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Development of a Software based on a Mathematical Model of the Renal System for Computer Physiology Practices for Biomedical studies

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Bachelor's Thesis UPF 2020/2021

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Acknowledgments

The following pages you are going to read are not only the fruit of my individual work.

First of all, I would like to thank my thesis supervisor, Dr. Rubén Vicente, for giving me the opportunity to work with him on this project and for offering me advice whenever I have asked for. I really hope this work ends up being a useful tool you can use in your classes.

Thanks (and congratulations) also to all my colleagues and friends who have gone through the same challenging process. Sharing our doubts and experiences has made the process more enjoyable.

Special thanks to my cousins, Tom and Maria for bringing me the most artistic point of view and being willing to help me at any time. It is always a pleasure to have such incredible artists like you both in the family.

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Summary/Abstract

A complete understanding of human organs and systems cannot be achieved only by theoretical classes. Practical lessons are also part of the curriculum of courses like Molecular Biology or Physiology. The great majority of vital processes and structures studied in these courses are not easy to reach and therefore, there is a need to develop realistic simulators based on mathematical models to work with.

One of these unreachable systems is the Renal System. The purpose of the present study is to program and develop a software intended to be used as a support tool in the study of the Renal System functioning of Medicine, Human Biology and Biomedical Engineering students. The software is developed in Python programming language and it includes a user-friendly interface created by Qt, a cross-platform software.

The Renal System regulates extracellular liquid volume, blood pressure or osmolarity, among others. The software reproduces one of the main renal processes; glomerular filtration. This procedure is primarily performed by the nephrons, the functional units of the kidneys. Glomerular filtration is conditioned by many different factors, like for example blood pressure or arterioles' radius located around the nephrons.

The program simulates different scenarios and shows how the factors mentioned affect important parameters such as the Single-Nephron Glomerular Filtration Rate (SNGFR), which refers to the volume of plasma filtered per unit of time in each nephron, the glomerular pressure or the urine volume, and at the same time, how these changes influence the renal function.

Keywords

Software, Mathematical Model, Simulator, Renal System, Glomerular Filtration, Nephron, SNGFR, Glomerular Pressure, Urine volume

Preface or prologue

The present Bachelor Thesis arose from the proposal of Dr. Rubén Vicente, who sought to create a new tool to implement in his Renal Physiology classes.

The Renal System is one of the most important systems in our body. Some of its main functions include regulating the extracellular liquid volume and blood pressure, the osmolarity, preserving the ionic balance or controlling hormone production and body waste excretion. The kidneys, despite their small size, filter about 180 litres of fluid every day. Due to the importance of the renal system in the functioning of our body, it is also vitally important to study and understand the processes that it carries out. However, the renal system is not easy to reach and work with, or at least not without using live animals or complex wet-lab experiments.

Thanks to the development of mathematical models reproducing vital processes, and more concretely renal processes, simulations can be performed while avoiding ethical and technical complications. The aim of this project is to develop an academic software based on a mathematical model simulating glomerular filtration, the first step in making urine. Moreover, the result will be packed into a good-looking and appealing graphic user interface to ease the learning process. The resulting program is aimed to be used only for academic purposes and wishes to be a useful tool for students of Medicine, Human Biology and Biomedical Engineering at UPF.

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1 Introduction

Following the educational currents that have emerged during the past two decades, practical lessons need to complement (or even lead) any teaching plans at all educational levels. When it comes to higher Biomedical studies, the full understanding of organs and systems cannot be achieved only with theoretical content and lectures. For a few years now, practical sessions are also part of the curriculum of courses like Physiology or Molecular Biology among others, in most universities. However, the great majority of vital processes and structures studied in these courses are not easy to reach and sometimes require the manipulation of live animals, thus raising serious technical and ethical limitations. Therefore, the use of mathematical models and computational simulators can be an extremely useful tool when it comes to study unreachable organs and their processes.

The renal system, among others, can benefit from these mathematical models and their approaches in order to understand its main processes and functioning. The kidneys play an essential role in the maintenance of total body homeostasis. By varying the amount and chemical composition of the urine, the renal system can regulate total body water, extracellular volume and tone, plasma electrolyte levels, plasma pH [1] and control body waste excretion. Kidneys can also produce and release into the circulation a large number of compounds, like angiotensin II or prostaglandin, which can affect blood pressure or flow among others. The kidneys keep blood water and ion concentrations within a suitable range thanks to the balance between the uptake and excretion of these substances. Despite their small size, about 180 litres of fluid are filtered by the kidneys every day [2]. Moreover, the kidneys have a huge reserve capacity, meaning that most people preserve full renal function even with only one kidney [3].

Anatomically, the renal system is formed by the kidneys, ureters, the bladder and the

urethra. The functional units of the principal organ, the kidneys, are the nephrons [3]. They are tubular structures made up of a single layer of epithelial cells and divided into four distinct segments: a glomerulus, a proximal tubule and a loop of Henle (Fig. 1). The nephron's distal end is connected to the collecting duct system, which delivers the remaining tubular fluid to the ureter.

