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Predicting Ageing: On the Mathematical Modelization of Ageing Muscle Tissue

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Abstract. The ageing of biological tissues can be accelerated by many factors, mainly of physiological and nutritional nature. In the case of skeletal muscle tissue, one of the main consequences of ageing is a progressive loss of muscle mass and a worsening of the quality of muscle tissue, termed "sarcopenia". The correlation between the deterioration of muscle tissue and what we usually refer to as the "lifestyle", although being the subject of several studies, up to now has been considered only from a clinical and a statistical viewpoint. However, the construction of a sound mathematical model of the muscle tissue, accounting for the changes due to ageing, can provide a more refined quantitative tool. Such a tool could determine in an improved way the variations of some measurable physiological parameters, such as the mass and the electrical impedance of the tissue, caused by the variation of other controllable factors, such as diet, physical activity, pharmacological treatments, air pollution exposure. A specific mathematical model, once implemented on a computer, makes it possible to perform "virtual" experiments, facilitating the search for a suitable treatment of sarcopenia. Moreover, test situations can be studied which would not be reproducible *in vivo*, such as drug overdoses, extreme nutritional deficiencies, environmental overexposure to harmful substances, and so on.

Keywords. Mathematical Modeling, Sarcopenia, Differential Equations, Stochastic Analysis

Introduction

Mathematical modeling is at the basis of the technological achievements of the last two centuries. Not only engines, aircrafts, and buildings have been designed and produced with the aid and guidance of mathematical modeling, but also communication media, electric appliances, and the whole digital world of computers would not have been possible without the deep understanding of physical processes and the predictive control provided by mathematical models of those processes. More recently, medical appliances and digital image processing have offered additional evidence of the positive impact that mathematics can have on the quality of life. In all of the mentioned applications the key for the success of mathematical modeling is the controllability of the system under consideration. Indeed, such a controllability (typical of engineered systems) may well be viewed as a necessary condition for the mathematical models to be of any use, since mathematics seems to be pretty controllable, at a first glance.

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Luckily enough, this is a misconception: on one side, the mathematical theory of deterministic chaos has shown us that unpredictability is inherent to even very simple mathematical models; on the other hand, many complex and poorly controllable systems have been subject to an effective mathematical modeling.

What kind of system is complex and poorly controllable? In a word, we could say that any *lively* system displays those features. And what kind of mathematical tools are needed to model lively systems? Those related with probability and stochastic analysis. Indeed, the best we can hope for is, in many cases, to achieve a predictive understanding of the average behavior of a complex system and of the degree of conformity to that behavior shown by small parts (or individual realizations) of the system.

In the last 60 years it has become more and more fashionable to try and apply mathematical models to lively systems such as turbulent flows, financial markets, biologically interacting populations, socially interacting human groups, neurological systems, living cells and tissues. All of these systems exemplify the three main features of lively systems: (1) it is impossible to follow in detail the behavior of each constituent of the system; (2) the collective behavior of the system is not a simple upscaling of the individual's behavior; (3) the time-evolution of the system displays deep reorganizations and modifications of the collective behavior due to both internal and external factors.

In attempting to develop a mathematical model for the behavior of a biological tissue and for its evolution over a long period of time, bringing ageing into play, we must be aware of the aforementioned issues, to choose the most appropriate modeling strategy and mathematical tools.

1. The Modeler's Task.

One of the main features of science is *capability of prediction*, that is, the possibility, starting from a known situation, to predict the values of some measurable quantities, enabling the scientist to have a fairly satisfactory picture of the future evolution of the situation. But this is not completely true. Indeed, the evolution which is predicted by the scientist is that of her own picture of reality, and reality often betrays our forecasts.

We can then see the importance of making a picture of reality, a *model*, as faithful as possible, but we must also cope with the limited nature of our resources. To build up a model that properly balances those needs is the main task of a scientist.

For instance, consider the properties of a steel bar used to reinforce a building. In seeking for accuracy, we could try and take into account all the atoms constituting the bar and all their interactions up to a certain distance. In other terms, we could picture the bar as a grid of atoms, using the laws of Quantum Mechanics to predict a rather accurate picture of the motion or of the response of the bar to an external load. But in doing that, we would immediately see that this is possible only for a very limited number of atoms (two or three, indeed) if we are looking for *exact* solutions, and perhaps a few hundred thousands of them if we are satisfied with *approximate* solutions, by using a computer. Since a real macroscopic bar is made of a huge number of atoms (billions of billions of billions), we see that this way is completely unfeasible.

