Kinetics of intravenous radiographic contrast medium injections as used on CT: simulation with time delay differential equations in a basic human cardiovascular multicompartment model

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Objectives: To develop a multicompartment model of only essential human body components that predicts the contrast medium concentration vs time curve in a chosen compartment after an intravenous injection. Also to show that the model can be used to time adequately contrast-enhanced CT series.

Methods: A system of linked time delay instead of ordinary differential equations described the model and was solved with a Matlab program (Matlab v. 6.5; The Mathworks, Inc., Natick, MA). All the injection and physiological parameters were modified to cope with normal or pathological situations. *In vivo* time–concentration curves from the literature were recalculated to validate the model.

Results: The recalculated contrast medium time–concentration curves and parameters are given. The results of the statistical analysis of the study findings are expressed as the median prediction error and the median absolute prediction error values for both the time delay and ordinary differential equation systems; these are situated well below the generally accepted maximum 20% limit.

Conclusion: The presented program correctly predicts the time–concentration curve of an intravenous contrast medium injection and, consequently, allows an individually tailored approach of CT examinations with optimised use of the injected contrast medium volume, as long as time delay instead of ordinary differential equations are used.

Advances in knowledge: The presented program offers good preliminary knowledge of the time–contrast medium concentration curve after any intravenous injection, allowing adequate timing of a CT examination, required by the short scan time of present-day scanners. The injected volume of contrast medium can be tailored to the individual patient with no more contrast medium than is strictly needed.

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The technical development of CT during recent years, not least with the introduction of fast multidetector CT and the consequent reduction in scan time duration, has resulted in frequent adaptation of acquisition protocols to take advantage of this technological improvement.

The very short scan time requires adequate timing of the intravenous contrast medium injection and an individually tailored contrast bolus that takes into account, for example, contrast medium concentration, volume and injection rate because many individual physiological parameters are beyond the examiner's control. This is certainly true for vascular examinations, but also, and increasingly, for parenchymal organ examinations.

Today's scanners are extremely fast. Therefore, contrast density thresholding can occasionally lead to examinations carried out too early in the enhancement phase. One means of handling this timing problem is to work with bolus-tracking systems [CARE (Siemens AG, Erlangen, Germany), Smart-Prep (General Electric, Milwaukee, WI), Sure Start (Toshiba, Tokyo, Japan) etc.] as provided by the different CT manufacturers.

Another approach studies “the patient factor” based on analysis of the injection of a small test bolus [1, 2] and the consequent determination of adequate injection factors. Yet others have proposed a pharmacokinetic compartmental model [3, 4]. This complex multicompartment model results in a system of many (>100) linked ordinary differential equations (ODEs) that can be solved numerically, yielding a time–concentration curve in the desired compartment.

It was the goal of this study to introduce a simplified and very basic multicompartment model, based on a system of linked time delay differential equations (DDEs), with modifiable physiological and injection factors and modalities. The number of differential equations to be solved in this model is markedly reduced with respect to previously proposed systems of ODEs [3, 4]. As shown, the solution of this system of DDEs provides good knowledge of the time–concentration curve for the projected injection, allowing correct timing of the planned CT examination. The model can be used for vascular and some parenchymal studies (liver, pancreas etc.), leading to an optimal individualised enhancement during the examination. The generated data enable the amount of contrast medium injected to be restricted to no more than is strictly required.

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Materials and methods

Compartments

In a hypothetical single physiological compartment (Figure 1), according to the principle of mass balance, the quantity of a substance within the compartment as a function of time is the difference between the amount of this substance entering the compartment and the amount leaving it, leading to the following basic differential equation:

$$\frac{d(V_c \cdot C_c)}{dt} = Q_{in} \cdot C_{in} - Q_{out} \cdot C_{out}$$

or

$$\frac{dC_c}{dt} = \frac{Q_{in}}{V_c} \cdot C_{in} - \frac{Q_{out}}{V_c} \cdot C_{out}$$

assuming that the volume of the compartment remains constant during the time of observation. This equation relates volume (V), concentration (C) and rate (Q), or the compartment (c), the incoming stream (in) and the outgoing stream (out).

