Patient-informed modelling of hepatic contrast dynamics in contrast-enhanced CT imaging

Setiawan, Hananiel, Abadi, Ehsan, Ria, Francesco, Fu, Wanyi, Smith, Taylor, et al.

Hananiel Setiawan, Ehsan Abadi, Francesco Ria, Wanyi Fu, Taylor B. Smith, Ehsan Samei, "Patient-informed modelling of hepatic contrast dynamics in contrast-enhanced CT imaging," Proc. SPIE 11312, Medical Imaging 2020: Physics of Medical Imaging, 1131214 (16 March 2020); doi: 10.1117/12.2548879

SPIE.

Event: SPIE Medical Imaging, 2020, Houston, Texas, United States

Patient-informed modelling of hepatic contrast dynamics in contrast-enhanced CT imaging

Hananiel Setiawan[a,b], Ehsan Abadi[a,e], Francesco Ria[a,e], Wanyi Fu[a,c], Taylor B. Smith[a,b], Ehsan Samei[a,b,c,d,e]

[a]Carl E. Ravin Advanced Imaging Laboratories, [b]Medical Physics Graduate Program, [c]Department of Electrical and Computer Engineering, [d]Department of Biomedical Engineering, [e]Department of Radiology,
Duke University, Durham, NC USA

ABSTRACT

Iodinated contrast agent is frequently used in computed tomography (CT) imaging to enhance organ contrast enhancement and improve diagnostic sensitivity. Despite this importance, there currently is a lack of standardization in contrast administration protocol across institutions, leading to many safety and clinical diagnostic risks. To solve this, we built three liver contrast enhancement/perfusion models: two using simple linear regression and another by combining a pre-existing pharmacokinetics mathematical model with clinical data with the eventual goal of individualizing contrast administration protocol to optimize contrast-enhanced CT imaging for each patient. These models primarily use patient attributes, such as height, weight, sex, age and contrast administration information, and bolus tracking information to make such predictions. 418 Chest/Abdomen/Pelvis CT scans were used in this study. 75% of cases were used to train these models and the rest were used to test the prediction accuracy. Pearson's correlation coefficient test was used to find the correlations between the patient attributes and contrast enhancement in liver parenchyma. Weight, height, BMI, and lean body mass were found to be statistically significant predictors for contrast enhancement ($P<0.05$), with weight as the strongest predictor. Of the predictive models, we found that including bolus tracking information increases predictive accuracy ($r^2=0.75$ v. 0.42) and that in the absence of bolus tracking information, combining clinical data with pre-existing pharmacokinetics model may provide the needed enhancement curve.

Keywords: contrast, image quality, patient-specific, neural network, modelling, prediction

1. INTRODUCTION

More than half of clinical CT imaging in the United States involves the use of iodinated contrast materials [1]. The use of such contrast agent in CT imaging enhances tissue contrast, particularly in soft tissue organs such as the liver, pancreas, spleen, and kidneys, and thus improves the depiction of a variety of disorders. Despite the critical role of contrast media administration in clinical practice, there is a lack of standardization in contrast administration techniques across institutions; for instance, a common approach is to use the same dose and injection rate in every patient, unless they are at the extremes of weight, while others make slight adjustment based on patient weight thresholds [2, 3]. As a result, many studies have indicated inconsistencies in contrast enhancement across different patients, posing serious safety and clinical diagnostic risk in over- and under-enhanced patient cases [4]. Therefore, there is a need to devise optimal and standard contrast media administration procedures to target clinically adequate organ contrast enhancement towards consistent diagnostic performance.

