

The iCoCooN: Integration of Cobweb Charts with Parallel Coordinates for Visual Analysis of DCE-MRI Modeling Variations

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Abstract

Efficacy of radiotherapy treatment depends on the specific characteristics of tumorous tissues. For the determination of these characteristics, clinical practice uses Dynamic Contrast Enhanced (DCE) Magnetic Resonance Imaging (MRI). DCE-MRI data is acquired and modeled using pharmacokinetic modeling, to derive per voxel a set of parameters, indicative of tissue properties. Different pharmacokinetic modeling approaches make different assumptions, resulting in parameters with different distributions. A priori, it is not known whether there are significant differences between modeling assumptions and which assumption is best to apply. Therefore, clinical researchers need to know at least how different choices in modeling affect the resulting pharmacokinetic parameters and also where parameter variations appear. In this paper, we introduce iCoCooN: a visualization application for the exploration and analysis of model-induced variations in pharmacokinetic parameters. We designed a visual representation, the Cocoon, by integrating perpendicularly Parallel Coordinate Plots (PCPs) with Cobweb Charts (CCs). PCPs display the variations in each parameter between modeling choices, while CCs present the relations in a whole parameter set for each modeling choice. The Cocoon is equipped with interactive features to support the exploration of all data aspects in a single combined view. Additionally, interactive brushing allows to link the observations from the Cocoon to the anatomy. We conducted evaluations with experts and also general users. The clinical experts judged that the Cocoon in combination with its features facilitates the exploration of all significant information and, especially, enables them to find anatomical correspondences. The results of the evaluation with general users indicate that the Cocoon produces more accurate results compared to independent multiples.

Categories and Subject Descriptors (according to ACM CCS): I.3.8 [Computer Graphics]: Applications—Applications; J.3 [Computer Applications]: Life and Medical Sciences—Life and Medical Sciences

1. Introduction

In cancer treatment, the efficacy of radiotherapy is hypothesized to depend on the specific characteristics of tumorous tissues. Tumor characterization requires the use of different imaging modalities, among which Dynamic Contrast Enhanced (DCE) Magnetic Resonance Imaging (MRI). These are time series of three-dimensional image volumes, i.e. 4D data, which reflect the absorption of a contrast agent by tissues. After DCE-MRI data acquisition, clinical practice uses one of the established models to derive per voxel a set of output parameters, which are indicative of tissue characteristics. However, different modeling approaches require dif-

ferent assumptions or choices. Depending on these choices, the resulting parameters might present different values.

It is difficult to decide beforehand whether different assumptions or choices lead to significant parameter differences and which assumption leads to better results. Therefore, it is valuable for clinical researchers to explore the variability in the parameter values, as given by the different alternatives. In this way, they can identify which anatomical regions are affected more by the modeling choices and whether this has an impact on the final clinical decision and treatment. Apart from exploring variations in the parameters independently, it is also important to know how the relation-

ships between parameters change. Still, these relationships are complex and the effect of different choices on DCE-MRI modeling is difficult to predict. To the best of our knowledge, there is no tool that allows this kind of inspection.

In this paper, we introduce a new application: the iCoCooN (Integrated Cobweb Charts and Parallel Coordinate Plots for Visual Analysis of DCE-MRI Modeling Variations). It is a visualization tool for the exploration and analysis of variability in the parameter values that result from different choices during DCE-MRI modeling. Within iCoCooN, we designed a representation, called Cocoon. For this, we integrated Parallel Coordinate Plots (PCPs) with Cobweb Charts (CCs - also called Star or Spider Plots, Radar Charts or Kiviats in literature), to simultaneously show different significant aspects of the data and to provide a more effective exploration. The interactive features of iCoCooN facilitate data exploration and improve anatomical interpretation. After the design, we conducted an evaluation of iCoCooN with clinical experts, where we performed two real-patient case studies. Due to the limited amount of field experts, we conducted an additional usability study with non-experts, to increase the statistical power of our evaluation.

Our work presents the following contributions:

- The iCoCooN is a new interactive application that enables the visual analysis of DCE-MRI modeling variations and, especially, the association of the observations from the parameter space to the patient anatomy.
- The Cocoon is a visual representation within the iCoCooN, which results from the integration of PCPs with CCs. It enables the exploration and analysis of the DCE-MRI modeling information in a single combined view.
- The evaluations demonstrate the potential of the iCoCooN for the analysis of DCE-MRI modeling variations.

