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Uncertainty, Probability, Functionality in contexts of Computational Biology and Bioinformatics

Abstract The present paper is dedicated to the cherished memory of Professor José Mira Mira, who prematurely passed away on August 13, 2008. In view of his deep scientific interests and professional expertise in bridging natural versus mechanical computation methods, we offer some remarks on the concepts of uncertainty, probability and functionality with special reference to two areas of particular current interest to researchers in the areas of computational biology and bioinformatics. Preliminarily, a sketch of undergraduate and graduate curricula in Computer Science at Federico II Naples University is provided.

Figure 1. José Mira Mira.

1. Introduction

Particularly appropriate to the topic of the present Meeting are the contributions of Professor Mira Mira both to Science and to his long, dedicated teaching. Among his numerous works, I would like to point out those in [11]and [12] co-authored by Ana E. Delgado, in which the areas of artificial intelligence and neuronal modeling in brain dynamics are approached with unsurpassed mastery. What, of course, cannot be reflected in their writing, is the enthusiasm and the conveyed strength of José's delivered talks directed to a highly competent audience in the occasion of his invited participation in the BIOCOMP2002 and BIOCOMP2005 International Conferences.

2. Informatics curricula in our Faculty

As specified by the national guidelines for all Italian state universities, the undergraduate curriculum in Informatics consists of a 3-year study program. It has the following aims: *(i)* to provide solid bases in the mathematical and informatics related areas; *(ii)* to offer know-how and technologies adequate to handle design, development and management of information systems; *(iii)* to realize a versatile cultural formation that would help to catch up in real time with the rapid evolution of informatics technologies; *(iv)* to pay particular attention to questions related to programming languages, to internet-related technologies, to date bases and to operating systems; *(v)* to dedicate time and teaching assistance to experiment planning and laboratory work; *(vi)* to guarantee opportunities for stages in companies in the area of computer science and technology in order to gain work experiences and in view of possibly interesting future employment occasions. More detailed information on the offered courses and on teaching staff can be found at http://informatica.dsf.unina.it/index.php.

A master course in Informatics is also offered. This consists of a 2-year program focusing on a technical and scientific formation that should allow to obtain jobs in the area of informatics technologies, with ability to catch up with the innovations in this area and with the skill to implement them in order to solve complex problems of current interest and to contribute to technological and scientific innovation.

Among the numerous existing graduate programs at Federico II Naples University, here we limit ourselves to sketch some of the essential features of one of them, that since the very first inception in 1982 has been chaired by the author of the present paper. The official name of this program is *Research Doctorate in Computation and Informatics Sciences (REDCIS)*. A brief outline of a newly established doctorate program in Computational Biology and Bioinformatics will also be provided.

Note that the Research Doctorate is the highest university degree which can be achieved in Italy in a particular subject. It is the equivalent of Doctor of Philosophy (Ph.D.) of Anglo-Saxon tradition. The main goal of our Research Doctorate programme is to teach the methods of pure or applied scientific research in the context of the particular chosen area.

REDCIS aims at training researchers who have an in-depth and integrated knowledge of essential tools and a basic cognizance of a wide range of mathematical and informatics disciplines. At the same time they should possess the ability to formalize problems in different applicable contexts and construct and analyze suitable mathematical models which require the use of numerical and data processing sophisticated techniques. In addition, a solid knowledge is required in the areas of probability, mathematical statistics and related applications. Therefore, those wishing to obtain this Degree will need to absorb different fundamental methodologies of applied mathematics and informatics as well as other methodologies pertaining to ancillary specialization areas.

All graduate students are expected to develop an aptitude in translating the realities of a concrete problem into mathematical models and to possess an excellent familiarity with those aspects of Informatics regarding methods and tools enabling to solve problems through the use of computers.

Furthermore, they will have to acquire, through analyses of meaningful sample problems, the tools and techniques necessary for solving realistic problems of different types in their entirety.

A period of basic overall training is followed, and partly complemented by, a period of progressive development which guides the students towards autonomous skills

of actuation and concludes with a thesis proposal in one of the areas of the training program. The enrolled student will have to demonstrate that by the end of the training program he/she is able to carry out *autonomously* and *efficiently* high level research projects.

REDCIS has always been regarded with great interest and high expectations by young graduates in the fields of Mathematics, Informatics, Physics and Engineering. The increasing involvement in ad-vanced research goes along diversified curricular directions (mathematical informatics, numerical analysis and optimization, applied analysis, mathematical physics). It should be highlighted that from the time of its inception, all Research Doctors have obtained rewarding jobs in universities, scientific institutions and in public and private enterprises, often even before the conclusion of their doctorate studies. The experience gained over the quarter of century of existence of this Doctorate curriculum has amply demonstrated that there are numerous and diversified productive and service sectors into which the recipients of this Doctorate have found employment. In fact, graduates of *REDCIS* are characterized as belonging to the managerial stratum, not only in the sphere of universities and public and private research bodies but also in sectors of public intervention with a potentially high demand for employment such as the management of environmental resources, planning and optimization of transport networks, informatics and telematic systems, optimization of combustion systems, management of resources and environmental control, processing of tele-tracking data, numerical applications in meteorology and diffusion of pollutants and design and development of technical informatics services. The interest of public research bodies in programs of this nature has been often stated both by scientific organs of the Italian National Research Council and by the management of the Council itself, even to the extent of granting special admission scholarships. The European Union has also shown interest by making concrete contributions in the form of financial resources and the allocation of study grants.

REDCIS is open to those graduates who owing a degree in Mathematics, Physics, Informatics, etc., or an equivalent qualification obtained at a foreign university, possess a sufficient basic knowledge in mathematical disciplines. This requirement is assessed by the entrance examination Committee. The doctorate course lasts three years and includes several training pathways which have been specifically

tailored to the participants and which are firmly centered in the fields of applied mathematics and informatics. A period of basic overall training is followed, and partly complemented by, a period of progressive development which guides the participants towards autonomous skills of actuation and concludes with a thesis proposal in one of the areas of the training program.

During the first year, the participants follow courses and seminars directed toward research and take related examinations. In order to be able to continue following the doctorate program, the participants, at the end of the first year or on another date established by the Teaching Board, must take and pass a qualifying exam.

During the second year, complementing the completion of their training through courses and seminars, the participants usually is expected to begin personalized work which is designed to lead them towards a proposal for a research topic which, usually at the end of the second year, is discussed and defended by the participants with the Teaching Board as well as with experts who may be designated by the Teaching Board. Following a successful conclusion, the Teaching Board formally approves the dissertation topic and nominates the Research Director.

Finally, it must be underlined that students of this Doctorate are strongly encouraged to spend a period of the three-year course in qualified scientific institutions both in Italy and abroad.

The Research Doctorate in Computational Biology and Bioinformatics (RDCBB), we point out that this has been conceived as a very wide interdisciplinary program, directed not only to graduates of Science and Engineering Faculties, but also to talented young people from the areas of biology and medicine. A full description can be found at

www1.na.infn.it/dottorat/PhDBioinformatica/index-en.htm.

Here, we limit ourselves to mentioning that its aim is to train young researchers in the fields of computational biology and bioinformatics, by merging research activities and expertises on the usage of information technologies and of chemical, physical and mathematical modeling in biology and medicine. The educational

programme is, for this reason, interdisciplinary and involves the competences of a wide number of departments of Federico II Naples University. Bioinformatics concerns the collection, storing, maintenance, dissemination and mining of biological data, mainly of molecular kind, by using methods developed in different research fields (mathematics, computer science, biology, medicine, physics, chemistry, engineering) with the goal to provide an interpretation key of biological phenomena. Computational Biology is aimed, also starting from a direct analysis of experimental results, to understand the structure and the function of biomolecules, and the relations among them both at molecular and cellular level. This discipline concerns even more complex systems, by studying the interactions between organisms and environment by means of the application of computational tools and the implementation of mathematical modeling. Such models can be used to test the biological systems in biotech and medical applications.

Among the main research subjects of *RDCBB* rank: storage, maintenance, organization and use of genetic data associated to normal and pathological traits; development of bioinformatical tools (software, hardware, algorithms) for the organization and the analysis of biological and bio-medical data, of specialized, integrated databases and of software for DNA and protein sequence analysis; set-up of methods for information retrieval and integration of heterogeneous bio-medical data and development of standards for biological and bio-medical data interchange; prediction of genes and other functional regions in DNA and proteins; simulation of metabolic and cellular processes; pattern formation and selforganization modeling; statistical approaches in bioinformatics; simulation of complex biological system dynamics, of evolutionary systems and artificial life.

3. Historical remarks

As is well-known, what nowadays we call Informatics is a field that stems its roots in some of the pioneering works by a number of mentors that I feel appropriate to mention here. Indeed, they have played a significant role in determining my own background and in orienting my research interests towards the field in which I still work. All this, however, with the proviso that, due to lack of space, I purposely skip over most of those whose names are indelibly carved on the pillars of that magnificent temple hosting informatics and all closely related subjects.

