamental objection (radiative collapse) to a realistic description of atomic physics through particles' trajectories. Here we illustrate how, using particle trajectories, typical "quantum phenomena" are in fact explained, starting with the absorption spectrum of a substance, in the case of ionic crystals.

To this end the first thing to do would obviously be to make available such trajectories as solutions of the equations (2). But, as already mentioned, the Wheeler-Feynman theory has a formal character, inasmuch as it doesn't discuss the convergence problem of the series defining the electromagnetic force acting on a charge. Indeed such series are not absolutely convergent, so that they make no sense, unless some suitable procedure is introduced. To our knowledge, no solution to this problem exists in the general case, whereas a solution was provided in the case of ionic crystals, as illustrated below.

2.1 Results Obtained Through Linearization: The Case of Ionic Crystals

The reason why the divergence problem can be concretely dealt with in the case of crystals, is that their equations of motion admit in a quite natural way an approximated treatment through linearization, since by definition crystals present a stable equilibrium, about which a linearization is feasible. The solutions of the linearized model are searched in the form of propagating waves. In the linear approximation, the field created by the ions turns out to be equal to that generated by a lattice of oscillating dipoles placed at their rest positions. As just mentioned, in such case Ewald was able to sum the series, so that a finite expression can be found both for the retarded and for the advanced fields.

Ewald found that each field can be thought of as the sum of two series having physical characters of completely different types. The first series forms the near field. This name is due to the fact that the only relevant terms in the series are those due to the charges located near the point at which the field is evaluated. Such field is obtained as a sum of spherical waves outgoing from any dipole and propagating with the speed of light c: however, since only the nearest charges are involved, the delays can be neglected, and, with a good approximation, that field can be dealt with as an instantaneous one. Instead, the second series, also absolutely rapidly convergent, is summed over the wave vectors *k* of the lattice. Such series represents a macroscopic field, and is due to the far charges. It can be represented as a combination of plane electromagnetic waves, each propagating with a given phase velocity equal to $\omega(k)/|k|$ rather than with the speed of light c.

Following such Ewald procedure, in the work (Lerose, 2014), a rigorous study could be performed for an ionic crystal model. It was shown that there exist traveling wave solutions, with a well definite dispersion relation $\omega(k)$ (with a certain number of branches), and that for such solutions the Wheeler-Feynman identity holds. Moreover, since the quantity $\omega(k)/|k|$ could be computed, such result shows that an evaluation of the refractive index can actually be produced in a purely theoretical way.

Additionally, it was shown that the dispersion relation $\omega(k)/|k|$ presents two further branches, with respect to a pure mechanical model of crystal (i.e. a model involving no delays, as occurs for c tending to infinity). Such additional branches, called *polaritonic branches*, were experimentally observed in the years seventies of the last century. For the occurring of such branches (due to the retardation of the forces), a quantum mechanical deduction is still lacking.

Concerning the model, a key remark is that, if one looks for the most relevant feature of ionic crystals, i.e., their behavior in the infrared, then the motion of the electrons can be ignored, and the force due to the electromagnetic fields produced by them on the ions can be approximated through a mechanical "effective potential'' having a short range character. This is one of the approximations usually performed in ionic crystal models (even in the quantum case), that goes back to the work of Born and Oppenheimer, and to the previous one of Born and Heisenberg for the classical case (see the works Born, 1924 and Born, 1927). So, in the equations of motion (2) for the ions (dealt with as point charges) such further short-range forces of a mechanical type due to the electrons come in. Moreover, due to the large mass of the ions, their equations of motion are taken in the *non-relativistic approximation*. In order for the equations to describe a crystal, an equilibrium point of the system has to exist, in which the rest positions of the ions form a well definite lattice. For example, in the case of Lithium Fluoride a cubic, face-centered lattice occurs with two ions, one of Lithium and one of Fluorine, in the primitive cell. So, if the displacements q_k from their rest positions are assumed to be small, in a first approximation the forces can be linearized, neglecting all terms nonlinear in the displacements, thus obtaining the system of equations

$$m_i \ddot{q}_i = F_i^{mech} + e_i \sum_{k \neq i} \frac{E^{ret,k} + E^{adv,k}}{2}, \qquad (3)$$

where F_i^{mech} is a force of a mechanical type (the electric field due to the electrons and of the Coulomb field due to the lattice of ions at rest), whereas the electric fields $E^{ret,k}$ and $E^{adv,k}$ are those generated by a dipole of moment $p_k = e_k\, q_k$ located at the equilibrium position of the k-th charge and evaluated at the equilibrium position of the i-th one (rather than at its actual position). Notice that the Lorentz force due to the magnetic fields is at least of a quadratic order in the displacements from the equilibrium positions, so that the magnetic field does not enter the equation, in the considered order of approximation. This approximation leads to an enormous simplification of the problem, since now the delays (and the anticipations) are fixed, rather than depending on the motions of the charges. However, one is still dealing with a formidable problem of infinitely many differential equations with delay and anticipation, for which existence and uniqueness theorems are unknown.

2.2 The Instantaneous Approximation: The Infrared Spectra of Ionic Crystals

However, the linearized model has limitations: first, in a certain band of frequencies it is absolutely opaque (the electromagnetic field cannot propagate), whereas in the complementary band it is absolutely transparent, i.e. the field propagates with no absorption at all.

Therefore, if one aims at computing, for example, the absorption coefficient, one has to go beyond the linear approximation. Taking non linearities into account, in a direct way without approximations, is at the moment impracticable. We resorted to study numerically the problem using a system of 4096 charges placed in a box, with periodic boundary condition. Now, we recall that the radiation reaction term is canceled for an infinite system, and moreover that the (retarded plus advanced) electromagnetic field is necessarily split into the sum of a near field, in which the delay is extremely small and can be ignored, and of a far field that instead presents the character of an external electromagnetic wave.

However, the propagation character of such wave are inappreciable in our model, because it can be felt only if the system has dimensions comparable to the infrared wavelengths (some microns), while the dimensions of our system (4096 ions) correspond to some tenths of Angstrom.

So, in the work (Carati, 2014) we proceeded with the apparently brutal approximation of working at a purely Coulomb level (i.e. with delays completely neglected), and so with purely Newtonian equations of motion. At such level, the electric susceptibility can be computed as the Fourier transform of the auto correlation of polarization, expressed in term of the position of the ions. Figure 1, taken from the work (Carati, 2018), reports the theoretical imaginary part of electric susceptibility, and the experimental data, for the main absorption line of Lithium Fluoride in the infrared. The most evident feature of the figure is that the computed values reproduce the data within about five orders of magnitude. It thus appears that the propagating wave plays no significant role for the computation of electric susceptibility (and thus of spectra). Propagation effects might however play a role for other phenomena.

2.3 Enters the Electron: The Chemical Bond in the H_2^+ Ion

We have seen that a pure Newtonian model allows one to reproduce the spectra of ionic crystals. One can ask whether it can reproduce other typical "quantum phenomena", in particular the chemical bond, a key ingredient in the ionic crystal model, since it accounts for the inter-ionic force due to the electrons. In light of the cancellation property that is expected to be produced by the Wheeler-Feynman identity, we proceed as is done in quantum mechanics, by neglecting the medium at all, and considering only the system of interest, as if the medium did not exist.

As at the moment we are unable to treat models with several electrons, we consider the case of the H_2^+ ion, i.e., a system with a single electron and two protons, that is the paradigmatic case in which a chemical bond (between protons) is formed. The idea, that goes back to Born and Heisenberg, is that, due to the small electron mass with respect to the proton mass, the electron moves much faster than the protons, which thus appear as "static". So the force the electron produces on the protons can be averaged along (a piece of) the trajectory, thus giving rise to an effective static attractive force between the two protons.

This was implemented in the paper (Carati, 2020), the most relevant result of which is shown in figure 2. The figure shows the effective potential between the protons due to the electron, as a function of distance (continuous curve), together with the results of quantum computations (crosses). The agreement is very good up to quite large distance, actually the double of the molecule size. Further investigations are needed for understanding the discrepancy at larger distances.

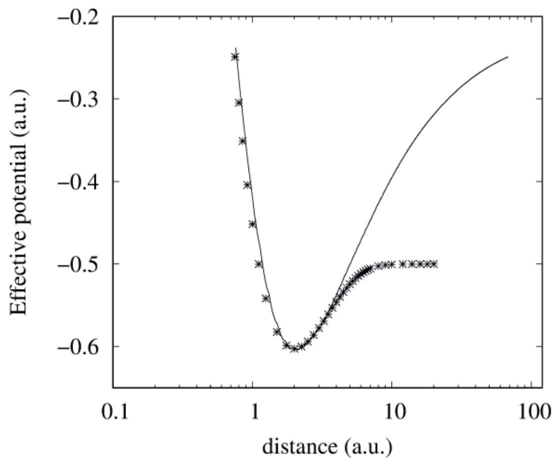

Figure 2: The result for H_2^+. Effective potential as a function of proton distance, computed for suitably chosen initial data (continuous line), together with the quantum potential in the Born-Oppenheimer approximation (stars). Distance and potential are given in atomic units (a.u.). Logarithmic scale is on the horizontal axis.

The equations of motion considered are a semi-relativistic extension of the standard three body problem with Coulomb forces, since the electron, due to its high speed, has to be treated relativistically.

No free parameters enter the model, except for the initial data. So an interesting point is to understand how Planck's constant $\hbar$ enters the problem. The point is that a bond, i.e. an effective potential, can be formed only if the motions are of a sufficiently ordered type, for perturbation theory to apply. Now, sufficiently ordered motions occur when the electron's angular momentum about the line through the protons is sufficiently large. And this is found to occur for an angular momentum of the order of $\hbar$.

Conclusions

We have shown cases where typical "quantum phenomena" (infrared spectra, chemical bond) can be explained in terms of trajectories of charges, solutions of Newton equations. Additionally, a phenomenon was explained (existence of polaritons, at the basis of the transparency properties of crystals), not yet explained in a quantum framework.

The approach used has a characteristic global feature, inasmuch as one deals with a macroscopic medium constituted by charges with mutual long-range electromagnetic interactions. In fact, the presence of the medium allows one to remove the main objection generally raised against the use of charges' trajectories in atomic physics, namely the radiative collapse of the charges, due to radiation emission caused by their accelerated motions. Such removal is in fact the main consequence of the Wheeler-Feynman identity, proposed by them through heuristic arguments, and now proven at least in the particular case of ionic crystals. By the way, it would be interesting to understand why such consequence was not drawn explicitly by Wheeler and Feynman themselves.

For what concerns the reductionist problem, one should point out that the results illustrated were obtained at the cost of dealing with Newton equations involving electromagnetic forces in a very special way, i.e. as semi-sum of retarded and of advanced forces. Consequently, the familiar Laplacian type of determinism (in which the present determines both future and past) is lost, and the problem of what determines what remains opaque. It should be mentioned that, nevertheless in their second work Wheeler and Feynman (Wheeler & Feynman, 1949) discuss such problem with nonchalance, as if it were somehow irrelevant. We are confident that the concrete applications presented here, with their impact on the relations between quantum and classical mechanics, may solicit the scientific community to take seriously into account the Wheeler-Feynman theory that apparently was ignored.

However, at least one exception exists. This concerns the works performed by J. Cramer in the years 1980 (see Cramer 1980 and 1986, and also Kestner 2012), that were brought to our attention by a referee. Such works are indeed relevant for our approach, and are addressed here through a final short comment, leaving possible further contributions for future work. Cramer's approach seems to be complementary to ours. Indeed, as explicitly stated even in the titles of his papers, his primary concern is with the *interpretation* of quantum mechanics. Instead, we work in the spirit of the extreme version of the Einstein Classical Program, aiming at *explaining* quantum mechanics in a completely classical framework, somehow as if it did not exist. To this end we start with concentrating on the explanation of concrete paradigmatic "quantum phenomena". Now, Cramer's argumentation is substantially based on the original version of the Wheeler-Feynman theory, which deals with classical electrodynamics of charges. On the other hand, the severest objection to the use of Newtonian trajectories in atomic physics–i.e. the radiative collapse—was eventually removed, and typical "quantum phenomena" were explained in terms of classical charges, just in virtue of the Wheeler-Feynman theory. Thus, it becomes at least conceivable that Cramer's interpretation may produce a relevant progress towards implementing the Einstein Classical Program itself in its extreme version, which aims at reducing quantum mechanics to pure classical electrodynamics.

These verifications could be the driving force for a transformation in a more inclusive sense of human consciousness as a whole.

Dedication

This paper is in memory of Giuseppe Pastori Parravicini, who suggested that the result obtained in the work (Carati, 2003) might be extended to a realistic model, in order to explain the phenomenon of polaritons, whose explanation in a quantum framework was lacking. In such way our research on the relations between quantum and classical mechanics passed, from the domain of ideal paradigmatic models, to the concrete one of theoretical predictions to be compared with experimental data, as occurred with the infrared spectra of ionic crystals, with polaritons and with the chemical bond in the H_2^+ ion.

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Data, Knowledge, and Theory: A Biostatistician's Perspective

Stuart G. Baker[a*]

[a] *Division of Cancer Prevention, National Cancer Institute [SGB], United Stets of America*

***Corresponding author:** Stuart G. Baker, Division of Cancer Prevention, National Cancer Institute, 9609 Medical Center Dr, Room 5E606, MSC 9789, Bethesda, MD 20892-9789 USA; e-mail: sb16i@nih.gov

Abstract

This commentary, inspired by a recent opinion piece of noted biologist Paul Nurse, overviews the interplay between data and various types of scientific knowledge within the realms of prediction, data patterns, causal inference, and scientific theory.

Keywords: prediction, cancer prevention, carcinogenesis, causal inference, machine learning

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Introduction

In a recently published opinion piece, the noted biologist Paul Nurse (2021) laments that the biological sciences are awash in data but sorely lacking in knowledge and theory. Less one think this is a new concern arising from our age of ubiquitous data, fifty years earlier, another British scientist, Leslie Foulds (1969), wrote

> "...Some investigators are fond of saying 'What we need is more facts'. The truth is that we have more "facts" than we know what to do with. Experimental analysis produced an alarming mass of empirical facts without providing an adequate language for their communication or effective concepts for their synthesis."

