

Research Article

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CompVision: An open-source five-compartmental software for biokinetic simulations

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Abstract: Simulations and numerical analysis of physical problems are important steps toward understanding underlying mechanisms of the processes. Important examples would be medical physics and medical imaging. Compartmental modeling has been found useful for estimating the transport and temporal variations of drugs/contaminants (commonly used in medical physics and medical imaging) in different organs, given that different organs would be modeled as compartments. Recycling among these modeled compartments (i.e., organs) was allowed through defining sets of constant transfer rates. In order to mathematically define these systems, one needs to use sets of differential equations (depending on the number of compartments) which would in fact be time-consuming and prone to mathematical error. Considering these issues, there is a need for a versatile computer program that is accurate, robust, and user-friendly to perform the required computations automatically. In the present work, we developed and benchmarked an open-source computer program entitled CompVision that was able to simulate five-compartmental systems. The present software had an easy-to-use graphical user interface (GUI) for the users. The executable program and the source codes were made available publicly under GPLv3 license, which would allow everyone to use, modify, and distribute

without any restriction. The present program would be useful in a variety of research fields and applications.

Keywords: compartmental modeling, numerical analysis, differential equations, computer programming, open-source software

1 Introduction

Compartmental modeling was found to be very useful in a variety of applications. For example, in the research field of medical imaging, we previously reviewed the employment and importance of compartmental models in positron emission tomography (PET) imaging [1]. Another field was nuclear medicine, e.g., the human body was represented using five compartments, namely, (1) blood, (2) kidneys, (3) urinary bladder, (4) other organs, and (5) tumor [2]. The variations of certain drugs or, more generally, the contaminant in these five compartments could be explained using sets of differential equations [1–4]. Setting up these differential equations in each compartment in the system would in fact be a tedious and time-consuming task. In addition, one might need to perform a more in-depth analysis of factors that had influence on the temporal variations in the concentration of drugs or contaminants in these five compartments. Considering these, availability of an open-source computer program that can simply be used by users would be crucial to the research community. The present work was the continuation of our previously published work [4], to develop an open-source computer program with graphical user interface (GUI) for modeling five-compartment systems. The present model is versatile and provides full access to users to control all the parameters such as (1) intake and fraction of intake rate, (2) depuration zone, (3) volume of compartments, (4) initial concentration in each compartment, (5) uptake/excretion rates, (6) transfer rates, and (7) time domain. The present program would be a useful tool for future investigations, considering the rapid growth in the field of nuclear medicine and imaging.

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2 Materials and methods

2.1 Mathematical derivations and equations

Considering the compartment i in the system, the rate at which the concentration is changing can be described as

$$\frac{dx_i}{dt} = \sum_{j=1}^N r_{ji}x_j - x_i \sum_{j=1}^N r_{ij}, \quad (1)$$

where x_i is the concentration in compartment i , N is the number of compartments in the system, and r_{ij} is the set of transfer rates among all the compartments that are present in the system. From equation (1), it can be seen that the concentration of a compartment in the system is related to the concentrations of its neighboring compartments. The intake rate of drugs/contaminants from an outside source to compartment i is P_i and the uptake/excretion rate is $\xi_i x_i$, given ξ_i and x_i are constants and the concentrations, respectively. In addition, considering the varying compartment volumes, it would be possible to relate the number of drug/contaminant molecules (M_i) with the concentration (x_i) and the volume (V_i), which is simply $M_i = x_i V_i$, and knowing which we can have

$$\frac{d(V_i x_i)}{dt} = P_i + \sum_{j=1}^N r_{ji}x_j - x_i \left(\sum_{j=1}^N r_{ij} \right) - \xi_i x_i. \quad (2)$$

