# Reflections on Curiosity[a]

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## Summary

***Objective***: The purpose of this article is to show that curiosity is the driving force behind all scientific endeavors. The second purpose is to show that all science is constrained on its underlying assumptions.
***Methods***: Three examples are used to illustrate the above theses: one from cosmology, the second from biomedical research, and the third from the formalization of human reasoning in a computer. The three examples are supported by quotes from Albert Einstein [1].
***Results and conclusions***: Research in cosmology shows that the horizon of our knowledge is continuously expanding but that major scientific questions remain to be solved. The second example from biomedicine explains that the more we discover of the details of living phenomena, the more complex they appear to be. The example involving human reasoning makes clear that the brain is still largely unknown territory. Like Einstein, who said he held '*humble admiration of the illimitable superior spirit who reveals himself in the slight details we are able to perceive with our frail and feeble mind*', I have a deep admiration for the Architect who reveals himself in the details that we are privileged to study in our research. As Albert Einstein said: *The important thing is not to stop questioning. Curiosity has its own reason for existing.*

## Keywords

Curiosity, scientific research, cosmology, perinatal research, ECG, human reasoning

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## Introduction

Curiosity is characteristic of children as well as researchers. Wondering about things was also for Plato the core of his philosophy [2]. This was—and still is—the main motivation behind the research I conducted all my life. Therefore, this article is on curiosity, but it spreads out further than just biomedical informatics. Because of my admiration for one of the greatest and most curious scientists who ever lived, I will highlight my paper with quotes from Albert Einstein, the physicist who fundamentally changed our view on the macrocosmos and the microcosmos. Curiosity and admiration for the non-living and living nature may start early in life. For me it began with astronomy. For that reason, the subject of cosmology will be the subject of the first part of my reflections. Soon after having completed the study of physics, I started my research in the biomedical field. One of the first subjects I studied was fetal circulation, to be able to monitor the condition of an unborn child in the perinatal period, in particular during birth. This will comprise the second part of my reflections. The third part will be an example of how human decision making could be formalized in a computer. This I will illustrate by another part of my research: the computer interpretation of the electrocardiogram, a subject that I had the privilege of investigating with many collaborators from within my country and abroad, over the course of many years. Regretfully, many other interesting subjects have to be left out, such as studies on brain and behavior, investigations on monitoring critically ill patients during and after cardiac surgery, or research on electronic health records. Nevertheless, I hope that the three examples will be representative for my curiosity in the non-living world, living organisms, and human reasoning.

## Cosmology

Let me start by discussing some aspects of astronomy and cosmology. By doing this I want to illustrate that all science is based on observations and that all theories are man-made and based on human assumptions or presuppositions. A true scientist knows that his observations are constrained, and that a theory should be modified or sometimes even rejected if it does not fit the observations. A genuine researcher is open to surprises, or serendipity.[b]

Being a student at Grammar School, I was an enthusiastic member of our

[a] 2nd IMIA/UMIT Medical Informatics Award of Excellence Lecture, given at the closing ceremony of IMIA's tri-annual World Conference MEDINFO 2007 in Brisbane, Australia, in August 2007.

[b] Coined by Horace Walpole (1754) after The Three Princes of Serendib (i.e., Ceylon), a Persian fairy tale in which the princes always make discoveries of things they were not searching for by accident and sagacity.

Dutch Amateur Association for Astronomy. I constructed my own telescope in the Fifties with the first Japanese lenses that came on the market, and spent long nights on the flat roof of my parental home. At that time there was not much stray light, as is nowadays caused by big cities and highways. It was fantastic to observe the moons of Jupiter in their orbits, the rings of Saturn, the red glow of Mars, the blue radiation of Sirius, and the slowly changing solar spots. And who is nowadays not impressed by the pictures taken by the Hubble telescope? I was also deeply impressed by the solar eclipse in August 1999 that I photographed in France (Fig. 1). An interesting feature of astronomy is that the formation of the cosmos unfolds itself, so to speak, before your eyes; the further away you look, the longer ago the cosmic events you see took place. Of course, one should have trust in the assumption that the laws of physics did not change during all these billions of years and are also valid throughout the entire universe.