2. Clinical Background

Dynamic-Contrast Enhanced (DCE) Imaging is a commonly used MRI technique in cancer diagnosis. DCE-MRI data are 4D data, i.e. 3D volume+time data, which depict the absorption and washout of a contrast agent (CA) in tissue over time. This technique is based on the idea that tumorous and healthy tissues have different CA uptake properties. Tumors tend to develop new, disorganized and permeable vessels, which have thinner and weaker walls [TTP*10]. Thus, they absorb and wash out CAs faster than healthy tissue.

A quantitative way of measuring tissue properties from DCE-MRI data is to use one of the established pharmacokinetic (PK) models [TBB*99, KVBH12, SB13]. These models are employed to derive per voxel an output set of PK parameters, which describe the distribution of the contrast agent inside the tissue and are indicative of tissue characteristics [SB13]. Each PK model considers a number of assumptions or crisp choices [PB05, TTP*10, CFY*11, KBO*11], depending on which, the values of the obtained

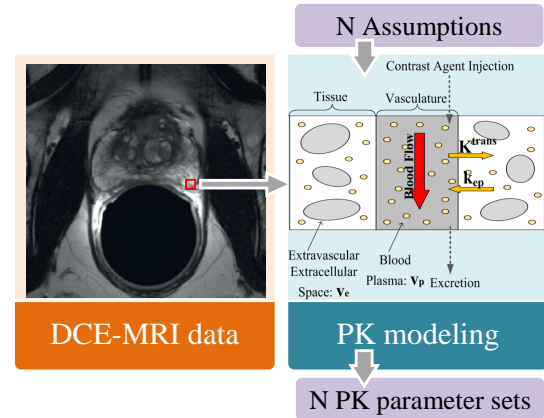


Figure 1: DCE-MRI data (orange) undergo pharmacokinetic (PK) modeling (blue: the extended Tofts model [PB05, Tof10]) using a number of input assumptions to derive per voxel the PK parameter sets (purple; also bold in model).

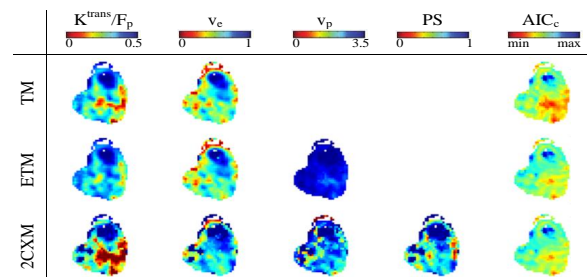


Figure 2: Standard layout for the inspection of PK parameter maps (columns) of a tumor, modeled using three different PK models (rows). Some parameters of the 2CXM are not involved in the TM and ETM models [SB13].

parameters may differ (Figure 1). Clinical researchers do not know a-priori whether there are significant differences among models or their modeling assumptions and which choice is the optimal to apply. Therefore, it is valuable for them to investigate how the derived PK parameters behave with different modeling choices. In this way, they can explore the impact of these choices on the precision of the treatment outcome.

Currently, clinical practice uses a slice-based technique, where the values of each PK parameter from the different assumptions are mapped to a colormap (Figure 2). Analysis using these so-called PK parameter maps is time consuming and does not provide the necessary insight, as clinical users need to manually inspect all slices of the different maps and to mentally perform the relationships, i.e. spatially and between assumptions. More specifically, in a real-world analysis, clinical researchers are required to explore at a voxel level the following data aspects:

1. **Identification of Variability** - The variations in each one of the PK parameters for different choices in modeling.

2. **Identification of Relations** - The relations inside each one of the PK parameter sets as a whole.
3. **Comparison of Behaviors** - The variations in the PK parameter set relations for different choices in modeling.
4. **Detection of Patterns** - The effect of different choices in modeling on patterns in the data.
5. **Exploration and Anatomical Reference** - The anatomical location of specific interesting behaviors or features.

To the best of our knowledge, there is no integrated tool with this complete functionality. For this reason, we designed the iCoCooN, with respect to the previously mentioned requirements, as defined by the users.

3. Related Work

There are numerous ways of visualizing multivariate data [Kei02]. In this section, we present the most relevant work related to the iCoCooN. Preim et al. [POM*09] presented a survey on applications for the exploration and analysis of perfusion parameters that characterize the shape of the DCE-derived enhancement curves and their correlation with the data. Yet, model-induced variability of PK parameters has not been addressed by any of these applications. The visualization of Nguyen et al. [NBYS12] focuses on the minimization of uncertainty in kinetic PET modeling parameters. This application allows the exploration of variabilities in the parameters, but the capabilities to show relations between parameters and the effect of variability on these are limited.