From equation (2), it can be noted that the diagonal elements are those at which $i = j$, so these can be defined as

$$r_{ii} = - \sum_{j=1}^N r_{ij} - \xi_i. \quad (3)$$

As mentioned in the previous work of Birchall and James [5], the diagonal elements could be replaced by the negative of the sum of every row element. Using equations (2) and (3), we can have a matrix form as

$$\frac{d(Vx)}{dt} = P + Rx. \quad (4)$$

In the present model, we considered the volume of each compartment to be a constant which did not change with time. Through defining $\mathbf{u} = \mathbf{x} + \mathbf{R}^{-1}\mathbf{P}$, where \mathbf{u} and \mathbf{R}^{-1} were column vector and the inverse matrix of \mathbf{R} , respectively, equation (4) could be written as

$$V \frac{du}{dt} = Ru. \quad (5)$$

Solving equation (5) and substituting the variable \mathbf{u} , the general solution to the time-dependent concentration $x(t)$ would be

$$x(t) = [\exp(V^{-1}Rt) - 1]R^{-1}P + \exp(V^{-1}Rt)x(0), \quad (6)$$

where V^{-1} was the inverse matrix of volume, R^{-1} was the inverse matrix of transfer rates, and t was the time. For a more detailed derivation, interested readers are referred to refs. [3,4] and references therein.

2.2 Program structure and implementation

The present computer program entitled CompVision was developed entirely using the FORTRAN90 programming language. The main reason behind this choice was its phenomenal computational speed and relatively low usage of system resources. CompVision had a GUI which allowed the users to input and control the required parameters such as (1) intake and fraction of intake rate, (2) depuration zone, (3) volume of compartments, (4) initial concentration in each compartment, (5) uptake/excretion rates, (6) transfer rates, and (7) time domain. Numerical simulations with a user-friendly GUI are important in a wide variety of research fields, e.g., dynamic food chain modeling of radionuclides [6–9], modeling of various pollutants in marine fauna [10–17], modeling of pollutant transport in the human respiratory tract [18,19], development of solar cells [20], etc. The main part of CompVision loaded the required modules for the GUI and the dialog control of the program. The dialog control called the dialog callback mainly in the form of synchronous callback. The dialog callback controlled and read the input of the program that was inputted by the user. These inputs were read in form of 256 character lengths and were then converted into double precision 8-byte real numbers which had 15 digits of accuracy. After the dialog callback obtained all the numbers, it would call the solver subroutine where all the parameters collected from the users' input would be passed to the solver function to perform the mathematical computations. There were multiple subroutines that would be called by the solver such as matrix exponential calculator, inverse matrix, etc. The main interface and the structure of CompVision are shown in Figure 1.

The GUI helped the user to input the required values for the program to function. The design and the structure of the GUI were kept minimal mainly for the ease of use and also to limit unnecessary code bloats. A total of 41 user input values were needed to be supplied to the present program. For the five-compartment system, we had a

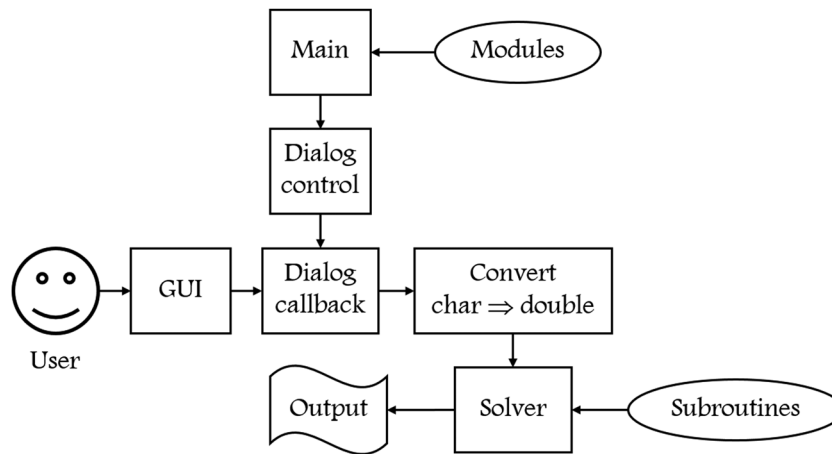


Figure 1: Main interface and structure of CompVision program elements.

5×5 transfer rate matrix (\mathbf{R}). As mentioned in the previous section, the diagonal elements of this 5×5 matrix were the negative of the sum of each row elements. Therefore, we ended up with a total of 20 ($5 \times 5 - 5 = 20$) transfer rates that required the input from the user. Other inputs to the program included the volume (total of 5 inputs), initial concentration (total of 5 inputs), and uptake/excretion rates (total of 5 inputs) of each compartment. In addition to these, the user would need to supply intake rate to compartment 1, fraction of the intake value which was actually supplied to the system, and the time at which intake to the system was halted. The time domain took the start value, the magnitude of the time steps, and the maximum cutoff time value. It should be noted that the time in this version of the program increased by multiplication of the step value with the preceding time point. The GUI of CompVision V-1.0 is shown in Figure 2. Microsoft PowerStation QuickWin run-time libraries and Microsoft Fortran libraries (using MSFLIB) were used in building the GUI.