In fact, over one hundred years ago, the mathematician and physicists Henri Poincare (1902) made a more fundamental point that "Science is built of facts the way a house is built of bricks; but an accumulation of facts is no more science than a pile of bricks is a house." In more contemporary terms, scientific knowledge is not just data, but how data are used to improve understanding or prediction. This commentary expands on the viewpoint in Nurse (2021), discussing the interplay between data and scientific knowledge in prediction, data patterns, causal inference, and theory.

1. Prediction

In clinical science, an important type of scientific knowledge is the prediction of a binary outcome, such as disease onset, based on non-modifiable predictors. Prediction models can involve traditional statistical models, such as logistic regression, or algorithms in machine learning. The predictors, called features in the machine learning literature, can include risk factors, such as age or smoking status, baseline biomarker values, and images.

Investigators fit prediction models in a training sample, measure reproducibility in an internal validation sample (a random sample from same population used to obtain training sample) and gauge generalizability in an external validation sample (a sample from a population different from the population from which the training sample was drawn) (Steyerberg & Harrell 2016). A prediction model that performs well in an internal validation sample can perform poorly in an external validation sample (Bleeker *et al.* 2003). Types of generalizability for external validation include different time periods, geographic regions, data collection methods, and clinical settings (Justice *et al.* 1999). Classification performance varying by clinical setting, which is known as spectrum bias, is an important consideration that is often underappreciated (Ransohoff & Feinstein 1978). A good example involves prediction based on carcinoembryonic antigen (CEA). Although CEA in the blood almost perfectly classifies specimens as diagnosed colorectal cancer or no cancer (Thomson *et al.* 1969), it poorly predicts the development of colorectal cancer in asymptomatic persons (Thomas *et al.* 2015). External validation is a prerequisite for recommending a prediction model for clinical use (Ramspek *et al.* 2020). On a fundamental level, external validation is analogous to testing a scientific theory to see how well it makes a prediction.

An underappreciated aspect of many clinical prediction models is the importance of feature selection. In this regard, computer scientist Pedro Domingos (2012) remarked "At the end of the day, some machine learning projects succeed and some fail. What makes the difference? Easily the most important factor is the features used." In terms of prediction, investigators should not be concerned if different sets of features predict outcomes equally well in the validation sample. The occurrence of many models with good prediction or classification performance is called the Rashomon effect, after the Japanese movie *Rashomon*, which depicted an event from multiple viewpoints (Breiman 2001). A possible explanation for the Rashomon effect is that the observed features are likely imperfect proxies for unobserved true predictors.

In clinical prediction with well-defined features (such as biomarker level, age, and family history), investigators may favor the standard statistical approach of logistic regression over complex machine learning algorithms because both approaches often perform equally well (Christodoulou *et al.* 2019) while logistic regression is easier to interpret. When the predictor is an image, feature selection by humans can perform poorly (Le Cun 1998). Fortunately, the development of optimization methods that took advantage of more powerful computing led to deep learning methods with automatic feature selection, yielding substantially improved performance with imaging data (Le Cun 1998; Krizhevsky, Sutskever & Hinton 2012; Cao *et al.* 2018). These algorithms typically make predictions in bizarre ways, using features not visible to humans or secondary to human recognition (D'Amour 2021). The result is an unusual but useful form of scientific knowledge involving good prediction (Cao *et al.* 2018) but lacking scientific interpretation. Conclusions about the performance of a clinical prediction model depend on the metric used to summarize performance. In recent years, there has been a growing appreciation of the value of decision analytic metrics (Baker 2018; Vickers *et al.* 2019).

2. Data Patterns

Another type of scientific information is what I call data patterns. The goal is to identify relevant patterns in high-dimensional data that can suggest new theories. One example is correlation networks to understand responses or biological adaptations to stress (Gorban *et al.* 2021). Another example is principal components analysis, which uses linear models to reduce dimensionality and has numerous applications in biology (Giuliani 2017). A third example involves biologically relevant longitudinal response in high dimensional data. For example, Baker (2014) compared biologically relevant changes (linear, sigmoid, and impulse) among thousands of genes at 14 times in the embryonic development of two species of frogs. Sigmoid curves suggest saturation effects while impulse curves suggest a transient response leading to a new steady state. Types of comparative results were heteromorphy (curves with different shapes), heterochrony (curves with the same shape but different transition times), and heterometry (curves with the same shape but different magnitudes). The training data were odd numbered time points, and the validation data were the even numbered time points (Baker 2014).

3. Causal Inference

Another major type of scientific knowledge is causal inference, which involves drawing conclusions about outcome after changing a modifiable variable, such as treatment. Conceptually, causal inference tries to determine the outcome if one went back in time and gave subjects a different intervention (Rubin, 2005). Causal inference is usually divided into methods for analyzing observational data and methods for analyzing data from randomized trials.

Most causal inference methods applied to observational studies involve a multivariate adjustment using data from concurrent controls (participants enrolled simultaneously with the treatment group and followed over the same time period). The multivariate adjustment is needed to control for confounders, which are variables that affect both intervention and outcome. For example, in estimating the causal effect of increased exercise on cancer incidence, it is important to control for obesity, which is a confounder because it affects both exercise and the cancer outcome. One useful technique for improving causal inference in these studies is the method of propensity scores, which matches on estimated probabilities of receiving treatment (Rosenbaum & Rubin 1983; Austin 2011). Causal graphs can be useful for identifying observed confounders in complex scenarios (Pearl 2010). However, there is always a nagging concern that no matter how many observed confounders are included in the analysis, there may be an important confounder that was not observed, and that lack of adjustment for this unobserved confounder could lead to incorrect conclusions.

An example of another type of causal inference from observational studies are results from the paired availability design for historical controls (Baker & Lindeman 1994, Baker, Kramer & Lindeman 2019). Standard historical controls are subject to selection bias, as persons who receive treatment later often differ from those who receive treatment earlier. The paired availability design avoids selection bias by comparing outcomes, in each medical center, before and after treatment becomes more available, with a causal adjustment (Baker & Lindeman 1994; Imbens & Angrist 1994) for changes in the availability of treatment. However, as with all observational studies, there is no free lunch. The paired availability assumes no systematic temporal changes unrelated to treatment. If data are available, bias from such temporal changes can be mitigated using outcomes from medical centers with no change in treatment over time.

During the recent pandemic, there was frequent debate as to the quality of evidence from observational studies versus randomized trials. The most convincing form of scientific knowledge in causal inference studies is the randomized trial, which avoids some critical assumptions needed for causal inference with an observational study. However, as with many types of observational studies, assumptions are required to accommodate missing-data, noncompliance, and extrapolation to a target population. A good illustration of the value of a randomized trial over an observational study involves the Alpha-Tocopherol, Beta Carotene trial that randomized male smokers to either control alpha-tocopherol, beta carotene, or both supplements with an outcome of lung cancer incidence (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994). Prior to the trial, there was considerable evidence from observational studies that these supplements could prevent cancer (The ATBC Cancer Prevention Study Group 1994; Peto *et al.* 1981). However, the results of the trial contradicted the observational evidence—alpha-tocopherol had no effect on lung cancer incidence and beta-carotene increased lung cancer incidence. Because the randomized trial is the gold standard of causal inference, the results of the ATBC trial trumped the previous observational results.

4. Scientific Theories

Scientific theories provide explanations. For examples, inflammation, radiation, and viruses can cause cancer but a theory is needed to explain how they cause cancer. Debates about theories are crucial to scientific progress and applications. The dominant theory of carcinogenesis is the somatic mutation theory. However, the somatic mutation theory has not been "scientifically tested" (Loomans-Kropp & Umar 2019) and does not explain many puzzling experimental results (Baker 2021). Alternative theories of carcinogenesis (Sonnenschein & Soto 1999; Soto & Sonnenschein 2011; Brücher & Jamall 2014; Baker 2020; Carvalho 2020) are worth considering not only for scientific value but because an understanding of tumorigenesis is a foundation for cancer prevention (Golemis *et al*. 2018; Loomans-Kropp & Umar, 2019).

Competition in theories, like competition in the marketplace, often leads to improvement. The 19th century geologist Thomas Chamberlin (1890) proposed the method of multiple working hypotheses, which involves evaluating several hypotheses and rejecting those that conflict with available data. One advantage of the method of working hypotheses is that

> "the reaction of one hypothesis upon another tends to amplify the recognized scope of each, and their mutual conflicts whet the discriminative edge of each" (Chamberlin, 1890).

A theory needs to be stated precisely to be useful. With a vague theory in which any outcome can be explained, there is no scientific knowledge (Feynman 1964). Band-aid approaches to modify a theory to explain puzzling phenomena are not convincing and will no longer hold as new challenges arise. For example, to try to explain puzzling aspects of the geocentric theory of planetary orbits, astronomers kept inventing new epicycles, small circles whose centers move around the circumference of larger circles, until the whole edifice became unwieldy (Maor 1998). The heliocentric theory of Copernicus (with later refinement by Kepler) obviated these ad hoc attempts to make theory fit the data. The somatic mutation theory of cancer, the prevailing paradigm of carcinogenesis, has become a patchwork of modifications to fit new observations (Soto & Sonnenschein 2007), which the mainstream cancer biology community has been slow to appreciate. For example, recent work on mutation fingerprints of cellular histories has shown that cells with three driver mutations are also readily found in normal tissue (Li *et al*. 2021; Moore *et al*. 2021; Naxerova 2021), a result that challenges the genetic definition of cancer. However, the mainstream response is not to consider non-genetic drivers of cancer but instead to speculate on new band-aids to the somatic mutation theory, namely, tissue-specific combinations of mutations in a more permissive microenvironment (Naxerova 2021).

Theories are useful in guiding experimentation and determining what quantities to observe. The noted economist Thomas Sowell (2012) said,

> "if there are two different theories, there should be some empirical evidence in principle that could distinguish what would happen under one theory from what would happen under the other."

For example, in cancer biology research, to "distinguish" the somatic mutation theory from the tissue organization field theory, Maffini *et al*. (2004) devised an elegant experiment involving rat mammary tissue recombination model. Their results showed that carcinogens target the stroma and not the epithelial tissue, which contradicts the somatic mutation theory of cancer and supports the tissue organization field theory.

Nurse (2021) advocates that scientists propose reasonable theories even if they later turn out to be incorrect. In a wonderful book on scientific investigation, Beverdige (1952) provides many examples of incorrect biological hypotheses that led to scientific progress. For example, the noted physiologist Claude Bernard hypothesized that nerve impulses induced chemical changes that heat the skin. To test this hypothesis, he experimented on rabbits, severing a cervical nerve to see if rabbit ear would become cooler. To his surprise, he found that ear became warmer, leading him to realize that nerves control the flow of blood through the arteries.

A challenge with proposing new theories is pushback related to the sunk cost fallacy. Individuals or institutions commit the sunk cost fallacy when they continue an endeavor solely as a result of previously invested resources including time, money, and effort (Arkes & Blumer 1985). Any unrecoverable sunk cost is irrelevant when deciding on future actions and ignoring the sunk cost fallacy can have dire consequences (Ronayne, Sgroi & Tuckwell 2021). Scientists are not immune to the sunk cost fallacy. A scientist who spends years designing experiments and writing papers based on particular theory would be inherently resistant to an alternative theory that jeopardizes the value of previous work. Proper skepticism is good, but it also important to be open to major shift in research directions if circumstances warrant. Government agencies can also suffer from the sunk cost fallacy. Because government agencies often value institutional interests above national interests (Sowell 2018), they may be reluctant to abandon a long-term research program for an initiative based on a compelling new theory. One organization that has successfully tackled the sunk cost fallacy is the research arm of the giant tech company Alphabet, which rewards teams for discontinuing projects that are unlikely to succeed (Teller 2016).

Another type of pushback to new scientific theories comes from the "Machiavelli effect" (Hall 2021). In his famous political treatise, *The Prince*, Machiavelli wrote "the innovator has for enemies all those who have done well under the old conditions, and lukewarm defenders in those who may do well under the new." According to Hall (2021), scientific funding rewards established researchers and who are then resistant to new ideas.

Nurse (2021) also suggests that teaching that science has ideas, and is not just a litany of data, will motivate students. Even elementary school studies can be motivated by ideas and theories. In the popular American children's cartoon television show, "The Magic School Bus" (Cole & Degan 1994), the science teacher, Ms. Frizzle, tells her students to "Take chances, make mistakes, and get messy." Taking chances (trying new experiments), making mistakes (proposing reasonable theories that may be incorrect) and getting messy (engaging in the practical details of experimentation and data analysis) is a good advice for all current and future scientific researchers.

Conclusion

There is a productive interplay between data, knowledge, and theory. Accurate and informative data are essential to prediction, data patterns, causal inference, and scientific theory. Consider Kepler's trial-and-error method to discover the motion of the planets around the sun. At first, Kepler thought the motion was circular. But with accurate data from Tycho Brahe, Kepler realized that a circular motion did not fit the data, and an ellipsis was required (Feynman 1965). In clinical prediction, investigators need informative features to develop good models, and they need data from an external validation sample to investigate generalizability. Data patterns can suggest new theories in the fields of network correlations, principal component analysis, and biologically relevant longitudinal response curves. For causal inference with multivariate models, investigators need to measure and adjust for all important confounders. For causal inference with the paired availability design, investigators need to select medical centers with no changes in relevant protocols over time except for the increased availability of treatment.

According to Nurse (2021), theory is needed to capitalize on today's data rich world. Similarly, Hand (2016) noted that focusing only on data misses the point of science, which is to develop theories. Following Nurse (2021), investigators should be encouraged to propose reasonable theories. Theories should be stated as precisely as possible with multiple theories welcome, and, ideally with relatively little pushback from the sunk cost fallacy or the Machiavelli effect. Facilitating such a culture can make scientific investigation more exciting and dynamic for both researchers and students.

The most underappreciated aspect of the interplay among data, knowledge, and theory is that theory can guide experimentation and thereby lead to important new data which can then lead to new knowledge and better theories.

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Competing interests

The author declares no competing interest.