The stability of the laws of physics cannot be proven, but there are no strong indications that this might not be the case. In its ability to look back in time, astronomy is radically different from the sciences of living nature, which bears even more secrets than astronomy. In many respects, the existence of the cosmos and all forms of life are a great mystery. As Albert Einstein said: '*The most beautiful thing we can experience is the mysterious. It is the source of all true art and all science. He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead: his eyes are closed.*'

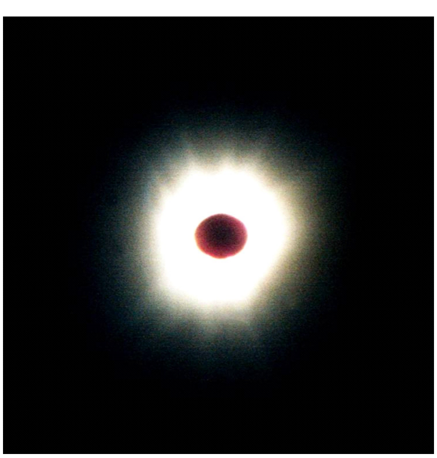

**Fig. 1** Solar eclipse, photographed by the author in northern France, August 1999

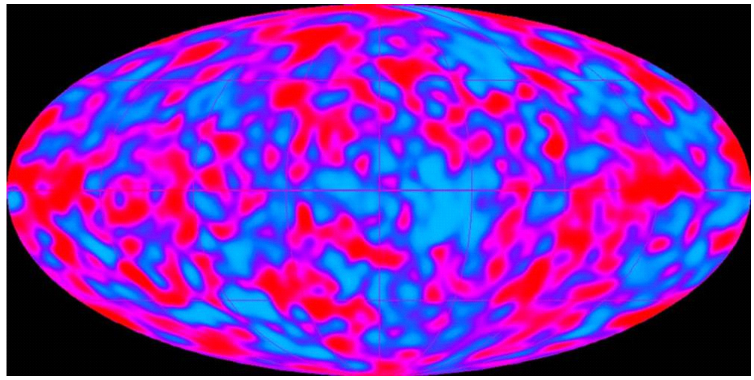

**Fig. 2** The weak background radiation, measured by the *COBE* satellite. The map shows the tiny relative differences in the measured temperatures, of the order of one-thousandth of a degree.

Everyone is acquainted with the Hubble telescope. It offers astounding pictures from space. Edwin Hubble was a great astronomer, who discovered in 1929 the relationship between the speed by which stellar systems are moving away from us and their distance to us. This is now known as Hubble's law [3]. His discovery was honored in 2003 by special postage stamps, 50 years after his death. Hubble's law says that the larger the distance of a galaxy is to us, the faster it speeds away from us. This speed can be measured by the so-called red shift, that is, a shift in the spectral lines of the light towards the lower frequencies. We know this phenomenon as Doppler shift. For instance, when hearing the sound of a vehicle first approaching us and then moving away, the sound frequency gets lower. For visible light this means a shift towards the red part of the spectrum. By using Hubble's law, the moment that the cosmos came into existence—known as the *big bang*—could be extrapolated to about 13.7 billion years ago.

The effect of the big bang is still detectable as weak background radiation, and was measured very precisely a few years ago by the *COBE* satellite.[c] Figure 2 shows the tiny relative differences in the measured temperatures, of the order of one-thousandth of a degree, with an average of 2.7 K [4]. The leader of the research team that made the discovery was astounded that he found traces of the *big bang* and said: *'If you are religious, it is as if you see God'*.

There are many researchers who point to a first cause or to God when they are confronted with the limits of their knowledge. One of them is Stephen Hawking in his book *A Brief History of Time* [5]. He ends his book with the claim that, once we know the explanation for the creation of the cosmos, we shall know the *'mind of God'* and shall have a '*theory of everything*'. I consider this assertion an illegitimate crossing of the borders of one's domain of research. The history of physics, but

[c] The background radiation is comparable to the radiation given off by a black object that was first heated to a high temperature.

also that of biology and geology, shows that all knowledge is finite. Crossing the borders of your discipline most often leads to speculation [6]. We should always be aware of this danger in our research. Some authors think that the 'end of science' has been reached. Horgan is one of them [7]. This view is, however, in sharp contrast with fundamental questions that still have to be solved, for instance, in cosmology and the physics of elementary particles, two areas that came together when the post-Newtonian era began with Albert Einstein, Niels Bohr, Hendrik Lorentz and Max Planck, the scientific giants of the first half of last century. Some basic questions for which answers are still fully unknown to us are, for instance [8]: (1) how did the universe begin? (2) what is 'dark matter'? (3) does Einstein have the last word on gravity? (4) are there additional space-time dimensions? (5) how were the elements from iron to uranium made?