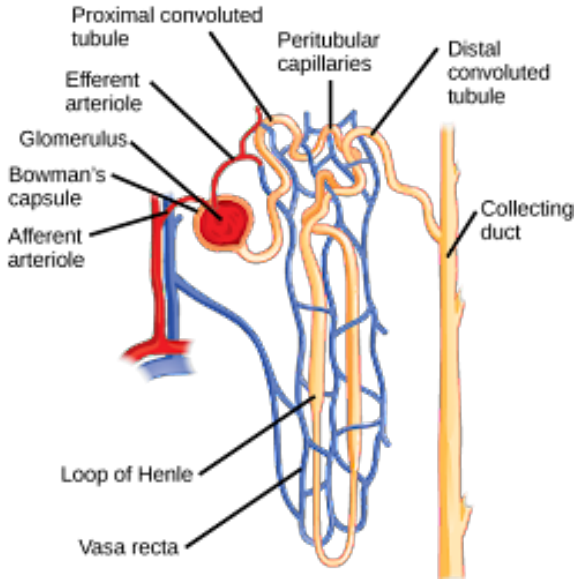

Figure 1: Nephron representation and its parts. Image extracted from Lumen Learning et al. [4]

Each nephron consists of an initial filtering component called the glomerulus. The glomerulus is formed by a network of capillaries enclosed by a capsule, the so-called Bowman's capsule, which is connected to the nephron's proximal tubule. The capillaries of a glomerulus are supplied by a single afferent arteriole and drained by a single efferent arteriole [5].

In the glomerulus, urine formation begins with the filtration of blood plasma across the capillary walls, the so-called glomerular filtration. The capillary walls permit the filtration of large amounts of fluid and small solutes while preventing the passage of large proteins and blood cells. The filtrate is collected by the enclosing capsule

and delivered to the proximal tubule [6]. The volume of plasma filtered per unit of time is referred to as single-nephron glomerular filtration rate (SNGFR) [5].
Normal renal function requires that the fluid flow through the nephron be kept within a narrow range. When tubular flow rate falls outside of that range, the ability of the nephron to operate may be compromised. Due to heart beat, breathing, movement, excitement, etc., the pressure on the renal artery is constantly under perturbations. To buffer these perturbations, the afferent arteriole responds by adjusting its radius (and consequently arteriolar resistance) to compensate for changes in the renal artery pressure. This phenomenon is known as renal autoregulation.

The subsequent process is reabsorption, during which water and solutes needed are returned back into the extracellular fluid and circulatory system. In addition to reabsorbing the substances needed, nephrons are able to secrete unwanted substances from the bloodstream into the filtrate [7]. Together, these processes complete the transformation of the glomerular filtrate into the urine.
The fluid passes through the components of the nephron as water and ions are removed as the fluid osmolarity changes. Of the 180L that are filtered in the glomerulus every day, only 1.5L of urine are secreted. Therefore, along the nephron, more than 99% of the fluid must be reabsorbed into the blood [5]. The most essential substances in the filtrate are reabsorbed in the proximal tubule. These include glucose, amino acids, phosphate, lactate and citrate [7]. Reabsorption can be active or passive, depending on the solute being transported.

Finally, secretion is the transfer of molecules from the extracellular fluid into the lumen of the nephron. During secretion, some substances will be removed from the blood through the peritubular capillary network into the collecting duct. Like reabsorption, it is mostly dependent on membrane transport systems. Secretion is

an active process because it requires the transfer of substances against their concentration gradients [5]. The end product of all these processes is urine, which is essentially a collection of substances that has not been reabsorbed during glomerular filtration or tubular reabsorption.

1.1 State of the art

Mathematical models and simulators are a relatively novel tool that is becoming increasingly popular when it comes to studying vital organs and processes. They are an outstanding tool since they avoid ethical debates regarding the use of live animals for research and they conduct experiments that may be difficult to perform in a wet lab environment due to time, cost, or safety concerns.

This trend has not left the educational sector behind. Higher Biomedical studies include practical lessons working with these tools as part of courses in their teaching plan. When it comes to studying the renal system, there is the need to develop a new and updated mathematical computerised model that reproduces different scenarios giving accurate and real output values.

The software used nowadays in Renal Physiology lectures at Universitat Pompeu Fabra is PhysioEx 6.0 [8]. This program was developed by Benjamin Cummings, a division of Pearson Education, in 2006 [9]. It consists of 13 modules containing 40 physiology lab simulations of different systems and processes that are used to supplement or substitute wet labs. The ninth module corresponds to the Renal System Physiology and the first experiment of this module is the one simulating glomerular filtration and which this study will focus on. Since the software itself was developed almost fifteen years ago, it is no longer compatible with current operating systems and there is undoubtedly scope for improvement when it comes to the digital design of the user interface.

1.2 Objectives

As briefly stated before, the purpose of this thesis is to program and develop a software intended to be used as a support tool in the study of the Renal System physiology for students of Medicine, Human Biology and Biomedical Engineering at UPF. The simulator will focus on reproducing the glomerular filtration process and on how altering different factors influence renal function.