Medical Imaging 2020: Physics of Medical Imaging, edited by Guang-Hong Chen, Hilde Bosmans, Proc. of SPIE
Vol. 11312, 1131214 · © 2020 SPIE · CCC code: 1605-7422/20/$21 · doi: 10.1117/12.2548879

This need will be achieved by building a model that prospectively characterizes contrast media perfusion and contrast enhancement in patients. Previous studies have indicated that contrast enhancement is correlated with patient weight and other body habitus metrics (i.e.: BMI and Lean Body Mass) [5-14]. The variability of such factors between patients may lead to significant variabilities in organ enhancements. However, the existing contrast perfusion models rely primarily on mathematical pharmacokinetics modeling and are not individualized to patient specific attributes, scanning parameters, and contrast media administration techniques. One of these models, the Physiology-based Pharmacokinetics (PBPK) model [15, 16] is a compartmentalized, differential-equation based model which predicts contrast enhancements in different organ as a function of injection time for an averaged population. While, the average result of the PBPK model has been shown to be in agreement with previously limited number of cases [15], we showed in a previous study that the result of the PBPK model is still clinically inaccurate due to its limited individualization to patient-specific attributes [17]. Therefore, to reduce inconsistencies in contrast enhancement in the clinic, there is a need to build a contrast perfusion model which primarily incorporates factors, such as patient attributes, scanning parameters, and contrast administration.

This study had two purposes: (1) to investigate the correlations between known pre-scan patient attributes, such as weight, height, age, and contrast enhancement in liver over time in clinical patient populations, and (2) to develop a patient-informed, machine learning-based contrast enhancement prediction model over time based on these correlations.

2. MATERIAL AND METHODS

2.1. Patient Library and Data Sources

This IRB-approved retrospective study included 418 adult patients (210 female) who underwent "Chest Abdomen Pelvis" CT exams with iodinated contrast performed with tube current modulation in 2018 at Duke University Medical Center. For each exam, patient's attributes (height, weight, age, and biological sex), scanner parameters (CT vendor/type, tube potential, slice thickness, scan times), as well contrast administration protocol (bolus volume, concentration, flow rate, injection duration) were collected using METIS patient information system (METIS, Duke University) and NEXO contrast management system (Bracco Diagnostic inc. Monroe Township, NJ). Considering a previous study which shows correlation between lean body mass and contrast enhancement [10], the lean body mass of each patient was calculated using the Boer formula based on patients' height and weight [18]. Contrast media was injected with uniphasic injection protocol using iodine-based contrast agent with concentration of 300 mgI/mL. In addition, the CT scanning exam included a bolus tracking contrast monitoring series to determine the appropriate scan start time; these images were repetitively acquired every 3 seconds, starting from 45 seconds post injection, to monitor whether the organ of interest has received proper contrast enhancement before the diagnostic scan commences. The summary of this dataset is reported in Table 1 and Table 2.

Table 1. Summary of Patient Attributes and Contrast Administration

	Mean	Median	Range [min, max]	Std. Dev.
Height (cm)	170.1	170.2	[135.9, 195.8]	10.2
Weight (kg)	84.9	83.9	[49.0, 137.9]	17.9
BMI (kg/m^2)	29.5	28.8	[18.0, 52.8]	6.4
LBM (kg)	48.2	44.6	[27.6, 72.9]	10.8
Age (y)	59.1	61.0	[19.0, 94.0]	15.0
Contrast Bolus Volume (mL)	145.6	146.0	[136.0, 154.0]	2.5
Average Injection Rate (mL/s)	2.9	2.9	[2.0, 3.0]	0.1
Start-of-Injection to Scan Duration interval (s)	69.2	69.0	[54.0, 98.0]	7.6

Table 2. Summary of examinations included in the study by clinical protocols, scanners and scan parameters; Noise Index (NI) for GE Healthcare; Reference Effective mAs (Q) for Siemens Healthineers.

Institution	Vendor	Models	Slice Thickness	NI, Q	kV	Pitch
Duke University Medical Center	Siemens Healthineers	SOMATOM Definition Flash, Force	0.6 mm	150, 200	120	0.8
	GE Healthcare	Discovery CT750HD, Revolution, VCT	0.625 mm	19,2, 22,0	120	1.38

2.2. Image Segmentation

Each patient case included 3 types of data: 1) Pre-monitoring image, taken before contrast injection starts, 2) Monitoring images, taken as contrast is being injected during the bolus tracking period, 3) Diagnostic image series. The livers were automatically segmented in the CT images using a deep learning-based algorithm [19]. This segmentation tool was previously trained on 200 expert manually segmented CT images. It is able to identify major body organs, including liver, with dice similarity coefficient values of > 0.85. The median HU value of the segmented livers was used to represent the enhancement value.