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The Enigma of Cancer Resistance to Treatment

Jekaterina Erenpreisa[a] Kristine Salmina[a], Olga Anatskaya[b], Alexander Vinogradov[b] & Mark Steven Cragg[c]*

[a] *Latvian Biomedicine Research and Study Center, Rātsupītes str 1-1k, Riga 1067 Latvia* - [b] *Institute of Citology RAS, Tikhoretsky pr. 4, Saint Petersburg 194064, Russia* - [c] *School of Cancer Sciences, Faculty of Medicine, University of Southampton, Tremona Road, Southampton S0166 YD, United Kingdom*

***Corresponding author:** Jekaterina Erenpreisa, e-mail: katrina@biomed.lu.lv

Abstract

Polyploid giant cancer cells (PGCC) are evaluated by histopathologists for cancer diagnosis, yet their role in cancer is poorly understood. In this essay, we highlight a particular aspect of these cells in relation to genomic self-organisation and transcriptional networks with relevance to treatment resistance. Embodying dynamic restructuring of the genomic network, epigenome and microenvironment, through explorative adaptation in response to sublethal challenge these cells operate at the edge of chaos and order. This state is manifested through oscillations in opposing cell fate pathways, with accelerated senescence coupled to reprogramming and an atavistic shift towards phylogenetically ancient unicellular genetic programs accessed through bivalent mediator genes. It recapitulates certain unicellular life-cycles in a cancer "life-cycle" which reciprocally connects the somatic mitotic cell cycle with the germline cycle of the PGCC.

Keywords: polyploidy giant cancer cells, mitotic slippage, cell senescence, reprogramming, self-organization, cancer

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1. How Are Malignant Tumors Inherently and Secondarily Resistant to Anticancer Drugs?

Polyploid giant cancer cells are assessed by histopathology for cancer diagnosis, yet their biological role in cancer is poorly understood and undervalued. The special issue in Seminars in Cancer Biology is devoted to these cells and different aspects of this emerging new field of cancer biology (Liu, Erenpreisa & Sikora 2021). Our article in this issue "Paradoxes of cancer: survival at the brink" (Erenpreisa *et al.* 2020) reviews the problems associated with cancer resistance to treatments under the lens of a "cancer life-cycle" (Erenpreisa & Cragg 2007) developed by us over two decades of research. In the present essay, we highlight a particular aspect of these cells relating to self-organization mechanisms which we believe under-pin the inherent and secondary resistance to anticancer treatments.

In spite of the huge diversity in the cellular origin of malignant tumors, all aggressive cancers ultimately evolve towards a similarly invasive EMT phenotype heralded by resistance to both genotoxic and targeted therapeutics (Pienta *et al.* 2020). Massive cell death is commonly seen in the first week after such treatments, followed by subsequent disease relapse. This begs the question "How are malignant tumors inherently and secondary resistant to these treatments?"

2. Explorative Adaptation at the Brink of Catastrophic Damage

Here we present a potential mechanism termed "explorative adaptation" which paradoxically is initiated in cancer cells only "at the brink" of catastrophic damage. Differentiated somatic cells are continually adapting to small fluctuations in their environment within the context of their deterministic genetic programs and die if these fluctuations elicit changes above the established threshold. In contrast, cancer cells can adapt to unforeseen environmental challenges using exploration by "trial and error", at the edge between order and chaos (Erenpreisa & Giuliani 2019). Faced with potentially lethal damage, they begin scanning their gene networks, revisiting hidden transcriptional configurations preserved in the mammalian genome memory spanning the 3.5 billion years of cellular evolution, which has survived catastrophes resulting in extinction of up to 75% of species. Such regulation by stochastic chance and vestigial transcriptional programs (termed also "predetermined chaos") seems the most likely way to facilitate the rare escape of "lucky" survivors from near-lethal damage. Uncertainty, fluctuations, duality of opposites involved in an intensive "dialogue with the environment"—the components of "self-organization" are the main features of this regulation. These concepts stem from the thermodynamics of unstable open systems discovered by Ilya Prigogine, the 1977 Nobel Prize winner in chemistry (*The Nobel Prize in Chemistry 1977*, n.d.). Studies of this nature demand relevant experimental settings, as this kind of regulation does not conform to the expected linearity between the severity of an applied drug and the final effect on cancer. This is perhaps why the reductionist gene-centric approach of targeted therapy has largely proved a failure during the 50 years of the "war on cancer" (Weinberg 2014; Bizzarri 2017; Brock & Huang 2017).

3. Cellular Senescence Coupled to Stemness Serves as a Tool of Explorative Adaptation

The process of explorative adaptation begins with premature cell senescence (induced by oncogenes, oxidative stress or anti-cancer drugs). Senescence, which interrupts proliferation and seemed initially a desirable outcome of anti-tumor therapy, paradoxically has now been established as a gateway to genome reprogramming and cancer cell survival. However, it acts not only in a paracrine manner through the senescence-associated inflammatory secretome as initially considered. It also opens the door for multipotency (stemness) allowing explorative adaptation of the genome in the stressed cancer cell. The period of premature cell senescence lasting for days, weeks and even months after the initial insult, is also characterized by heterogeneous dual phenotypes marked by the concurrent expression of opposing regulators, pairing senescence and stemness (self-renewal), through molecular regulators such as p21 versus OCT4 and Nanog versus p16INK4a (Erenpreisa *et al.* 2020). Expression of p16, in turn, supports the reprogramming loop of the inflammatory cytokine IL-6 (Mosteiro *et al.* 2018). Physical oscillations manifest between these opposing states, literally between immortal life and terminal death. An immediate consequence of this mechanism is that traditional drug screening assays, such as 3-day viability tests, may be uninformative for treatment outcome many weeks afterwards whereas a clonal assay may be much more appropriate (Mirzayans, Andrais & Murray 2017).

4. Reversible Polyploidy of Giant Cancer Cells Provides a Platform for Clonogenic Survival

Senescent cancer cells, particularly those with defective/absent TP53, while temporarily interrupting cell divisions after genotoxic treatments, usually do not interrupt DNA replication and thus shift through aborted mitosis ("mitotic slippage") into transient polyploidisation cycles. The polyploid state has the advantage of increased gene dosage, tolerance to apoptosis, toxicity, and immunity evasion. Interestingly, IL-6 activates embryonic stemness during the initiation of PGCCs and can reprogram normal fibroblasts into cancer-associated fibroblasts (Niu *et al.* 2021). Moreover, the PGCC can undergo epigenetic diversification of their subnuclei, even redistributing DNA damage into those undergoing autophagy and then executing asymmetric division to remove damage, followed by symmetric division of the repaired daughter cells (Erenpreisa *et al.* 2017). Polyploidy through senescence provides cells with additional options and

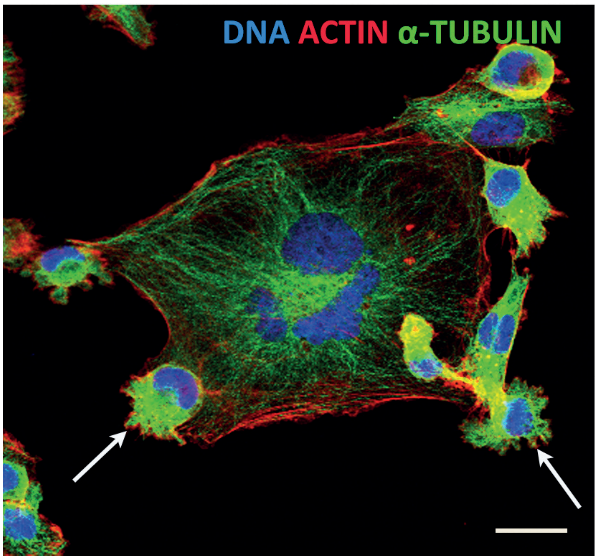

Figure 1: Budding of mitotic progeny starting mitotic divisions from a polyploid giant cancer cell (PGCC). MDA MB 231 cancer cell after 20h doxorubicin treatment, on the 7th week. Bar=25 µm (republished from Salmina *et al.* 2020).

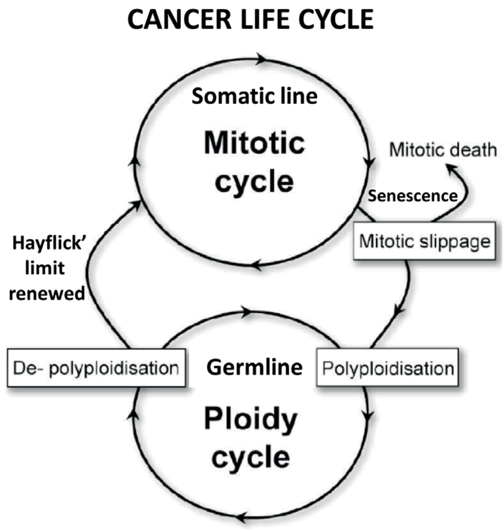

Figure 2: Schema of the "cancer life-cycle" reciprocally uniting through senescence and mitotic slippage the mitotic and the ploidy cycle of giant cancer cells (modified from Erenpreisa & Cragg, 2007).

time for repair, including recovery of the telomere attrition by alternative telomere lengthening (Salmina *et al.* 2020). Finally, this process raises the conditions for depolyploidisation and the return to the mitotic cycle by budding, which immediately starts mitotic divisions (from two weeks to several months after treatment) as seen in Figure 1.

This behavior is akin to the life-cycle of certain unicellular organisms alternating between a vegetative and generative phase with cycling polyploidy; the latter supporting the immortality of the former by renewing the Hayflick limit of telomere shortening (Figure 2). These life-cycles are likely recapitulated by cancer cells from the unicellular phylogeny.

5. Evolutionary Origin of "Cancer Life Cycle" from Unicellular Organisms

The phylogenetic origin of gene ancestry helps to understand how this can occur. The human genome possesses nearly 23,000 genes; 60% of them provide essential cell functions (DNA replication, DNA damage repair, RNA synthesis, ribogenesis, etc.). These highly conserved genes appeared in Prokaryotes and unicellular forms. Subsequently a relatively small number of new genes were added at the transition to multicellularity, where transient polyploidy and syncytia played an important role. The Cambrian explosion (ca. 500 million years ago, with atmospheric oxygen raising over 5%) was heralded by a burst of many, complex, multicellular species, while humans (the last in this 16-18 phylostrata range) contributed only an additional 0.3% of new genes.

Recent studies of gene phylostratigraphy testified that human cancers have an imbalance in the expression of these various genes—i.e. "old" genes of unicellular-origin are overexpressed, while "new" genes belonging to more recent phylostata coding for intercellular communication and complexity of higher multicellular organisms are underexpressed. The underlying rationale is that aggressive, high-grade cancers obtain some unifying phenotype present also within unicellular organisms, with mesenchymal and amoeboid features (Trigos *et al.* 2017). Moreover, the so-called cancer driver proto-genes appeared in evolution mostly in early multicellular organisms and even earlier (Domazet-Lošo & Tautz 2010). Therefore, their dysfunction in cancer may cause an imbalance between the unicellular and multicellular parts of the human genome network, collapsing it towards a more densely wired unicellular core (Trigos *et al.* 2018). Furthermore, polyploidy as such, particularly instigated by hyper-activated non-mutant *c-myc*, which also epigenetically "opens" the chromatin for multiple targets and particularly by activating bivalent genes—capable to quickly shift from poised to active state—was shown to shift cells to unicellular and cancer-linked gene ontology modules

(Anatskaya *et al.* 2020). Therefore, *myc*, this well-known stemness master gene (one of the Yamanaka reprogramming transcription factors (Takahashi & Yamanaka 2006) is an important player for inducing cancer by self-organization, coupling polyploidy with stemness through senescence (which in turn, may be also induced by over-expressed (often mutant) *ras*-family gene, the oncogenic partner of *c-myc*). It is no surprise then, that knockdown of *c-myc* in mice can cure even metastatic cancer (Morton & Sansom 2013).

6. Cancer Aneuploidy: Order from Chaos or Chaos from Order? The Role of Meiosis

Cell fate change by self-organization of the whole genome raises the question of how genomic aberrations, such as aneuploidy, fit into this model. Aneuploidy should interfere with cell division and accumulate lethal mutations, restricting tumors, but in fact accompanies aggressive cancers and is their hallmark. The most general solution of this conundrum is that polyploid genomes are unstable and lead to aneuploidy and that explorative adaptation (by trial and error) is impossible without the variability initially produced by the ensuing genome chaos. This stress-induced chaos for cell fate change often occurs in one cell division (chromothripsis) (Ye *et al.* 2018), which may result from or during mitotic slippage. By contrast, in the longer time-course, the recovered mitotic clones with aneuploidy can undergo stepwise selection of mutants more fit for survival. This represents a satisfying solution reconciling genome chaos with embryonality through "McClintock heredity" and the atavistic features of PGCCs (Liu 2021).

Another facet of this problem is an understanding of the role of the germline (primordial germ and meiotic) genes—which are also a hallmark of cancer (Bruggeman *et al.* 2018) and diagnostic or prognostic for certain cancer types (e.g. *MOS*, *SCP3*, *SOX11*, and *DMC1*). Meiotic genes (at least some of them) are also up-regulated during polyploidy in response to genotoxic stress. Although they may facilitate aberrant mitosis they may also drive non-conventional meiosis and parasexual processes coupled with polyploidy and thereby help to counteract the loss of heterozygosity (Salmina *et al.* 2019; Archetti 2020). In conclusion, these largely overlooked PGCCs, may represent a bridge between many of the paradoxical observations seen in cancer and its resistance to treatment. Hopefully, a greater focus on systems-wide understanding will help unlock deeper understanding of cancer and thereby more effective means to treat it in the forthcoming decade.

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Complexity: the Role of Information in Organizing Chance

Alberto Strumia [a]*

[a] *Istituto Nazionale di Alta Matematica "Francesco Severi", Italy*

***Corresponding author:** Alberto Strumia, albertostrumia@gmail.com

Abstract

This paper reviews some of the more relevant results arising from the crisis of reductionism, which have lead to complexity theory and the problem of foundations in different contexts of sciences, starting from the late 19th century. It focuses on the relation between complexity and mathematical non-linearity, and suggests a comparison between Chaitin's compressible/incompressible strings and the philosophical notion of universal. It also suggests a comparison between the notion of information, especially in its algorithmic version, and the Aristotelian-Thomistic concept of form. It shows how chance can generate stable order and organization only if some information drives the process dynamics. Starting from random initial conditions, suitable information leads the evolution trajectories of each cell (element) of some system (either simple or complex) towards a precise attractor. Examples of fractals, galaxies, and models of a biological organ in a living system, like a human heart, generated by stem cells are proposed. The fact that ancient Aristotelian-Thomistic logic/ontology appear to be more close to contemporary science than in the past centuries may contribute to both philosophy and science.