Here, I wish to pay my tribute to Eduardo R. Caianiello (left of Fig. 2) under whom I graduated and who first directed my interests towards the new area of Cybernetics. Through his kind encouragement and his multifaceted relationships with mathematicians, engineers, physicists and biologists crowding the scientific panorama at that time, I was able to meet and enjoy lectures and discussions by people such as Norbert Wiener (right of Fig. 2), Warren McCulloch (Fig. 3), Gordon Pask (left of Fig. 4) and Ross Ashby (right of Fig. 4), just to mention a few.[1]

The subject of my talk today is centered on the notion of "uncertainty" and of various possible interpretation of it. Of course, the pathway of the scientist is paved by uncertainties of a variegated nature. The transition from a cloud of uncertainty to well defined conclusive remarks is what scientific research is all about. Without the claim of being exhaustive, hereafter I shall briefly outline some examples showing different possible types of uncertainty.

Figure 2. Eduardo R. Caianiello (left) and Norbert Wiener.

1 The three photos in which McCulloch appears have been taken from [13]. It is interesting to take note that the young man (center of photo on the right of Fig. 3), delivered yesterday the introductory talk in this Workshop and is with us today.

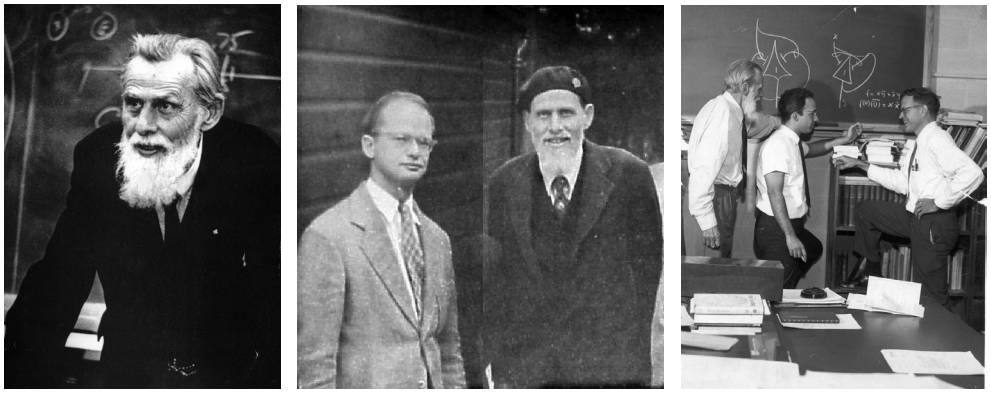

Figure 3. Warren S. McCulloch (left), with Walter Pitts (center), with Roberto Moreno Díaz Sr. and Louis Sutro.

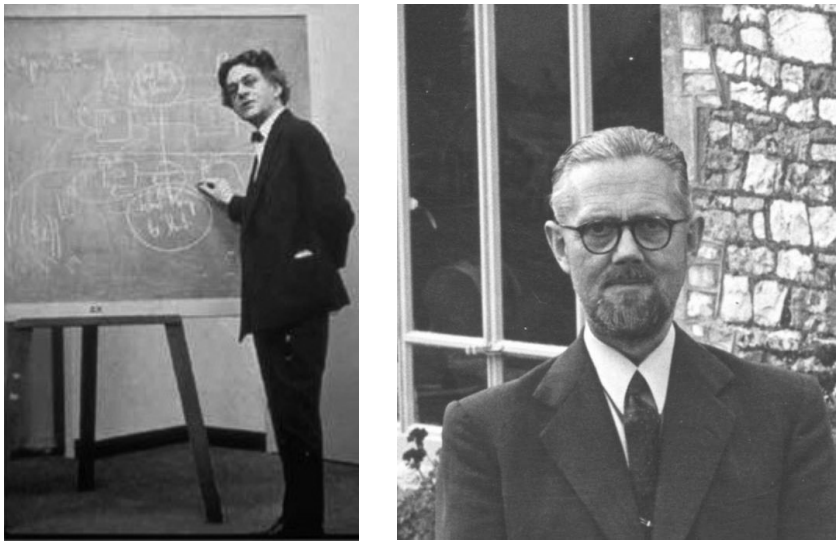

Figure 4. Gordon Pask (left) and Ross Ashby.

3.1 Uncertainty by complexity

In everyday's life we face events that take place in very restricted ranges of lengths, masses and times. It is thus inconceivable, on the grounds of sole human experience, the "perception" of lengths (see table 1) ranging from the distance 2×10^{22} m of the closest nebula, Andromeda, to 5×10^{-11} m, the radius of hydrogen atom.

Table 1. Lengths (m).

Distance of closest nebula (Andromeda)	2×10^{22}
Radius of our galaxy	6×10^{19}
Distance of closest star (Alfa Centauri)	$4{:}3 \times 10^{16}$
Mean radius of Pluto's orbit	$5{:}9 \times 10^{12}$
Radius of Sun	$6{:}9 \times 10^{8}$
Height of Mount Everest	$8{:}9 \times 10^{3}$
Man's mean height	$1{:}8 \times 10^{0}$
Thickness of an overhead transparency sheet	1×10^{-4}
Size of the Polio virus	$1{:}2 \times 10^{-8}$
Radius of Hydrogen atom	5×10^{-11}
Effective radius of proton	$1{:}2 \times 10^{-15}$

What about *masses* ? In this case we face values that, expressed in kilograms, to our dismay have order of magnitudes ranging between 10^{41} to about 10^{-30}. (See table 2.) Similar is the situation concerning the dimension "time" and our total inability to "metabolize" the duration of the life of an elementary particle (for instance of the order of 10^{-14} seconds) or 10^{18} seconds, expressing the estimated age of the Universe. (See table 3.)

Table 2. Masses (Kg)

Our galaxy	2.2×10^{41}
Sun	2×10^{30}
Earth	6×10^{24}
Luna	7.4×10^{22}
Water of all Oceans	1.4×10^{21}
Cruise liner	7.2×10^{7}
Elephant	4.5×10^{3}
Man	7.3×10^{1}
One grape	3×10^{-3}
Grane of dust	2.3×10^{-10}
Virus	6.7×10^{-13}
Penicillin molecule	5×10^{-17}
U^{238} atom	4×10^{-25}
Electron	9.1×10^{-31}

Table 3. Times (s)

Age of Universe	1.0×10^{18}
Age of Earth	1.3×10^{17}
Age of Cheope's pyramid	1.5×10^{11}
Mean life of a person	2.0×10^{9}
Earth's revolution period (1 year)	3.1×10^{7}
Earth's rotation period (1 day)	8.6×10^{4}
Neutron's mean life	7.0×10^{2}
Heart beat period	8.0×10^{-1}
Tuning fork's period (*A, La*)	2.3×10^{-3}
Muon's mean life	2.2×10^{-6}
Microwave oscillation period (*3cm*)	1.0×10^{-10}
Mean life of neutral pion	2.2×10^{-16}
Oscillation period of a 1 - *MeV* γ ray	4.0×10^{-21}

The above remarks stress that we are able to get the feelings of physical dimensions in a very restricted ranges of values. Still, all quantities mentioned above are uniquely and precisely expressed by exact numbers. However, the amount of immediately perceivable information conveyed to us by such numbers is extremely poor or, equivalently, extremely large is the amount of uncertainty carried by them. Another quite surprising discovery takes place when we refer to the well-known notion of n! and look at the growth of it as n moderately increases. Indeed, $2! = 2$, $4! = 24$, $7! = 5040$, and so on. However, already $9!$ is close to a half million, $13!$ is over six billions and $20!$ is greater than a billion of billions. (See Table 4, reminding us of a "Christmas Tree", and Table 5 in which, as customary, for instance the notation $e + 118$ indicates that the number $7{:}156945\cdots365$ must be multiplied by 10^{118} to yield $80!$)

Note that from the view point of the numerical representation everything is precise and uniquely determined. Still, the "information content" of the above numbers fades away as far as our pesonal perception is concerned.

Hence, a kind of "uncertainty by dimension" is seen to emerge, despite the absolute absence of uncertainty by "representation". This is, in my view, one of those cases falling within the more general area of what I like to call "uncertainty by complexity". By such wordings I refer to those situations that, though precisely described in quantitative terms, do not yield any directly perceivable information. Some other examples will be provided hereafter.

3.2 The Ornstein-Uhlenbeck process

As is well-known, in 1828 in the "Philosophical Transactions" ([1]) appeared a paper by Robert Brown (see Fig. 5) in which the existence of a very peculiar and unsuspected type of motion of particles in water, discovered the year before, was described.

The first explanation of the physical origin of such a motion, ever since denominated "Brownian motion" was proposed by Einstein in 1905. Successively, refinements of Einstein's theory were obtained by several mathematicians and physicists. Here

we limit ourselves to referring to the work by G.E. Ornstein ed L.S. Uhlenbeck. In it, a mathematical model was proposed according to which the particles underlying Brownian motion were viewed as subject to a stochastic diffusion process such that the density $U(x, t)$ of particles at each point x and at each instant t was assumed to satisfy the following

Table 4. Factorial

$n! = 1 \cdot 2 \cdot 3 \cdots\cdots n$

0!	1
1!	1
2!	2
3!	6
4!	24
5!	120
6!	720
7!	5040
8!	40.820
9!	362.880
10!	3628.800
11!	39.916.800
12!	479.001.600
13!	6.227.020.800
14!	87.178.291.200
15!	1.307.674.368.000

Table 5. Factorial

20!	2,432902008176640e+018
30!	2,652528598121927e+032
40!	8,159152832478897e+047
50!	3,041409320171298e+064
60!	8,320987112741137e+081
70!	1,197857166996979e+100
80!	7,156945704626365e+118
90!	1,485715964481719e+138
100!	9,332621544394454e+157
150!	5,713383956446549e+262
170!	7,257415615307826e+306

THE

PHILOSOPHICAL MAGAZINE

AND

ANNALS OF PHILOSOPHY.