2.3. Algorithm/Model Development

In this study we explored and developed 3 models: two using simple linear regression method and one using a combination of pre-existing pharmacokinetics model (PBPK) with clinical data. We randomly selected 75% of the patient cases as the training set (in which we used 15% for validation) and the remaining 25% as testing set. The output label is taken from the median of the HU reading from each patient's liver as segmented by our segmenter tool. The goodness of fit was evaluated in terms of R^2, Mean Absolute Error, and Mean Squared Error. We also compared our result to the result of the PBPK model.

2.3.1 Linear Regression Models

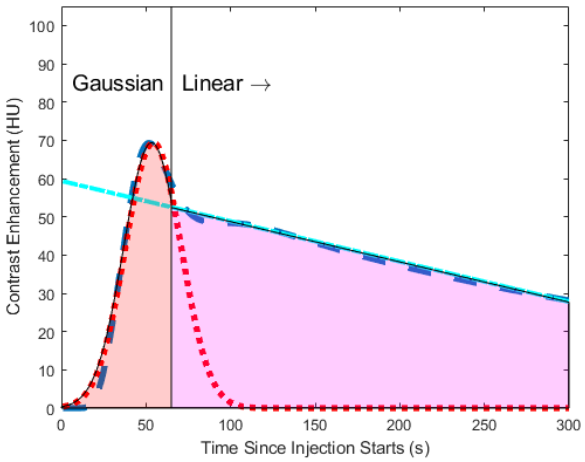
The first model (model A) predicts liver contrast enhancement at a particular time using input features such as: height, weight, sex, age, BMI, calculated lean body mass, contrast bolus volume, contrast injections rate, and scan time. Similarly, the second model (model B) is a simple linear regression model which predicts liver contrast enhancement at a particular time using all the input features used in model A, with the addition of the monitoring/bolus tracking data.

2.3.2 Hybrid Model

The hybrid model combines the input features used in model A with prediction curve from the PBPK model for each patient. We do this by first parameterizing these curves into two phases; the first phase as a Gaussian function, while the second phase as a linear function:

- $Ae^{\frac{-B(x-C)^2}{D}}$ Phase 1: **Gaussian** function
- $G\,e^{Hx}$ Phase 2: **Linear** function

We then adjusted these curve parameters according to the clinical data of each patient before training them with patient features to predict an output curve for liver contrast enhancement.



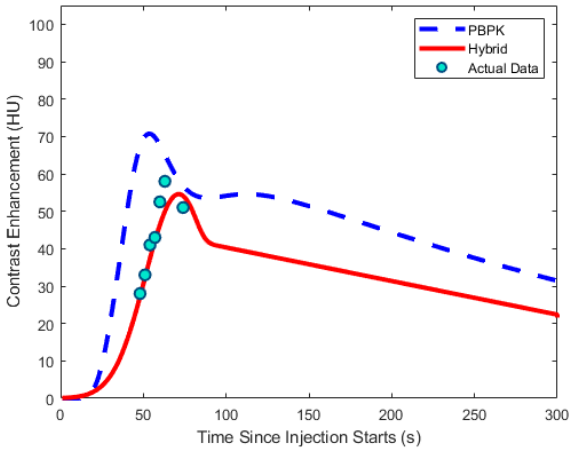


Figure 1a (Left) Illustration of the parameterization of the PBPK prediction curve for the hybrid method

Figure 1b (Right) An example of predicted curve using the hybrid method

to the model (model A), whereas the second model predict contrast enhancement at diagnostic time without the monitoring data (model B). The training outcome was set to be the contrast enhancement in Hounsfield Unit (HU). The goodness of fit was evaluated in terms of R^2, adjusted R^2, mean absolute error, and mean squared error. We also compared our result to the result of the PBPK model.