The CompVision V-1.0 program and its source code could be downloaded from https://figshare.com/articles/software/CompVision_An_open-source_five-compartmental_software_for_biokinetic_simulations/14654118. The current version of our program is executable on Microsoft Windows systems. In addition, we have tested the present program in GNU/Linux environment using Wine and it worked well. CompVision does not require any installation and it can run in the portable mode. The executable file has a size on disk of about 516 kB. The CompVision is

distributed under GNU General Public License version 3 (GNU GPLv3).

3 Benchmarking and numerical tests

3.1 Case study 1: Extreme range of transfer rates

Similar to our previous work [4], we used the five-compartment model with extreme ranges of transfer rates introduced by Birchall and James [5]. The extreme transfer rates and time intervals that were used here were hypothetical to test the numerical performance of the present computer program. It is remarked here that these large and short time intervals might not correspond to real-life scenarios. These extreme ranges in the transfer rates would in fact challenge the numerical accuracy and stability of our program. The system setup and transfer rates for this numerical example are shown in Figure 3.

The temporal variations of concentrations in the five different compartments obtained by Birchall and James [5] and by CompVision are compared in Table 1. Good agreement between the reported results was shown. It is remarked here that the model developed by Birchall and James [5] was relatively more simplified, for example, the volume of each compartment and the uptake/excretion

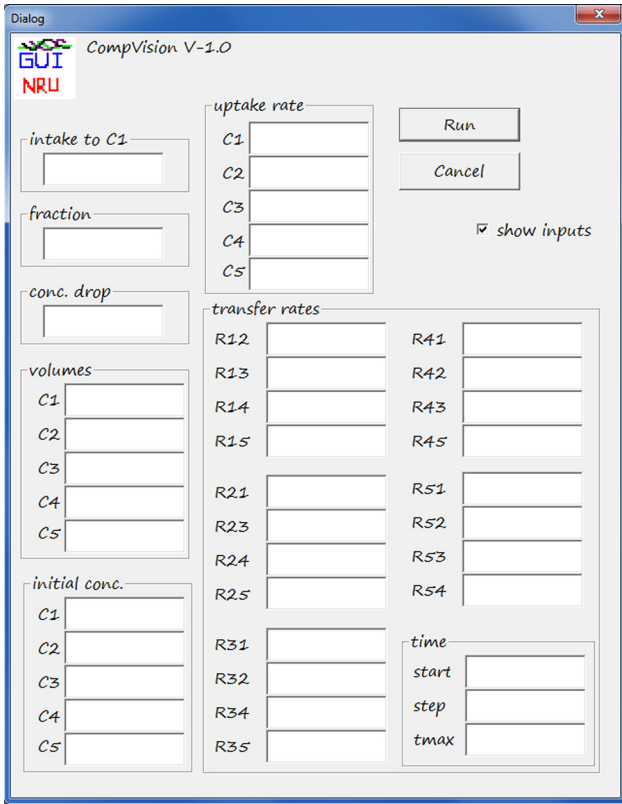


Figure 2: Graphical user interface (GUI) of CompVision V-1.0 program.

rates were not considered. Such a difference in the mathematical models led to some discrepancies between the results shown in Table 1.

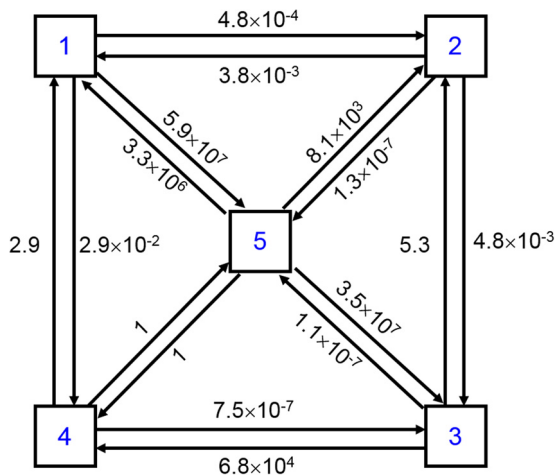


Figure 3: Simulated five-compartmental model of Birchall and James [5] with extreme ranges of transfer rates.