Indeed, the main objective of this project is to achieve accurate and real output values, based on a mathematical model, that allow students to complete their understanding of the renal system and glomerular filtration in different simulated scenarios.

Moreover, the software should be compatible with most current operating systems and needs to be presented through a user-friendly interface in order to ease and make the learning process more appealing.

2 Methods

2.1 Modelling Glomerular Filtration

The dynamics of the mathematical models, as well as certain parameter values and approximations, have been borrowed from Sgorualis et al. [6]. Glomerular filtration starts when blood flow arrives at the glomerulus capillaries. The blood flow is commonly modelled by the Poiseuille's law [10]:

$$\triangle P = QR \tag{1}$$

where P refers to the pressure drop along the vessel, Q the volumetric flow and R the vascular resistance [6]. Following the analogy with Ohm's law [11], the so called vascular resistance is related to the vessel's luminal radius (r), the vessel's

length (L) and blood viscosity (μ) by:

$$R = \frac{8\mu L}{\pi r^4} \tag{2}$$

During the glomerular filtration process, practically all of the pressure drop between the renal artery (P_A) and the renal vein (P_V) occurs between the afferent and efferent arterioles [6]. Therefore, the pressure drop along the pre-afferent arteriole, glomerulus and post-efferent arteriole segments, along with fluid loss due to filtration is considered negligible. The final circuit is shown in Fig. 2.

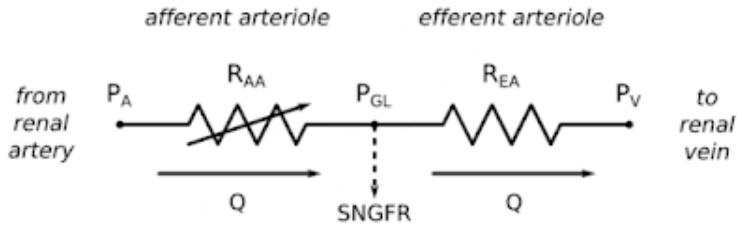

Figure 2: Equivalent circuit of renal vasculature. Glomerular pressure equals both afferent arteriole outlet and efferent arteriole inlet pressures, and blood flow is the same in both vessels. Figure extracted from Sgorualis et al. [6]

Moreover, following with Eq. 1, it is found:

$$Q = \frac{P_A - P_V}{R_A A + R_E A} \tag{3}$$

$$QR_{AA} + QR_{EA} = P_A - P_V \tag{4}$$

$$P_A - QR_{AA} = P_V + QR_{EA} \tag{5}$$

$$P_{GL} = P_V + QR_{EA} \tag{6}$$

where P_{GL} denotes the glomerular pressure and R_{AA} and R_{EA} correspond to the afferent and efferent arteriolar resistance.

Additionally, SNGFR can be calculated from P_{GL} following Starling's law [12]:

$$SNGFR = K_f(P_{GL} - P_b + \pi_g) \tag{7}$$

where K_f is the filtration coefficient and P_b and π_g are the pressure in the Bowman capsule and the colloid osmotic pressure, respectively. These last two magnitudes are considered to be constant. It is known that if the sum of the Bowman capsule and the colloid osmotic pressures exceeds glomerular pressure, filtration will not be possible since it cannot occur against the gradient. For that reason, when glomerular pressure attains values below 45 mmHg, glomerular filtration does not take place and SNGFR is null [6]. All the parameters used in the mathematical model applied are summarised in Table 1.

μ	3.5 cP
L_{AA}	18.23 μ m
L_{EA}	15.82 μ m
P_V	3.7503 mmHg
P_b	15 mmHg
π_g	55 mmHg

Table 1: Standard parameter values of the model. Values extracted from Sgorulis et al. [6], Nader et al. [13] and Neal et al. [14].

Finally, urine volume can be logarithmically related with SNGFR. This relationship was extracted by compiling data from several scenarios simulated with PhysioEx

6.0 [8] and plotting both magnitudes. The resulting graph is shown in Fig. 3.

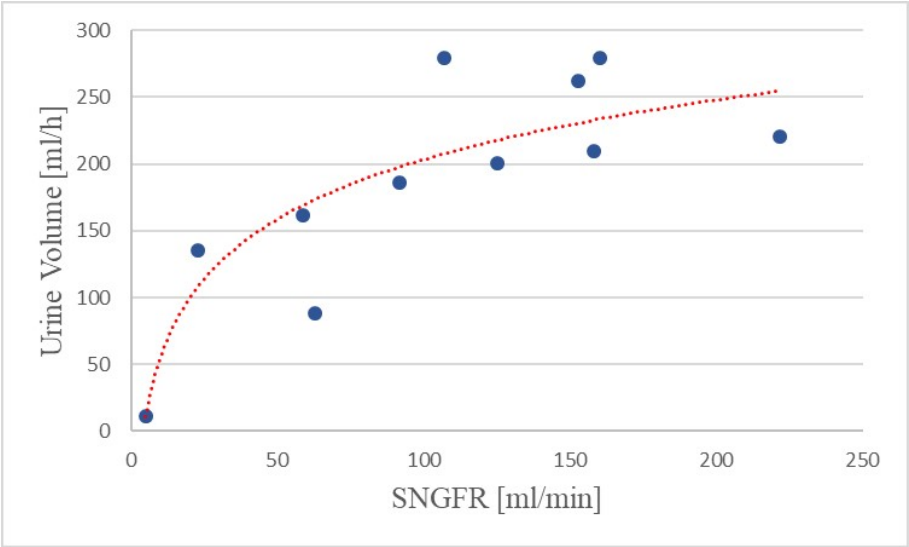

Figure 3: SNGFR and Urine volume relationship. Data extracted from PhysioEx 6.0 [8] software.