Keywords: crisis of reductionism, complexity, chance and order, fractals, cellular automata, stem cells, organ generation

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1. Complexity: the Role of Information in Organizing Chance

Where is science going? From a practical point of view, this is a hard question because of the philosophical, ideological, and economical-political constraints imposed by several (or unified?) powers on concrete scientists. A sort of unpredictable bifurcation between dangerous scenarios and marvelous perspectives appear on the horizon of the future.

From a theoretical point of view, it is easier to guess what the new paradigms—emerged in the 19th century and developed along the 20th and the 21st century—are requiring for scientific disciplines to advance.

This paper will provide a small contribution in trying to answer the theoretical question. Which positive or even unavoidable *scenarios and perspectives* seem to emerge for science to widen its own subject of investigation and renew its own methods?

In §2 something is said about the paradigm of *complexity*, arisen from the so called "crisis of reductionism."

§3 is devoted to emphasize some relevant steps in science theories—from Einstein's Relativity to the more recent approaches to complexity—and their philosophical interpretations. These show a drive toward some logical and metaphysical notions by Aristotle and Aquinas rather than the conceptions of modern philosophers.

In §4 an §5 we attempt to demonstrate that a stable order and organization may arise from either order or chance—a system is given random initial conditions in the evolutive trajectories of its constitutive parts (cells), where some leading information (a law) drives the entire process. Chance (randomness) alone only generates chance. Computer simulation examples involving 3D-fractals and a model of a spiral galaxy are presented.

In §6 an application to biology is proposed. This shows the stem cell generation modelling of an organ in a living system, such as the human heart. We offer a rough example, based on algorithmic information coded into a *compressible* string, and a more realistic model, where information is coded into a string considered as *incompressible*. The Conclusion offers some remarks and perspectives.

2. Complexity from the Crisis of Reductionism

An educational sentence describes complexity as follows: *the whole is not equal to the sum of its parts* (Polkinghorne, 2002). The scientific effectiveness of this sentence relates to the mathematical concepts of *linearity* and *non-linearity*. These allow to represent the "philosophical" concept of complexity into mathematical equations. In fact, it is well known that only *linear differential equations* feature the following property: the sum (more properly, a linear combination) of two or more of their solutions (which we may interpret as *parts*) provides a new solution (which we may interpret as a *whole*) of the same differential equation. In wave theory, such a property is equivalent to the superposition principle of wave amplitudes. This allows for a simple solution of any linear system of differential equations. Hence, before the discovery of complexity, physics and mathematics' theorists were supposed to find the *linear equations* that govern natural phenomena or, at least, to approximate any problem to a linear one. Even the so called *perturbative methods* aim at progressively approximating solutions of non-linear equations by means of linear techniques—the only ones people could manipulate at the time. The introduction of computer has enormously improved the power of numerical methods. However, it has also highlighted odd instability phenomena, such as *deterministic chaos* (Lorenz 1963). Linearization techniques resemble the attitude of a traveler who joints the pieces of information acquired in each neighborhood from different points of observation along the road.

Unexpectedly, the emergence of complexity has revealed that some *global properties* of things exceed the capabilities of these extensions of linear methods.

During a confidential conversation, several years ago, the well-known astrophysicist Nicola Dallaporta (1910-2003) said that, in the end, the *harmonic oscillator* and the *two-body problem* are the only two genuine physical problems we can solve with exactness. Both are governed by the same linear differential equation!

Reductionism is the scientific method that attempts to reduce all our scientific knowledge to linear problems, decomposing any *wholeness* into a sum of simpler *parts*. Thus, the universe is a set of different kinds of galaxies; a galaxy is stars and planets and other celestial bodies; a living body is cells; a cell, or any kind of physical body, is molecules; a molecule is atoms, and an atom is elementary particles (*fermions*). Everything is interacting thanks to fundamental fields, which in turn are carried by another kind of elementary particles (*bosons*).

The adventure of this science resembles the exploration of the sole portion of a plane confined in the neighborhood of the tangency point with a wider non-linear manifold (the complex real world).

Now, it is legitimate and unavoidable for a human being to adopt a reductionistic approach to reality, since our mind cannot know everything in a single, all-embracing act, as divine mind does. Our mind needs to put together a sequence of acts of knowledge partially localized in space and time, step by step.

However, in some lucky circumstances, through attempts, one can reach one or more exact solutions of a non-linear equation, even if no general method can obtain a general solution that encompasses, as a family, all the solutions to that equation.

After exploring the entire neighborhood of the point of contact between the tangent plane (the range of linear investigation) and the manifold (the non-linear world or reality), scientists seem to have discovered that the great majority of real phenomena need to be represented and must be governed by non-linear laws. The sum of their solutions (provided that they are individually known) generally is not a new solution. Indeed, the discovery of *complexity* has gained not only new problems about the *structure of things*, but also surprises about the *dynamics* of their behavior in time, such as unpredictability. This depends on the high sensibility toward the initial conditions of the solutions (Poincaré 1892-1899; 1905-1911). Stability theory is just concerned in such topics, involving also *qualitative analysis* of the *topology* of trajectories when a quantitative one is no longer fully possible. Among the first pioneering and most relevant studies on these topics we remember (Thom 1972) and (Arnold 1992).

A new approach to reality seems to require a sort of enlargement of mathematics so that it becomes capable of dealing not only with number and extension (i.e., quantity), function, equation and inequality (i.e., relation), but also with quality and other properties (De Giorgi 2013). This means approaching a more comprehensive ontology formalized by symbols like usual mathematics, but widened respect to its object of investigation (Strumia 2012). As a consequence all mathematized sciences will result widened.

– *Set theory*, e.g., represents a first step in that direction, enlarging mathematics from numbers to collections of any kind of things (Tapp 2005).

– *Topology*, formerly (significantly) known as analysis *situs*, within set theory, is another step in attempting to rediscover the old Aristotelian category of situs (Poincaré 1895), catching global (*topological*) properties of sets and classifying them into different irreducible species, depending on the number of holes and handles (Wall 2016).

– *Biology, informatics, cognitive sciences*, and the so-called *artificial intelligence* are discovering unexpected, tight relationships between the notions of Aristotelian form and information (Marks II 2014).

– Furthermore, the new branch of the so-called *humanities*, according to some authors, is interested in following a demonstrative approach in dealing with humanistic disciplines, similar to what Aristotle did, so that the old opposition between hard science and human disciplines is overridden (Burguete-Lam 2008).

In that sense, we can say that contemporary science is progressively approaching an Aristotelian method to investigate reality. The predicted formal approach to ontology is now seen as a sort of rediscovery and re-building of metaphysics as a *theory of foundations* of science. The most recent interest—documented by several articles in literature recalling the names of Aristotle and Aquinas—is a symptom of such a change of mind in scientific methodology (Modrak 1990; Simpson-Koons-Teh 2019).

3. Relevant Steps in Science towards Aristotle and Aquinas

3.1 General Relativity and Aristotelian Space

Einstein himself (Einstein 1969) maintained that in his theory of gravitation, space-time is no longer a sort of pre-existing box that contains the bodies in the old Cartesian-Newtonian fashion. On the contrary space-time *is made* by bodies, i.e., matter and fields (energy-momentum distribution), since the latter determine, as a source, the metric, the connection, and the curvature of space-time. This alternative conception of space (including time) is rather close to the Aristotelian idea of space defined by the intimate contact relations between bodies (Koyré 1971).

3.2 Proper Classes in Set Theory and Analogy

Since *sets* (in *set theory*) are more generic entities than numbers, being collections of any kind of things and not of just numbers, several paradoxes and contradictions emerged while dealing with them. These paradoxes recall the ones of the Aristotelian-Thomisitic notion of *entity* (Latin, *ens*). Georg Cantor (1845-1918) discovered the contradiction arising in attempting to introduce the notion of universal set, or set of all sets (Cantor 1932). Later, Bertrand Russell (1872-1970) solved the paradox (Russell 1938) introducing *non-univocal definitions* of sets (theory of *types*). More simply, Kurt Gödel (1906-1978) introduced the distinction between *proper* and *non-proper classes* or sets in the usual sense (Gödel 2001, orig. 1938). Both made a relevant step in rediscovering the Aristotelian-Thomisitc notion of *analogy* (Bochenski 1961, Strumia 2010).

3.3 Gödel's Undecidability and its Informatic Implications (Turing *et al.*)

With his *undecidability theorem* (1931), Kurt Gödel showed that not all the propositions one is able to formulate with the symbols and rules of an axiomatic system as that of Russell's *Principia Mathematica*, can be demonstrated either as consistent or non-consistent with the axioms. So, they are *undecidable* (Gödel 1931). More, very ingeniously, he was able to relate bi-univocally any proposition to a number (*Gödel's number*), and any demonstration procedure to a computation, labelled in its turn, bi-univocally, by a number. Therefore, if there exist undecidable propositions, then the corresponding numbers are non-computable, i.e., they cannot be evaluated by any formula. They can be obtained only by listing sequentially their digits, one after the other.

3.4 Turing and the Halting Problem

Applying Gödel's theorem to computer science, Alan Turing (1912-1954) discovered the halting problem. If not, any number is computable through a computational procedure, a computer should not halt when attempting to evaluate such a number through any possible program (Turing 1937).

3.5 Wiener and Information Theory

In the meanwhile (1948) Norbert Wiener (1894-1964), one of the fathers of information theory, realized that information would have played, in science, the role of a new principle of explanation of reality, being irreducible to the known principle of *matter* and *energy*. He claimed: "Information is information, not matter or energy. No materialism which does not admit this can survive at the present day" (Wiener 1965).

Later information acquired a more and more relevant role in science, which was largely exceeding the field of telecommunications, within which the main problem was that of minimizing the noise disturbing radio broadcastings (Shannon 1948). The role played today by information in biology strongly resembles that of the Aristotelian *form*, as the governing principle of living organisms' structure, organization, and *dynamics* (*individual behavior* and *species evolution*). In philosophical terms, the scientific notion of *form/information* as organizing principle of the *structure* remembers the Aristotelian-Thomistic notion of *essence*, and the scientific notion of *dynamics* recalls the Aristotelian-Thomistic notion of *nature*, philosophically defined as *essence*, *principle of action* (Strumia 2012).

3.6 Chaitin's Irreducible Strings and the Problem of Universals

Gregory Chaitin (born in 1947), applied the aforementioned results to the programming languages and computer algorithms. He discovered that if we deal with a computer program like a *string* that sequentially collects all the characters required to write down the instructions, then the strings corresponding to a computable number could be compressed into shorter ones, corresponding to more efficient programs. However, the strings corresponding to a non-computable number, could not be compressed, and only the sequence of their digits listed one after the other could identify them (Chaitin 1992, p. 141; Strumia 2020).

A similar situation suggests a direct comparison with the philosophical topic of the *universals* as developed by Aristotle and Thomas Aquinas (followed by many other philosophers).

A universal, in fact, is a *concept/name* under which one collects a lot of individuals, in order to avoid to list them one after the other. From the cognitive point of view, Aristotle and Aquinas discovered that our mind, being finite, can know the world only through universals (*immaterial information*), since it cannot know everything as singulars caught by the same cognitive act. Only the divine mind, being infinite, can know all singulars together by one act. On the contrary we need to compress information into shorter strings (*the universals*).

3.7 Cognitive Sciences, Human and Artificial Intelligence, and Self-Consciousness

Another intriguing and wide topic where science meets the Aristotelian-Thomistic tehory of knowledge is the field of cognitive sciences, in its different branches. Here the immaterial character of information, which allows to transfer it from one matter support to another one (as it happens, e.g., from the hardware peripherals of our computer toward the network), plays a crucial role. The same information, which organizes the structure of an observed material body, is caught by our external senses thanks to electro-chemical signals, and travels across our neural system to reach our brain. Being immaterial, according to Aquinas, it is extracted by our mind and fixed in it immaterially, as a universal. According to Aquinas the immaterial operation of such extraction (Latin, *abstractio*), requires an immaterial self-subsisting operating subject, which is the immortal soul of man. Our science, at present, is just investigating the lower levels of that process, concerning the five senses, the neural system, and the brain. It is barely discovering that the mind seems to be irreducible to the sole material brain (Basti 2002).

3.8 Heisenberg and the Aristotelian Potency

In a completely different context, i.e. quantum mechanics, and several years before, another fundamental principle of Aristotelian metaphysics had been tangentially taken in consideration by Werner Heisenberg (1901-1976). According to his first interpretation of the "new physics", at that time, the probabilistic character of the wave function suggested a correlation with the Aristotelian notion of potency. In his own words: "It was a quantitative version of the old concept of 'potentia' in Aristotelian philosophy." (Heisenberg 1962, p. 12, Strumia 2021)

Here, we will rather focus on simple examples (mainly taken from Strumia 2020) of the role of information as a driving principle in generating order and organization in both non-living and biological systems.

In particular we aim to show how algorithmic information plays a leading role in generating any ordered structure starting either from already sequentially ordered initial conditions, or from random initial conditions. The final organized and ordered structure emerges as an attractor toward which the trajectories—solutions to the dynamics driven by some law (information)—converge.

In living systems, a contiguity constraint is to be imposed to random multiplication of cells that reproduce one near to the other, in order to generate the organs of a living body. The simple scheme of *cellular automata* (Wolfram 1982, Wolfram 2018) will be used to model such a behavior.

4. Order from Order and Information (Generation of a Spherical Shell, Fractals, and Galaxies)

There is no surprise if we generate an ordered structure starting from an already sequentially ordered distribution of initial conditions, either in the case of a simple structure (like a spherical shell, see Figure 1) or in the case of a complex structure such as a fractal set (e.g., a *3D-Julia set*, see Figure 2).

Generation of *order from order* and organization assigning a *law* (*information*) is quite a usual experience. Animations linked to Figures 1 and 2 show clearly the possible dynamics of the processes.