Table 1: Comparisons among contaminant concentrations in five different compartments obtained by Birchall and James [5] and those obtained by our present model

Time	1 (ref. [5])	1 (CompVision)	2 (ref. [5])	2 (CompVision)	3 (ref. [5])	3 (CompVision)	4 (ref. [5])	4 (CompVision)	5 (ref. [5])	5 (CompVision)
10^{-8}	1.16×10^1	1.16×10^1	2.00×10^1	2.00×10^1	2.73×10^1	2.73×10^1	2.00×10^1	2.00×10^1	2.11×10^1	2.10×10^1
10^{-7}	2.79×10^{-1}	2.79×10^{-1}	2.00×10^1	2.00×10^1	5.73×10^1	5.73×10^1	2.03×10^1	2.03×10^1	2.15×10^1	2.15
10^{-6}	1.32×10^{-6}	1.34×10^{-6}	2.00×10^1	2.00×10^1	5.61×10^1	5.61×10^1	2.38×10^1	2.38×10^1	2.64×10^{-6}	2.67×10^{-6}
10^{-5}	2.74×10^{-6}	2.76×10^{-6}	2.00×10^1	2.00×10^1	3.04×10^1	3.04×10^1	4.95×10^1	4.95×10^1	5.51×10^{-6}	5.54×10^{-6}
10^{-4}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	7.15×10^{-2}	7.15×10^{-2}	7.99×10^1	7.99×10^1	8.90×10^{-6}	8.93×10^{-6}
10^{-3}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
10^{-2}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
10^{-1}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
1	4.44×10^{-6}	4.46×10^{-6}	1.99×10^1	1.97×10^1	4.59×10^{-3}	4.62×10^{-3}	8.01×10^1	8.03×10^1	8.92×10^{-6}	8.97×10^{-6}
10^1	4.47×10^{-6}	4.59×10^{-6}	1.93×10^1	1.75×10^1	4.63×10^{-3}	4.75×10^{-3}	8.07×10^1	8.25×10^1	8.99×10^{-6}	9.22×10^{-6}
10^2	4.70×10^{-6}	5.11×10^{-6}	1.52×10^1	8.03	4.86×10^{-3}	5.29×10^{-3}	8.48×10^1	9.20×10^1	9.45×10^{-6}	1.03×10^{-5}
10^3	4.86×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.77×10^1	9.39×10^1	9.77×10^{-6}	1.05×10^{-5}
10^4	4.86×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.77×10^1	9.39×10^1	9.77×10^{-6}	1.05×10^{-5}
10^5	4.88×10^{-6}	5.22×10^{-6}	1.24×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.81×10^1	9.39×10^1	9.82×10^{-6}	1.05×10^{-5}
10^6	4.84×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.01×10^{-3}	5.40×10^{-3}	8.73×10^1	9.39×10^1	9.73×10^{-6}	1.05×10^{-5}
10^7	4.97×10^{-6}	5.22×10^{-6}	1.26×10^1	6.11	5.14×10^{-3}	5.40×10^{-3}	8.97×10^1	9.39×10^1	9.99×10^{-6}	1.05×10^{-5}
10^8	1.12×10^{-5}	5.22×10^{-6}	2.83×10^1	6.11	1.16×10^{-2}	5.40×10^{-3}	2.02×10^2	9.39×10^1	2.25×10^{-5}	1.05×10^{-5}