Only those body regions in which contrast medium exerts an opacifying effect [5], which are necessary for the analysis of the time–concentration curve after an intravenous injection, were included in a simple multi-compartment model (Figure 2).

The vein used to inject the contrast medium and its collaterals constitute a compartment on their own.

The driving force of the circulation (right heart, left heart), together with the lungs, is simulated by three distinct compartments in which individual blood volumes can be allocated for any individual patient.

The liver is included in this model because the analysis of the different phases of its enhancement is important in many pathological situations; consequently, the presence of the intestines (seen as a compartment including the pancreas and the spleen) as a separate compartment is mandatory because the portal vein return is, together with the hepatic artery, responsible for the special time-related enhancement of the liver. The description of the liver necessitates the implementation of the intravascular compartment and the extravascular extracellular compartment; indeed, radiographic contrast medium does not penetrate the intracellular space, so that two spaces

Figure 1. In a one-compartment model, the quantity of a substance at a given point in time equals the difference between the amount of the substance coming in and the amount going out. C_c , concentration of the considered substance in this compartment; V_c , volume of the considered compartment.

Figure 2. Scheme of the implemented multi-compartment model. IV, intravenous; LH, left heart; RH, right heart.

or volumes (intravascular and extravascular extracellular) suffice.

The system compartment represents the remaining part of the body. The liver and the system return their blood to the right heart.

Physiological data

The average volumes of the different compartments (Table 1) were taken from the literature [1, 2, 6–8]. These volumes can be altered as required and are adjusted for patient height (H) and weight (W) in relation to the blood volume: blood volume = $a \times [(H/2.54)^{0.725} \times (W/2.2)^{0.425}] - b$, with $a = 33.164$ and $b = 1.229$ for male patients, and $a = 34.85$ and $b = 1.954$ for female patients [3]. An organ can be described with essentially three spaces: namely, an intravascular space, an extravascular extracellular space and an extravascular intracellular space. The passive diffusion between these two extravascular spaces can be described by Fick's law, as will be done in the proposed model; the permeability factor in the equations describing Fick's law is set to 4, with the interstitial volume fractions of blood (0.48) and tissue (0.04) in the computation of the time–iodine concentration curve [7].

The flow rates are as follows [3, 4]: the venous flow rate is 4.2 ml s^{-1} , the cardiac output (CO) in ml s^{-1} is calculated by $36.36 \times [(H/2.54)^{0.725} \times (W/2.2)^{0.425}] / 60$, where

Table 1. Volumes of the different compartments of the model

Compartment	Volume (ml)
Veins	35
Right heart	250
Lungs	250
Left heart and aorta	450
Liver intravascular	71
Liver extracellular	524
Intestines, portal system, spleen and pancreas	2500
Kidneys	300
System	7000

height is in centimetres and weight is in kilograms. The CO is corrected for age with $CO \times [1 - (\text{age} - 30) \times 1.01 / 100]$ [9].

The fraction of the CO going to the systemic circulation is 0.43, to the hepatic artery 0.07, to the kidney 0.20, and to the intestines and spleen 0.30 [6, 10].

The renal clearance is calculated with the Cockcroft and Gault formula: $\text{clearance} = \{[(140 - \text{age}) \times W] / (72 \times \text{serum creatinine})\} \times Q$, where $Q = 1.00$ for male patients and $Q = 0.85$ for female patients [11]. The volume of urine excreted is set to 2000 ml per 24 h.

Injection parameters

The injection parameters under consideration are the concentration of the contrast medium, the volume and the injection rate.

The injection modalities available are continuous rate (the only one considered in this communication), exponential deceleration and biphasic. These modalities are programmed with corresponding step functions in the differential equation describing the injected venous compartment. The step function takes account of the injection duration(s) in the differential equation under consideration.