Although our tool was designed specifically for dealing with DCE-MRI modeling variations, the general idea of combining PCPs with CCs is not new. In Temporal Stars [NF02], discrete multiples of radial graphs, with each axis representing a variable, are set along a central time axis to describe variation with time. This representation is useful for comparing different star glyphs or for monitoring time evolution of the variables. As an extension, the 3D Kiviat [TAS05] combines variable axes circularly arranged to a central time axis and a surface rendering around the 2D Kiviat for each time step to show time evolution of the variables, i.e., the evolution of the 2D Kiviat in time. In this way, 3D Kiviat shows correlations between attributes, while preserving the focus on time evolution. The visualization proposed by Fanea et al. [FCI05] employs a combination of PCPs and Star Glyphs in a single configuration, to address clutter in the former. Each Star results from PCP polylines unfolding around the central axis and depicts a data item or a data dimension, thus, maintaining the total number of dimensions. The PCPs of this visualization do not provide additional dimensions with additional information or insight in data relations or patterns. Finally, in VisLink [CC07], interrelationships between multiple visualizations can be interactively explored, with the form of multiple 2D layouts positioned in space and linked together to show data associations.

Our approach combines specific attributes of the previous

work with new ones, to accommodate all the requirements of our application, as mentioned in Section 2. We keep the Star Glyphs for the exploration of relations and behaviors in each parameter set [NF02, FCI05, TAS05], but we provide additional dimensions with PCPs for the exploration of trends and relations in each one of the parameters across these different choices. In this way, the PCPs provide additional information and are not restricted to time representation [NF02, TAS05] or to linking multiple representations [CC07]. Finally, we incorporate functionality to link observations from the parameter space to the anatomical space, which is not provided in any previously mentioned work.

4. The design of iCoCooN

After DCE-MRI acquisition, different output parameters are derived per voxel during PK modeling, using one or more of the established models and/or a number of assumption alternatives. In order to visualize all data aspects, as described in Section 2, we employ the workflow proposed in Figure 3.

For the visualization of each one of the PK parameters across the different choices, we decided to employ **PCPs** [Ins85] (Figures 3 and 4). This representation allows the user to visualize multiple data dimensions in limited space and to detect trends and patterns. In our case, each line in the PCPs corresponds to a location in the medical volume and each dimension to a PK parameter value for the different modeling choices. It is a suitable choice for the identification of model-induced variability in each of the PK parameters. For the vi-

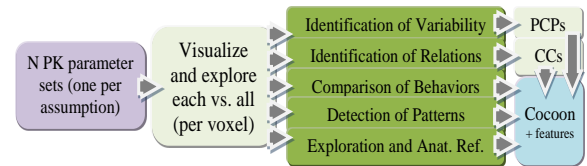


Figure 3: Workflow considered for designing iCoCooN. With dark green, we denote the five requirements discussed in Section 2, for the visualization and exploration of the required data aspects.

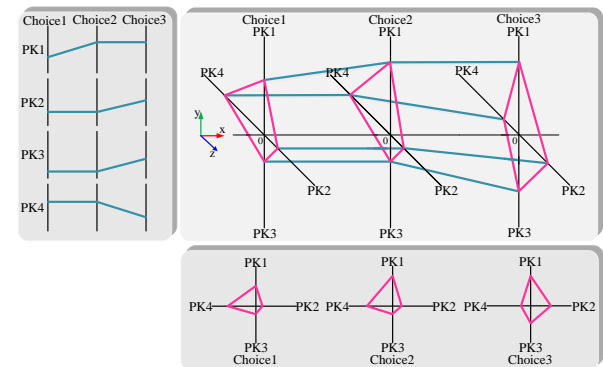


Figure 4: Configuration of Cocoon from perpendicular integration of PCPs (cyan) and CCs (magenta). Here, we consider four PK parameters for three assumptions (choices).

