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Mathematical modeling in medicine

-Prospects of lifesaving technology

Introduction

In the previous century, industrial engineering was revolutionized with the growing capabilities of computers. With the aid of computers, it became possible to make accurate predictions of various physical phenomena and situations. Often, such predictions are obtained by constructing approximate solutions to a certain type of mathematical equations; partial differential equations. Though most of the partial differential equations used in industry today were already well established before the 20th century, their complexity rendered the task of finding an exact solution impossible. In fact, even establishing that there exists a solution is not trivial. Consequently, it is necessary to construct good approximations. Today, the modern computer is capable of performing billions of basic math operations each second (e.g. adding two numbers). Clearly, it would take one man a life time to perform a similar number of computations. In this respect, the computer is a superior tool for constructing approximate solutions. However, the computer is not intelligent and needs to be told exactly what to do. In most situations, this is not easy.

The art of combining mathematics, physics, and computers into a predicative tool for industrial engineers is consequently both many folded and interdisciplinary. In addition to an appropriate physical description, in terms of mathematical equations, one needs to design efficient computer programs to compute their solution.

In spite of the success mathematical modeling has enjoyed in Physics, similar approaches to other disciplines have until recently remained few and with little practical impact. Traditionally, other disciplines are descriptive and qualitative: From experimental or empirical studies, a description is deduced and a possible explanation is given. There have been few or no attempts to formulate underlying dynamics in the language of mathematics. This is now changing. Especially in the Life sciences, where studies using mathematical modeling are receiving large funding and attention. To quote one of the optimists in this direction;

*"Mathematics is Biology's next microscope, only better;
Biology is Mathematics' next Physics, only better."* – J. E. Cohen.

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When applied to medicine, the revolutionary potential of the mathematical modeling approach becomes clear. In medicine, mathematical modeling can radically improve both drug development and hospital technology.

In this contribution, the author aims at equipping the reader with a perspective on current and future applications of mathematical modeling in medicine. It is the author's hope that the reader will obtain an insight that stretches far beyond actual examples.

First, two applications of mathematical modeling of Cardiovascular diseases are considered. Then, we end this contribution by a discussion of mathematical modeling of cancer.

Cardiovascular diseases

Mathematical modeling of blood flow and electric heart activity have been researched extensively throughout the previous decades. There are multiple reasons for this focus. Firstly, cardiovascular diseases are the leading cause of death in the developed part of the world. Secondly, electric heart activity and arterial blood flow can be appropriately described by equations already known from Physics. Consequently, the major research effort is now on the design of efficient computer programs for obtaining accurate approximations.

For the untrained in mathematics, it can be unclear exactly what a mathematical model is. In Figure 1, an approximate solution to a mathematical model of blood flow is shown. It is a snapshot of the flow at a given time and from a given angle. Observe that only the flow in a slice of the artery is shown. The mathematical model, and the algorithm used to approximate a solution, is independent of such choices (time, angle, slice, etc.). Thus, the same computer program can be used for any set of choices. Consequently, very detailed studies of the flow can be performed. Moreover, the mathematical model does not depend on the actual geometry of the artery. Thus, the same computer program can be used on any artery and any patient. One can even apply modifications to an artery and see how this will change the flow. In this way, it might be possible to predict the outcome of a surgery without actually having to perform it.

For further discussion, see [6]. For a more detailed exposition of the mathematics and numerical solution approaches, see [2].

Application 1: Aneurysm on the Circle of Willis

The Circle of Willis (CoW) is a system of arteries located at the base of the brain (see Figure 2 for an illustration). It constitutes the most common location for aneurysms. It has been estimated that 5-6% of the population is living with one or more aneurysms on the CoW. Most of these are luckily very small and unlikely to rupture. In Figure 2, a CT image of a real case is shown. Clearly, if such an aneurysm were to rupture, the chances of survival are next to none.