Mathematics

A system of 10 coupled differential equations (one for each compartment, except for the liver, which needs two equations—one intravascular and one extravascular) can

be determined using the models stated above. Table 2 summarises the differential equations. In Matlab (Matlab v. 6.5; The Mathworks, Inc., Natick, MA), these 10 ODEs can be numerically solved with the Runge–Kutta method. It became possible to include time lags in the model by using DDEs; it has become possible recently to solve these numerically in Matlab with the “dde23” algorithm [12].

These time lags (Table 3), based on known circulation times [13], allow for a more physiological description of the circulation (*e.g.* realistic delays between the onset of the injection and the arrival of the contrast medium in a target organ, and a realistic simulation of the venous return to the right heart), creating coupled DDEs in the system of simultaneous equations. These DDEs depend on the system state at earlier times, whereas in ODEs the derivatives depend only on the current value of the independent variable. For the sake of comparison, all data were also examined with a system of ODEs with the same data as the DDEs, except for the time delays.

Analysed data

We attempted to validate the solution of the coupled DDEs by recalculation of the injection results (time–concentration or time–attenuation curves) reported in the literature. Acquisition of time–concentration data from serial scans after a specific injection at a specific anatomical point or region only for investigational reasons was considered ethically inappropriate in this setting for patients undergoing only diagnostic CT.

Table 2. Summary of the delay differential equations describing the mass of contrast medium in the different compartments of the model (venous, right heart, pulmonary, left heart, intestine, liver intravascular, liver extravascular extracellular, system, kidney, urine) varying with time (dt)

$$\begin{aligned} \frac{d(V_r \cdot c_r)}{dt} &= H(Q_{cm} \cdot c_{cm}) - Q_v \cdot c_r \\ \frac{d(V_r \cdot c_r)}{dt} &= Q_v \cdot (\text{lag}) c_v + F_{sys} \cdot Q_l \cdot (\text{lag}) c_{sys} + (F_{ah} + F_{int}) \cdot Q_l \cdot (\text{lag}) c_{iv} + F_{ki} \cdot Q_l \cdot (\text{lag}) c_{ki} - Q_r \cdot c_r \\ \frac{d(V_{pu} \cdot c_{pu})}{dt} &= Q_r \cdot (\text{lag}) c_r - Q_{pu} \cdot c_{pu} \\ \frac{d(V_l \cdot c_l)}{dt} &= Q_{pu} \cdot (\text{lag}) c_{pu} - Q_l \cdot c_l \\ \frac{d(V_{int} \cdot c_{int})}{dt} &= F_{int} \cdot Q_l \cdot (\text{lag}) c_l - F_{int} \cdot Q_l \cdot c_{int} \\ \frac{d(V_{iv} \cdot c_{iv})}{dt} &= F_{ah} \cdot Q_l \cdot (\text{lag}) c_l + F_{int} \cdot Q_l \cdot (\text{lag}) c_{int} - (F_{ah} + F_{int}) \cdot Q_l \cdot c_{iv} - P.S. \cdot (c_{iv} - c_{ec}) \\ \frac{d(V_{ec} \cdot c_{ec})}{dt} &= P.S. \cdot (c_{iv} - c_{ec}) \\ \frac{d(V_{sys} \cdot c_{sys})}{dt} &= F_{sys} \cdot Q_l \cdot (\text{lag}) c_l - F_{sys} \cdot Q_l \cdot c_{sys} \\ \frac{d(V_{ki} \cdot c_{ki})}{dt} &= F_{ki} \cdot Q_l \cdot (\text{lag}) c_l - F_{ki} \cdot Q_l \cdot c_{ki} - \frac{Cl}{60} \cdot c_{ki} \\ \frac{d(V_{ur} \cdot c_{ur})}{dt} &= c_{ki} \cdot \frac{Cl}{60} \end{aligned}$$