Although the quest for answers to such questions may require an entirely new paradigm, but one thing is for sure: we observe an impressive order in reality. This order is seen both in the non-living and the living nature. You may wonder about such order; but nobody knows its origin. Einstein wrote: '*I consider the comprehensibility of the world as a miracle or an eternal mystery. One should expect a chaotic world which cannot be grasped by the mind in any way. This could not be expected a priori. That is the "miracle" which is being constantly re-enforced as our knowledge expands.*' [9]

Unquestionably, we can *observe* reality more and more, but don't we also understand its underlying fundamentals less and less? Reality as we know it appears to be infinitely complex, diverse, and dynamic, and possesses impressive beauty and—regretfully—sometimes awful grief and suffering as well. We are acquainted with the latter in medicine and health care.

In the past decades, impressive discoveries were not only made in astronomy, but also in biomedicine and medical informatics. Who could have thought at the time that I started my research in the biomedical domain—now almost 45 years ago—that we would be able to look inside the body without using a surgical knife or an endoscope, in three dimensions and in real time? Isn't it amazing that we can look in a non-invasive way at obstructions in the arterial system to prepare for surgical interventions? And there is much more to come. It all just depends on our creativity and imagination, driven by our curiosity. Another expression from Albert Einstein is that '*imagination is more important than knowledge*.'

Let me now change the subject from cosmology to my earliest research, perinatal monitoring; another exciting area for curious researchers.

## Perinatal Monitoring

An example of a highly complex physiological process is the transformation, within seconds to minutes, of the circulation of the fetus to that of the youngborn child. This transformation takes place at the moment that the fetus leaves the womb and begins breathing. In some respects this transformation shows similarities with the countdown during the launch of a space vehicle; all sequential steps must be thoroughly prepared and carried out in the right order.

In our research we developed instruments and information processing methods to monitor this process [10]. We also developed computer models to simulate the fetal circulation and conducted animal studies with unborn lambs [11]. Between the fetal and the adult circulation there are fundamental differences. To mention some of them:

- The fetal lungs are not yet in operation—they unfold at birth.
- The fetal blood gets oxygen via the umbilical cord.
- The fetal blood has a type of hemoglobin that binds oxygen far better than in the adult. The two genes that code for adult hemoglobin are located on chromosome 11; the genes that code for fetal hemoglobin are on chromosome 16.

As mentioned, the lungs are as yet unfolded and only a small amount of blood flows through the lungs. So, the fetal blood cannot follow the same pathway as in the adult. For that reason three shunts are in operation (Fig. 3):

1. the *Foramen ovale,* an opening between the left and the right atrium;
2. the *Ductus venosus,* for the supply of oxygen-rich blood from the placenta; and
3. the *Ductus arteriosus,* connecting the pulmonary artery with the aorta.

Because of these shunts, the fetal heart has in essence only one atrium and one ventricle.

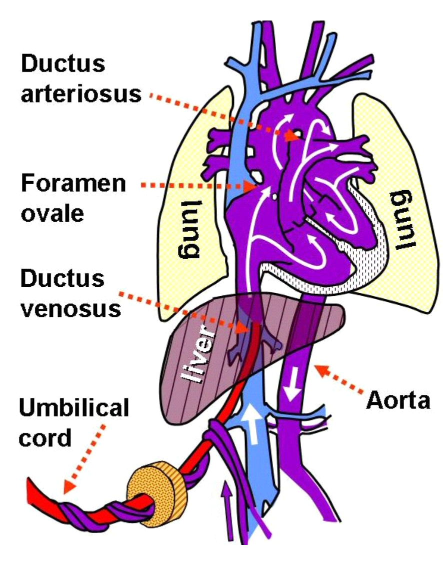


**Fig. 3** The fetal heart and part of the fetal circulation. The three shunts, only operational in the fetal circulation, are depicted (see the text).

The shunts have to be closed as soon as possible after birth and the lungs have to be opened immediately, if the child is not to suffocate and die.
At birth, *chemoreceptors* stimulate the lungs to open. These chemoreceptors continuously measure the $pCO_2$. When the fetal lungs start breathing, the arterial lung pressure drops quickly and the valve in the *Foramen ovale* closes automatically. The *Ductus arteriosus* is closed with the help of *bradykinin*, a protein that is secreted by the fetal lungs at the time they unfold. It has a strong contracting effect on the *Ductus arteriosus*. The umbilical cord starts contracting about 30 to 60 seconds after birth, somewhat delayed in order to donate as much as possible blood from the also contracting placenta to the fetal circulation. Can you see the dramatic changes that take place during birth? Can you see the comparison with the countdown of the launch of a space vehicle? The fetal countdown is even more impressive.
Why am I telling you about the fetal circulation at birth? By this I want to show that at birth two fully different circulations are simultaneously present.