Urine volume is then expressed, in ml/h, by the following equation:

$$UrineVolume = 64.395ln(SNGFR) - 93.263 \tag{8}$$

being Eq. 8 the trend line with an R-squared value of 0.7303. Logarithmic relationship was chosen because it was the one with a higher R-squared value. Similarly to the SNGFR behaviour, when glomerular pressure drops below 45 mmHg, there is no urine formation happening.

2.2 Software development

The software was developed in Python [15] programming language, more concretely, using the Spyder [16] environment. All of the previously defined equations, as well as their corresponding parameters, were defined in a *.py* file. The use of additional packages and libraries, such as NumPy [17] extension or XlsxWriter module [18], was also needed for a complete programming of the model.

The input parameters of the software were defined to be the afferent and efferent

arterioles' radius and the blood pressure. These inputs are introduced by the user. From these magnitudes, glomerular pressure, SNGFR and urine volume are measured and extracted as output values of the model.

The program can also perform other functions. For instance, the software includes some data managing options to compile and handle a data set with all the simulations run. These extra functions were added to the software to ease and complete its future educational application.

2.3 Graphic User Interface design

The user-friendly interface was created using Qt [19]. Qt is a cross-platform software for creating graphical user interfaces (GUI) that run on various software and hardware platforms with no change in the underlying code base [20]. Qt offers a design tool named Qt Designer [21] in which the programmer can compose and customise windows and dialogues in a what-you-see-is-what-you-get (WYSIWYG) manner. This tool makes the interface creation a much more intuitive process by adding different widgets, defining colours, sizes and choosing all visual aspects in a very simplified way. Additionally, all properties set in Qt Designer can be changed dynamically within the code, transforming the *.ui* file into a *.py* file. Regarding the main window of the GUI, the GIF that appears at the centre (Fig. 4) was created using Adobe Illustrator [22]. Inspired by the experiment in PhysioEx 6.0 [8], a nephron is represented along with the vascular system around it, as a set of pipes. Its movement shows the path blood follows once it has filtered through the glomerulus, and until the formation of urine. In these tubes, it is marked the radius of the inlet pipe (equivalent to the afferent arteriole), the radius of the outlet pipe (referencing the efferent arteriole) and the pressure at which the blood reaches the glomerulus. These values are entered by the user in the box on the left of the screen. The values and ranges of these input quantities have been extracted from PhysioEx 6.0 [8].

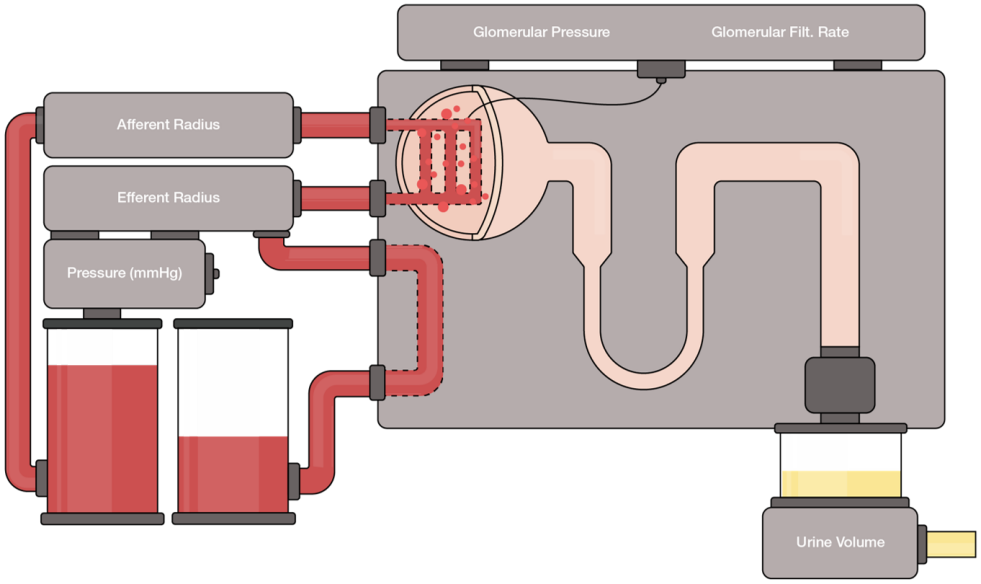

Figure 4: Central GUI Illustration. Main illustration of the graphical interface representing the nephron and the vascular system as a set of pipes. Illustration created with Adobe Illustrator [22].