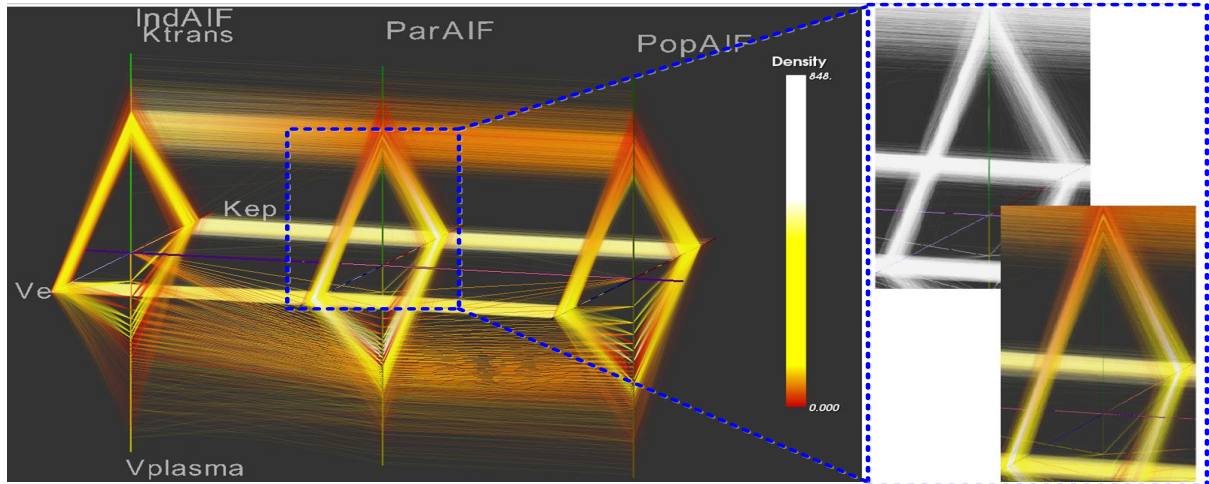


Figure 5: An implementation of the Cocoon for four PK parameters (K^{trans} , v_e , v_{plasma} and k_{ep}) and three assumptions (IndAIF, PopAIF and ParAIF). Zoomed view: using the density colormap for better line visibility (red: very low density or outliers; yellow: low density; white: high density).

sualization of each modeling choice, we decided to employ CCs [CCKT83] (Figures 3 and 4). This compact iconography representation combines the advantages of PCPs with glyphs for the easy detection of patterns among different plots [Kei02], based on the human perceptual ability to easily discern shape differences. In our case, each line in the CCs corresponds to a location in the medical volume and each dimension to a PK parameter value derived from one modeling choice. It is a proper choice for comparing qualitatively a whole PK parameter set against another, or for locating relations, similar and dissimilar behaviors or outliers in a parameter set.

Using a single PCP with each axis reflecting the PK parameter values and an additional discrete axis reflecting the different modeling choices is not an appropriate option. This solution adds clutter in the PCP due to an increasing number of overlapping lines from the different modeling choices. Furthermore, it can only provide an overview on global shifts in the parameters, while it disregards spatial relationships between parameter sets and does not satisfy all the requirements of Section 2. Therefore, for visualizing and linking both intra- and inter-model information, both PCPs and CCs are needed. However, if many variables are involved in the exploration, independent multiple PCPs and CCs might be visually cumbersome, due to the amount of windows.

For these reasons, we decided to create a new representation, the **Cocoon**, from the perpendicular integration of PCPs and CCs in a single 3D view with orthographic projection [Mun09]. With the 3D Cocoon, we improve exploration by conveying different views of the data in an equal context. This is also one of our main differences with respect to previous work [NF02, FCI05, TAS05, CC07, POM*09, NBYR12]: the PCPs of the Cocoon are not linking multiple CC representations, but they show additional dimensions of the data.

In this way, we facilitate linking between parameters and modeling choices in a compact view, without forcing the user to use his memory during tasks, as in the case of the independent multiples. Figure 4 depicts the concept behind the configuration of the Cocoon, when we have four parameters to compare across three assumptions. For our application, we need to show a limited number of different modeling choices and a maximum of six independent parameters [SB13]. The optimal number of parameters is four, but for more than four parameters in the CCs, the user can selectively switch on and off axes in the representation. Therefore, the scalability of the Cocoon is adequate for this concrete application and we consider out of the scope of this paper to study higher dimensionality. Figure 5 shows an implementation of the Cocoon for the concept of Figure 4.

We needed to address three main issues concerning the Cocoon: (1) complexity of interaction, (2) perception constraints due to limited short term memory [PW06] and (3) clutter [Mun09, DCK12, HW12]. For the first issue, we facilitate interaction by **reducing the degrees of freedom**. Not all orientations of the Cocoon are sensible, so the user can rotate the Cocoon only around two axes (longitudinal and latitudinal) to adapt the view. For the second issue, the specific tasks in our application field do not require to rely on short term memory. In an opposite case, the user can still **selectively** show the independent multiple PCPs and CCs to clarify information from the Cocoon, since all components are linked [War01, Mun09]. For the last issue, we increase the visibility of the polylines of the Cocoon using **low alpha values**, but also a colormap based on the **lines density** (Figure 5). The density colormap enables better discernibility of overlapping bundles, giving an impression of texture and an idea of the variability of the data; for example, high density lines that highly vary throughout the assumptions may in-