3. RESULTS

3.1. Correlations of Different Attributes to Contrast Enhancement

The Pearson correlation coefficients between different patient attributes are shown in Table 3. We found that patient weight has the strongest correlation, while age does not seem to have statistically meaningful correlation with contrast enhancement over time. In addition, we observed that correlation between these patient attributes and contrast enhancement varies over time.

Table 3. Correlation table between patient attribute features with contrast enhancement. P-values below 0.05 are highlighted in bold.

	45-50 seconds				50-55 seconds				55-60 seconds			
Features	r	*P* value	95% LL	95% UL	r	*P* value	95% LL	95% UL	r	*P* value	95% LL	95% UL
Weight	-0.19	3.20E-03	-0.31	-0.07	-0.23	4.22E-04	-0.35	-0.11	-0.31	1.55E-06	-0.42	-0.19
BMI	-0.11	**8.85E-02**	-0.24	0.02	-0.13	4.93E-02	-0.26	-4E-04	-0.20	1.90E-03	-0.33	-0.08
LBM	-0.22	6.90E-04	-0.34	-0.10	-0.24	2.22E-04	-0.36	-0.12	-0.31	1.45E-06	-0.43	-0.19
Height	-0.17	1.19E-02	-0.29	0.04	-0.19	4.30E-03	-0.31	-0.06	-0.19	3.60E-03	-0.31	-0.06
Age	0.01	**8.21E-01**	-0.11	0.14	-0.07	**3.09E-01**	-0.20	0.06	-0.12	**6.19E-02**	-0.25	0.01

	60-65 seconds				65-70 seconds				70-80 seconds			
Features	r	*P* value	95% LL	95% UL	r	*P* value	95% LL	95% UL	r	*P* value	95% LL	95% UL
Weight	-0.33	8.65E-06	-0.46	-0.19	-0.42	2.01E-06	-0.56	-0.26	-0.43	5.88E-06	-0.58	-0.26
BMI	-0.20	8.70E-03	-0.34	-0.05	-0.34	1.56E-04	-0.49	-0.17	-0.40	4.21E-05	-0.55	-0.22
LBM	-0.36	2.00E-06	-0.48	-0.22	-0.32	3.41E-04	-0.47	-0.15	-0.30	2.50E-03	-0.47	-0.11
Height	-0.22	3.50E-03	-0.36	-0.08	-0.12	**1.80E-01**	-0.30	0.06	-0.08	**4.42E-01**	-0.27	0.12
Age	-0.04	**6.36E-01**	-0.19	0.11	0.05	**5.78E-01**	-0.13	0.23	0.13	**1.80E-01**	-0.06	0.32

3.2. Prediction Models

Figures 2 shows the plot of predicted v. actual contrast enhancement along with the 1:1 line and the error probability density function for Model A, while Figures 3 refers to Model B, Figures 4 refers to the Hybrid model, and Figure 5 refers to the PBPK model result. Table 4 reports the comparison summary of the four models' goodness of fit.

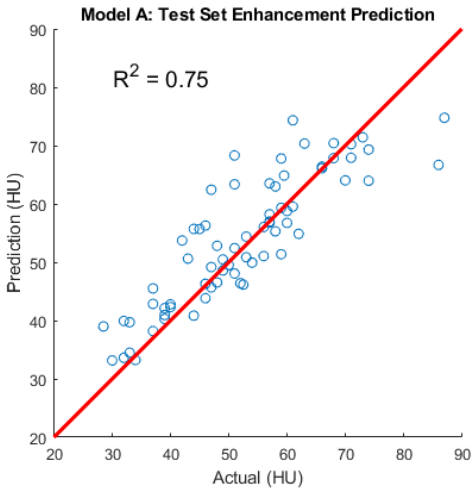


Figure 2 Scatter plot of the Predictions v. Actual HU values of test set for Model A (includes monitoring data). The red line shows the perfect prediction, 1:1 line