The central illustration also shows where the outputs are measured and their values are displayed in the box on the right side of the window. Moreover, at the bottom of the screen, there is a table in which all the results of the simulations can be collected and a dataset can be edited and downloaded, thanks to the functions previously programmed and already mentioned in the previous section.
Finally, the entire graphical interface is accompanied by a common and consistent appearance. This corporate image is completed with a personalised logo, shown in Fig. 5, where the name of the simulator is displayed. The program is titled RenPhy Simulator.

Figure 5: Logo of RenPhy Simulator software.

Illustration created with Adobe Illustrator [22].

In addition, the software contains an initial window and a screen with additional information regarding the description of the software, its theoretical background and credits.

3 Results

3.1 Mathematical output values

The mathematical model developed in this study can be used to simulate and measure three output variables; glomerular pressure, SNGFR and urine volume. In the following subsections, some figures plot the output values calculated versus the input variables, which are defined by each user and include afferent and efferent arterioles radius, and blood pressure.

The software should provide coherent and meaningful output values in order to ensure a correct learning for students with its use.

3.1.1 Glomerular pressure variable behaviour

In this section, it is explored how glomerular pressure is affected by the alteration of all three input variables. In Fig. 6a, an increase is seen dependent on higher radius. On the other hand, in Fig. 6b, the same opposite effect is observed when the efferent arteriole radius is plotted. Finally, in Fig. 6c, a linear dependence is clearly shown between the glomerular pressure and the blood pressure variables.

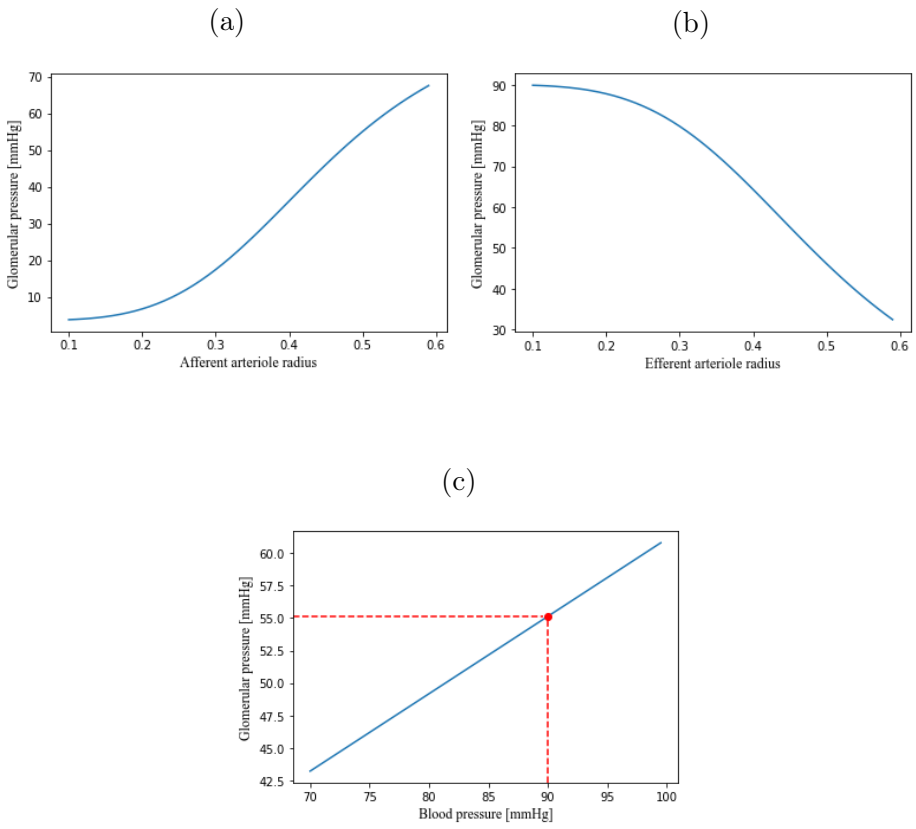

Figure 6: Glomerular Pressure relation towards model input variables. 6a (Top-left): Afferent arteriole radius vs Glomerular pressure. 6b (Top-right): Efferent arteriole radius vs Glomerular pressure. 6c (Bottom): Blood pressure vs Glomerular pressure. The red dashed line marks the value of glomerular pressure considering a physiological blood pressure.

3.1.2 SNGFR variable behaviour

Furthermore, Fig. 7 contains the same plots taking SNGFR as the dependent variable. Larger afferent arteriole radii also imply larger values of SNGFR, as it can be seen in Fig. 7a. When decreasing the efferent arteriole radius, SNGFR diminishes too, as shown in Fig. 7b. Moreover, Fig. 7c demonstrates that the linear dependence is also maintained between SNGFR and blood pressure. All three plots include ranges containing null values of SNGFR.