Of people developing a life threatening CoW aneurysm, about 10% die before reaching medical attention. Another 50% die within one month. Of the

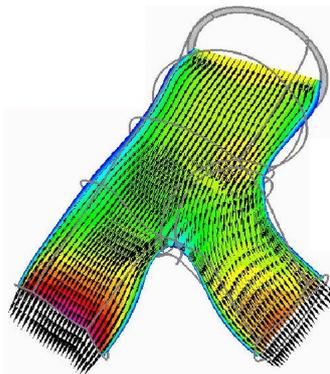


Figure 1. Computer simulation of blood flow in a segment of an artery. The arrows denotes the direction of the flow. The length and color of each arrow denotes the velocity. @University of Colorado.

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survivors, about 50% suffer from neurological defects.

Once an aneurysm have been discovered, there are basically two treatment options (see Figure 3). One option is to perform a craniotomy, exposing the aneurysm, and closing the base of the aneurysm with a clip. This procedure is known as surgical clipping. The other option is to fill the aneurysm with a special kind of thread, called coil. In that case, a catheter is passed into a groin artery and moved along the arteries until the aneurysm is reached. Both procedures are considered highly risky as there is a chance that the patient will die during surgery. In the case of clipping, chances of complication are high since it is extremely hard to reach the area surgically and since the aneurysm might rupture during surgery. In the case of coiling, there is a large chance that the aneurysm will continue to grow even after the procedure. This is complicated even further as the risks associated with surgical clipping of previously-coiled aneurysms are even higher.

For the physician faced with a case of aneurysm, the following questions needs to be answered:

1. What are the risks of rupture? When will it rupture?
2. Which of the two treatment options should be used?
3. In the case of coiling, how much should be filled?
4. In the case of clipping, where should the aneurysm be clipped?

Today, there are no good answer to any of these questions. In the future however, there is a great chance that the physician can use mathematical modeling, in the form of a computer program, to answer all of these questions. In fact, several research institutions are already developing such software. See for instance [1].

Application 2: Ischemic heart disease

Ischemic heart disease is the western world's largest cause of death and is characterized by reduced blood supply to the heart muscle (Figure 4). It is usually caused by a blockage in one of the arteries (coronary) on the outer wall of the heart. When this happens, the muscle tissue in the affected region of the heart muscle starts to die. As a consequence, the heart no longer functions optimally. However, the consequences are even more severe as the electrical current coordinating heart contractions no longer spreads correctly through the affected tissue. If the blood supply reaches a critically low level, the heart muscle no longer contracts in a coordinated manner and thus no blood is pumped through; the heart stops beating.

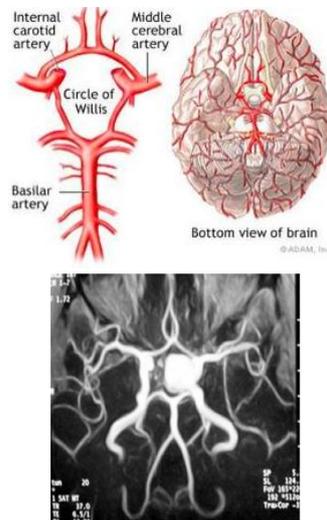


Figure 2. The drawing on top illustrates the location of Circle of Willis. On the bottom, the figure shows a CT scan of a real patient's Circle of Willis. The large apple shaped white region is an aneurysm. Drawing to the left is property of ADAM Inc. Image on the right was first published in [5].

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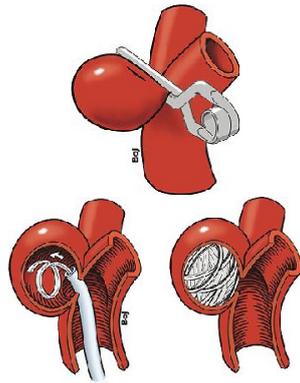


Figure 3. The two ways of treating an aneurysm on the Circle of Willis. Surgical clipping (top) or coil filling (bottom). @ Rigshospitalet, Denmark.