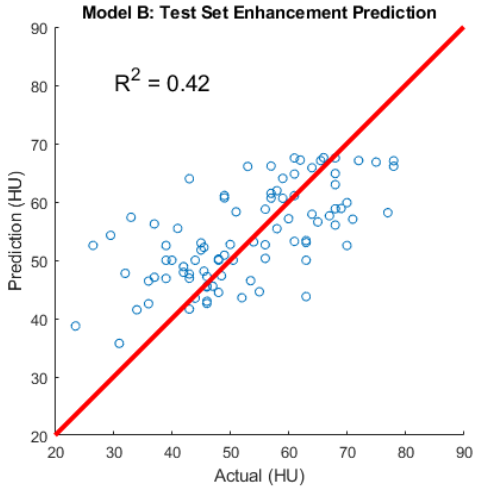


Figure 3 Scatter plot of the Predictions v. Actual HU values of test set for Model B (excludes monitoring data). The red line shows the perfect prediction, 1:1 line

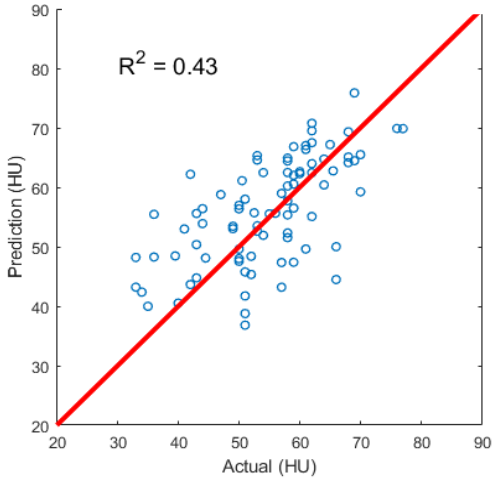


Figure 4 Scatter plot of the Predictions v. Actual HU values of test set for the Hybrid model. The red line shows the perfect prediction, 1:1 line

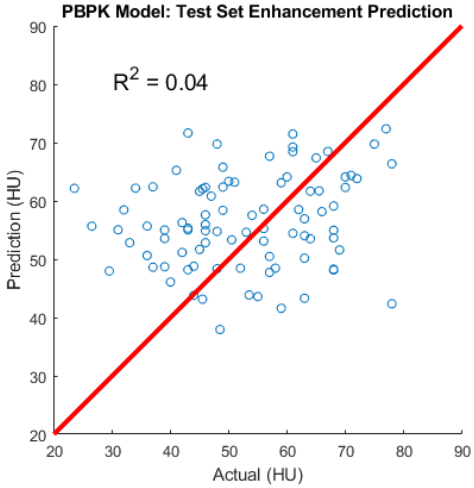


Figure 5 Scatter plot of the Predictions v. Actual HU values of test set for the PBPK model. The red line shows the perfect prediction, 1:1 line

Table 4. Summary of the goodness-of-fit of the predictions

	Model A	Model B	Hybrid	PBPK
Test R^2	0.75	0.42	0.43	0.04
Train R^2	0.96	0.61	0.49	N/A
Mean Absolute Error	4.79	7.6	12.1	16.2
Root Mean Squared Error	6.58	9.64	14.5	21.4

4. DISCUSSION

In this study, we show that a patient's weight is inversely correlated and is the strongest predictor for contrast enhancement among the attributes we evaluated, while age does not seem to show any statistically meaningful correlation and other attributes we investigated showing weaker correlation than weight. We also build two preliminary models to predict contrast enhancement over time, one using the bolus tracking contrast monitoring data (model A) and the other one without (model B). Understanding these correlations and having a robust contrast model is an essential step in our attempt to individualize contrast-enhanced CT imaging protocol for every patient. Previous studies have shown the potential benefit of individualizing such protocol in reducing safety risk, such as increased-risk of contrast-induced nephrotoxicity, heart failure, dehydration, or unnecessary additional dose from repeated scans for under-enhanced patients [20-22]. However, we would like to additionally highlight that individualizing contrast administration and scanning protocol can reduce inconsistencies in contrast enhancement and image quality across patients.