[NEW SERIES.]

SEPTEMBER 1828.

XXVII. *A brief Account of Microscopical Observations made in the Months of June, July, and August, 1827, on the Particles contained in the Pollen of Plants; and on the general Existence of active Molecules in Organic and Inorganic Bodies. By* Robert Brown, *F.R.S., Hon. M.R.S.E. & R.I. Acad., V.P.L.S., Corresponding Member of the Royal Institutes of France and of the Netherlands, &c. &c.*

[We have been favoured by the Author with permission to insert the following paper, which has just been printed for private distribution.—Ed.]

THE observations, of which it is my object to give a summary in the following pages, have all been made with a simple microscope, and indeed with one and the same lens, the focal length of which is about $\frac{1}{3\frac{1}{2}}$nd of an inch*.

The examination of the unimpregnated vegetable Ovulum, an account of which was published early in 1826†, led me to attend more minutely than I had before done to the structure of the Pollen, and to inquire into its mode of action on the Pistillum in Phænogamous plants.

In the Essay referred-to, it was shown that the apex of the

* This double convex Lens, which has been several years in my possession, I obtained from Mr. Baneks, optician, in the Strand. After I had made considerable progress in the inquiry, I explained the nature of my subject to Mr. Dollond, who obligingly made for me a simple pocket microscope, having very delicate adjustment, and furnished with excellent lenses, two of which are of much higher power than that above mentioned. To these I have often had recourse, and with great advantage, in investigating several minute points. But to give greater consistency to my statements, and to bring the subject as much as possible within the reach of general observation, I continued to employ throughout the whole of the inquiry the same lens with which it was commenced.

Figure 5. Front page of the article containing the description of the observations by Robert Brown privately communicated in 1827.

equation:

$$\frac{\partial U}{\partial t} = \Big(-\frac{x}{\theta} + \mu\Big)\,\frac{\partial U}{\partial x} + \frac{\sigma^2}{2}\,\frac{\partial^2 U}{\partial x^2} \tag{1}$$

with θ, μ, and σ suitable parameters. Despite the simplicity of this equation, unsuspected mathematical difficulties arise when one asks for some closely related questions. For instance, when for the first time a particle will reach a specified point S starting from a given position y. (The so-called first-passagetime problem) The quantitative answer to such a simply stated question is very complicated. It is indeed possible to prove that the Laplace transform of the associated density function $g(S,t|y)$ is given by

$$g_\lambda(S|y) = \exp\Big[\frac{(y-\mu\,\vartheta)^2 - (S-\mu\,\vartheta)^2}{2\,\sigma^2\,\vartheta}\Big]\;\frac{D_{-\lambda\,\vartheta}\Big[\sqrt{\dfrac{2}{\sigma^2\,\vartheta}}\;(\mu\,\vartheta - y)\Big]}{D_{-\lambda\,\vartheta}\Big[\sqrt{\dfrac{2}{\sigma^2\,\vartheta}}\;(\mu\,\vartheta - S)\Big]}\,, \tag{2}$$

in which $D_\nu(\cdot)$ denotes the parabolic cylinder function defined as follows:

$$D_\nu(z) = \sqrt{\pi}\,2^{\nu/2}\,e^{-z^2/4}\Big[\frac{1}{\Gamma[(1-\nu)/2]}\;\Phi\Big(-\frac{\nu}{2},\frac{1}{2};\frac{z^2}{2}\Big) - \frac{\sqrt{2}}{\Gamma(-\nu/2)}\;z\;\Phi\Big(\frac{1-\nu}{2},\frac{3}{2};\frac{z^2}{2}\Big)\Big],$$

where

$$\Phi(a,c;x) = 1 + \sum_{n=1}^{\infty}\;\frac{a\,(a+1)\,\cdots\,(a+n-1)}{c\,(c+1)\,\cdots\,(c+n-1)}\;\frac{x^n}{n!},$$

$$\Gamma(z) = \int_0^{+\infty} e^{-t}t^{z-1}dt$$

are Kummer and Euler gamma functions, respectively. We are thus facing a problem that is formally solved once the function $g(S,t|y)$ has been obtained as the inverse of the above Laplace transform. However, this is not feasible. The apparent simplicity of formula (1) is indeed a carrier of absolutely no information in the sense that, though rigorously exact, it does not yield any hint that would help to guess outlook and features of the desired density $g(S,t|y)$. Neither, more helpful appear to be the

exact expressions of the moments of the first passage time obtained from (2), as shown by the expressions of the first three moments:

$$t_1(S|y) = \vartheta \left\{ \sqrt{\pi} \left[\varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_1\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] + \psi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \psi_1\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right\} \tag{3}$$

$$\begin{aligned} t_2(S|y) = {} & 2\,\vartheta\, t_1(S|y) \left[\sqrt{\pi}\, \varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) + \psi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & + 2\,\vartheta^2 \left\{ \sqrt{\pi}\, \ln 2 \left[\varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_1\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \right. \\ & \left. - \sqrt{\pi} \left[\varphi_2\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_2\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] - \psi_2\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) + \psi_2\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right\} \end{aligned} \tag{4}$$

$$\begin{aligned} t_3(S|y) = {} & 3\,\vartheta\, t_2(S|y) \left[\sqrt{\pi}\, \varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) + \psi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & + 6\,\vartheta^2\, t_1(S|y) \left[\sqrt{\pi}\, \ln 2\, \varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \sqrt{\pi}\, \varphi_2\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \psi_2\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & + 3\,\vartheta^3\, \sqrt{\pi} \left(\ln^2 2 + \frac{\pi^2}{12}\right) \left[\varphi_1\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_1\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & - 6\,\vartheta^3\, \sqrt{\pi}\, \ln 2 \left[\varphi_2\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_2\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & + 6\,\vartheta^3\, \sqrt{\pi} \left[\varphi_3\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \varphi_3\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right] \\ & + 6\,\vartheta^3 \left[\psi_3\left(\frac{S-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right) - \psi_3\left(\frac{y-\mu\,\vartheta}{\sigma\sqrt{\vartheta}}\right)\right], \end{aligned} \tag{5}$$

where we have set

$$\varphi_1(z) = \int_0^z e^{t^2}\, dt = \sum_{k=0}^{\infty} \frac{z^{2\,k+1}}{(2\,k+1)\,k!}$$

$$\varphi_2(z) = \sum_{n=0}^{\infty} \frac{z^{2n+3}}{(n+1)!\,(2n+3)} \sum_{k=0}^{n} \frac{1}{2k+1}$$

$$\varphi_3(z) = \sum_{n=0}^{\infty} \frac{z^{2n+5}}{(n+2)!\,(2n+5)} \sum_{k=0}^{n} \frac{1}{2k+3} \sum_{j=0}^{k} \frac{1}{2j+1}$$

and also

$$\psi_1(z) = 2\int_0^z du\, e^{u^2} \int_0^u dv\, e^{-v^2} = \sum_{n=0}^{\infty} \frac{2^n}{(n+1)\,(2n+1)!!}\, z^{2n+2}$$

$$\psi_2(z) = \sum_{n=0}^{\infty} \frac{2^n z^{2n+4}}{(2n+3)!!\,(n+2)} \sum_{k=0}^{n} \frac{1}{k+1}$$

$$\psi_3(z) = \sum_{n=0}^{\infty} \frac{2^n z^{2n+6}}{(2n+5)!!\,(n+3)} \sum_{k=0}^{n} \frac{1}{k+2} \sum_{j=0}^{k} \frac{1}{j+1}.$$

Equation (3) yields the mean value of the first passage time, from (3)and (4) one obtains the variance Var $(S|t) = t_2 - t_1^2$, and , finally, (5) allows to calculate the asymmetry coefficient $\Sigma(S|y) = t_3(S|y)/\left[\mathsf{Var}(S|y)^{3/2}\right]$. We stress that we are again facing exact expressions whose inspection does not provide any sort of useful or understandable information. In conclusion, we are offered here one more instance of "uncertainty by complexity ".