The primary symptom of ischemic heart disease is a certain type of chest pain (angina). Diagnosis of ischemic heart disease is performed by reading the results of an electrocardiogram (ECG). ECG is a method to measure the electric activity of the heart and hence it is possible to see if the electric current is spreading as it should. There are basically two methods used to treat ischemic heart disease. The first method consists of removing the blockage. This is commonly achieved by expanding the artery at the blockage. The second method is known as bypass surgery. It consists of constructing a new artery leading blood from a different source to the area with reduced supply.

For the physician faced with a case of ischemic heart disease, the following questions need to be answered:

1. Where is the blockage located?
2. Which of the two treatment options should be used?
3. What is the optimal bypass construction?

Today, mathematical modeling is actually being used to determine the latter. However, the result is then only optimal with respect to the amount of blood supplied to the region. It is not optimal with respect to the electrical activity of the heart.

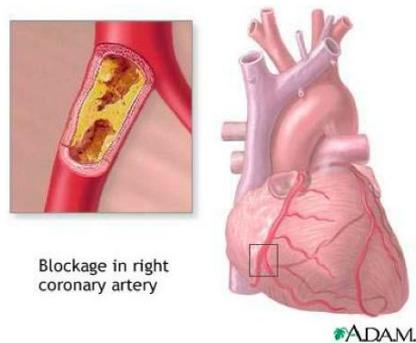


Figure 4. Ischemic heart diseases. @ADAM Inc.

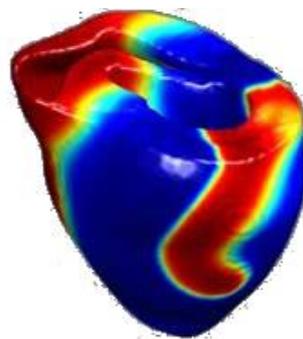


Figure 5. Computer simulation of the electric activity in a heart. The simulated heart is at the onset of cardiac arrest. @Richard Clayton, University of Sheffield (<http://www.dcs.shef.ac.uk/~richard/>).

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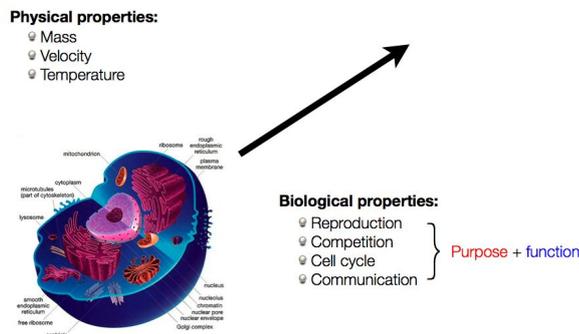


Figure 6. Living material is difficult to model since it cannot be characterized by a small set of parameters. As opposed to inert material, it has a function.

Thus, it does not help to determine what solution yields the best heart function.

In the future, mathematical modeling of the entire heart can give answers to all of the above questions. See for instance [4].

Cancer

In contrast to the case of cardiovascular diseases, mathematical modeling of cancer is still in its infancy. While mathematical models of the cardiovascular system are very similar to models of industrial systems (e.g flow of water in a pipe), even a good approach for modeling cancer growth is unavailable.

For models of the cardiovascular system, it does not really matter that the system consists of living material. When modeling cancer growth, the aim is to model the evolution of billions of living cells. In addition to having physical properties, such as mass and temperature, a cell has biological properties (Figure 6). These biological properties renders the possible behavior of each cell complex. For instance, a cell can communicate across distances to other specific cells causing these to change behavior. Furthermore, through random mutation in a cells DNA, a cell can radically change behavior. In fact, it can change the behavior of a large number of cells. Consequently, the behavior of a random event in one cell can change the evolution of an entire tumor. Today, there does not exist any good mathematical description of biological properties. In fact, it seems like the available mathematical tools are not appropriate for the task.

Through the search for a good mathematical model of cancer, it is actually predicted that fundamentally new mathematics will be developed. Indeed, a vast number of researchers expects the great mathematical revolution of this century to be the mathematical formalization of phenomena in the Life Sciences, as was the case with Mathematics and Physics in the previous centuries.

The interested reader is strongly encouraged to consult [3, 6, 7], and the references therein, for more on this material.

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