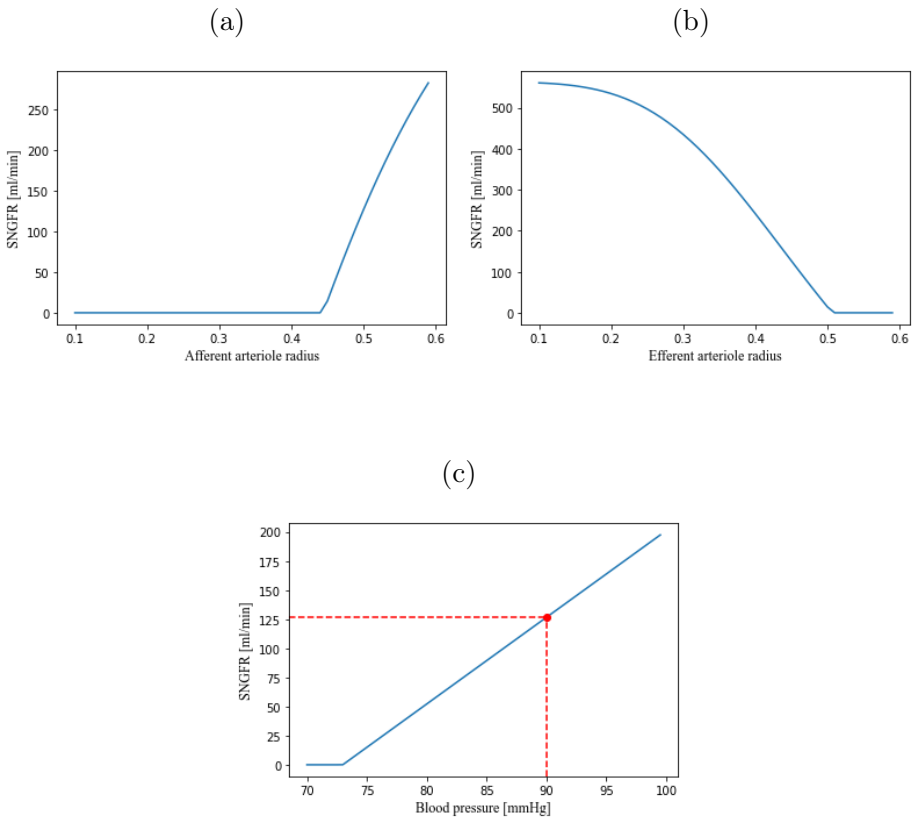

Figure 7: SNGFR relation towards model input variables. 7a (Top-left): Afferent arteriole radius vs SNGFR. 7b (Top-right): Efferent arteriole radius vs SNGFR. 6c (Bottom): Blood pressure vs SNGFR. The red dashed line marks the value of SNGFR considering a physiological blood pressure.

3.1.3 Urine volume variable behaviour

Fig. 8 reflects how urine volume is affected by varying the inputs of the software. The urine volume variable shows a similar behaviour to the previously presented SNGFR variable towards the first two input variables of the model. In Fig. 8a, it is shown that an increase in afferent arteriole radius value implies also an increase in the urine volume. Conversely, when increasing the efferent arteriole radius, the urine volume diminishes, as it can be seen in Fig. 8b. Furthermore, Fig. 8c illustrates that the relation towards the blood pressure input variable is now a logarithmic dependence.

The same behaviour is observed with respect to the SNGFR variable (see Fig. 8d), as it was previously stated in Eq. 8. All the plots include ranges containing null urine volume values.