4.1 Order from Order: Spherical Shell

The information is now given by the parametric equations of the shell:

$$x = r\cos\theta\sin\varphi,\ \ y = r\sin\theta\sin\varphi,\ \ z = r\cos\varphi,$$

where the parameters θ, φ are assigned in sequential order, within the respective intervals:

$$0 \le \theta \le 2\pi;\ \ 0 \le \varphi \le \pi.$$

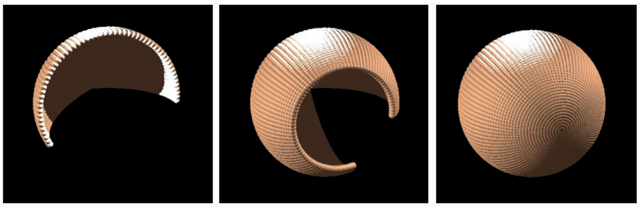

Figure 1: Generating a non-complex structure (spherical shell) starting from sequentially ordered initial conditions. Computer simulation. https://tinyurl.com/5n8r8p9u

4.2 Order from Order: A 3D-Julia Set

Here the information is provided by the recursion rule: $q_{n+1} = q_n^2 + c$, which generates each term of the series $\sum_n q_n$ of the quaternions q_n, the convergence domain of which defines the set. For details see (Strumia 2017, chapter 8).

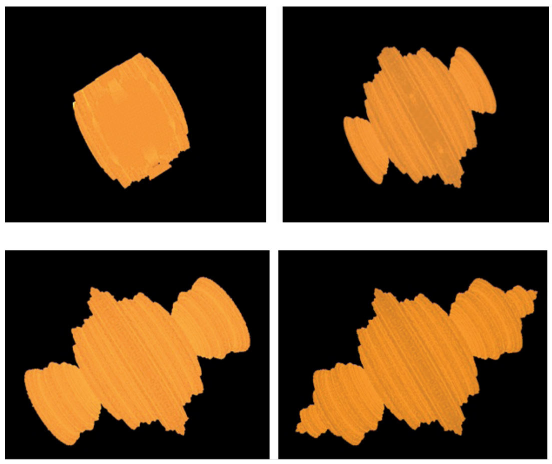

Fig. 2. Generating a complex fractal structure (*3D Julia set*) starting from sequentially ordered initial conditions - Computer simulation https://tinyurl.com/2tcf7hkx

4.3 Order from Order: A Spiral Galaxy

The same process generating order from order through an assigned law can be implemented also in the case of a more physical system, like the generating model of a spiral galaxy.

Here, the simplest law (playing the role of driving information) is provided by the Geodesic equations of motion of particles:

$$\frac{du^{\mu}}{ds} + \Gamma^{\mu}_{\alpha\beta} u^{\alpha} u^{\beta} = 0$$

in Schwarzschild metric:

$$g_{00} = 1 - \frac{r_s}{r},\ g_{11} = -\frac{1}{1-\frac{r_s}{r}},$$
$$g_{22} = -r^2,\ g_{33} = -r^2 \sin\theta,$$

which is a static solution to Einstein's equations of General Relativity.

Figure 3 compares a computer-generated image with an astronomical photo of the spiral galaxy Arp 273-d3d1cbb96446.

In our computer simulation the initial conditions are assigned in a sequential order, at regular identical angles.

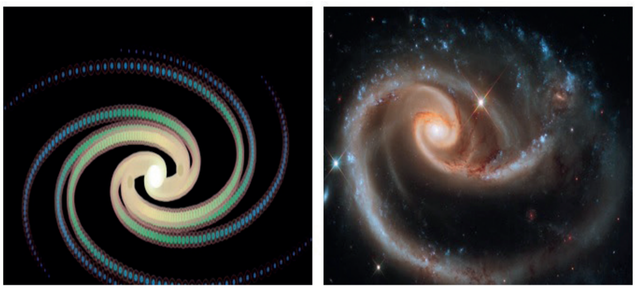

Fig. 3. Generating a spiral galaxy structure starting from sequentially ordered initial conditions.
https://tinyurl.com/yc352rhx

5. Order from Chance and Information (Generation of a Spherical Shell, Fractals, and Galaxies)

In Figure 4, 5, and 6 the same structures are generated by computer programs starting from random initial conditions. The information involved in a suitable mathematical law drives the trajectories toward *attractors* that lead to final ordered structures.

The animations show initial random distributions of points that step by step reveal an emergent organized and ordered structure.

5.1 Order from Chance & Information: A Spherical Shell

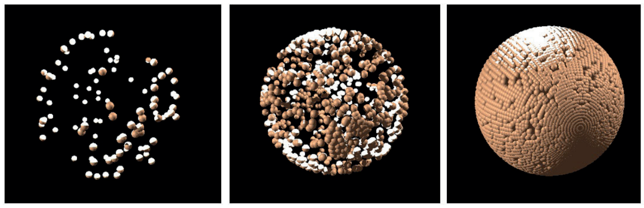

Figure 4: Generating a non-complex structure (a spherical shell) starting from random initial conditions. Computer simulation. www.youtube.com/watch?v=NBiTiJsPqLo&list=PLwSewYMk4YzGHORxIVvHrQlQ-uwIGsDuO&index=3

5.2 Order from Chance & Information: A 3D-Julia Set

Figure 5: Generating a complex fractal structure (3D-Julia set) starting from random initial conditions. Computer simulation. https://tinyurl.com/59c6atk8

5.3 Order from Chance & Information: A Spiral Galaxy

Figure 6 shows the same spiral galaxy as in Figure 3, yet this is generated starting from initial conditions at random angles and random distance from the center.

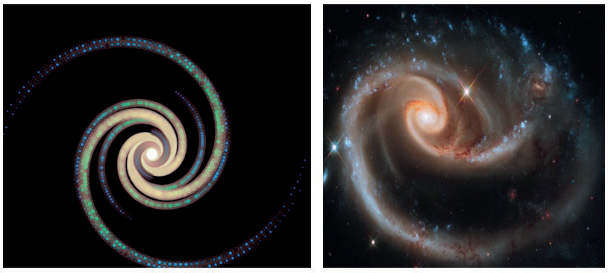

Figure 6: Generating a spiral galaxy structure starting from random initial conditions. https://tinyurl.com/yvz3aacf

6. Random Cellular Automata: Stem Cells and Heart Models Generation

What we have shown in the previous sections has relevance in biological applications. The methodology that implies random initial conditions and a driving information leads to an organized and ordered structure, such as a living body's organ. This model of an organ emerges as an attractor. In order to respect the dynamics of cell generation, we need to impose the constraint of space contiguity between each mother cell and its immediate daughter cell. A simple useful way to model such a constraint is provided by *cellular automata*, which we have suitably adapted to our problem. It is remarkable that when chance is left alone in governing the dynamics, the probability to get an ordered and organized system at the end of the generation process is so small that the result looks more similar to a cancer rather than an operating organized system. On the contrary, when a driving information is added to chance, even starting from random initial conditions, within the suitable basin of attraction, the system shows emergent organization.

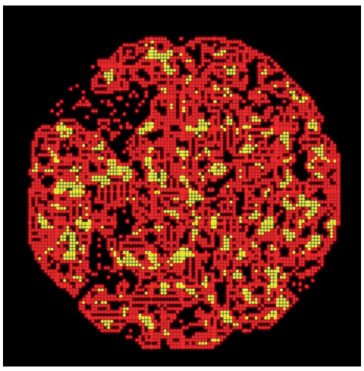

Figure 7: Generating a disordered cell formation by random cellular automata. Computer simulation. http://albertostrumia.it/sites/default/files/Animations/MeteorGuns.m4v

6.1 A 3D-Julia set generated by random cellular automata

A simple mathematical example is offered by the same Julia set examined before, which has been generated by random cellular automata constrained by contiguity condition.

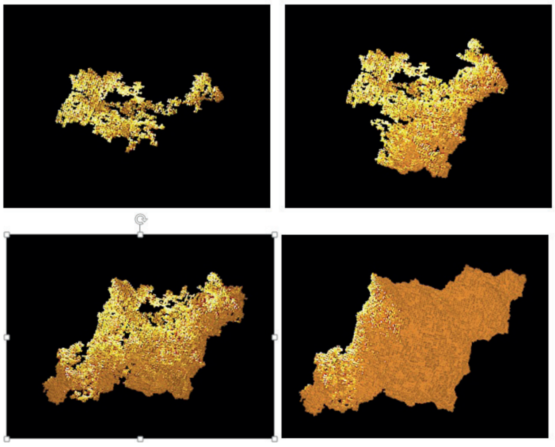

Fig. 8. Generating a 3D-Julia set by random cellular automata. Computer simulation. https://tinyurl.com/2mp2d8et

We can apply the same method of governing chance by some leading information driving cellular automata, in order to model the generation of a biological system, like an organ of a living body.

For the sake of simplicity, we limit ourselves to the generation of the exterior surface of the organ. We choose two heart-like models.

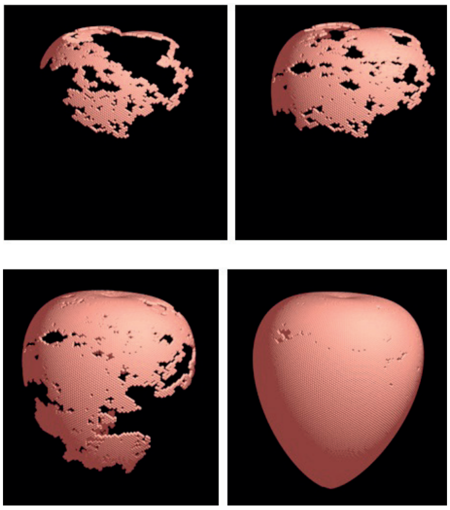

Figure 9: Generating a rough model of a heart by random cellular automata. Computer simulation. https://tinyurl.com/2p9xxad5

6.2 A "Compressible" String for a Rough Model of Heart-like External Surface

A first, very rough scheme tries to start from the idea of "compressing" the required information into a simple set of parametric equations of the organ (*compressible string*), as follows:

$$x = \pm R \sin\theta \sin\varphi + ay^2,$$
$$y = \pm b\, R \cos\theta \sin\varphi, \quad \theta, \varphi \in [0, \pi],$$
$$z = c\, R \cos\varphi\, e^{d\varphi},$$

with a, b, c, d parameters to be suitably adjusted (see Figure 9).

An 6.3 An "Incompressible" String for a Realistic Model of a Human Heart External Surface

A more realistic shape of an external surface of a human heart can be obtained starting from a true anatomic model such as the one that Bob Hughes elaborated by means of vectorialization (Strumia 2020, chap. 9) and that we have suitably adapted.

In such model, the coordinates of each small block of cells (not each single cell, for evident reason of visual scale) are mapped one by one, into a sort of "*incompressible*" string of information, and painted as random *cellular automata* (see Figure 10).

We ignore if the information string within the DNA of a biological living system is compressed or incompressible. At present, perhaps nobody still knows.

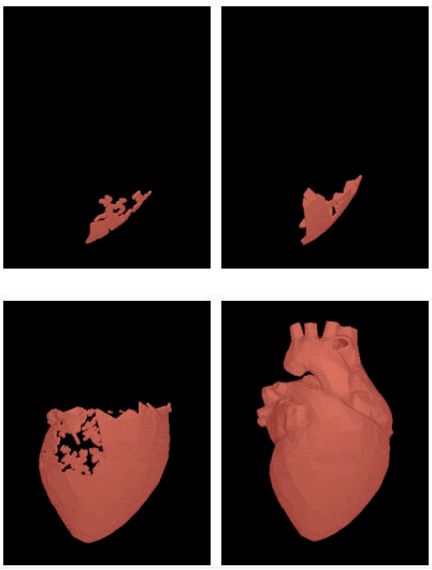

Figure 10: Generating an anatomic heart model by random cellular automata. Computer simulation. www.youtube.com/watch?v=9gZi87yojJ8

Conclusions

We have sketched how information plays a determinant role in generating order and organization in complex systems. In doing so, it resembles the ancient Aristotelian-Thomistic *form*.

Today's approach to the role of algorithmic information in driving chance towards organized and ordered structures as attractors is a sort of philosophically poorer, mathematized version of the ancient form.

The models presented in pictures and animations are enough illustrative.

All the mathematical and programming details (definitions, equations, and program lists) can be found in (Strumia 2020).

Future research should focus on modeling, beside the structure of complex systems, also their dynamics, corresponding to the Aristotelian-Thomistic notion of nature (*the essence as principle of action*).

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Science and the Dragon: Redistributing the Treasure of Knowledge

Ugo Bardi[a], Ilaria Perissi[b], Luisella Chiavenuto[c] & Alessandro Lavacchi[d]*

[a] Dipartimento di Chimica 'Ugo Schiff', Università di Firenze, Florence, Italy - [b]Global Sustainability Institute, Anglia Ruskin University, Cambridge, United Kingdom- [c]Independent Researcher, Aosta, Italy - [d]Istituto di Chimica dei Composti Organo Metallici del Consiglio Nazionale delle Ricerche (ICCOM-CNR), Area della Ricerca di Firenze, Sesto Fiorentino, Italy

***Corresponding author:** Ugo Bardi, Email: ugo.bardi@unifi.it

Abstract

We start from an analogy: science can be seen as one of the dragons of Western mythology, described as sitting on their hoard of gold but not using it for any useful purpose. Similarly, scientists seem to be content with accumulating knowledge, doing little or nothing to use it outside their restricted domain of expertise. We argue that this attitude is one of the elements causing the ongoing decline of science as a way to produce innovative knowledge. We propose that the situation could be improved by encouraging scientific communication and the redistribution of the scientific treasure of knowledge in the form of "mind-sized" memes.

Keywords: knowledge distribution, memes, specialization, h-index

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Introduction

There are several reasons for the evident decline of science: unreliability, falsifications, cronyism, elitism, politicization, hyper-specialization, aversion to innovation, and more. This decline is not just reducing the capability of science to produce culture and innovation. It is also generating a serious disconnection of science from society as a whole. Non-scientists are developing an ideological aversion toward the dominating "technoscience," seen as representing the entire scientific process.

In part, these problems can be attributed to a few (or maybe not so few) bad apples in the basket. But there is one profound problem affecting the whole scientific enterprise: science has grown so much that by now it produces an unmanageable mass of data and results which are incomprehensible except to people working in the narrowly specialized fields in which the results were produced.