4. Uncertainty by representation

Consider the sequence

$$3,7,3,0,9,\ \ 5,0,4,8,8,\ \ 0,1,6,8,8,\ \ 7,2,4,2,0,\ \ 9\ldots\ . \tag{6}$$

Can it be viewed as a "random" sequence of decimal digits? Probably YES, since all digits from 0 to 9 are involved and no clear evident presence of regularities emerges. A similar remark also holds for the sequence of binary numbers

$$1,0,1,1,0,\ \ 1,0,1,0,0,\ \ 0,0,0,1,0,\ \ 0,1,1,1,1,\ \ 0,\ldots, \tag{7}$$

whereas the sequences

$$1,1,1,1,1,\ \ 1,1,1,1,1,\ \ 1,1,1,1,1,\ \ 1,1,1,1,1,\ \ 1,\ldots, \tag{8}$$

and

$$0,1,2,3,4,\ \ 5,6,7,8,9,\ \ 0,1,2,3,4,\ \ 5,6,7,8,9,\ \ 0,\ldots \tag{9}$$

evidently exhibit regularity features so that for both of them it would be unreasonable to talk about randomness whatever meaning one may wish to associate to such a word. Actually, (6) is the sequence of the $\sqrt{2}$ digits of the decimal representation of p2, in the positions from the tenth to the thirtieth after dot ($\sqrt{2}$=1.414213562 373095048801688724209698078569 6. . .), while (7) is extracted from the binary representation of $\sqrt{2}$. However, (6) and (7), quite independently of their origin, could as well be viewed as generated via 21 independent throws of a hypothetical 12-faceted "die" (better, by a regular dodecahedral "die" with a suitable interpretation of the 12 possible results of each throw), just alike sequences (8) and (9). In other words, each one of the above sequences could well be viewed as generated by the outcomes of 21 throws of this hypothetical dodecahedric die, so that each of such sequence would have probability 10^{-21} of occurrence. Neither a slightly biased die would significantly change such probabilities. In conclusion, there is no way to establish a *priori*, by looking at these sequences, whether they have been generated by throwing a die, whether the die was biased or whether the successive throws were independent.

Common sense suggests that it should be reasonable to identify "randomness" with the absence of regularities. With this in mind, one could then again ask whether the mathematical object consisting of the sequence (6) of the decimal digits that provide the decimal representation of $\sqrt{2}$ is a good candidate to be viewed as random, or not.

The fact is that here we are meeting what I feel reasonable to call "uncertainty by representation". This appears even more clearly justified after noting that a different type of representation may destroy the irregularity or the assumed randomness of a sequence of numbers. This is for instance highlighted by the specific case of p2. Indeed, a well-known theorem states that the square root of an integer number admits a continuous fraction representation consisting of a sequence of integers a_0, a_1, a_2,..., that is periodical after the first term:

$$a_0 + \cfrac{1}{a_1 + \cfrac{1}{a_2 + \cfrac{1}{a_3 + \cfrac{1}{\ddots}}}}.$$

In the case of $\sqrt{2}$ one has:

$$1 + \cfrac{1}{2 + \cfrac{1}{2 + \cfrac{1}{2 + \cfrac{1}{\ddots}}}}$$

so that the corresponding representative sequence is

$$1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2 \ldots$$

in which no longer elements of irregularity or randomness are present.
Out of the many interesting problems concerning the level of irregularity of certain ubiquitous mathematicalconstants we mention the following: To establish which of the trascendental numbers

$$\pi = 3,14159\ 26535\ 89793\ 23846\ 2643\ldots$$
$$e = 2,71828\ 18284\ 59045\ 23536\ 0287\ldots$$
$$e^{\pi} = 23,14069\ 26327\ 79269\ 00572\ 9088\ldots$$
$$\pi^{e} = 22,45915\ 77183\ 61045\ 47342\ 7153\ldots$$
$$\gamma := \lim_{n\to\infty}\left(1 + \frac{1}{2} + \frac{1}{3} + \cdots + \frac{1}{n} - \log n\right) = 0,57721\ 56649\ 01532\ 86060\ 6512\ldots$$

should be considered as "most random". In this respect, various computations ([10]) have indicated that for instance " π is more "random than e"

5. Determinism and uncertainty

Consider a population of individuals characterized by discrete reproduction times $\tau_1, \tau_2, \ldots$ that, after the choice of a suitable "clock" we shall identify with the instants $1, 2, \ldots$. Let 0 denote the initial observation time and let N_i be the number of individuals present at time i. The simplest, somewhat unrealistic, well-known mathematical model for the population growth is

$$N_{i+1} = cN_i \quad (i = 0, 1, 2, \ldots), \tag{9}$$

where N_0 denotes the initial number of individuals in the population. Note that (10) can equivalently be written as

$$\frac{N_{i+1} - N_i}{N_i} = \lambda \tag{10}$$

where $\lambda \equiv c - 1$ denotes the constant population growth rate.

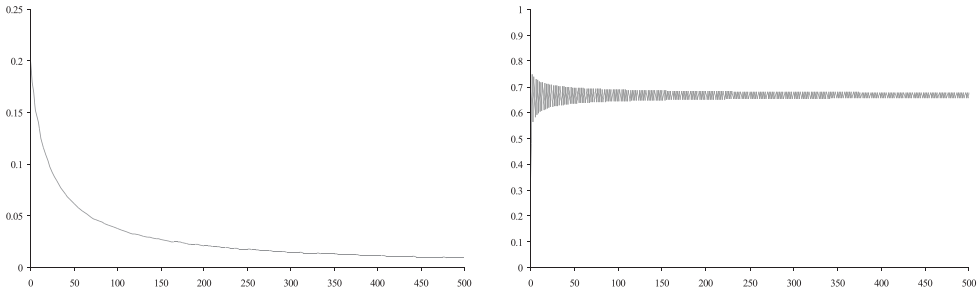

Figure 6. Plots of $x_{n+1} = x_n(1 - x_n)$, $x_0 = 0.2$ (left) and of $x_{n+1} = 3x_n(1 - x_n)$, $x_0 = 0.2$ (initial value hardly visible here).

Such a model (Malthusian growth) implies that the population size exponentially increases as the number of generations increases. However, in any real situation the limitation of environmental resources available to the population, as well as competition, predation, accumulation of toxic substances, etc., limit the growth process,

so that the number of individuals sharing the habitat cannot exceed a value, say N_{max}, depending on the considered species and on the environmental characteristics. The above equation should consequently be modified. For instance, we may set

$$N_{i+1} = cN_i\,(N_{max} - N_i) \tag{12}$$

implying a linear decrease of the growth rate $\rho(N_i) \equiv c(N_{max} - N_i) - 1$ as N_i approaches N_{max}.
As is customary, it is convenient to normalize the involved quantities in a way to be able to refer to the finite interval (0, 1) by setting

$$\begin{cases} x_i = \dfrac{N_i}{N_{max}}, \qquad (i = 0, 1, 2, \ldots) \\ \\ \alpha = cN_{max} \end{cases} \tag{13}$$

Hence,

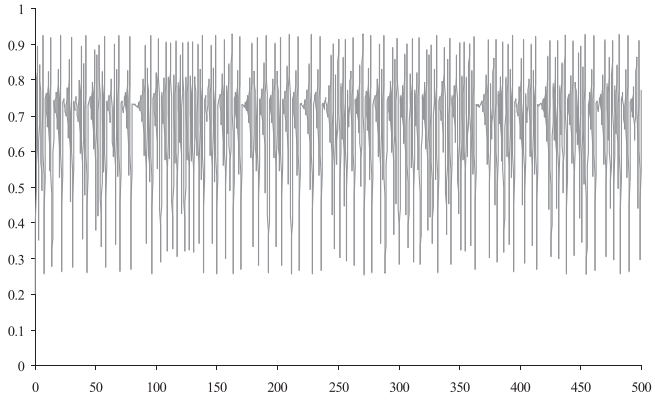

Figure 7. Plot of $x_{n+1} = 3.7x_n(1 - x_n)$, $x_0 = 0.2$ (initial value hardly visible here).

$$x_{i+1} = \alpha x_i(1 - x_i) \qquad (i = 0, 1, 2, \ldots) \tag{14}$$

is now the transformed growth equation in which the environmental "carrying capacity" is unit. Making use of (13), or graphically as sketched in Fig. 8, after spe-

cifying the initial value $x_0 = N_0/N_{max}$, one can iteratively calculate the successive (normalized) population sizes:

$$\begin{cases} x_1 = \alpha x_0(1 - x_0) \\ x_2 = \alpha x_1(1 - x_1) \\ \dots \\ x_n = \alpha x_{n-1}(1 - x_{n-1}) \\ \dots \end{cases} \tag{15}$$

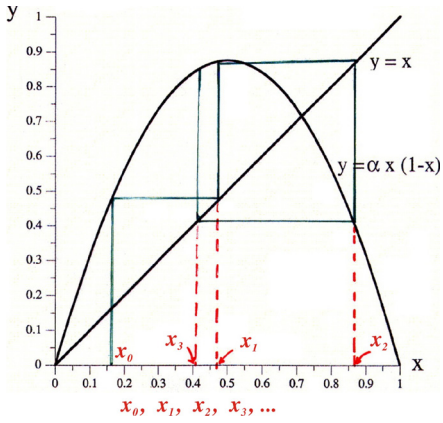

Figure 8. Geometrical method for determining the population sizes.

Hence, the obtained values x_1, x_2,... are the (normalized) number of individuals present in generations 1, 2, ... starting from x_0 initially present individuals. Note that equation (14) admits the equilibrium point $\rho = 1 - 1/\alpha$. It is interesting to monitor the behavior of x_n for some values of α. For instance, $\alpha = 1$ implies that the equilibrium point is 0, so that the population monotonically goes to extinction (left of Fig. 6). For $\alpha = 3$, the population decreases towards the equilibrium point $\rho = 2/3$ via damped oscillations (right of Fig. 6). Similarly one can monitor the time course of the population size for other values of parameter α. It is interesting to point out in this respect that a new, surprising kind of behavior emerges for certain choices of α. For instance, $\alpha = 3.7$, as n increases x_n tends to the equilibrium point $\rho = 0.7297$ in a sort of "chaotic" way, in the sense that the sequence of values x_1, x_2, ... appears to be really random, as shown by Fig. 7. By inspection of such a figure, it is for instance

impossible to establish whether the observed values are the result of a stochastic process or if, as we know, they have been obtained via an equation describing the rigorously deterministic evolution of a system.