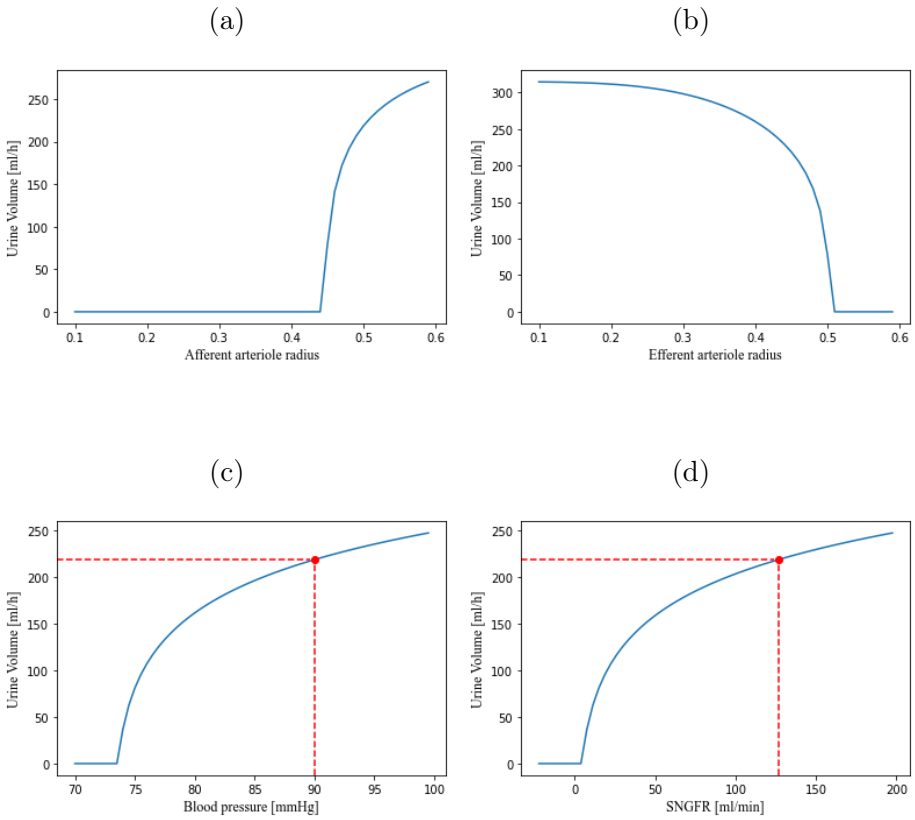

Figure 8: Urine volume relation towards model input variables and SNGFR. 8a (Top-left): Afferent arteriole radius vs Urine volume. 8b (Top-right): Efferent arteriole radius vs Urine volume. 8c (Bottom-left): Blood pressure vs Urine volume. 8d (Bottom-right): SNGFR vs Urine volume. The red dashed line (in Fig. 8c and Fig. 8d) marks the value of glomerular pressure considering physiological values of the independent variable.

3.2 RenPhy Simulator

The complete software has been packed in a distributable *.exe* file with its corresponding Windows Installer, created with InstallForge [23]. The EXE application, as well as the *.py* files and icons, have been delivered to the tutor of this project, Rubén Vicente, who is also the teacher of Renal Physiology at UPF. The idea is to make this software available to every student uploading it to MyApps [24]. MyApps is a cloud platform that allows students to access certain applications for academic use, without having to have them installed on their devices. It can be used from any device and browser, it is only necessary to have access to the Internet [25]. The transfer of RenPhy simulator to MyApps [24] has been performed by the UPF IT department.

As mentioned in the previous section, the software contains three interconnected windows. A simple initial panel, shown in Fig. 9, displays the logo of the program and two buttons. The button on the left, the one with the *play* icon opens the main window. And the right button with the *question mark* icon opens the additional information screen.

Regarding the main window, as it has been previously described in the Methods section, it contains a central illustration. On the left side, the user can introduce the input parameters, run the simulation or restore the default parameters. Moreover, on the right side of the screen, a box displays the output values calculated by the software. At the bottom part of the window, a table is displayed with some buttons on the right. These buttons activate some data management functions; the user can record or delete data of simulations, export or clear all the dataset saved. Finally, in the upper right corner, the button with the question mark connects again with the third window. An overlooking of this main window is provided in Fig. 10.

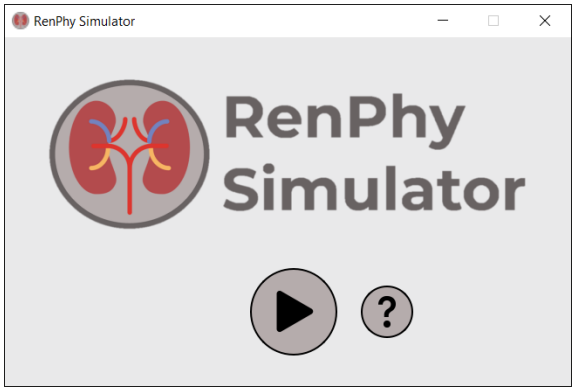

Figure 9: Initial window RenPhy Simulator. This welcoming window contains two buttons; one for starting the main page of the simulator (down-central button), and a second one to open the additional information window (down-right button).