- One with the placenta as its ‘lung’ and one with the child’s own lungs;
- One with a heart that essentially consists of two chambers and one with a heart with four chambers;
- There are even two different sets of genes, present on chromosomes 11 and 16, for two different types of hemoglobin before and after birth, respectively;
- But already during gestation the lungs are prepared to launch a *shot* of *bradykinin* at the first breath, in order to quickly close the *Ductus arteriosus*.

The second circulation is not functional during pregnancy, but is fully prepared to become immediately operational at birth. It is like the firing of the second stage of a space vehicle.
Aren’t we astonished by the phenomena that we study in our research? Now you also understand the reason why we developed perinatal monitoring and, perhaps, you understand my curiosity. As Albert Einstein said: ‘*There are two ways to live your life. One is as though nothing is a miracle; the other is as though everything is a miracle.*’

## ECG Interpretation

Thus far we looked at observations in the non-living and the living nature. I want to conclude by a last example, borrowed from my research in biomedical informatics. It illustrates how we deal with the processing of biomedical knowledge. I will give an example from our research on decision-support for the diagnostic interpretation of ECGs. It took us many years to develop the interpretation system in which many sequential processing steps are carried out, involving signal analysis and pattern recognition [12, 13]. Nowadays, systems for the interpretation of ECGs have been successfully introduced in clinical practice and are also used for population screening.
The electric field, generated by the heart, can be measured on the body surface (see an example of a body surface map in Fig. 4). Nobody is able to interpret such complex and continuously changing body surface maps. Therefore, the electric field is sampled in space and time by electrodes, resulting in the common 12-lead electrocardiogram. These ECG signals can be interpreted by cardiologists or can be used as inputs for computer interpretation. We invested much of our research in the formalization of the knowledge, reflecting the thinking and reported by expert cardiologists, so that ECGs could also be interpreted by computer. In a later project we investigated in the framework of an international study how reliable ECG computer interpretation is compared to that carried out by human experts. All existing ECG computer systems in the world participated in this latter study. For that purpose we collected a large database of well-documented ECGs [14].
The overall results can be expressed in a graph, in which the performance of the participating ECG interpretation systems and that of the experts is plotted against the ‘true’ diagnosis (Fig. 5). The ‘true’ diagnoses were obtained in two different ways:
(1) the diagnosis derived from ECG-independent clinical data, depicted horizontally, and

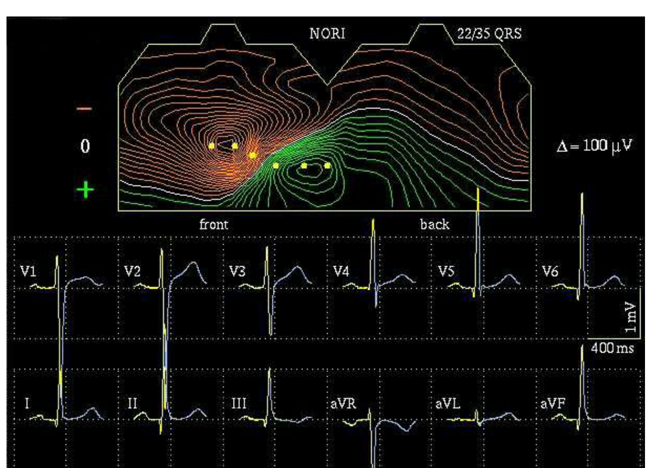


**Fig. 4** Body surface map of the electric field, generated by the heart, consisting of equipotential lines. The map shows an instant during ventricular depolarization, 44 msec after the onset of the ventricular depolarization. At the left we see the map on the front and at the right on the back of the chest. The 12 common ECG leads are seen below the map. The six locations of the chest electrodes are seen on the front side as solid dots.

(2) the joint ECG interpretations from cardiology experts, depicted vertically. The dots represent the overall outcomes of 16 interpretation systems. The open circles are the overall interpretations by 13 experts from different countries.

One may compare a test like this one with a chess match between grandmasters and computers. The question is whether the computer can beat the grandmaster. We found in our study on ECG interpretation that the best experts performed still better than the best interpretation systems. I think this study is a beautiful illustration of knowledge processing in medicine. But, as in computer chess, the match is not yet over and I am most curious to see how far we will finally come. The challenge is, whether the fullest human knowledge and expertise in this domain are transferable to machines. There is, however, an important caveat to be made.