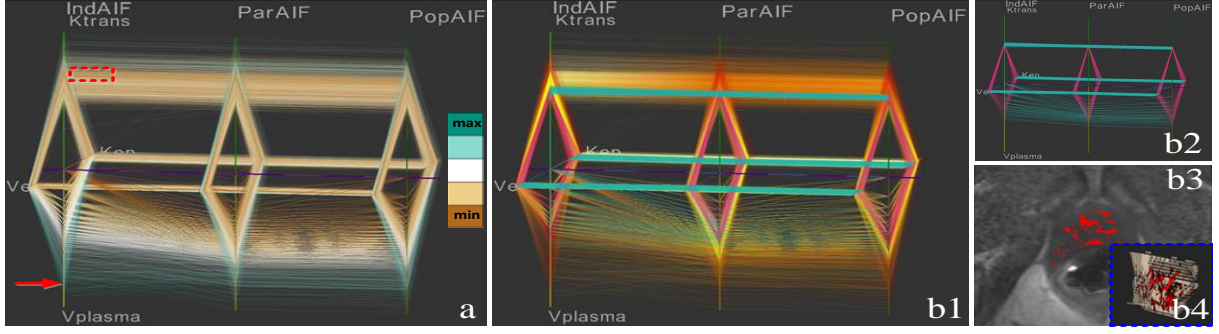


Figure 6: Two features: (a) - Band coloring on the axis with the red arrow for the identification of trends in the data. The zero values of V_{plasma} for the first AIF (brown lines), correspond to the values of K^{trans} in the red box. The legend shows the employed colormap. (b) - Brushing the Cocoon. (1) - Cyan brush in PCPs and magenta in CCs to reduce occlusion due to overlapping polylines and glyphs. (2) - Visualization of the brushed bundles only. (3) - Linking to 2D anatomy and (4) - to 3D model.

indicate that the assumptions have a strong impact on parameters, while very low density lines that highly vary throughout the assumptions may indicate outliers.

Clinical researchers usually look at specific combinations of PK parameters, which we offer as the default view in the axes configuration. To improve the view and to increase visibility further, we use a number of **interaction features**. **Axes reordering** often affects positively the view and the ability to see relations and trends in the data [WPWR03], while **scaling** allows to pull apart dense parts of the representation for better discernibility. Although automatic algorithms for axes reordering can be helpful, given the dimensionality of our application, they were not considered further. **Band coloring** allows the user to extend a primitive clustering from the values of one dimension of the Cocoon to all. We employ a divergent colorblind safe colormap from ColorBrewer, in order to differentiate between low, medium and high parameter values. Figure 6-a shows how band coloring aids rough detection of trends in the data, visualized as color bands. **Brushing** allows the users to explore, analyze and detect interesting trends and relations by selecting areas or values of specific interest in the Cocoon [War94, Kei02] (Figure 6-b:1,2). Finally, **linking** the brushed observations to the medical data, by highlighting the corresponding regions in a 2D slice viewer and a 3D model (Figure 6-b:3,4), establishes correspondence to the patient anatomy. We implemented iCoCooN in Python as a DeVIDE module [BP08], employing the Visualization Toolkit (VTK).

5. Evaluation Results

In order to assess the value of the iCoCooN, we conducted an evaluation, inspired by the article of Lam et al. [LBI*12]. It consists of two parts: (1) an evaluation of the iCoCooN with clinical researchers and (2) a general evaluation to test the usability and effectiveness of the Cocoon and to increase the statistical power of the evaluation, given the limited availability of field experts. For the second part, we abstracted the tasks from the clinical field to a more general domain, so that they could also be performed by non-experts.

5.1. Evaluation with Clinical Researchers

In order to evaluate whether the designed visualization meets its requirements, we conducted individual evaluations with intended users: four field experts from different institutions, representing two types of clinical researchers, i.e. two clinical physicists and two biomedical engineers. As a proof of concept, we used two cases: (1) a prostate tumor case, where clinical researchers want to explore and analyze the effect of different clinically established choices of arterial input function (AIF) [PRM*06, CFY*11, KBO*11] within the same model on the PK parameters and their in-between relationships; and (2) a cervical tumor case, where clinical researchers want to explore and analyze how the parameters and their in-between relationships vary when derived using three different established models [TBB*99, KVBH12, SB13]. These datasets were provided by the clinical researchers themselves and are described in Table 1.