In conclusion, this is an example showing the existence of situations in which "uncertainty" is a consequence, so to say, of the very nature of certain solutions of equations derived to describe the evolution of systems subject to strictly deterministic laws (see also [7]).

6. Probabilistic certainty

Quite natural is to view as uncertain the possible outcomes or results generated in a probabilistic context. Are we sure about the occurrence of an event such as the outcome of the throw of a die, or the draw of a card from a well shuffled deck? Of course no, as these are situations governed by the "empirical law of large numbers". Still, against intuition, the uncertainty level of certain random phenomena can progressively fade out, to lead eventually to situations of "practical" certainty. A first, simple example is provided by the so-called problem of the birthdays coincidence: *What is the probability* P_n *that all of* n $(n < 365)$ randomly chosen persons have different birthdays? A simple argument, under the reasonable equal probability assumption, yields (here we do not consider leap years):

$$P_n = \frac{365 \times 364 \times \cdot \times (365 - n + 1)}{(365)^n}. \tag{16}$$

Hence, the probability Q_n that at least 2 of the n persons have the same birthday is $Q_n \equiv 1 - P_n$.

Table 6. Probabilities of birthdays coincidence. For 60 persons this exceeds 99%

n	$1 - P_n$
1	0.000000
5	0.027139
10	0.116950
15	0.252900
20	0.411440
25	0.568700
30	0.706320
35	0.814380
40	0.891230
45	0.940976
50	0.970374
52	0.978005
54	0.983877
56	0.988332
58	0.991665
59	0.992990
60	0.994123

Table 6 indicates that in the case of only 50 persons the probability of coincidence is over 97%, while it exceeds 99% in the case of 60 persons. (Neither these probabilities would change much if someone lies about his birthday!) Fig. 6 is an illuminating plot of such probability of coincidence.

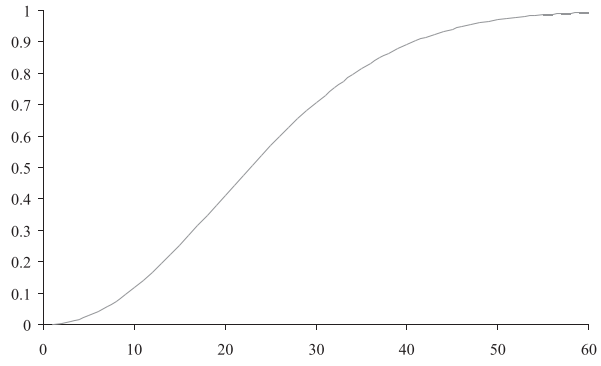

Figure 9. Plot of the probability of birthdays coincidence as a function of the number of persons.

Quite interesting is also the following example: *What is the probability* P_n *that by inserting at random* n *letters directed to different people into as many pre-addressed envelops, at least one of them is delivered to the right person?* Against intuition, it can be shown that the highest uncertainty level (0:5 corresponding to the case of only 2 letters) is slightly reduced in the case of 3 letters, and that not much is gained in randomness as the number of letters progressively increases. Indeed, there results

$$P_n = \sum_{k+1}^{n} \frac{(-1)^{k+1}}{k!}$$

with

$$\lim_{n\to\infty} P_n = 1 - e^{-1} = 0.6321205.$$

Table 7. indicates the rapid stabilization of the values of P_n as n increases.

n	P_n
1	1.0
2	0.5
3	0.6666666
4	0.6250000
5	0.6333333
6	0.6319444
7	0.6321428
8	0.6321180
9	0.6321208
10	0.6321205

Table 7. Table of coincidences

We are thus facing two situations in which practical certainties emerge in contexts regulated by purely random laws ($Q_n \simeq 1$ for $n > 60$ and $P_n \simeq 1 - e^{-1}$ for $n > 9$).

One more example showing that sure results may emerge out of situations characterized by intrinsic uncertainty is the so-called Parrondo paradox, that can be stated as follows: *The participation of a player to a game consisting of two alternate individually losing games can turn out to be winning* (surely quite in contrast to in-

tuition!). [2] To sketch this paradox, let us assume that a player possessing an initial capital X_0 (in arbitrary currency units) plays a game consisting of two randomly alternating games A e B. For simplicity, we assume that each game consists of flipping an unfair coin with the following rule: The payoff is 1 if the outcome is Head, and -1 (namely the player loses 1) if the outcome is Tail. In addition, again for simplicity, we assume that the two games are played in succession in random order, as determined by a generator of random numbers uniformly distributed in (0; 1).We shall arrange things in such a way that $P(A) = \pi_A$ and $P(B) = 1 - \pi_A$ are the probabilities of playing games A and B, respectively.

Assume now that games A and B are characterized as follows.

GAME A

Let

$$P(H) = 0,5 - \epsilon := p_A$$
$$P(T) = 0,5 + \epsilon := 1 - p_A$$

be the probabilities of Head and Tail, respectively, where denotes a suitably chosen positive real number.

GAME B

This, in turn, consists of two alternating games that are specified as follows. Let X_n be the the player's capital at the time of n-th repetition of the game; then, Head and Tail probabilities are taken according to the following recipe: If $X_n \bmod 3 \neq 0$ then,

$$\begin{cases} P(H) = 0,75 - \epsilon := p_{B_1} \\ P(T) = \ 0,25 + \epsilon := 1 - p_{B_1}. \end{cases} \tag{17}$$

2 Hereafter we refer to losing and winning games on the average.

If, instead, $X_n \bmod 3 = 0$, then

$$\begin{cases} P(H) = 0,10 - \epsilon := p_{B_2} \\ P(T) = \ 0,90 + \epsilon := 1 - p_{B_2}. \end{cases} \tag{18}$$

Let us separately analyze the features of games A and B.

GAME A

In the presence of Game A alone, $P(A) = \pi_A = 1$. To be specific, as an example let us set $\epsilon = 0,005$ and let us denote by V_i^A $(i = 1, 2, ...)$ the player's capital at the i-th bet. This is a random variable whose probability distribution is:

$$V_i^A = V^A = \begin{pmatrix} -1 & 1 \\ 0,5 + \epsilon & 0,5 - \epsilon \end{pmatrix}.$$

It is easy to calculate the average payoff:

$$E\left(V^A\right) = -2\epsilon \tag{19}$$

and to realize that X_n satisfies

$$X_n = x_0 + \sum_{i=1}^{n} V_i^A. \tag{20}$$

Hence, X_n can be viewed as a random walk starting at x_0. The average capital at n-th bet is thus:

$$E(X_n) = x_0 + nE(V^A) = x_0 - 0,01n \tag{21}$$

where use of (19) and of (20) has been made. In conclusion, Game A produces steady losses in time, i.e. it is is a losing game.

GAME B

In the presence of Game B alone, $\pi_B \equiv P(B) = 1$. Hence, rules (17)and (18) must be applied. Set again $\epsilon = 0,005$. Then, for $i = 1, 2,...$ there results:

$$V_i^{B_1} = V^{B_1} = \begin{pmatrix} -1 & 1 \\ 0,25 + \epsilon & 0,75 - \epsilon \end{pmatrix}$$

$$V_i^{B_2} \equiv V^{B_2} \sim \begin{pmatrix} -1 & 1 \\ 0,90 + \epsilon & 0,10 - \epsilon \end{pmatrix}.$$

Hence,

$$\begin{aligned} E\left(V^{B_1}\right) &= 0,5 - 2\epsilon \\ E\left(V^{B_2}\right) &= -0,8 - 2\epsilon. \end{aligned} \tag{22}$$

It is not difficult to convince oneself that capital X_n can now be expressed as

$$X_n = x_0 + \sum_{i=1}^{n} \left(V_i^{B_2} I_{X_{i-1} \bmod 3=0} + V_i^{B_1} I_{X_{i-1}, \bmod 3=1} + V_i^{B_1} I_{X_{i-1} \bmod 3=2} \right).$$

To obtain its mean, the probabilities of $\{X_i \bmod 3 = k\}$ for $k = 0, 1, 2$ must be calculated. To this purpose, we must resort to some technicalities, and formalize our problem into mathematical terms by introducing a 3-state Markov chain, with states 0, 1, 2 representing the classes $[0]_3 \equiv X_i \bmod 3 = 0$, $[1]_3 \equiv X_i \bmod 3 = 1$ and $[2]_3 \equiv X_i \bmod 3 = 2$, respectively. By virtue of (17) e (18), the corresponding transition probabilities are seen to satisfy

$$\begin{bmatrix} p_0(n+1) \\ p_1(n+1) \\ p_2(n+1) \end{bmatrix}^T = \begin{bmatrix} p_0(n) \\ p_1(n) \\ p_2(n) \end{bmatrix}^T \begin{bmatrix} 0 & p_{B_2} & 1 - p_{B_2} \\ 1 - p_{B_1} & 0 & p_{B_1} \\ p_{B_1} & 1 - p_{B_1} & 0 \end{bmatrix}$$

or, explicitly:

$$\begin{bmatrix} p_0(n+1) \\ p_1(n+1) \\ p_2(n+1) \end{bmatrix}^T = \begin{bmatrix} p_0(n) \\ p_1(n) \\ p_2(n) \end{bmatrix}^T \begin{bmatrix} 0 & 0,10-\epsilon & 0,90+\epsilon \\ 0,25+\epsilon & 0 & 0,75-\epsilon \\ 0,75-\epsilon & 0,25+\epsilon & 0 \end{bmatrix}. \tag{23}$$