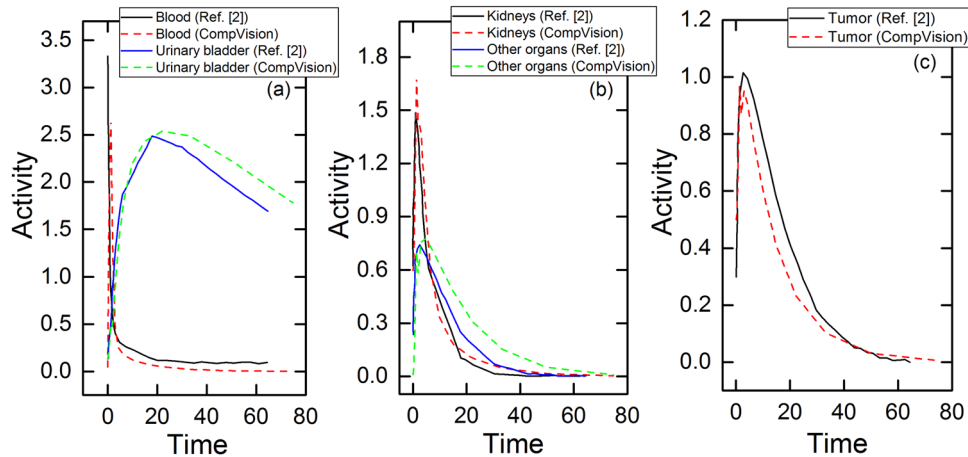


Figure 4: Comparisons between temporal activity curves of ^{90}Y -DOTATOC obtained by Jeremic *et al.* [2] and CompVision for (a) blood and urinary bladder, (b) kidneys and other organs, and (c) tumor.

3.2 Case study 2: Biokinetics of ^{90}Y -DOTATOC in human body

For this case study, we used the five-compartmental model introduced in the previous work of Jeremic *et al.* [2]. The human body was modeled using five-compartments, namely, (1) blood, (2) kidneys, (3) urinary bladder, (4) other organs, and (5) tumor (see Figure 4). The drug was administered into compartment 1 (i.e., blood), from which the drug would then be transferred to other compartments. In this example, the activities in these five-compartments were determined and compared with the previously reported results, and the comparisons are shown in Figure 4.

The obtained temporal activity curves from CompVision were in good agreement with results previously reported by Jeremic *et al.* [2]. The intake was supplied through the blood compartment and therefore the activity for this compartment increased rapidly in the early time intervals. Other compartments such as kidneys, tumor, urinary bladder, and other organs were also interconnected with the blood compartment, so that in later time intervals the activities in these compartments started to increase. After some time, the intake to blood was stopped and therefore the activity in this compartment was reduced. For other compartments, smoother decreases in the activities with time were noticed, which were attributed to recycling among these compartments with different transfer rates. In addition, as a result of excretion, the activities versus time for all compartments in general followed a descending trend. Interested readers are referred to ref. [2] for more details. Some noticeable differences were attributed to employment of different mathematical models, since Jeremic *et al.* [2] did not consider the volume of compartments. The volume of different

compartments (i.e., in this case would be organs) could be vastly different in realistic scenarios, so these parameters were considered in our model. To facilitate more direct comparisons, we set the volumes of these five-compartments to unity. In addition, we chose the best initial concentrations from the reported curves and excretion rates to obtain a good estimate of these results. The intake rate value into compartment 1 (i.e., blood) was set to 4.5 GBq as reported by Jeremic *et al.* [2] and therefore the obtained results of time-activity would also be in GBq unit. In addition, the time unit is in hour, given that the transfer rate units were in h^{-1} [2].

4 Conclusion

In the present work, we introduced and discussed the development of an open-source five-compartmental computer program entitled CompVision. The present program could simulate temporal changes in the concentrations of drugs/contaminants in the considered compartments. An open-source program was presented here, which could be changed/modified by users to perform computations specific to their studied systems. The present program would be useful in a variety of applications, ranging from environmental physics to medical physics and imaging. We hope to further expand this program to be used for multi-compartmental cases (i.e., cases with more than five compartments). This user interface can be used in various research fields including biokinetics and pharmacokinetics simulations, tracer tracking, physiological modeling, environmental-radioactivity modeling, pollutant modeling, nuclear medicine and imaging (e.g., PET), and

internal dosimetry. In particular, the present user interface would be useful if one would like to track the temporal changes of a studied substance in different spatial sections. The important features of this user interface include the ease of use, low usage of system resources, small size of the program, ability to execute in portable mode (no installation required), cross platform support (can run on both Microsoft Windows and Linux machines), and its optimized computational speed. Last but not the least, the present program is open-source which enables users to modify, debug, and execute the program for their desired specific application. In the future, we aim to further develop the present user interface by incorporating different numerical techniques.

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