The evaluation consisted of four phases. One of the phases, i.e. the third, was task-specific, while the others were general and aimed at clarifying three broader aspects:

- Does the proposed Cocoon offer new understanding in the data, in comparison to current practice and also the independent multiple PCPs and CCs? If yes, how? If no, why?
- Do the features of the Cocoon contribute to the visualization and facilitate cognition? If yes, how? If no, why?
- Does brushing and linking contribute to the exploration and interpretation of the data? If yes, how? If no, why?

In the **first phase** of the evaluation, we simulated the visual environment for the exploration of the PK parameter space in prostate and cervical data. In this phase, we were interested in a first opinion on the individual features of iCoCooN. This part was also used as training, so the tool was initially operated by the first author, while the test subject first observed a demonstration and then explored the functionality. We asked the test subjects with a questionnaire to comment on the clarity and potential usefulness of each one of these features, but also to quantify their value using

Table 1: Description of the datasets used in the evaluation with clinical researchers. We work on the whole prostate region, but only on the specific tumor region in the cervix, due to the high anatomical variability of the organ between individuals.

	DCE-MRI data (4D)				Modeled data (3D)			
	Resolution (voxels)	Voxel size (mm ³)	Time resolution (s)	ROI size (voxels)	Modeling choices	PK maps	PK maps resolution (voxels)	PK voxel size (mm ³)
Prostate dataset	256 × 256 × 20 for 120 timepoints	1 × 1 × 3	2.5	80 × 80 × 20 (usual prostate size)	3 AIF alternatives	4 3D maps per choice	256 × 256 × 20 (as in DCE-MRI)	1 × 1 × 3 (as in DCE-MRI)
Cervix dataset	176 × 176 × 20 for 120 timepoints	2.273 × 2.273 × 3	2.5	33 × 33 × 18 (specific tumor size)	3 different models	3, 4 and 6 3D maps per choice	176 × 176 × 20 (as in DCE-MRI)	2.273 × 2.273 × 3 (as in DCE-MRI)

a grading scale (1-5). The **second phase** required from the test subjects to grade (1-5) the ability to identify variations and relationships in the data, but also to relate them to the anatomy and pathology of the patient. The **third phase** required a more detailed hands-on exploration of the data, aiming at evaluating the insight provided by iCoCooN. In this phase, the test subjects operated the tool exclusively themselves and they were asked to explore the data in iCoCooN and to analyze their observations, as they would do in a real case, performing the tasks of Section 2. In the **last phase**, they evaluated the tool as a whole, based on their experience, commenting also on the strengths, limitations and missing features of iCoCooN.

5.1.1. First Phase: the iCoCooN Features

In the first phase, the test subjects evaluated the features of iCoCooN individually, following a questionnaire. The quantitative results from this evaluation are summarized in Table 2, with a convention of 1 for negative to 5 for positive. All features of iCoCooN received scores above 4, apart from two cases with a neutral grade (3), where the subjects commented that they needed to form a more concrete opinion by performing an actual task.

Using a questionnaire, we also asked for general comments on each one of the features. First of all, the **Cocoon** was considered understandable and relatively easy to use. The test subjects confirmed that it enables the identification of variations, relations and trends in the multidimensional data in a combined view, even for parameters that do not seem to have an obvious association in the independent multiple views. The **restricted manipulation of the Cocoon** in space is according to the test subjects appropriate. Yet, the Cocoon requires training for learning how to obtain the most adequate view and to interpret the conveyed information. They were inclined, though, to say that there is no need to additionally inspect the **independent multiples**.

Table 2: Evaluation of the features of iCoCooN by clinical researchers, using a grading scale (1=negative, 5=positive).

	#1	#2	#3	#4
Cocoon	3	4	4	4
Cocoon Manipulation	5	4	5	4
Cocoon inst.of Ind.Mult.	5	3	4	4
Scaling/Reordering	4	5	5	4
Band/Density Coloring	4	4	5	4
Brushing/Linking	4	5	5	5

The independent multiples might be used selectively, only for details-on-demand or for easier tasks that involve single parameters. However, they stated that they needed to confirm this impression with a more exploratory task. The advantages of **reordering** and **scaling** the Cocoon axes are also straightforward for data interpretation, while **band coloring** provides a visual context of how the values of one parameter behave in respect to the rest of the parameters and aids the detection of basic patterns in the data. The application of the **density** colormap was considered useful for distinguishing overlapping lines and for deciding on the importance of the variations, relations or trends. This feature requires training, but was regarded as easy to learn. Finally, according to the test subjects, there is no currently used tool with **brushing and linking** functionality for their purposes. They described it as potentially easy to learn and use; an appropriate and appealing feature for data exploration, especially for relating observations from the Cocoon to the patient anatomy.