Since the maximum modulus eigenvalue of the transition matrix is 1, the stationary distribution exists. Hence, setting $P([0]_3) = p_0$, $P([1]_3) = p_1$, $P([2]_3) = p_2$, system (23) becomes

$$\begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix}^T = \begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix}^T \begin{bmatrix} 0 & 0,10-\epsilon & 0,90+\epsilon \\ 0,25+\epsilon & 0 & 0,75-\epsilon \\ 0,75-\epsilon & 0,25+\epsilon & 0 \end{bmatrix}, \tag{24}$$

whose solution is:

$$\begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix} = \begin{bmatrix} 0,383612 \\ 0,154281 \\ 0,462108 \end{bmatrix}. \tag{25}$$

During its evolution, the Markov chain converges to the three stationary states characterized by the probabilities (25). Therefore, one must expect that the average capital decreases roughly in a linear fashion as the number of iteration of Game B increases:

$$E(X_n) \cong x_0 + n\left[E\left(V^{B_2}\right) \cdot p_0 + E\left(V^{B_1}\right) \cdot p_1 + E\left(V^{B_1}\right) \cdot p_2\right] \cong x_0 - 0,008695 \cdot n. \tag{26}$$

In conclusion, in the long run B is a losing game.

To summarize, when individually considered, both A and B are losing games.

Let us now go back to the initial problem, namely to the global game consisting of a random switching of games A and B. We can again resort to a 3-state Markov chain with states $[0]_3$, $[1]_3$ and $[2]_3$, whose transition matrix M is

$$\begin{bmatrix} 0 & \pi_A p_A + \pi_B p_{B_2} & \pi_A(1-p_A) + \pi_B(1-p_{B_2}) \\ \pi_A(1-p_A) + \pi_B(1-p_{B_1}) & 0 & \pi_A p_A + \pi_B p_{B_1} \\ \pi_A p_A + \pi_B p_{B_1} & \pi_A(1-p_A) + \pi_B(1-p_{B_1}) & 0 \end{bmatrix}.$$

The (existing) stationary distribution $P([0]_3) = p_0$, $P([1]_3) = p_1$, $P([2]_3) = p_2$ is obtained by solving

$$\begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix}^T = \begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix}^T M, \tag{27}$$

after specifying π_A. As a concrete case, let us make games A and B equally likely by setting $\pi_A = 0,5$. Then,

$$\begin{pmatrix} p_0 \\ p_1 \\ p_2 \end{pmatrix} = \begin{pmatrix} 0,345070 \\ 0,254108 \\ 0,400822 \end{pmatrix}.$$

Recalling (19) and (22), the capital at the $n-th$ bet can be represented as follows:

$$X_n = x_0 + \sum_{i=1}^{n} \left(V_i^A I_A + V_i^{B_2} I_{X_{i-1} \bmod 3=0} + V_i^{B_1} I_{X_{i-1}, \bmod 3=1} + V_i^{B_1} I_{X_{i-1} \bmod 3=2} \right).$$

Thus, for $i \gg 1$ there holds:

$$\begin{aligned} E(X_n) &\cong x_0 + n \left[E\left(V^A\right) \cdot \pi_A + E\left(V^{B_2}\right) \cdot p_0 + E\left(V^{B_1}\right) \cdot p_1 + E\left(V^{B_1}\right) \cdot p_2 \right] \\ &\cong x_0 + 0,0015704 \cdot n. \end{aligned}$$

This result is surprisingly in contrast with intuition, and thus paradoxical, in that the random alternation of the two considered individually losing games has led us to an overall winning game. Once again, a deterministic result (the average win) has stemmed out of a strictly random context. In other words, out of the uncertainty of

the results of each of the two games, a result that can be called "sure" has emerged: The increase of the average capital as the number of bets increases.

7. Uncertainty by structure

It is not difficult to find situations from the realm of computational biology and bioinformatics that immediately exhibit behaviors characterized by high uncertainty levels. Two specific and fascinating examples are offered by the structures and working mechanisms finalized to accomplish functions that are essential for a large part of living organisms, synthesized by the two words "brain" and "muscles": Thinking processes and ability to move. Hereafter, we shall provide a bird's eye view of some of the surprising features that characterize the above-mentioned functions in a general uncertainty context.

7.1 Uncertainty by structure

As is well-known, nervous systems are made of a large number of cells, the neurons, interconnected in a way to form structurally very complicated networks whose detailed "cartography" is still far from having been specified. The electric signals that travel in these networks are the carriers of the information that neurons send off, receive and process. They are ultimately responsible for the so-called "thinking processes" and for the reactions of organisms to the stimulations received from the environment.

Human nervous system includes some ten billion neurons, essentially located on a surface of about 1200 cm^2 (the brain cortex) wrapping a mass (encephalus) occupying a volume of about 1 liter, which implies a neuronal density of 10^7 cm^{-3}. A few more data: the volume of a neuron is about 10^{-7} cm^3, and is accompanied by a large variety of shapes; the "transmission line " (axon) that carries information from a neuron to other elements of the network, whose length varies between some tenth of a micron to about 1 meter, allows for electric signals propagation speeds ranging between 0.6 to 120 m/s; the neuron's body (soma) out of which the axon stems, though exhibiting a large variety of forms, has linear dimensions of the order of ten microns. Finally, during its activity a neuron can be thought of as a "physical gadget" having the power of 1 billionth watts.

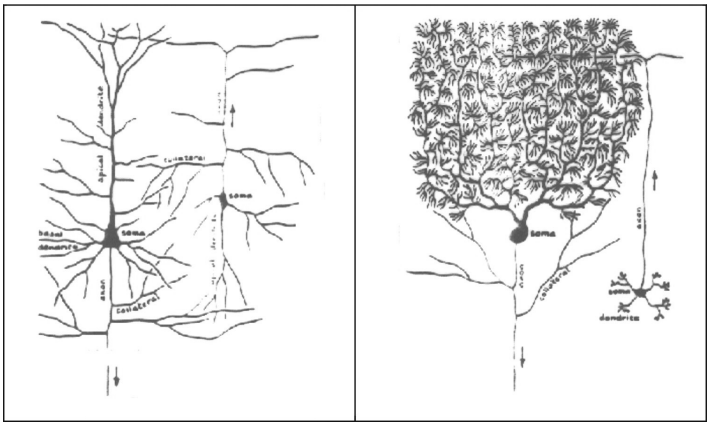

Figure 10. Different types of neurons. On the left a pyramidal cell and a cell of Martinotti in the cortex cerebri are depicted. Note the typical dendritic arborizations of the neuron on the right (Purkinje cell in the cortex cerebelli).

Fig. 10 shows in a pictorial way two different types of neurons in the brain (left) and in the cerebellum. It indicates the large degree of variability especially in the shapes of somas and of the dendritic arborizations; these act as "antennas" able to receive signals from other elements of the net. Fig. 11 is a sketch of a pair of interconnected neurons including some self-explained terminological indications.

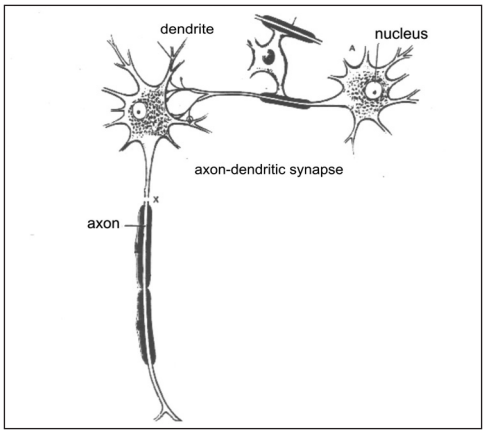

Figure 11. Some details of a pair of neurons.

Immagine now of interconnecting these 10 billion neurons to "construct" the network representing the nervous system, as pictorially shown by Fig. 12. We ask ourselves: How many distinct nets can be obtained with these neurons? We remark that in the case of only 100 neurons one obtains 2^{100}, namely about 10^{30}, distinct networks. If one wished to label each of them with a speed of 10 billion nets per second, the necessary time to accomplish this job would be 10^{20} seconds, which is about one thousand times longer than the estimated age of the Universe!

We are thus facing enormously and incredibly complex systems escaping any possibility of accurate descriptions, characterized by a large variability of shapes and by very small components.

In conclusion, in order to understand and to mimic the dynamics of such a system it would be necessary to write down and solve an astronomical number of coupled equations (for instance one equation for the description of the activity of each neuron); in addition, one should attain a detailed specification of network, which is far from being feasible on the grounds of the currently available neuroanatomic data.

This is a suggestive example of what I feel appropriate to denominate "uncertainty by structure".