On the other hand, we could view the bar as a sort of “homogeneous material”, finding out what kind of response the bar has to an applied load, without deriving that from physically established and detailed principles. Anyway, we have to use appropriate hypotheses: for instance, we may assume that a piece of bar behaves the same way if it is pulled in a direction or in another one, or that it recovers its initial shape whenever unloaded, and so on. In other words, we have to make a *model* of what our situation is, and proceed from it applying appropriate *hypotheses*. As we all know, a steel bar is not homogeneous at all if we magnify it enough (even long before getting to atomic scales), but we can assume that the inhomogeneities of the material are negligible if one aims at predicting the behavior of the bar, at least if the loads are not too heavy. Of course, leading physical principles such as conservation of energy may help in the construction of the model, but in general they are not enough for a complete description. Driven by a need for simplification, scientists have been able to deal with a great number of phenomena, just trying to minimize the number of necessary assumptions, using symmetry considerations, dropping negligible quantities, and so on.

It should be stressed that every model is not only a partial picture of the phenomenon, but also a choice, namely the choice of what features are negligible for the study that one has in mind. As we have said, the choice is usually made pursuing essentiality: for instance, if we picture our bar as a homogeneous material, we could describe it with a smaller number of parameters and perhaps end up with a simpler problem, easier to solve, even if it is far from being complete. Only the experience of the modeler may lead to the right amount of simplifications.

2. How to Model Living Systems

A living organism has a peculiar organization which makes it very different from both a bunch of atoms and a macroscopic material. Living tissues exhibit a great variety of self-organization mechanisms and show radically different pictures at different scales. A skeletal muscle, for instance, shows a very complicated (but not random) structure at smaller and smaller scales: from fascicles to fibers, to sarcomeres, to myosin and actin. Moreover, a living tissue is usually growing, thus showing a feature which is not shared with ordinary macroscopic materials.

Therefore, if one wants to predict a future situation, the type of models that she is been using may be crucial for the accuracy of the prediction. It is very important to remind that predictions may depend on the model used and some lack of matching with real life is not a matter of wrong basic laws, but rather of a wrong or insufficient modeling.

2.1. Deterministic and Non-Deterministic Models

Models may be, in essence, divided into two classes: *deterministic* and *non-deterministic* ones. Deterministic models usually lead to mathematical problems that are treatable only when a limited number of unknowns comes into play. Let us make a simple example: suppose that we want to describe bacteria on a substrate. Clearly, the number of living bacteria at a certain time is an integer number: they cannot be fifteen and half. But, if their number exceeds a million, or if their birth rate and mortality rate are sufficiently high, it could be even meaningless to consider the exact number of bacteria at a certain moment as an integer number: we may not be able to count them, since they die and are born too quickly. We therefore admit that an error of one part on a million will not affect the final picture that we would like to have, and then we can assume the number of bacteria to be also non-integer. This is the starting point in setting up a *differential equation*, that is, an equation relating the speed at which a quantity increases or decreases with the quantity itself.

A differential equation is in general difficult to solve explicitly, but it is often easily approximated to within a given error, and then it may produce a nice prediction of the situation we want to model. However, suppose that we are dealing with several species of bacteria on the same substrate: each species, namely each individual, will interact with the others in a very complicated way, which has to be modeled itself. If the number of species of bacteria increases, the deterministic problem that comes out may rapidly become intractable, both because the mathematics is too complicated and because the number of interactions is difficult to describe.

In such a situation, a non-deterministic model may be more useful. We could speak of a sort of "bouquet" of bacteria and specify only the relative percentage of the species in a given point. In doing so, we only know the probability of finding one bacterium or another in a given point. We could alternatively speak of "many different bacteria in the same point", which evolve under laws to be modeled. The sentence "the bacterium is here now" becomes meaningless in this context, but the prediction may be easier to obtain.

Another important point is the *knowledge of the initial situation*. This is often taken for granted, but if the phenomenon under study shows *instability*, it is very likely that a small error in the initial conditions will produce a great error in the predicted situation, what is sometimes referred to as the "butterfly effect". This is the reason why, for example, it is possible to predict precisely a total eclipse of Sun many years before it happens, but it is very difficult to forecast the weather for the next week.