5.1.2. Second Phase: Information Identifiability

In the second phase, the test subjects had to grade (1-5) the ability to identify specific information using the iCoCooN, i.e. variability and relations or trends, and the ability to relate findings from the iCoCooN to anatomy. The quantitative results from this evaluation are summarized in Table 3, with a grading convention of 1 for easy to identify to 5 for difficult. All but one gradings were below 2, indicating that the test subjects considered the three tasks easy. In only one case, the relation to the anatomy received a neutral grade (3), as the test subject explained that he would need to interact with the Cocoon more, to form a more concrete opinion.

Table 3: Evaluation of the identifiability of information in iCoCooN by clinical researchers, using a grading scale (1=easy, 5=difficult).

	#1	#2	#3	#4
Variability identifiability	2	2	1	2
Relations identifiability	2	1	2	2
Relation to anatomy	2	1	2	3

5.1.3. Third Phase: Case Studies

In this phase, the test subjects used iCoCooN for the exploration and analysis of a prostate dataset and a cervical dataset, as they would do in a real case, executing the tasks of Section 2. The patient-specific findings presented below are observations of the clinical researchers.

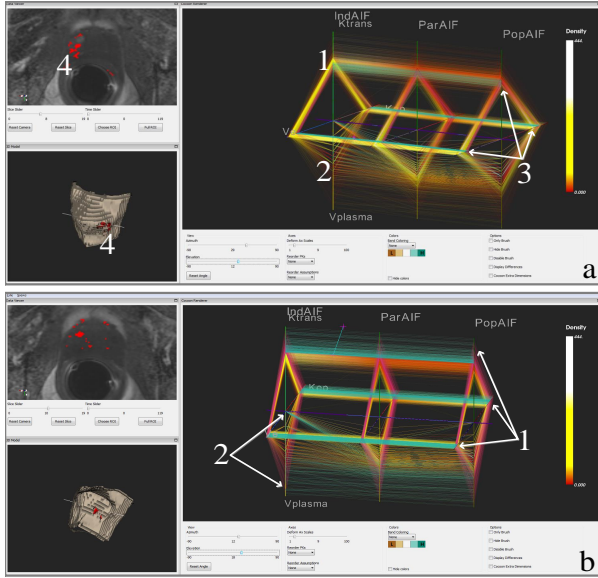


Figure 7: Exploration and visual analysis of a prostate tumor case with iCoCooN during the third phase of the evaluation with clinical researchers.

Case study: Prostate The test subjects were interested in exploring how the four PK parameters of the extended Tofts model (K^{trans} , v_e , v_{plasma} and k_{ep}) [TBB*99], vary across three different AIF choices (Individual, Population-based and Parker-based AIF) [PRM*06, CFY*11, KBO*11]. The AIF is used as an input assumption to the model and there are different options for its precise shape [KBO*11]. The behavior of the parameters for the different AIF choices, presented these major patient-specific findings:

1. **Identification of Variability** - The K^{trans} parameter, which relates to the tissue permeability, remains highly unaltered throughout the different AIF choices (Figure 7-a:1). Minor changes in the distributions are reflected by changes in the density colors. Also, the v_{plasma} , which relates to the blood plasma volume, presents significant variations throughout the AIF choices (Figure 7-a:2).
2. **Identification of Relations** - Lower and slightly decreasing v_e , which relates to the volume of the extracellular extravascular space, is associated to slightly increasing k_{ep} and lower values of K^{trans} (Figure 7-a:3).
3. **Comparison of Behaviors** - Although the general behavior of the parameter sets seems stable across the AIF choices, the differences in the density colors of the CCs reflect slight changes in K^{trans} , v_{plasma} and k_{ep} (Figure 7-a).
4. **Detection of Patterns** - The highest values of K^{trans} are related to high values of k_{ep} and v_e in all three AIF choices (Figure 7-b:1); and to values of v_{plasma} that are highly variable between the AIF choices (Figure 7-b:2).
5. **Exploration and Anatomical Reference** - Low v_e and low K^{trans} regions reflect the necrotic core of the tumor and some outliers at the border of the prostate (Figure 7-a:3,4).