Only when we try to imitate human decision making in a computer, we become aware of the fact that we have no idea how a reasoning process evolves in the brains of experts, either grandmasters or cardiologists. We know that the reasoning in a human brain is fully different from the formal, 'brute force'

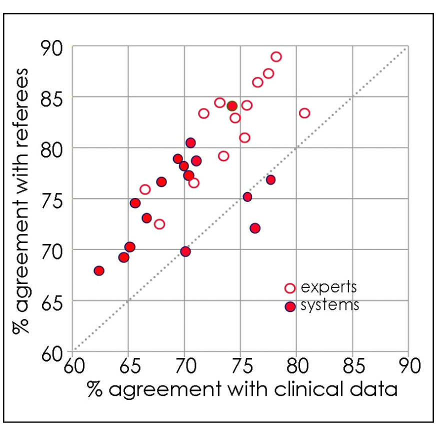


**Fig. 5** Assessment of the interpretation of a large database of ECGs by 16 different computer systems (solid dots) and by 13 cardiology experts (open circles). The interpretations are plotted against the diagnoses derived from ECG-independent clinical data (horizontally) and the joint ECG interpretations by cardiology experts (vertically). Ideally, all dots and circles should fall on the diagonal, also depicted in the graph.

approaches we frequently encode in a computer. In general, the brain is still a great mystery. Although we understand more and more about the nervous system at the neuronal level and possess much experience gained from studies with functional MRI, from which we know what cortical areas are operational for certain tasks, the bridge between the microscopic and the macroscopic level is almost entirely *terra incognita*.

In the neurosciences, as in cosmology and physics, there are several major subjects that are still open for basic research, such as [15]: (1) why does it seem that recognition memory, unlike recall memory, is essentially infinite? (2) how does the 'scanning process' in our brain operate when we try to remember something? (3) why is there a loss of short-term memory after an injury? (4) how are physiological and biochemical processes related to psychological phenomena? (5) how and in what form are memories stored in the brain? (6) is human memory bounded or infinite? (7) what are intelligence and consciousness? Such questions are not only very intriguing, but some answers will also be of great relevance for medical decision making and human reasoning in general. Who is not downright curious to find some answers to such questions?

In all our research endeavors we should be aware that human initiative and insight is always in the lead. *Research is people*, is an expression I borrowed from Hubert Pipberger, many years ago. And Einstein remarked: '*The whole of science is nothing more than a refinement of everyday thinking*.'

## Closing Remarks

My presentation was on *Reflections on curiosity*, in particular related to biomedicine. To quote Einstein again: '*Only a life lived for others is a life worthwhile*.' Is this not the motivation for all our research in the biomedical field?

Yes, we are motivated by curiosity, but foremost we are stimulated by our concern for better health care. By the way, do we, researchers and workers in biomedical informatics, still have the time to reflect? Do we ever question ourselves on what are our deepest motivations and what we are living for? As we saw, the leader of the COBE project, Albert Einstein and Stephen Hawking were all of them most interested in such questions and were most interested in the origin of all that is.

Was Albert Einstein a religious person? Some say he was, others deny it. But here is what he said himself: '*My religion consists of a humble admiration of the illimitable superior spirit who reveals himself in the slight details we are able to perceive with our frail and feeble mind*.' I fully agree. I myself have a deep admiration for the Architect who reveals himself in the details that we are privileged to study in our research. Our discoveries make us think about what lies behind the laws of physics, what or who caused the big bang, who created two simultaneous circulations in a fetus, and who designed the human brain with its superb image processing and decision making powers that we try to imitate in our computers.

We try to unravel in our research the structure behind what we observe in living and non-living nature. Was there a 'superior spirit' or architect behind this structure? Personally I think the answer is 'yes'. But you recognize the hand of the architect only when you have learned to know him. It is as with the work of a famous artist: once you know the style of Rembrandt, you recognize most of his paintings; once you became a lover of the songs of Schubert, you recognize the composer also from a song you never heard before. The same applies to the Architect of life forms and the cosmos. He is easily recognizable from his material, its forms and its endless variations. It makes you curious to see more of it and to study the composition of His creations. There is no end in research and wondering. As Albert Einstein said: '*The important thing is not to stop questioning. Curiosity has its own reason for existing*.'

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