Our results in Table 3 suggest that weight serves as the strongest predictor of liver parenchyma contrast enhancement compared to other features. In general, patient weight is inversely correlated with the contrast enhancement; greater weight implies lower enhancement. This observation is supported by previous studies which suggests similar conclusion regarding weight features [5-9]. Despite this concurrence, it is important to note that our data do not show stronger correlations between weight derivative features (calculated BMI and Lean Body Mass) or age and contrast enhancement, unlike other studies have shown previously [9, 10].

Between the models demonstrated in this study, we found that including bolus tracking monitoring data increases the accuracy of the model. This was expected as monitoring data can inform the model about the early dynamics of the liver contrast enhancement. Clinically, this supports the importance of acquiring bolus-tracking monitoring data before the diagnostic scan. While having such model can assist the administrator in determining the optimal time to conduct the diagnostic scan, relying on monitoring data limits the possibility of having a truly personalized contrast administration protocol for each patient (e.g. impossible to adjust bolus volume, injection rate, contrast media concentration). Thus, in the absence of monitoring data, our hybrid model can deliver the needed liver enhancement prediction curve. We also found that our models showed higher predictive accuracy than the regular PBPK model (r^2 of 0.42, 0.75, and 0.43 for our models and 0.04 for PBPK) when tested on our patient library test set as shown as in Figure 5.

This study had several limitations. First, we used Chest/Abdomen/Pelvis related protocols which restrict the variability in the contrast media administration and scanning protocols, two important factors in this study. We also need to make the library institution-agnostic by including data from other institutions. Future studies will include clinical dataset from different clinical protocols and institutions. Second, although we have demonstrated that weight is an important feature to predict contrast enhancement, there are other factors, such as heart rate, hydration level, and other cardiac function indicators, which theoretically thought as important factors that we

did not consider due to unavailability of data. Furthermore, we mostly included patients with no known liver problems in this study. Liver abnormalities (e.g. Hepatic cirrhosis) may influence contrast perfusion both in livers and other organs of interest, making it challenging to truly predict the dynamics of contrast enhancement. The described model can be extended to include also vital signs and other patient specific features. Lastly, while the model predicts enhancement of liver parenchyma at a certain time point, the model's predictive capability will always be constrained within a short time window (approximately from 60 to 75 seconds after injection starts), preventing us from modeling a complete contrast enhancement curve. To solve this shortcoming, future studies should include perfusion imaging data to provide additional data points to train the model, especially during early arterial and delayed phases. When this is not possible, another alternate solution may be to combine existing mathematical model to help inform the missing sections of the enhancement curve of an organ.

5. CONCLUSION

Patient attributes, especially a patient's weight, can be used to predict contrast enhancement over time. The performance of the prediction model can be further improved when bolus tracking contrast monitoring data are included. In the absence of monitoring data, a combination of pharmacokinetics method with clinical data can provide such prediction.

REFERENCES

[1] Sahbaee, P., Samei, E., Segars, W., "SU-C-12A-03: the impact of contrast medium on radiation dose in CT: a systematic evaluation across 58 patient models," Med. Phys. 41(6), 106–106 (2014).

[2] Laurent, L., Zamfirova, I., Sulo, S., And Baral, P., "Weight-based contrast administration in the computerized tomography evaluation of acute pulmonary embolism: challenges in optimizing imaging quality," Medicine 96(5), E5972 (2017).

[3] Kessler, R., Hegenscheid, K., Fleck, S., Khaw, A., Kirsch, M., Hosten, N., & Langner, S., "Patient body weight-tailored contrast medium injection protocol for the craniocervical vessels: a prospective computed tomography study," PloS one 9(2), e88867 (2014)

[4] Sahbaee, P., Segars, W.P., Samei, E., "Patient-based estimation of organ dose for a population of 58 adult patients across 13 protocol categories," Medical Physics 41(7), 072104 (2014).

[5] Bae, K.T., "Optimization of contrast enhancement in thoracic MDCT," Radiol. Clin. North Am. 48, 9–29 (2010).