We could compare science to the dragon Fafnir of Norse mythology or to one of its modern versions, such as Smaug of Tolkien's novel *The Hobbit*. Dragons are said to sit on immense hoards of gold that they do not use and that nobody else can use. Science seems to be doing the same with the knowledge it creates, a treasure kept hidden in the darkness of scientific journals, inaccessible and incomprehensible to the majority of people and to most scientists as well. It has been said that a typical condition of scientists is to know more and more about less and less. If the trend continues, eventually they will know everything about nothing. Indeed, the dragon is not just sitting on the treasure of knowledge, but it is dominating its way of production by means of controlling science funding as well as the career of scientists. Science is becoming more and more like a dragon locked in its giant cave.

A recent paper by Chu and Evans (2021) offers a dramatic illustration of the current impasse of science. These authors found that the larger a specific research field is, the more unequal the impact of a scientific article becomes in terms of the number of citations. In other words, in science there holds the rule that "the rich becomes richer," just as it happens in the financial world (this is also called the "Matthew Effect" from the parable of the talents in Matthew's gospel). The result is that new entries in the field do not succeed in removing obsolete research from the top places of interest, if they ever manage to see the light on a scientific journal. The Matthew effect takes place with grant applications. Those scientists who can accumulate research grants in an early stage of their career tend to keep being successful (Bol *et al.* 2018). Also, this effect discourages innovative new entries in research.

In this paper, we examine the question and propose a tool inspired by Seymour Papert's book *Mindstorms* (Papert, 1980). According to Papert, the learning process for humans is based on unpacking complex concepts into easily understandable sub-units that he calls "mind-size" (or "mind-sized") bites. The author proposed this idea mainly in the framework of teaching geometry to children (Abelson *et al.* 1974). However, its value applies also to adults (Maedi 2013).

We propose here to enlarge Papert's concept of "mind-size learning" to match the current scientific enterprise. We do not aim at renouncing specialized knowledge, but valuing the transmission of ideas using a language that is mutually understandable by scientists working in different fields and, at the same time, not just by scientists but also by practitioners of humanities and by the public. In other words, we propose to redistribute the dragon's gold to the people.

1. Creativity and Knowledge

Mainly, we owe the concept that creativity is an emergent property of knowledge to Jean Piaget (Maedi 2013; Gruber & Vonèche 1977), who expressed it in the sentence "creativity is knowledge." There follows that if we want to restart the progress of science, we need "cross-fertilization" from one scientific field to the other, including humanities. This idea is also known as "interdisciplinarity," a concept that is often praised but rarely practiced.

Several factors tend to discourage interdisciplinarity in modern science. One is the attempt to classify scientific research in specific sectors. Hence, research is forced inside sealed compartments that discourage exchanges of ideas between different fields. Another factor is the use of various "indices" developed with the purpose of measuring productivity and the competence of an individual scientist or of an academic journal. These indices assume that competency is proportional to the number of papers that a scientist produces ("publish or perish"), taking also into account the number of citations received. In general, a paper will most likely be published if it deals with well-known ideas and concepts. Also, people who work in the same field as the author will cite it more than others. This encourages scientists to remain within the limits of their fields in order to maximize the number of their publications and the number of citations (Migheli & Ramello 2021). Venturing outside one's area of specialization and producing actually innovative research would mean stepping into the darkness where a scientist's work is likely to be ignored. No citations, no career—no career, no scientist. Indeed, it would be useless to blame bureaucrats for having developed indices that, in large part, are well integrated with the way scientists behave and the way the scientific process is performed. The problem lies deep in science.

The lack of interdisciplinarity in science is not just a matter of quality, as we can measure it. (Chu & Evans 2021) report that

> "Examining 1.8 billion citations among 90 million papers across 241 subjects, we find that a deluge of papers does not lead to turnover of central ideas in a field, but rather to ossification of canon. (…) A novel idea that does not fit within extant schemas will be less likely to be published, read, or cited."

Chu and Evans propose that this phenomenon is due to the large number of papers published in every field, which makes it impossible for researchers to keep abreast with the general work. We also need to take into account a parallel phenomenon that Chu and Evans do not mention: as a certain field becomes larger, it also becomes more fragmented. That is, a large field spawns smaller subfields, which in turn will spawn smaller fields. The set of scientific fields is fractal.

The Web of Science database includes 241 subjects of study. Such a classification is arbitrary. For instance, Wikipedia lists 1475 fields. Even the finer Wikipedia subdivision is rather “macro” in comparison to the way certain fields are perceived by their practitioners. Note also that the fractalization of science does not take place just across different fields: it also takes place at the temporal level. The basic concepts of single disciplines can be progressively forgotten not because they have been invalidated, but simply because they suffer a sort of de-facto obsolescence that condemns them to oblivion. This phenomenon was clearly seen during the past two years of the epidemics that saw the rediscovery and sometimes the rejection of some basics of medicine that somehow had been forgotten. Just as an example, a recent review (Ashby & Best 2021) reports how “misconceptions about herd immunity and its implications for disease control are surprisingly common.” This loss of scientific memory is the local version of the wider dissociation occurring between scientific and humanistic disciplines, which gradually lose their common roots until they become completely alien to each other.

The result is that whenever scientists of two separated fields happen to discuss the same subject, they tend to behave like enemy ships exchanging broadsides against each other before vanishing in the fog. There have been several examples of this aggressive behavior. One is that of the study *The limits to growth* (Meadows *et al.* 1972). The study originated from the field of engineering control systems, but its method applied to describing the global economic system. As a result, it fit the field of economics. As argued in the book *The limits to growth revisited* (Bardi 2011), the debate occurred among people who did not understand each other. Hence, the study was demonized based on an insufficient debate and little evidence. Another example is the remarkable scientific quarrel between physicists and geologists about the cause of the “Cretaceous–Paleogene extinction event, ‘’ some 66 million years ago. In 1980, a group of researchers, most of them physicists, proposed that the impact of an asteroid had caused the extinction (Alvarez *et al.* 1980). Geologists, instead, mostly attributed the event to a large-scale volcanic eruption (Bond & Wignall 2014). The row that followed is by now legendary and the two groups involved had difficulties in understanding each other (Alvarez 1988).

These examples show how different scientific fields can split in views, methods, and terminology. They become ossified, with scientists belonging to different subfields unable, and often uninterested, to speak to each other. A blatant example of such a fractalization and hyper-specialization of science may be the recent Covid-19 crisis, with the birth of a hierarchical view of human health that saw one specific ailment as separated and more important than all the others. The emergence of the pandemic led to a rush to publish that created a large number of poor quality papers—a rush described as a “carnage” (Bramstedt 2020). Kendrick (2021) reported a similar outcome when statins became a popular subject of research in the 1990s: other fields involving the prevention of cardiovascular disease were practically abandoned.

These phenomena are the cause of a chain of troubles and incomprehension transmitted from one scientific field to another. This generates diffidence and mistrust not just within science, as it is understood nowadays, but also among people working in humanities, and the public. If the sad state of science is not recognized, we will continue financing and producing poor science, useful to nobody.

2. Science as Language: Mind-size Concepts

Nowadays, a great number of different people speak international languages, such as English. The result is that widely spoken languages tend to incorporate new terms from other cultures (e.g *pizza* from Italian, *ubuntu* from Bantu, *perlage* from French, and many others). The increase of the size of the vocabulary generates, probably as a compensation, a reduction of its grammatical and syntactic complexity (Reali *et al.* 2018).

These trends are typical of ordinary languages but can also be seen in science. The huge number of terms developed in different fields generates a simplification in the grammatical structure of the scientific language. Scientific papers are written in a standardized form of English that avoids clichés like the plague. Such a language tends to be simple, especially when used by non-native speakers, by now probably the majority of the active scientists in the world. There have been proposals for the use of a codified and simplified form of English for instance, the ASD-STE100 Simplified Technical English (STE).

However, the grammatical simplification of scientific English does not solve the problem of the proliferation of concepts. This is a gigantic problem: the human mind has limits. So, how to make a mass of concepts available outside the specific fields that produced them? Here, we can take inspiration from the work of Seymour Papert, who proposed the concept of "mind-size" (or "mind-sized") models (Papert 1980).

Papert's idea is in itself "mind-sized." It implies breaking down complex ideas into sub-units that can be easily digested, just the way we do when we take bites from a too big chunk of food. In approaching a field of science, we try to break it down in mind-size bites that represent the essence of the story.

In fields other than hard sciences, this method is known as "slogans," which are the political equivalent of mind-size concepts. As an example, the sole first volume of Karl Marx's *Das Kapital* is 1134 pages long. Nevertheless, many people defined themselves as Communists without having read Marx's text, just on the basis of slogans. For instance, "Soviet power plus electrification" was proposed as a synthetic definition of Communism by Vladimir Ilich Lenin (Lenin 1919), and that seems to have been sufficient for many people.

Can we do something similar with science? Answering this question can only be made in qualitative terms. So we now present a number of case studies to illustrate how it is possible to communicate complex scientific ideas in the form of mind-size bites.

3. Case Studies

3.1 Darwin's Natural Selection

Darwin's book, *The origin of species* (1859) is a series of mind-size concepts. It contains some tables and some calculations, but not a single equation (and note that he uses the term "plot" only with the meaning of a parcel of land). The book is easily understandable by people not trained in biology and not even in science. Yet, it was a milestone in understanding not just the behavior of Earth's biosphere, but the more general concept of "complex systems."

Darwin's ideas are easy to condense into mind-size statements. A classic one is "The survival of the fittest:" a synthetic interpretation of the mechanism of evolution. This is not the only possible way to express Darwin's ideas in a single sentence. Another one is "Nature in red tooth and claw" a poetic interpretation written by Tennyson (actually before the publication of Darwin's book). Another somewhat poetic interpretation is *The blind watchmaker*, the title of a book by Richard Dawkins (1986).

These mind-size explanations are not necessarily excessive simplifications and can also illustrate different interpretations of the theory. For instance, "The survival of the fittest" is not equivalent to "Evolution by natural selection." The second statement may imply that evolution maintains the stability of the genetic endowment of a species without individuals striving to become "better." The latter interpretation seems to be more popular nowadays (Gorshkov *et al.* 2004).

A good example of how a mind-size interpretation of Darwin's theory can be profitably used in real life is about a well-known problem in medicine: that of the growing antibiotic resistance of bacterial pathogens (Aslam *et al.* 2018). There is no need of being experts in molecular biology or genetics to understand the problem: when bacteria are attacked using antibiotics, natural selection will favor forms that are resistant to the attack. These will rapidly become the major component of the bacterial population. The new variants may be highly dangerous, not because natural selection favors more lethal species–the opposite is actually true–but because the task of fighting the infection has been entrusted to the antibiotic, preventing the immune system from developing appropriate defenses. If the antibiotic fails to provide protection, then the body has no defense to fight the new infection. This general problem affects all medical factors. If a vaccine is not 100% effective in eradicating a virus, then it may favor the development of new, vaccine-resistant, viral variants.

These concepts have been known for a long time, nevertheless antibiotics have been used freely and in large amounts, not just to cure human illnesses, but as a preventive measure to keep farmed animals healthy with the result that antibiotics have been spreading along the food chain, affecting the whole ecosystem (Kumar *et al.* 2020). Not only has it been impossible to control the growth of antibiotic production up to now, but the industry gleefully forecasts a 300%

increase in sales for 2027 (Data Bridge Market Research 2020).

One of the reasons for the antibiotic spread is that the public and most physicians do not understand that natural selection is more than just a theory mentioned in textbooks, but a reality of everyday life. Among others, Andersson *et al.* (2020) made this point recently. If people knew the basic concepts of evolutionary biology, then the current problem could have been at least mitigated.

3.2 Mind-size Dynamic Models

The recent pandemic has put to severe strain the capabilities of the world's governments to manage the situation. Their reaction highlighted how little of the basic elements of the epidemic cycles were known by decision-makers and by their advisors alike. Some scientists have been maintaining that the growth of the epidemic was expected to be "exponential," extrapolating it at absurdly high levels. Even specialists in epidemiology were often unable to provide sound advice, mainly owing to the failure of complex, multi-parameter models that consistently overestimated the diffusion of the Covid-19 epidemic (Saltelli *et al.* 2020). This was the result of a phenomenon known as "creeping overparametrization," the tendency of modelers to tinker with the model by adding "ad hoc" parameters.

This is a widespread issue of modeling complex systems. Models are not prophecies, they are computing machines designed to explore the "cause and effect" space. The result is that less detailed models can often provide better long-term forecasts than complex ones. For instance, the "base case" model of the 1972 study *The limits to growth*, one of the first "integrated assessment models" in the history of modeling, has described reasonably well the trajectory of the principal parameters of human economy over 50 years (Bardi 2011; Turner 2008; Herrington 2021). Note that the model used in *The limits to growth* was relatively "mind size" because it was based on just five principal stocks and their simple interactions.

Even simpler models provided reasonably good results. Bardi and Lavacchi (2009) as well as Perissi and colleagues (2017) experimented with system dynamics-generated "mind size" models and found that their results are comparable with those of more complex models. In fact, even simpler models were useful as descriptors of future events. For instance, Marion King Hubbert (1956) described the production peak of crude oil in the United States with a simple model involving only two parameters. In general, all these models provide similar results in terms of "bell-shaped curves," which can describe apparently different phenomena such as epidemic cycles (Kermack *et al.* 1927), oil extraction (Bardi & Lavacchi 2009), and fisheries (Perissi & Bardi 2021).

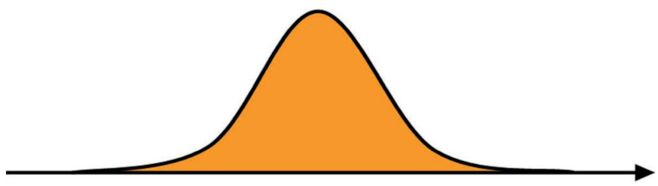

Figure 1: The Hubbert peak: a "mind size" result of dynamical models of complex systems.

3.3 Network Analysis

Many modern models are based on the concept of "network". A network can be defined as a graphical representation of either symmetric or asymmetric relations between discrete objects/individuals. The objects are called nodes or vertices, and usually represented as points. We refer to the connections between the nodes as edges, and usually draw them as lines between points.