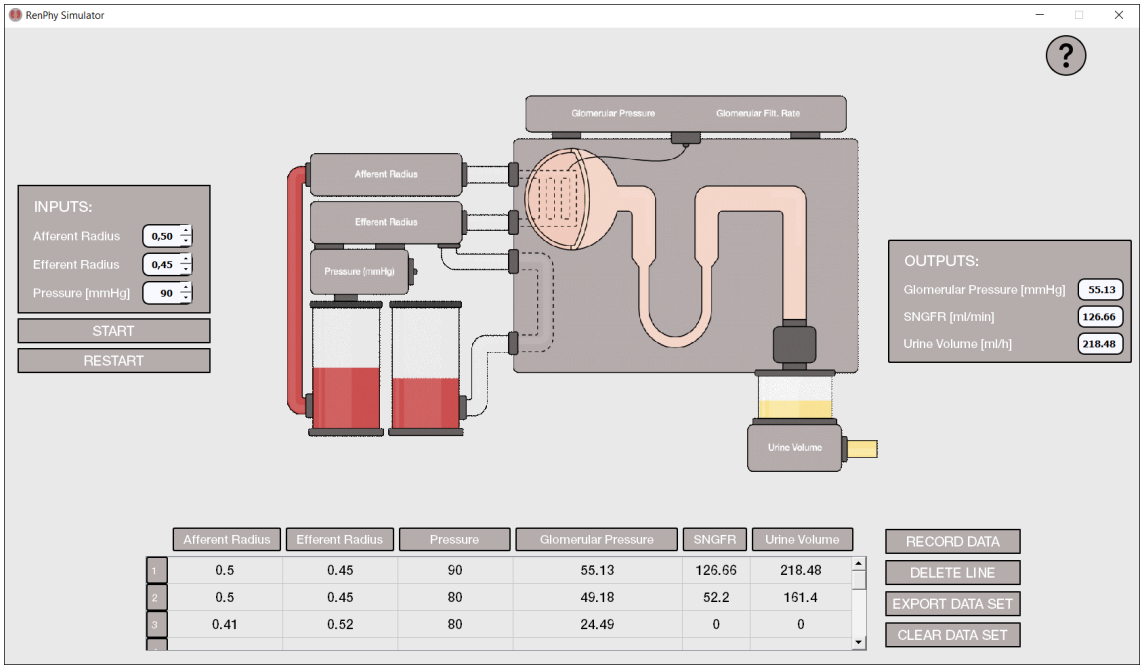

Figure 10: Initial window RenPhy Simulator. This welcoming window contains two buttons; one for starting the main page of the simulator (down-central button), and a second one to open the additional information window (down-right button).

Lastly, a third window was created in order to provide some additional information about the use of the software and some theoretical background notes. This third screen is shown in Fig. 11.

Figure 11: Additional information window RenPhy Simulator. This screen includes a software description, a theoretical background and credits.

4 Discussion

The numerical output values obtained from RenPhy Simulator end up being coherent and having appropriate magnitudes. When increasing the afferent arteriole radius, the inflow of blood to the glomerulus also increases, as the afferent resistance diminishes since it is inversely proportional to the radius of the vessel. These alterations lead to an increase in the glomerular pressure (see Fig. 6a) and, consequently, more filtrates and a rise is also observed in the SNGFR values (see Fig. 7a). Urine volume also increases (see Fig. 8a) as more blood has been filtered. On the other hand, an afferent arteriole radius reduction causes a diminution in the three model outputs; glomerular pressure (see Fig. 6a), SNGFR (see Fig. 7a) and urine volume (see Fig. 8a).

The modification of the efferent arteriole radius produces the exact opposite effect. When it diminishes, the outlet resistance increases, making the outflow of the glomerulus more complex. Therefore, glomerular pressure rises (see Fig. 6b), more blood plasma is filtered and finally, SNGFR and urine volume increase too (see Fig. 7b and Fig. 8b).

Similar to the afferent arteriole radius behaviour, with higher blood pressure values, the pressure in the glomerulus is also greater (see Fig. 6c). This leads to more filtration and an increase in both the values of SNGFR and urine volume (see Fig. 7c and Fig. 8c).

The relation between SNGFR and urine volume has also been plotted (see Fig. 8d) to show the logarithmic dependency already stated in Eq. 8. In some of the figures, a red dashed line was added to mark where the physiological magnitudes are located. All of the measurements evaluated have achieved consistent and realistic values.

Regarding the software itself, this new version resulted in an easy-to-use program with clear advantages over its predecessor, PhysioEx 6.0 [8]. The execution time

has been reduced and simulations can be performed much faster. Moreover, the data management functions added, offer new possibilities of learning activities, like plotting the magnitudes or making calculations with the complete dataset using complementary programs such as Excel [26]. In addition, the GUI appearance and all the corporate image work make the program more attractive for users.

The installation process has also been simplified as now there is no need to execute the program from a virtual Windows desktop. The application can be executed directly from MyApps [24] and will be available for all students taking the Physiology courses at UPF.

4.1 Limitations

This study has some limitations that should be noted. First of all, the mathematical model applied does not fully represent the functioning of the renal system since its autoregulation capacity has not been modelled. Autoregulatory mechanisms maintain a stable SNGFR for perfusion pressure between 90 and 180 mmHg [6] creating a plateau form in the pressure plot.

Furthermore, this software is only simulating glomerular filtration, leaving behind other important renal processes, such as reabsorption or secretion, which would also be very interesting to simulate and study while using the software.

4.2 Further work

As mentioned in the Limitations section, this software could be completed with a second simulation experiment reproducing renal reabsorption and secretion. Moreover, many other systems could be modelled and integrated into a good-looking platform. The methodology and proposal defined in this study could be implemented to any other vital process. For sure, these kinds of tools would be useful and interesting to apply in many other body functions.

5 Conclusions

In conclusion, a simulator based on a mathematical model of renal glomerular filtration was developed in order to be used only for academic purposes. It aims to be a useful tool for students of Biomedical studies taking Renal Physiology courses. The results showed that it presents numerous advantages over older similar alternatives, including new functions that would like to make the user learning experience even more complete. So far, the use of design platforms has helped in creating an attractive, good-looking interface that, at the same time, provides the user with consistent values.

As a final personal opinion, it has been a rewarding experience working on this thesis. I have been able to join together knowledge acquired from very different courses taken during my degree. I applied on this study physiological concepts, modelling and programming skills. It has been a nice way to end these four years at UPF, demonstrating the multidisciplinarity of Biomedical Engineers.

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