Besides the instability phenomenon, which is in some sense unavoidable, there is another, maybe less known, problem in modeling that influences scientists' attitude rather deeply. When complex, or to be more precise, lively situations are under investigation, such as those concerning living or economic systems, not only are the predictable values known within an error, but also some *laws* may be partially unknown. For instance, in the case of bacteria one may suppose that species A eats species B, but the rate of that can be very difficult to measure. Or, in an economic problem, even if it is plausible that the mean propensity to consume increases when the gross national product increases, and one can simply assume that the two quantities are proportional, it may be very difficult to estimate the proportionality constant.

2.2. Numerical Simulations

After achieving good theoretical stability results for the model, some simulations can be performed, trying to have a clue of the unknown constants which have to be chosen. Usually simulations are performed by implementing the model on a computer (the so-called *numerical simulations*, often referred to as *in silico*). For example, a simulation may be used to predict the private expenses with different values of the internal product and to determine a possible value of the unknown proportionality constant. Next, with that value, other simulations may be able to predict several features of the phenomenon. In this sense, modeling is useful to modeling itself, without being a circular procedure. But, for the same reasons, simulations of complicated or chaotic phenomena must be always used with caution, and the awareness of all the simplifications made must guide the interpretation of the results. Moreover, even if numerical simulations may lead to huge money savings, for example by replacing a wind tunnel with a computer, and therefore they are very useful, sometimes they may be badly employed, especially when they are passively assumed as truth, as for some partial climate predictions.

Anyway, numerical models are often the unique way to discover and/or explain features which otherwise remain inaccessible, and they probably will be the major tool for predicting and decrypting our life in the next future.

3. A Model for Sarcopenia.

Finding the causes and the mechanisms which lead to the ageing of biological tissues has always been an important task for the medical research. Indeed, the quality of life of elderly people could be greatly improved by slowing down or blocking such mechanisms.

Among the various elements of human body, the one which is severely subject to ageing is muscle tissue, especially that related to skeleton. A significant degeneracy of such tissues entailing loss of muscle mass and reduced functionality of the muscular fibers, often associated with ageing, is a syndrome named *sarcopenia*.

3.1. What is Sarcopenia

Sarcopenia is a so-called *geriatric syndrome*, that is, a complex clinical situation which is quite common in the old age and which does not fit into the definition of a specific disease. Although there is no general agreement on the parameters defining the syndrome, primary sarcopenia refers to a progressive loss of skeletal muscular mass in adults, which can become dramatic (loss of 50% of muscular mass) after the age of 80. In the last ten years it has been suggested to use the term sarcopenia referring generally to the loss of muscle functionality, and not only muscle mass. In 2010 the European Working Group on Sarcopenia in Older People [1]

> "recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia." (p. 413)

Someone proposed to use the term *dynapenia* for the loss of the sole muscle function, but the denomination did not achieve a widespread use.

Needless to say, sarcopenia has a great impact on the quality of life of elderly people: the loss of muscle functionality greatly reduces mobility and consequently reduces autonomy; moreover, the risk of injuries and bone breaking considerably increases, causing disabilities and hospitalization.

3.2. Diagnosis of Sarcopenia: How to Measure Some Quantitative Parameters

In order to describe and to diagnose sarcopenia, there is a strong need to find some quantitative markers of the disease, an obvious candidate being the actual amount of skeletal muscle tissue in a human body. However, measuring such a quantity in a reliable and not invasive way is not easy, and several techniques have been proposed in the last few years. Apart from MRI, which is quite slow and expensive, two tests have been considered as a widespread diagnostic tool: BIA (Bioelecrical Impedence Analysis) and DEXA (Dual-Energy X-ray Absorptiometry). Unfortunately, both of them can measure only the mass and are inappropriate to evaluate the quality of muscle tissue: this is one of the main points which makes so difficult any clinical diagnosis of sarcopenia. The usual methods to test the efficiency of the muscles (hand grip strength test, six-minute walk test, knee extension strength test) are much less precise and must be adapted to elderly people. For instance, the six-minute walk test, which is quite demanding for an 80-year-old person, is usually replaced with the four-meter walk test, which is a lot easier and can be performed in any room, but it is even too quick and cannot precisely measure the performance of the leg muscles in a prolonged exercise.