This kind of approach can lead to a clearly mind-size representation of the diffusion of an epidemic: each node in the network represents a person. The edges between nodes represent social connections over which a disease can be transmitted (Dottori & Fabricius 2015) Ashby & Best 2021). In itself, the network representation does not generate a mind-size model of how the infection grows and then declines in time. Nevertheless, the mathematical implementation of the model can take into account the probability of infection spread through the neighbors of an infected node and that of the recovery of already infected people. The resulting cycle is the same "bell-shaped" curve described in the previous section, as shown in Figure 1.

Networks can represent all sorts of systems in the real world. For example, one could describe the Internet as a network whose nodes are computers or other devices and whose edges are physical (including wireless) connections between the devices. The World Wide Web is a huge network where pages are the nodes and links

Figure 2: SIR dynamics simulated by network analysis based on graphs theory (Courtesy of the University of Graz, http://systems-sciences.uni-graz.at/etextbook/networks/sirnetwork.html).

are the edges. Other examples include social networks of acquaintances or other types of interactions, networks of publications linked by citations, and transportation, metabolic, and communication networks.

At the basis of a network analysis (Barnes & Harary 1983), *graphs are an intuitive way of representing and visualizing the relationships between many objects* even more than stock and flows. The dedicated branch of discrete mathematics called graph theory provides the formal basis for network analysis, across domains. It represents a common language for describing the structure of all those phenomena that can be modelled by networks.

However, as previously commented for the case study in 3.2, a large and complex modelling network requires a huge number of differential equations to describe the system. This is the case of large genetic networks (Bornholdt 2005). In fact, extrapolating the standard differential equations model of a single gene (with its several kinetic parameters) to large systems would render the model prohibitively complicated. One possible way to simplify such models would be to find a "coarse-grained" level of description for genetic networks. This means focusing on the system behavior of the network while neglecting molecular details wherever possible.

3.4 The Schrödinger equation

The Schrödinger equation describes a variety of phenomena involving quantum particles. This deceptively simple equation, in most cases, turns out to be impossible to solve, except in terms of approximations. In chemistry, it can describe the distribution of the electric charge around atomic nuclei and in a complex molecule. The procedure to determine this distribution is as far as it can be from a "mind-size" concept, and the same is true in terms of understanding the results. Nevertheless, over the years, chemists have developed graphical concepts to help non-specialists to understand the electron distribution around nuclei. These graphical objects are called atomic or molecular "orbitals," a term that derives from the old interpretation of electrons "orbiting" around the nucleus. Although you need a certain level of training in chemistry to use orbitals as mental tools, they mercifully spares us from the details of the underlying quantum physics.

A solution of the Schrödinger's equation for one of the possible states of an electron associated with a hydrogen nucleus is given in Figure 3 as a "mind size" representation. These representations makes sense for chemists, who use them to grasp some of the chemical

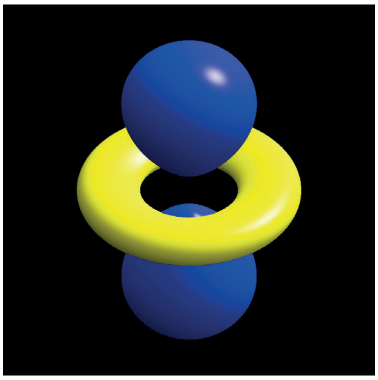

Figure 3: Calculated 3d orbital of an electron's eigenstate in the Coulomb-field of a hydrogen nucleus. https://en.wikiquote.org/wiki/Atomic_orbital#/media/File:Hydrogen_eigenstate_n3_l2_m0.png. CC BY-SA 3.0.

properties of atoms and molecules without the need of being experts in quantum mechanics. For instance, usually the interpretation of the aromatic properties of some organic molecules is understood in terms of these graphical representations of the electronic distribution.

Conclusion: How to Improve Communication in Science?

The global number of published scientific reports was estimated at ca. 50 million in 2010 (Jinha 2010). At a rate of 2-3 million papers published every year, nowadays this number may be closer to 100 million. Assuming that an article has an average length of 5 pages, we have a corpus of knowledge spanning some 500 million pages, with good possibilities of reaching one billion pages in the near future. The Bible, with about 1400 pages in its English version, is a leaflet in comparison.

What is the value of this giant mass of data? On this, we may cite Henry Poincaré who said, "Science is built up of facts, as a house is built of stones. But an accumulation of facts is no more a science than a heap of stones is a house" (Poincaré, 1905). Of course, databases index scientific publications, but that does not necessarily create knowledge, just like a list of the shape and weight of each stone in the heap does not create a house.

Science is, after all, a human enterprise and it has to be understood in human terms, otherwise it becomes a baroque accumulation of decorative items, just like gold in the paws of a dragon. The accumulated knowledge of science must be somehow made "alive" if it has to generate further knowledge.

This is the key insight that Papert generated in 1980 in terms of "mind size models." In order to be alive, science must have a comprehensible form. That does not mean renouncing the conventional accumulation of data and results in the form of specialized papers. It means that scientists should feel their duty to express results in the form of mind-size bites, understandable by their colleagues and, as much as possible, by the public. Scientific production and communication cannot be seen as separate tasks: they are one and the same thing.

Of course, this idea will not make any inroads in science if it is not supported in some way, for instance by specific legislation aimed at redefining the parameters that control scientists' careers and their salaries, especially avoiding the deadly trap of the "h-index." But, more than legislation, perhaps what is needed is just a different attitude. Among other things, we need to reconcile modern "science" and humanism, as it used to be not long ago. We need to stop thinking that there exist "two cultures," in the view of Charles Snow (1959). There is only one culture: the human culture, in the sense that ancient philosophers, such as Plato, had clear.

A return of "science" from the realm of the dragons' caves for both scientists and the public to appreciate it is possible. The job of the dragonslayer is a little out of fashion nowadays, but it could still be useful (Heinlein 1961).

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Habeas Mentem and Neurotechnology: A Brief Introduction to the Ethical Problem of Neurorights Protection

Julie Bicocchi[a*]

[a] *Sociologist, Switzerland*

***Corresponding author:** Julie Bicocchi, Email: juliebicocchi@gmail.com

Abstract

Over the last twenty years neuroscience has evolved much more rapidly than the ability to update national and international human rights law. In this regulatory vacuum new and potentially dangerous market niches have been created for more and less invasive devices dedicated to our mental activities. How, and in which contexts, it is still possible to fill this serious gap is a topic that the scientific community and civil society must discuss as soon as possible. Otherwise, dystopian scenarios might open up, in which algocracy and technocracy could converge into a regime of perpetual overpowering of our humanity.

Keywords: Habeas mentem, neurorights, AI, neuroscience

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Introduction

The world is rapidly filling with interface-controlled games, wearable technologies, smart fabrics, submillimetre semiconductors, injectable technologies. However, while the future is approaching fast, the law is not evolving as quickly: the need to recognize and protect neurorights arises from the (increasing) gap between scientific progress and the law's capability to understand and regulate it. Unfortunately, although the human desire to understand (and sometimes condition) the mind is old, the ethical debate on such themes has not yet grown enough, neither in terms of contents nor in relation to the subjects involved.

Here I will try to sketch the issue, hoping to contribute to the examination of a problem that might soon prove to be extremely relevant.

1. Mind Control: The Holy Grail of Neuroscience

This essay will try to introduce the controversial relationship between scientific progress and *habeas mentem*, understood as the right to protect the human mind from unconscious exploitation and manipulation, so that it cannot be used for any purposes without the explicit consent of the person concerned.

Until the early 2000s, the notion of psychophysical integrity was decomposable into the two categories of physical (external limit) and mental integrity (internal limit), each of which could be separately analyzed. This categorization worked very well from a legal perspective. For example, it could be used in court to assess the extent of a damage and obtain proportional compensation. That was one of the reasons consumer protection (and the provision of specific instances of compensation) conditioned technological design (and partly scientific research) for several years.

However, what would happen if the victim of an injury were unable to understand that he or she had suffered a damage? How to prevent people from being blackmailed into neurologically invasive practices (e.g., giving up certain mental functions or activities in exchange for employment)?

Modern science timidly faced the problem from an ethical point of view between the end of the 19th century and the 1930s: at that time the polygraph (i.e. lie detector) seemed to allow for overcoming boundaries, such as mind reading, which until then had been considered impassable. Notwithstanding, the ethical debate soon faded, because the machine promised more than it could actually deliver.

The history of the attempts at mental and neuronal interference is rooted in times far more distant (archaeologists tell us, for example, of the electric catfish used by Ancient Egyptians to treat arthritis) (Royal Society 2019). But none of these practices had, until now, exceeded the legal perimeter of the society that had produced them. Current technological advancements and the contemporary climate of legal, physical, and biopolitical uncertainty, however, present us with unprecedented challenges. In fact, it is not always possible to assess the condition of subordination of those who make use of neurotechnologies: the "informed" consent in this case is not always truly such.

In other words, promoting neurorights protection means clashing with the ethical inadequacy of the available scientific investigation tools and legal possibilities.

In a not too distant past, scholars used to reflect about *habeas mentem* only in psychological terms, as a right to escape mental manipulation in a more equitable and cognitively advanced society (Sanford 1956). Such a naive vision depended on the modest clinical efficacy of the brain-implant technology of the times. During the 1970s, the Spanish scholar Jose Manuel Rodriguez Delgado shocked his Yale colleagues with the hypothesis of a "psychocivilized society" formulated on the pages of *The New York Times*. Delgado had been student of John Fulton, who practiced the surgical destruction of the prefrontal lobes in animals. He was determined to avoid the invasive interventions of the Portuguese neurologist Egas Moniz, who won the 1949 Nobel Prize thanks to the practice of lobotomy. Hence, Delgado proposed the implantation of electrodes in the brain as a more effective and conservative practice. In 1952 he was among the co-authors of the first paper dedicated to long-term electrodes in humans. Today we would say that the results of his research were greatly overestimated. But at the time, more than one scholar (including the psychiatrist Peter Breggin) raised a moral issue about the technocratic drift underlying the heuristic approach of the Spanish researcher. Since then, the goal of wresting the power of neurotechnology from authoritarian governments or terrorist groups has been periodically emphasized as a future eventuality, both within utopian visions and within less reassuring governmental projects. In less than half a century we have seen Natalia Petrovna Bekhtereva's multiple electrode implantation (1963), William House's cochlear implant (1969), Jacques Vidal's Brain-Computer Interface (1973), Medtronic patent TENs for pain control (1974), robots controlled by EEG signals (1988), the treatment of Alzheimer's disease through DBS (1997, followed by DBS use against dystonia in 2003 and against epilepsy in 2018), the first tetraplegic person controlling an artificial hand by using a BCI (2005), the retinal implant Argus II, and the NeuroPace RNS system of responsive DBI, both approved by FDA (2013). Furthermore, over the last twenty years, the advancement rate has surged, especially in neurosurgery and the military, also thanks to the birth of large companies such as Facebook (2004), Kernel (2016), Neuralink (2016), and dedicated programs promoted by DARPA.

Whether these are invasive technologies (ECoG, cortical implants, neural dust, neuropixels, DBS, retinal implants, etc.), or non-invasive technologies (EEG, MEG, fMRI, tDCS, TENS, etc.), and whether they are medical or recreational practices, or even suitable for specific work activities, scientific research is now at a crossroads: is it better to contain the risk or optimize the opportunities?

In this context, neurorights emerge as a new typology of human rights that the Morningside Alliance Group proposed, as early as 2017, for inclusion in the *Universal declaration of human rights*.

2. Neurorights as New Human Rights?

One of the liveliest ethical debates currently underway concerns neuroenhancement, that is, the use of technologies for improving non-impaired cognitive, affective or behavioral functions. Neroenhancement can be achieved through surgical, technogenetic, electromagnetic or pharmacological techniques, or through the combination of two or more of them. This practice poses an ethical dilemma because its recipient is not a patient but a healthy person—comparable to the intact person who undergoes cosmetic surgery. On top of this, secondary objections include the lack of fairness of those who resort to it, for example, in sports competitions. In any case, in different jurisdictions a conflict might arise between the alleged right of a healthy person to decide how to modify their own mental faculties and the harm of human dignity if this practice irreversibly modifies the cognitive abilities typical of the human species.

It may be useful to mention an observation that Harvard University Professor Jeff Lichtman proposed to his students of molecular and cellular biology in order to introduce them to the study of the brain: if the advance towards the total understanding of our neurological functioning were a mile, today scientists would have travelled ca. three inches (National Geographic 2014).

Indeed, so many questions cannot be answered with a reasonable degree of certainty. These include the following: can I be sure that I will keep my self-determination ability intact while using certain devices? How are we going to be certain that we have not suffered any form of mental violation or manipulation? How can we assert our right to be forgotten, if we download our personal memories on digital media?

Contemporary mental manipulation can occur through a distorted use of goods and services usually considered to be of general interest (television, Internet, social media) or through a misinformed use of specific tools. One solution (recently identified in Chile, the first nation in the world to have included the protection of neurorights in the constitutional charter) could be the introduction of the *Opt-in* model (prior and explicit consent) already applied to organ donations. Therefore, not only would an explicit authorization be a *sine qua non* for accessing a citizen's brain data but, above all, their transfer should be bound to an altruistic purpose (which would make them unsaleable). Putting these kinds of limits in a market as attractive as that of brain-machine interaction (and, in short, brain-AI interaction) could affect many states in terms of loss of investments: big tech companies, as it has already happened in the fiscal field, are constantly looking for "heavens (of violation) of neurorights". Also there are those who believe that such a protection's specific fault would be a "mereological fallacy", caused by the insufficient distinction between what is neuronal, what is psychological, and what is mental. In fact, it focuses almost exclusively on the brain, as if the body (and not the person as a whole) felt emotions or exercised free will (an aspect that could be relevant when assessing the seriousness of a crime).

3. Transparency versus Digital Authoritarianism

Further important political aspects are involved where the issue of obtaining consensus proves to be key. The social credit system implemented in China since 2014, officially on an experimental basis and in order to combat petty crime, is one of the possible points of no return with regard to the violation of neurorights, insofar as government decisions become *de facto* non-questionable, regardless of how pervasive, discriminatory, and even harmful they may be.