To pinpoint the above remarks by an example, let us implement a classical approach by which the neuron is represented as a linear threshold element (see Fig. 13). It is thus a system having a certain number n of input lines along which travel signals X_1 ,X_2, ..., X_n incoming from other neurons or from the environment. These signals, due to the synapses S_1, S_2 ..., S_n, by some biochemical processes

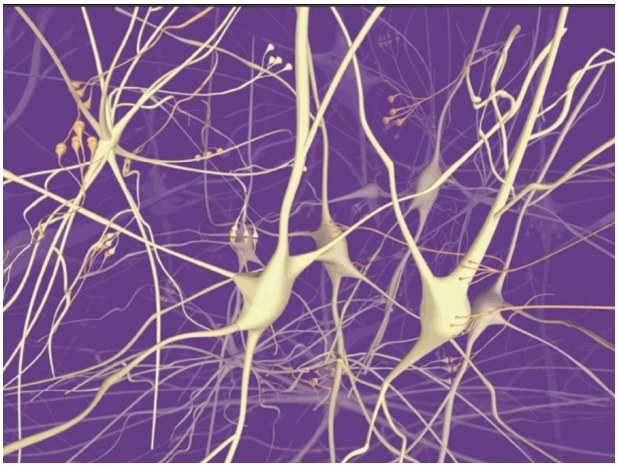

Figure 12. Representation of a fragment of neuronal net.

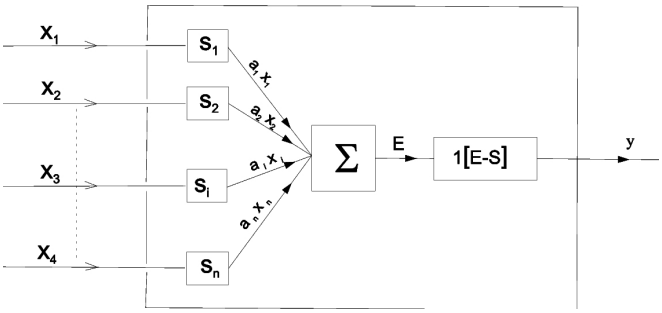

Figure 13. A neuron viewed as a linear threshold element.

are changed into excitatory and inhibitory signals a_1X_1, a_2X_2,..., a_nX_n that, acting on the cell body, are summed up to yield the total stimulation $E = \sum_{i=1}^{n} a_iX_i$. If this exceeds a characteristic value (the neuron's "firing threshold") the neuron releases an output signal y that, in turn, by traveling along the axon will reach the synaptic branches of other neurons, including, possibly, itself. If, instead, the total

stimulation is less than the threshold value, no output is produced by the neuron. In mathematical terms, we can thus write:

$$y = 1\left[\sum_{i=1}^{n} a_i X_i - S\right],$$

where $1(z)$ denotes Heaviside unit step function:

$$1(z) = \begin{cases} 1, & z > 0 \\ 0, & z \leq 0. \end{cases}$$

With such a background, let us refer to a net made out with such neurons that, as shown in [9], we shall represent by the diagram of Fig. 14. In such a net there are four input neurons i_1, i_2, i_3, i_4 (neurons

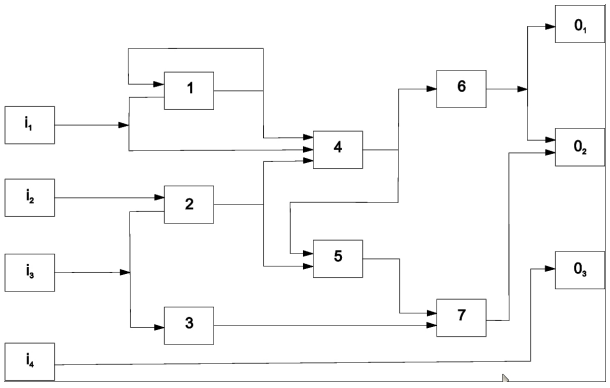

Figure 14. An example of a small neural network: input neurons are denoted by i_k's, output neurons by o_i's. The remaining neurons are the so-called internal or central neurons.

affected by environmental stimulations) and three output neurons o_1, o_2, o_3, representing, for instance, neurons acting on the motor system of the organism. The signals coming from input neurons generate the responses of the organism: these consist of the signals produced by the output neurons under the effect of the activities of the "central" neurons (seven neurons in Fig. 14). Under the further simpli-

fication that the net's evolution is synchronous in the sense that there exists a sort of internal clock by virtue of which time consists of a discrete sequence 1, 2, ... , n, ... of instants, the description of the network's dynamics requires to solve the highly nonlinear system of the $N + n$ equations

$$u_k(p+1) = 1\left[\sum_{h=1}^{N} a_{kh}u_h(p) + \sum_{h=1}^{m} b_{kh}i_h(p) - S_k\right] \quad (k = 1, \ldots, N)$$

$$o_k(p+1) = 1\left[\sum_{h=1}^{N} c_{kh}u_h(p) + \sum_{h=1}^{m} d_{kh}i_h(p) - S'_k\right] \quad (k = 1, \ldots, n)$$

that has been written down including the specification of the different types of neurons: input neurons (i_k), $(k = 1, 2, \ldots, m)$, internal neurons (u_s), $(s = 1, 2, \ldots, N)$;and output neurons (o_l), $(l = 1, 2, \ldots, n)$: Coupling coefficients are indicated as follows: a_{kh} (internal neuron h - internal neuron k), b_{hk} (internal neuron h - input neuron k), c_{hk} (output neuron h - central neuron k) and d_{hk} (output neuron h - input neuron k). It is easy to guess what kind of difficulties would be met when realistically dealing with networks comprising thousand or million neurons. In addition, if time is for instance measured in multiples of the "synaptic delay" τ , the equations describing the evolution of an "autonomous network" (namely a network without input and output neurons) should be written in the following form:

$$u_h(t+\tau) = 1\left[\sum_{k=1}^{N}\sum_{r=0}^{l(h)} a_{hk}^{(r)}u_k(t - r\tau) - S_h\right] \qquad (h = 1, 2, \ldots, N;\ k = 1, 2, \ldots, N),$$

where $a_{hk}^{(r)}$ denote the coupling coefficients (generally time-dependent in order to be able to account for phenomena such as "adaptation" or "learning"). Note that the delays between the release of a signal and its effect on the neuron on which it impinges, due to the different fibres lengths, are considered. The above-written equations thus assume that the simplifying assumption of "adiabatic approximation" has been made($a_{hk}^{(r)} = a_{hk}$) and that the signal transmission is instantaneous, the only present delay being the synaptic delay τ .

Without elaborating further on the structural uncertainty that stems out of brain-related mathematical considerations, a few remarks are in order on non-structural, but rather dynamical, aspects that contribute to increase even more the level of uncertainty related to such an area.

Nervous systems are prime examples of systems with collective dynamics. Even at the most primitive levels there are sensory-motor interactions and the higher one goes on the evolutionary ladder, the more one finds cell assemblies and regions tuned to circumscribed functions which must interact dynamically in a collective fashion in order to subserve the identity or one-ness of the organism. Thus, while there are universal features in nervous systems, different species have evolved different solutions which are best adapted to their ecological niche. We emphasize that the brain is a prototype of collective dynamical systems: Cooperation and competition occurring at different levels of neural organization, from molecules via neurons, synapses, neural networks to neural centers, are the key driving forces of brain dynamics. Studying such collective dynamical aspects of the spatio-temporal activity of single neurons, neural networks and neural systems, and their role in neural information processing, has attracted a lot of attention also in recent years. We expect contributions now not only for understanding the normal operation of specific neural systems, but also new and better mathematical models of neurological and psychiatric disorders, and models to foster brain-inspired computation and robotics. From a macroscopic, phenomenological level of study, one should also be able to pass to the consideration of subtended multiple microscopic phenomena.

In short, a brain should be viewed as organized into successive hierarchical levels ranging from the microscopic level (molecules, receptors, ion channels, synapses) to macroscopic level (nuclei, cortical areas, neuronal networks), and vice versa. The kind of possible inferences when passing in a "topdown" strategy to each successive level, namely moving from the macroscopic towards the microscopic, or vice versa by implementing a "bottomup" approach, are a fundamental matter for the study of complex biological systems, such as the brain.

From the above consideration, it clear emerges a picture that leads one to realize that neuronal transmission and brain function involve independent and/or coordinated activities of numerous agents, among which are ion channels and ion pumps.

Axonal and cytoplasmic transports of proteins and other classes of molecules are mostly directional, and rapid beyond passive diffusion. All these processes require input and usage of energy and are thus, performed and controlled by molecular motors. Just as a human being is made up of billions of interacting cells, each individual cell consists of billions of interacting molecules. Our aim is to understand biological processes also at the level of individual molecular interactions. Biological systems consist of large molecules like proteins and DNA and also small molecules that act as substrates and signals to drive and control the cellular processes. The activity of healthy and diseased cells is determined by complex interactions between these different molecules. Some molecules can cause illness whereas others (e.g. therapeutic drugs) can cure. A study of molecules in isolation is mandatory in order to be able to understand the basic mechanisms of disease as well as of normal function. In such a context, the two main research themes are cell motility and cell signaling.