[6] Kormano, M., Partanen, K., Soimakallio, S., Kivimaki, T., "Dynamic contrast enhancement of the upper abdomen: effect of contrast medium and body weight," Invest. Radiol. 18, 364-367 (1983).

[7] Platt, J.F., Reige, K.A., Ellis, J.H., "Aortic enhancement during abdominal CT angiography: correlation with test injections, flow rates, and patient demographics," AJR 172, 53–56 (1999).

[8] Kondo, H., Kanematsu, M., Goshima, S., et al., "Body size indexes for optimizing iodine dose for aortic and hepatic enhancement at multidetector CT: comparison of total body weight, lean body weight, and blood volume," Radiology 254(1), 163-169 (2010).

[9] Tan, S., Ng, K., Yeong, C., Raja Aman, R., Sani, F., Abdul Aziz, Y., & Sun, Z., "Personalized administration of contrast medium with high delivery rate in low tube voltage coronary computed tomography angiography," Quantitative Imaging In Medicine And Surgery 9(4), 552-564 (2019).

[10] Ho, L.M., Nelson, R.C., DeLong, D.M., "Determining contrast medium dose and rate on basis of lean body weight: does this strategy improve patient-to-patient uniformity of hepatic enhancement during multi–detector row CT?" Radiology 243(2), 431-437 (2007).

[11] Arana, E., Martí-Bonmatí, L., Tobarra, E., Sierra, C., "Cost reduction in abdominal CT by weight-adjusted dose," Eur. J. Radiol. 70, 507–511 (2009).

[12] Ichikawa, T., Erturk, S., Araki, T., “Multiphasic contrast-enhanced multidetector-row CT of liver: Contrast-enhancement theory and practical scan protocol with a combination of fixed injection duration and patients' body-weight-tailored dose of contrast material,” Eur. J. Radiol. 58, 165–176 (2006).
[13] Yamashita, Y., Komohara, Y., Takahashi, M., Uchida, M., Hayabuchi, N., et al., “Abdominal helical CT: evaluation of optimal doses of intravenous contrast material–a prospective randomized study,” Radiology 216, 718–723 (2000).
[14] Yanaga, Y., Awai, K., Nakayama, Y., Nakaura, T., Tamura, Y., et al., “Pancreas: patient body weight tailored contrast material injection protocol versus fixed dose protocol at dynamic CT,” Radiology 245, 475–482 (2007).
[15] Sahbaee, P., et al. “The effect of contrast material on radiation dose at CT: Part I. Incorporation of contrast material dynamics in anthropomorphic phantoms,” Radiology 283(3), 739-748 (2017).
[16] Bae, K.T., Heiken, J.P., Brink, J.A., “Aortic and hepatic contrast medium enhancement at CT: Part I. Prediction with a computer model,” Radiology 207(3), 647-655 (1998).
[17] Setiawan, H., et al., “Patient-informed and physiology-based modelling of contrast dynamics in cross-sectional imaging,” Proc. SPIE. 10948 (2019)
[18] Boer, P., "Estimated lean body mass as an index for normalization of body fluid volumes in man," Am. J. Physiol. 247, F632-5 (1984).
[19] Fu, W., et al., “From patient-informed to patient-specific organ dose estimation in clinical computed tomography,” Proc. SPIE 10573, 1057315 (2018).
[20] Solomon, R., and Deray, G., “How to prevent contrast-induced nephropathy and manage risk patients: practical recommendations,” Kidney International Supplement 100, S51–53 (2006).
[21] Feng, S. T., Zhu, H., Peng, Z., Huang, L., Dong, Z., Xu, L., Li, Z. P., “An individually optimized protocol of contrast medium injection in enhanced CT scan for liver imaging,” Contrast Media & Molecular Imaging 2017, 7350429 (2017).
[22] Kessler, R., Hegenscheid, K., Fleck, S., Khaw, A., Kirsch, M., Hosten, N., & Langner, S., “Patient body weight-tailored contrast medium injection protocol for the craniocervical vessels: a prospective computed tomography study,” PloS one 9(2), e88867 (2014).