This system is already causing important violations of human rights through "simple" mental manipulation: for now, we are talking about censorship, but the distance separating it from the crime of opinion is short. Unfortunately, digital authoritarianism is insidious and does not require such striking situations, to gain ground. Let us take the case of AI: it is submitted to us as a black box, since the combination of the algorithms that compose it often remains obscure even to its creators. However, as Cynthia Rudin's studies have showed, this apparent necessity is a precise market choice (Rudin *et al.* 2021). In fact, with some precautions and greater economic investments, in many cases we could make use of interpretable machine learning. This has a high predictive value and, perhaps, can even be cleaned of the prejudices already outlined by O'Neal (2017).

Chile experienced thirty years of dictatorship. The nation has sensed the dangers concealed by deregulation in this field and set specific limits in its constitutional charter in 2021.

> "Scientific and technological development will be at the service of people and will be carried out with respect for life and physical and mental integrity. The law will regulate the requirements, conditions and restrictions for its use by people, and must especially protect brain

> activity, as well as the information from it" (Official Journal of the Republic of Chile 2021).

Still on the subject of neurorights protection, a Chilean bill project is also extremely interesting. It regards "the protection of neuro-rights and mental integrity, and the development of research and neurotechnologies" (Official Journal of the Republic of Chile 2022).

This should be an important point of reference for any democracy. Unfortunately, so far, this level of sensitivity has emerged only in Delgado's homeland, beside Chile. The Spanish *Charter of the Digital Rights* (2021)—which is descriptive, not normative, and subjected to the legal system in force,

> "[...] does not seek to discover new fundamental rights, but rather to specify the most significant ones in the digital environments and spaces, or to describe instrumental or ancillary rights pertaining to such fundamental rights. It is a naturally dynamic process given that the environment is in constant evolution with consequences and limits that are not easy to predict." (Gobierno de España 2021).

However, the Spanish point of view on the problem (that is, finding useful elements to protect neurorights in the existing legislation) is slightly different from that of Goring and Yuste who were inspired by the *Belmont commission report* (1979). These scholars worked along withh multidisciplinary study groups and proposed to integrate neurotechnological innovations with our fundamental human and societal values already in 2016. At the time of the *Belmont commission report* ethics in biomedical research followed the three principles of respect for persons, beneficence, and justice. Instead, the BRAIN initiative (sponsored by the White House in 2013) proposed a very practical approach to the new management of issues such as informed consent, risk-benefit assessment, and subject selection:

> "Technological advances must be shaped by our collective moral sensibilities in order to ensure that these advances are smoothly incorporated into our culture and indeed contribute to the common good" (Goering & Yuste 2016).

We have clarified what needs to be defended and how it needs to be defended. But who should be in charge of defending?

To find the answer, it is important to adopt an international perspective. On the one hand, we have both the technological advancement we previously referred to, and the worrying neuroweapons, about which too little is still known, compared to all the matters covered by military secrecy in the major world powers. On the other hand, we have a scientific community that can and must begin to consider not only its own aspirations, but also the current concrete possibilities through a neuroethical filter. Obviously, this should not be an anachronistic Luddite stance.

According to the Morningside Alliance Group, it is time to add new human rights to the *Universal declaration of human rights* to protect mental privacy, personal identity, personal agency, equal access to cognitive augmentation, and protection from algorithmic biases. One of the most innovative ideas discussed in early 2021 concerns the hypothesis of a "Technocratic Oath" modelled on the Hippocratic Oath. This idea seems popular in the United States. However, is not the risk we take by trusting an oath disproportionate in terms of the irreversibility of the potential and often unknown damage?

To date, the major national and international ethical committees on AI and neurorights include—in a direct or indirect way—the so-called stakeholders: subjects (usually large companies) that might have an economic, when not political, interest in managing as unilaterally as possible the infinite potential of AI and mass mind control. But what guarantees do we have today that human-oriented computing technology, neuroscience, and AI can be contained within precise limits, when the companies that develop them have a turnover exceeding the GDP of entire nations? Can we therefore act on what is already technologically possible without a clear and urgent legal boundary?

Conclusions

Neurotechnology advances at ever-increasing speed. We urgently need an independent ethics committee to control both the neurotechnology production and its affordance for mind control and consciousness manipulation. Current legislation worldwide fails to foresee all possible human rights violations that we might face in the near future.

Political and cultural issues add to the legal one. In fact, this insidious and pervasive mental manipulation represents one of the worst dangers that political decision-makers and ordinary citizens have faced. Unfortunately, the subjects who would have the greatest concrete possibilities to prevent it and fix any damage could also be the least interested in shedding light on the issue. The result of this legal and cultural backwardness is worrisome: we cannot accurately measure how many and what kind of *habeas mentem* violations are already taking place, all over the world. If the law and the scientific community do not take action in the short term, these types of violations may not even be considered as such anymore in the future.

From this point of view, only national and international ethical organizations completely free of conflicts of interest can try to stem the technocratic drift already in place. Otherwise, methods of regimentation and invasive control of entire populations, such as the Chinese social credit system, might represent the point of no return for any sort of human right.

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RNA-based Vaccines against SARS-CoV-2: A Word of Caution and an Analysis of Potential Long-term Adverse Events

Carlo Gambacorti-Passerini[a*] *& Andrea Aroldi*[a]

[a] *University of Milano-Bicocca, Department of Medicine and Surgery, Hematology Division, ASST Monza, Italy*

***Corresponding author:** Carlo Gambacorti-Passerini, Email: carlo.gambacorti@unimib.it

Abstract

This paper briefly discusses the mechanism and potential of still unknown side-effects of RNA-based vaccines against SARS-CoV-2.

Keywords: RNA-based vaccines, SARS-CoV-2, LNP, S protein

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Introduction

The COVID-19 pandemic saw the introduction of new types of vaccines, i.e. DNA- and RNA-based products. These vaccines were developed and released based on an emergency authorization, where many steps related to the development of a vaccine or of a drug were shortened or completely eliminated. The urgent need to make them available to be public justified this expedited approach. However, such an approach risks to become an excuse to omit a much needed surveillance activity.

We will not deal with DNA-based vaccines. In fact, their use is dwindling because of Vaccine Induced Thrombocytopenic Thromboses (VITT), a rare (1/100,000 event) but often fatal adverse event (AE) (Pavord *et al.* 2021).

RNA-based vaccines are instead gaining widespread use to prevent SARS-CoV-2 infection, and offer an excellent tool to prevent serious COVID-19 signs and related deaths (Public Health England 2021; Evans & Jewell 2021).

Vaccinated people enjoy a high degree of protection against serious COVID-19, Intensive Care Unit (ICU) admission, and COVID-19 related death. They however can become infected and transmit SARS-CoV-2, although with reduced viral loads.

RNA-based vaccines are formed by injecting the RNA coding for the S protein (or part of it) admixed with lipid nanoparticles (LNP) that protect it from degradation and increase its cellular uptake. This in turn lead to RNA transcription and production of the S protein. The S protein then induces an immune response consisting of both a cellular (T-based) and long-lived response, and in a humoral (B-based) short-lived one with the production of anti-S antibodies (Dan *et al.* 2021).

Upon intramuscular injection, the RNA gets distributed to the injection site, the draining lymph node(s), and the liver. The presence of the RNA usually lasts 48-72 hours (European Medicines Agency 2021).

The S protein of SARS-CoV-2 was chosen because it mediates virus entry into cells through the binding of Angiotensin Converting Enzyme 2 (ACE2), present on the membrane of epithelial and endothelial cells

(Guney & Akar 2021). Therefore, antibodies against the S protein should be able to block the fusion of the virus with a cell membrane, thereby blocking its entry and subsequent viral replication and cytolytic effects.

RNA-based vaccines represent also a new type of medical tool, as traditional vaccines contain the entire microbiological agent (either attenuated or inactivated) or proteins derived from it.

Because of the global emergency linked to COVID-19, no long-term safety analysis of RNA-based vaccines was undertaken. Hence, caution should be exercised, as for any new medical treatment.

Three items need to be considered when examining the potential AEs linked to the use of RNA-based vaccines: the lipid nanoparticles (LNP), the RNA, and the protein being produced.

1. LNP

Lipid nanoparticles make the RNA able to resist degradation, and allow them to be picked up by cells in an endosome and finally be released into the cell cytoplasm for translation (Schoenmaker *et al*. 2021). They are composed by cationic (ionizable) lipids whose positive charges bind to the negatively charged backbone of mRNA, pegylated lipids that help stabilize the particle, and phospholipids as well as cholesterol molecules that contribute to the particle's structure. Cationic and pegylated lipids have showed safety problems as they could accumulate in the liver and cause hepatotoxicity. They could also elicit an innate or conventional immune response (Ndeupen *et al*. 2021).

Indeed, some generalized inflammatory response, including myocarditis, were observed with a prevalence of approximately 1-5/100,000 and are being monitored (Haaf *et al*. 2021). The cause might be the LNP, alone or combined with RNA.

2. RNA

It constitutes the core of the vaccine, as it is translated into the S protein, the real immunogen in an RNA-based vaccine. RNA itself can be toxic upon injection in cells because it can activate Toll-Like Receptors (TLR), usually in late endosome, thus initiating a cytokine storm (Dalpke & Helm 2012). It appears that the conversion of uridine into pseudouridine in the RNA strand reduces this risk (Dolgin 2021).

Another risk linked to the intracellular presence of RNA is its ability to form DNA and to integrate into cellular DNA. Although conventional wisdom indicates that the RNA –> DNA direction is not possible in cells, we need to remember that our cells contain many retrotransposons (or class I transposons). Under certain circumstances, these can activate and produce reverse transcriptase and catalyse the reverse transcription of RNA into DNA. This, in turn, can anneal to homologous sequences in the genome and cause genetic damage (Pray 2008). This fact was proven recently in vitro for SARS-CoV-2 (Zhang *et al*. 2021), and proposed as the mechanism by which patients clinically cured from COVID-19 can remain positive by SARS-CoV-2 PCR assay for months (Zhang *et al*. 2021). Indeed, this hypothesis was recently questioned (Smits *et al*. 2021). In addition, it was demonstrated in vitro that the use of RNA to modulate the transcriptome profile of cells for producing pluripotent stem cells was the safest tool available, but was still associated with the development of some genomic alterations in transduced cells (Steichen *et al*. 2014).

It can be argued that the virus itself can induce a similar phenomenon during a natural infection as well as through the spontaneous activation of transposons themselves. This is certainly true but pertains to two different types of contexts: virus infection and transposon activation occur naturally, while the injection of a vaccine is a human activity, which requires an informed consent.

The most common disease following insertional mutagenesis is represented by the development of a malignancy, which requires a minimum of 2-3 years to become clinically detectable. In this case, we lack information simply because an insufficient amount of time elapsed. Most possibly, such a risk will be absent (included in the "background noise" of present cancer rates) or very low. However, it is essential that we put in place an adequate and efficient monitoring system for it.

3. S Protein

A safety analysis must consider the protein produced by the injected RNA, although it is not yet present in the RNA-based vaccine. In the case of SARS-CoV-2, the S protein plays an important pathogenetic mechanism in determining COVID-19.

The S protein, in fact, binds to ACE2 and cause its down-regulation. ACE2 plays an important role in cell homeostasis: its product (mainly angiotensin 1-7) has anti-inflammatory, vasodilation and anti-thrombotic effects that balance the opposite effect of angiotensin II, i.e. the product of ACE1 in physiological conditions. This unbalance produces important effects typical of severe COVID-19, such as the cytokine storm and the production of sFLT1, which causes endothelial damage and coagulation activation (Giardini *et al.* 2020).

A work performed with SARS-CoV-1 elegantly demonstrated that injecting the S protein (more precisely, the ACE2 binding part of it) in animals caused the pathogenetic changes typical of lung and endothelium viral infections (Imai *et al.* 2005). Therefore, one could argue that the RNA-based vaccines that drive the production of S protein could cause similar effects in vaccinated people.

Two lines of evidence are against this hypothesis:

1. The injection site of the vaccine involves a minimal part of the body. Usually, the injection site involves a volume of a few ml and 30-100 micrograms of RNA. It is true that in the case of RNA-based vaccines it is impossible to predict how many micrograms of protein will be produced. However, these figures pale in comparison with an entire lung involved by SARS-CoV-2 infection. Even in the aforementioned animal model, it took tens of milligrams of S protein to cause COVID-like pathological changes.

2. The S protein is produced in cells transduced by the RNA-based vaccine. It contains a single stop-transfer, membrane-spanning sequence located at the C terminus, which prevents it from being fully released into the lumen of the ER and subsequent infected cells' secretion. Consequently, it remains stuck in the cell membrane, similarly to the S protein produced during an infection. However, the mature virus formed inside the infected cells is released into the circulation upon cell lysis. When cells are transduced by the RNA-based vaccine, the S protein is not released into the circulation and remain in the cell, where it is subsequently degraded into peptides and presented to CD4 lymphocytes. These then initiate the immune response. The final development of the immune response leads to the production of anti-S antibodies.

The above-mentioned data strongly object to the possibility that the S protein can be released into the blood stream in significant amounts and damage cells.

Conclusions

RNA-mediated vaccines offer a new but not fully tested vaccination tool. Some of the possible AEs require closer monitoring. Any toxicity of the LNP and the S protein itself would manifest in the form of acute AEs. Thus, short-term follow up programs would be able to spot them timely.

On the contrary, any insertional mutagenesis operated by the retrotrascription and genomic integration of the RNA itself would require a substantial amount of time (2 to 6 years) to manifest as an increased incidence of neoplasias (mostly lymphomas, sarcomas, and leukemias). This effect remains hypothetical at present, but cannot be discounted *a priori*.

In our opinion, a successful immunization strategy needs to convince, not coerce people. Many have suggested that we should bar these arguments from public view and knowledge, in order "not to scare people away from vaccines." We think this is a short sighted and counterproductive view. In the long term, transparency, reliability, and science-based opinions win people's trust.

It is essential however that the separation of powers be maintained even when COVID-19 pandemic is concerned. Scientists must retain their independence from politicians, similarly as judiciary must remain separated and independent from legislative and executive powers.

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Organisms

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