Hereafter we shall outline some facts concerning muscle contraction, which is, among other things, also propedeutic to the locomotion, as a second example in which uncertainty originates from the complexity of the involved structures and from the context in which they operate. Figures 15 and 16 show the essentials of the levels of structural organization in a typical skeleton muscle and the innervation of some muscle fibres by a single motor nerve. It must be emphasized that the ability to move is a feature

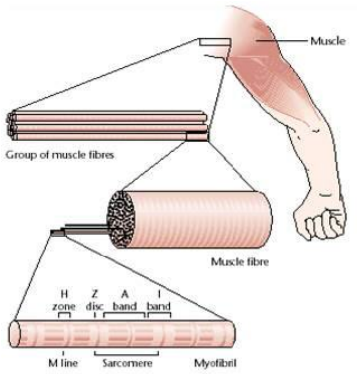

Figure 15. Sketch of the innervation of several muscle fibres by a single motor nerve to form a motor unit.

common to cells. Evolutionary processes gave origin to a variety of proteins able to generate forces and motion. Right this is the main role of protein motors that are essential for life: In their absence all cellular transports would indeed come to an irremediable stop and thus lead any organism to death.

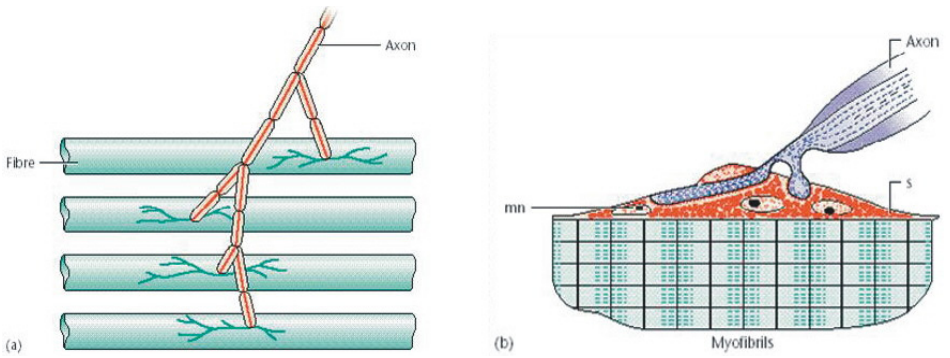

Figure 16. Levels of structural organization in a typical vertebrate skeletal muscle.

These proteins can be looked at as nanomotors that make use of the chemical energy released by a "fuel molecule" (ATP) to produce mechanical work. These motors are of two types: linear (myosins, kinesins, dineins) and rotating (flagellar motors in bacteria, ATPase). Linear motors produce sliding along specific filaments in specified directions; they are involved in muscles contractions and in transportation of materials in cells via idrolization of ATP with ensuing energy transfer due to the release of phosphor anions.

The forthcoming considerations concern the sliding process of Myosin II (a protein belonging to the so-called myosin family) over an actin filament. They are meant to offer some details on the way in which these protein motors transform into force, movement and mechanical work the chemical energy provided by ATP. Such "sliding machines" transform the input flux (consisting of free chemical energy and hydrolized ATP molecules) into the output flux in the form of the force necessary to determine the sliding process. Here the main questions are to establish (a) whether input and output of these molecular machines are rigidly coupled, and (b) whether a chemical reaction at the input always produces a unit of mechanical movement at the output.

The a priori difficulty in finding sure answers to these questions is due to the very context in which molecular motors operate: displacements, energies and times of the order of nanometers (1 nm = 10^{-9} m), piconewtons (1 pN = 10^{-12} N) and milliseconds (1 ms = 10^{-3} s). In short, the overall sliding consists of a sequence of steps, as sketched in the top of Fig. 19. The length, roughly constant, of a each step is equal to the distance (5:5 nm) between each pair of consecutive actin monomers. Under low load condition applied to an end point of the myosin consisting of a characteristic "head", most steps occur in the same direction, that we shall call "forward direction", and only a small fraction of them (about 10%) take place in the opposite, or "backward" direction. It is conceivable that, due the presence of some intermediate processes, a "loose coupling theory " is appropriate to explain the observed inputoutput relation. According to F. Oosawa (see Fig. 17), who was the first sustainer of the loose coupling theory and the responsible of the first experimental evidence of the bidirectional motion of the myosin, the available free energy is not significantly greater of the energy ($k_{\mathrm{B}}T \sim 4$ pN nm) of the thermal bath in which the sliding process takes place. Indeed, this molecular motor operates in the water at room temperature, and its structural units are not rigid and are sensible to thermal fluctuations. Actually, it appears that living cells have "discovered" a way to efficiently convert into movements small quantities of chemical energy via a mechanism that fruitfully harness the forces originated by the thermal molecular agitation.

Figure 17. F. Oosawa.

The final confirmation of the initially very controversial two-directional feature of the actin-myosin sliding process is a recent discovery due to T. Yanagida (v. Fig. 18) that was made available world wide by an article on an issue of Nature ([8]) whose front page shows Yanagida next to the title "Swimming against the tide". [3]

Figure 18. Front page of Nature, Vol. 408, pp. 764-766, (2000).

The extremely high uncertainty level that is exhibited by the operating modalities of so much complex structures appears to be further emphasized when one realizes that certain macroscopically very simple and familiar acts are in fact the final result of a myriad of synergetically cooperating mechanisms. For instance, in order to generate a force of 10 N, such as the one necessary to hold a 10 Kg heavy object in equilibrium against gravity, some 10 trillions of simultaneously working molecular motors of the kind described above are necessary.

This is a paradigmatic examples pinpointing the unexpected degree of complexities of structures and related operating mechanisms that emerge when

3 The author has had the privilege of collaborating with Yanagida and his team thanks to an international cooperation program between the Japan Science and Technology Corporation and Frederic II Naples University. (Seehttp://www.jst.go.jp/icorp/english/past proj/single-e.html).

universally familiar actions, such as thought processes or mechanical movements, are considered in connection with their ultimately underlying microscopic processes.

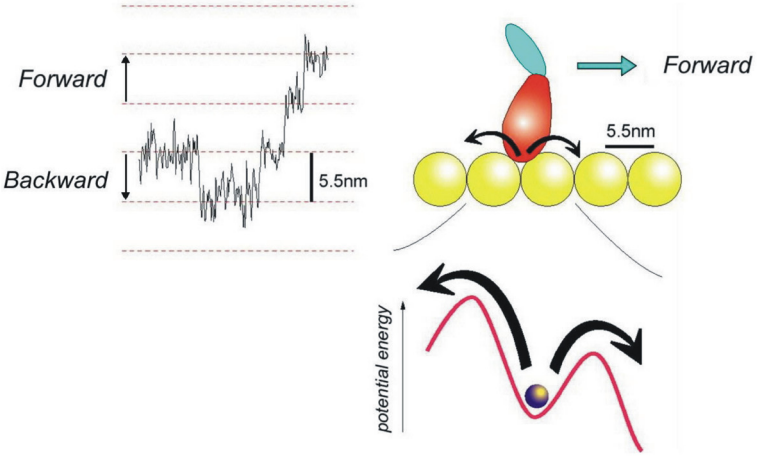

Figure 19. Some records and a sketch of the motion of a single myosin head in a hypothetic washboard-type potential.

We conclude this bird's eye view of the acto-myosin motor by briefly outlining a simple phenomenological model, originally proposed in [2], that is able to provide a quantitative description of the available experimental data and that is in agreement with the loose coupling assumption. The basic idea is to describe the myosin sliding over the actin filament as the motion along an axis of a Brownian particle in a highly viscous fluid. Under reasonable assumptions, supported by physical and dimensional considerations, after denoting by x the position of the particle, and assuming that its mass is such that the inertial term can be disregarded, one is led to the following equation of motion:

$$\dot{x} = -\frac{1}{\beta}\frac{d}{dx}\left[U(x) - Fx\right] + \sqrt{2\frac{E}{\beta}}\,\Lambda(t), \tag{28}$$

where

$$U(x) = \frac{K}{2}\left(x_L - \frac{L}{2}\right)^2, \qquad x_L = x(\mathrm{mod}L) \tag{29}$$

the other parameters (β, F, K, L) being suitably specified (see [2]). In this equation, $\Lambda(t)$ denotes a delta-correlated stationary Gaussian process with zero mean that synthesizes the effects of the collisions suffered by the particle from the molecules of the liquid in which the sliding phenomenon takes place. Note that Eq. (28) contains a periodic potential whose period equals that of the distance between the pairs of consecutive actin monomers, as well as the term $-Fx$ whose role is to tilt this potential. Actually, such a tilting is ultimately responsible for the privileged direction of the observed sliding steps. In successive papers ([14], [3], and [4]) the possible origins of such a tilted potential have been investigated, and in all cases Brownian motors have been suggested that are able to harness and efficiently use a part of the energy provided by the underlying thermal bath. In particular, in [5] a model has been constructed that has yielded a very satisfactory agreement with the essential dynamical and energetic characteristics that experimental evidence has disclosed.

Summing up, a picture has emerged in which very accurate predictions of the features of the actinmyosin molecular motor have been possible despite the very high level of structural and dynamical uncertainty. Particularly significant has been the discovery that functionally efficient and reliable molecular motors can be thought of, that take advantage of the chaotic features of the environment in which they operate. This leads one to re-consider the role of noise in such a "wet" environment: instead of being a disturbing agent for the accomplishment of certain tasks, in some cases, such as the presently outlined one, noise can appear to be a powerful and useful cooperating agent.

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