3.3. Mathematical Models of Muscle Tissue

The first mathematical models of some of the functionality of muscles appeared in the scientific literature long ago. The pioneering work of the Nobel laureate A. V. Hill in the decade 1920-30 tried to describe some experimental results about the muscle contraction by using a few ordinary differential equations. Later on, in 1954, another Nobel laureate, A. F. Huxley, discovered the so-called "sliding filament" mechanism of muscle contraction and in 1971, together with R. M. Simmons [2], proposed a mathematical equation describing some quantitative parameters involved in the contraction of muscles. Since then, a lot of mathematical literature has been developed on the subject of muscle contraction. Recent important instances are the papers by L. Truskinovsky and coauthors [3-5], where it is proposed a refinement of Huxley's model which is capable to better fit the experimental data in a wide range of physiological situations. The model by Truskinovsky is based on a mathematical description of the behavior of a single cross-bridge between myosin and actin and takes into account also some stochastic fluctuations, which cannot be neglected at the molecular level, by inserting suitable terms in the equation. Then, many such equations (~2000) are coupled in order to describe the behavior of a single sarcomere, and, via some numerical simulation, the output of the model is related to experimental measurements.

Another approach to muscle modeling has been undertaken by using the tools of Continuum Mechanics: the muscle tissue is viewed as a homogeneous material and all the microscopic details are coded in the equations describing the material. With this approach one can hope to model a larger system, such as an entire biceps or triceps, taking into account also the typical orientation of the muscular fibers. Among the authors which followed this method, we like to mention Holzapfel and Ogden [6], who have proposed several models of the heart as a muscle, accounting also for the geometry of the ventricles.

4. Our Research Activity: Modeling the Quality of Muscles

The main goal of our research activity, which started a few months ago at the "Niccolò Tartaglia" Department of Mathemetics and Physics of the Università Cattolica del Sacro Cuore, is to produce a mathematical model capable of quantitatively describing the evolution of sarcopenia. In order to do this, we need two main ingredients:

- a sound model of the skeletal muscle tissue, which can keep into account also the possible loss of muscular mass;

- a descriptor of the quality of muscle tissue, that is, some quantity which can summarize the physiological changes due to the ageing into a quantitative parameter.

For instance, a possible strategy could be to introduce in an existing model, such as an adapted version of the model by Truskinovsky, a time-dependent parameter measuring the strength of the cross-bridges between actin and myosin. Tuning the value of the parameter by imposing an increasing weakness of the bonds as time passes could result in a sarcomere which is deteriorated and which has a worsening in the performance. In such a way we would have a descriptor of the quality of muscles, and the model could be coupled with other equations describing the evolution in time of the quality parameter. Clearly, those equations should account for nutritional and environmental factors, as well as drug assumptions and training activity of the subject.

As a starting point, we are looking for some quantitative parameters which can be used in the diagnosis of sarcopenia. The main parameter is the total skeletal muscle mass, but also the electrical impedance of the tissue, which is easily measured, can be a good indicator, as well as the muscle fat content, although this is much harder to evaluate. In doing this, we are studying the correlations between the electrical resistance of the muscle tissue and the muscular performance, in order to test whether the electrical impedance can be a good quantitative parameter on not. A good electrical model of the human arm or the human leg, capable to account for the electrical capacity of the cells and the geometry of the appendicular muscles, would be very useful at this stage.

4.1. The Role of Stochastic Phenomena

If we are interested in the mechanical properties of the muscle tissue, we can safely make use of deterministic continuum mechanical models, which only capture the collective behavior of the system. But, when it comes to assessing the quality of the tissue as it evolves with ageing, a number of "randomizing" phenomena influence the system. In particular, the degenerative process of ageing acts in a stochastic way on the individual cells of the tissue, and the macroscopic effects of that process can be traced and simulated only by a careful analysis of that stochastic process. Moreover, the response of each person to external factors (diet, medications, lifestyle, etc.), and even the response of different muscles, may be very different, and a probabilistic approach is necessary in assessing suitable parameters to diagnose sarcopenia.

5. Conclusions

Sarcopenia is a serious syndrome related to human ageing and one of the main causes of frailty and inability in elderly people. It shows up as a gradual loss of skeletal muscle mass and functionality. Far from finding a medical therapy, even the diagnosis of the disease is problematic, due to the scarcity of quantitative parameters (besides the total muscle mass and strength) and the difficulty to measure them. In order to help the active ageing and healthy living, we started an ambitious scientific project aiming to produce a mathematical model of the behavior of the human skeletal muscle capable to describe also the quality of the muscular tissue. Such a model would be very helpful in the search for the mechanisms causing the disease and could suggest also possible therapies. As a starting point, we are trying to simplify the evaluation of the total skeletal muscle mass by comparing segmental BIA measures of the limbs with other anthropological measures.

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