c_{cm} , concentration of the contrast medium; c_{ec} , contrast medium concentration in the extravascular extracellular liver compartment; c_{int} , contrast medium concentration in the intestinal compartment; c_{iv} , contrast medium concentration in the intravascular liver compartment; c_{ki} , contrast medium concentration in the kidney compartment; c_l , contrast medium concentration in the left heart compartment; c_{pu} , contrast medium concentration in the pulmonary compartment; c_r , contrast medium concentration in the right heart compartment; c_{sys} , contrast medium concentration in the system compartment; c_{ur} , contrast medium concentration in the cumulated 24 h urine; c_v , contrast medium concentration in the venous compartment; Cl , clearance of contrast medium (calculated as per second); F_{ah} , fraction of the cardiac output to the hepatic artery; F_{int} , fraction of the cardiac output to the intestine compartment; F_{ki} , fraction of the cardiac output to the kidney compartment; F_{sys} , fraction of the cardiac output to the arterial intestinal circulation; H , step function; lag , use of time lag in delay differential equations; $P.S.$, permeability factor in Fick's law; Q_{cm} , flow rate of the contrast medium into the venous compartment; Q_l , flow rate of the left heart; Q_{pu} , flow rate in the pulmonary compartment; Q_r , flow rate of the right heart; Q_v , venous flow rate; V_{ec} , volume of the extravascular extracellular liver compartment; V_{int} , volume of the intestinal compartment; V_{iv} , volume of the intravascular liver compartment; V_{ki} , volume of the kidney compartment; V_l , volume of the left heart compartment; V_{pu} , contrast medium concentration in the pulmonary compartment; V_r , volume of the right heart compartment; V_{sys} , contrast medium concentration in the system compartment; V_{ur} , volume of urine in 24 h; V_v , volume of the venous compartment.

Table 3. Time lags to different target compartments

Target	Delay (s)
Vein to right heart	3
Right heart to lung	2
Lung to left heart	1
Left heart to liver	3
Intestine to portal vein	4
Liver to right heart	1
System to right heart	15

To replace these serial acquisition data, seven aortic [3, 14–19] and three hepatic [3, 18, 19] enhancement curves were borrowed from the literature. One author [16] provided standard deviations for the measured data; these are shown in Figure 6. Some authors give the standard deviation of the mean peak enhancement (382.6 ± 49.9 HU in the aorta and 52.6 ± 9.0 HU in the liver [19]; 210 ± 43 HU in the aorta after an injection at 2 ml s^{-1} and 364 ± 70 HU after 5 ml s^{-1} [18]).

Statistical analysis

To compare the experimental (measured) and calculated (or predicted) data, the median prediction error (MDPE) and the median absolute prediction error (MDAPE) values were computed [20–22] and expressed as a percentage. A value $<20\%$ was considered acceptable [23]. The MDPE, a signed value, is a measure of the goodness of fit and represents the direction of over- or underprediction; the MDAPE is a measure of the accuracy or the size of the error [20, 23].

In the data from the literature one finds either an enhancement difference between an enhanced and unenhanced organ or an absolute enhancement value, both Hounsfield unit values being kilovoltage dependent. The program that we used calculates a kilovoltage-independent time–iodine concentration curve in mgI ml^{-1} . For comparison, however, an interconversion factor of 22.65 HU per mgI ml^{-1} was used [24].

Results

For the seven aortic [3, 14–19] and three hepatic [3, 18, 19] data point graphs from the literature, the corresponding patient and injection parameters were fed into the program. The time–concentration (expressed in mgI ml^{-1}) curves in the selected compartments were calculated and added to the individual graphs (Figures 3–11).

The curves calculated with the DDE systems fit well visually to the experimental data. Indeed, the times of maximum contrast medium concentration correspond, and the overall shape of the curves fits well. The times of maximal enhancement, both measured and calculated, are compared (Table 4).

The MDPE and MDAPE between the experimental and calculated data are shown (Table 4). They are well situated below the accepted maximum 20% limit, indicating an at least acceptable goodness of fit, as far as the DDE data are concerned. The fit with the ODE calculated data is less good, as is shown by the MDPE and MDAPE data regularly being greater than the accepted 20%.

Figure 3. Computed data (continuous curve) and Bae et al [3] measured data (+) (125 ml at 2.5 ml s^{-1} of 320 mgI ml^{-1}).

Figure 4. Computed data (continuous curve) and Knollmann and Coakley [14] measured data (+) (160 ml at 3.5 ml s^{-1} of 370 mgI ml^{-1}).

Figure 5. Computed data (continuous curve) and Fleischmann et al [15] measured data (+) (120 ml at 4.0 ml s^{-1} of 300 mgI ml^{-1}).

Figure 6. Computed data (continuous curve) and Platt et al [16] measured data (+) with standard deviations (150 ml at 4.0 ml s^{-1} of 300 mg l ml^{-1}).

Figure 7. Computed data (continuous curve) and Kim et al [18] measured data (+) (90 ml at 2.0 ml s^{-1} or at 5.0 ml s^{-1} of 300 mg l ml^{-1}).

Figure 8. Computed data (continuous curve) and Awai et al [17] measured data (+) (95 ml at 2.7 ml s^{-1} or at 3.8 ml s^{-1} of 300 mg l ml^{-1}).

Figure 9. Computed data (continuous curve) and Tatsugami et al [19] measured data (+) (100 ml at 5.0 ml s^{-1} of 300 mg l ml^{-1}).

Figure 10. Computed data (continuous curve) and Kim et al [18] measured data (+) (90 ml at 5.0 ml s^{-1} of 300 mg l ml^{-1}).

Figure 11. Computed data (continuous curve) and Tatsugami et al [19] measured data (+) (100 ml at 5.0 ml s^{-1} of 300 mg l ml^{-1}).

Table 4. Time ($T_{\max}$) of maximum enhancement (s) for the measured data and the calculated values. Median prediction error (MDPE) and median absolute prediction error (MDAPE) results for the different control studies, as computed with a time delay differential equation (DDE) or ordinary differential equation (ODE) system

Data source	Reference	Volume (ml)	Rate (ml s ⁻¹)	Content (mg ml ⁻¹)	$T_{\max}$ measured (s)	$T_{\max}$ DDE calculated (s)	$T_{\max}$ ODE calculated (s)	MDPE DDE	MDAPE DDE	MDPE ODE	MDAPE ODE
Aorta											
Bae et al	3	125	2.5	320	53		53	2.7	7.9	7.7	7.7
Knollmann and Coakley	14	160	3.5	370	55		48	-3.3	7.1	-2.5	6.3
Fleishmann et al	15	120	4.0	300	41		34	-6.2	6.9	-1.0	32.8
Platt et al	16	150	4.0	300	45		41	0.4	1.6	-0.4	11.4
Awai et al	17	95	2.7	300	42		49	-4.9	9.3	34.7	38.6
Awai et al	17	95	3.8	300	30		39	-0.3	8.7	17.1	32.5
Kim et al	18	90	5.0	300	26		22	-1.8	6.9	34.9	36.7
Kim et al	18	90	2.0	300	50		48	-2.2	3.8	10.5	21.1
Tatsugami et al	19	100	5.0	300	27		24	-0.6	5.6	16.1	25.6
Liver											
Bae et al	3	125	2.5	320	83		70	-6.8	9.7	-16.1	31.0
Kim et al	18	90	5.0	300	56		38	-4.0	5.9	>100.0	>100.0
Tatsugami et al	19	100	5.0	300	60		39	0.0	1.3	-4.2	4.2

Discussion

Although current non-ionic radiographic contrast media are generally considered safe, there are still exceptional acute adverse reactions, and radiologists are responsible for volume-related complications including contrast-induced nephropathy [25]. The use of the lowest possible volume of contrast medium is thus imperative to avoid, where possible, these volume-related adverse events.

It is the radiologist's responsibility to make the best possible use of the injected dose of iodine. This can be done by tailoring the CT examination to the time-concentration curve of the injected contrast medium, or by adapting the injection parameters and consequent time-concentration curve to the projected examination.

In both cases, an optimal CT examination can be performed with a lesser volume of contrast medium, reducing the patient's contrast load and, consequently, the cost of the examination.

Previous computer simulation models were based on the solution of a system of up to 100 ODEs [3]. The presented solution is a simplified multicompartment model of the human cardiovascular system. These compartments are described with the necessary DDEs, based on the mass balance principle, allowing for time delays between successive compartments to be more realistically simulated. The simplification of the model and the incorporation of time delays and the consequent use of DDEs differentiate this study from other similar studies.

Besides the parameters governing contrast medium administration (volume, injection rate and concentration), individual patient parameters such as height, weight, sex and age can be modelled.

To validate the presented program, data from time-concentration curves were retrospectively modelled. It was not considered practical to prospectively test the model on patients as this required enrolling them in a single-level serial CT examination, without further clinical benefit [18]. These literature results were remodelled using as many parameters as possible when available. This had the advantage of offering a variety of data and settings. Some curves were means of small patient groups; where tabulated standard deviation data were available, they were added to the graph.

To compare statistically the results of the calculated time-concentration curves and the literature data, the MDPE and the MDAPE values were computed and expressed as percentages [20, 21]. The goodness of the fit (MDPE) of the predicted values with the observed literature data is considered good, as is the accuracy with an MDAPE <10% in all control cases. An MDAPE value <20% is generally considered to be good. This is not the case for the calculated ODE data. The differences between the measured and calculated data are the result of several factors, including individual factors other than weight, age etc. that are difficult to capture in physiological data [1, 2]; Fleischmann [26] tried to include these in his "patient factor" after mathematical analysis of a test injection. Perhaps contributing even more to the difference between the measured and calculated data are the scan parameters that influence largely on the attenuation of iodine—the literature data are mostly expressed in Hounsfield units, and not in iodine concentrations—and on the other hand the small empiric measurement noise and errors. The times

of maximum enhancement, both measured and calculated, correspond well. The physiological time lags incorporated in the DDEs (Table 3) also produce aortic time–concentration curves with a realistic recirculation peak as can be seen in Figure 3. The results of this study suggest that time–concentration predictions are better formulated after calculations with a DDE system than with ODEs.

There is a body of literature concerning clinical studies of varying injection regimens and their effect on CT imaging of different body regions; these studies are mostly based on empirical findings. However, the wide physiological variability between patients results in subsequent variability in examinations.

The availability of a well-predicted time–concentration enhancement curve for a particular region or organ, with a given set of injection parameters, makes the exact timing of a CT examination possible in any desired compartment. The use of the injected contrast medium bolus can be optimised or, when a desired contrast medium concentration is *a priori* selected, the bolus can be tailored accordingly.

As a further development of the program, data resulting from aortic flow measurements during preliminary ultrasound Doppler examination could be incorporated; this would require a new validation study. The acquisition of more patient results in everyday clinical practice with this program, and with knowledge of more clinical data such as cardiac status, is a subject for future research.

Finally, this program could also be used for the time–concentration calculation of other pharmacological agents with initially identical kinetics and distribution, such as gadolinium-based contrast media.

Conclusion

The presented program is based on the mass balance principle. This principle is applied to the different compartments of a simple cardiovascular and splanchnic model. Accordingly, the compartments are described with time DDEs. The solution of this system of equations produces a time–concentration curve in any desired compartment of the model for a given contrast medium intravenous injection.

The results suggest that a system of DDEs is superior to an ODE system in the prediction of time–concentration data.

This knowledge allows an individually tailored CT examination to be performed. The contrast medium volume injected can be reduced, contributing to the prevention of volume load-related adverse events, such as contrast-induced nephropathy.

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