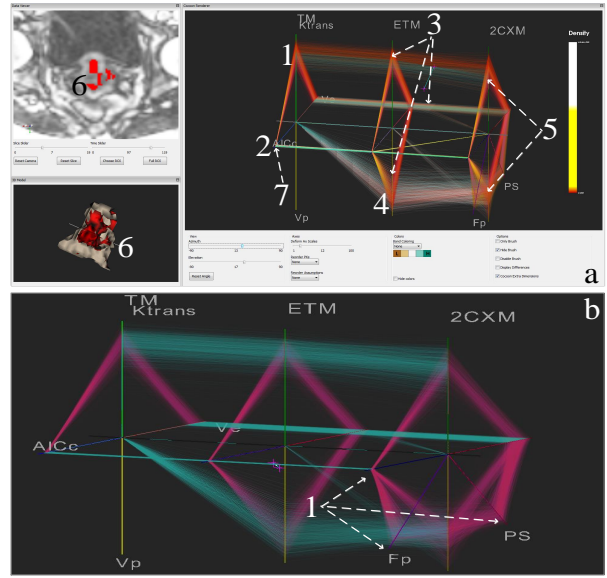


Figure 8: Exploration and visual analysis of a cervical tumor case with iCoCooN during the third phase of the evaluation with clinical researchers.

Case study: Cervix The test subjects explored how the application of different models (Tofts model: TM, Extended Tofts model: ETM and Two-Compartmental Exchange model: 2CXM) [SB13] affects the behavior of the respectively derived PK parameters in the tumor. The first model results in two parameters (K^{trans} and v_e); the second, in three (K^{trans} , v_e and v_p); and the third in five (K^{trans} , v_e , v_p , F_p and PS) [SB13]. An opposite Akaike information criterion (AIC_c) that relates to the relative quality of fit of each model, i.e. high values of AIC_c mean high relative quality, is additionally included to each PK set. The test subjects identified the following major patient-specific findings:

1. **Identification of Variability** - The K^{trans} parameter does not present significant changes despite the application of different models, apart from slight decreases between the ETM and the 2CXM (Figure 8-a:1). This, together with high and stable AIC_c in the TM and ETM models (Figure 8-a:2), is an indication that these models had a reasonable fit.
2. **Identification of Relations** - In the 2CXM, high AIC_c is highly correlated with high flow F_p and permeability-surface area product PS (Figure 8-b:1).
3. **Comparison of Behaviors** - Regions with lower K^{trans} and lower v_e present lower v_p (Figure 8-a:3, brushed) in the ETM and 2CXM. In the ETM model, v_p presents a big spread; bigger than in the 2CXM (Figure 8-a:4). This variability in the v_p values of the 2CXM is related to the slight variability in K^{trans} values (Figure 8-a:5).
4. **Detection of Patterns** - In regions, where the K^{trans} and the v_e values are low, the AIC_c values do not present significant changes across the three models (Figure 8-a:2&3, brushed), meaning that clinical researchers expect that they will all give similar classifications.

Table 4: Translation of clinical tasks to tasks with the synthetic datasets, for the controlled study.

	Clinical Study (with experts)	Controlled Study (with general users)
<i>Data Dimensions</i>	<i>A number of PK parameters for different modeling assumptions.</i>	<i>A number of parameters from different measurements.</i>
Identification of Variability	Identify which of the PK parameters remains unaltered/presents variability throughout the different modeling assumptions.	Identify which of the parameters remains unaltered/presents variability throughout the different measurements.
Identification of Relations	Find a relationship or trend between two or more parameters throughout the different modeling assumptions.	Find a relationship between two or more specific parameters throughout the measurements.
Comparison of Behaviors	In which of the assumptions do we encounter a specific behavior of two or more parameters?	In which of the measurements do we encounter a specific behavior of two or more parameters?
Detection of Patterns	Find a specific pattern in the parameter behaviors. How does it change throughout the assumptions?	Find a given pattern in the parameter behaviors. How does it change throughout the measurements?
Exploration	e.g. Which assumption do you trust more for each zone of the tumor based on all the parameters?	e.g. Which measurement do you choose if you demand specific characteristics?

5. Exploration and Anatomical Reference - A usual indication of malignancy is the combination of low v_e and low K^{trans} . This is the necrotic core of the tumor (Figure 8-a:6) and has the worst responses to treatment. In these parts, the model that fits better is TM, which is confirmed by slightly higher AIC_c values in the Cocoon (Figure 8-a:7).

With this data, we confirmed that iCoCooN fulfills all the requirements of the intended users, as described in Section 2.

5.1.4. Fourth phase: the iCoCooN Overall

In the last phase of the evaluation, the test subjects commented on iCoCooN overall and, mainly, on its strengths, limitations and missing features. According to their experience, they positively judged the application as useful: the Cocoon in combination with its features provides the necessary information and the user requirements are met. They were also asked to compare the tool to current clinical practice, i.e. the slice-based inspection of all alternative parameter maps. To that, they commented that current practice is mainly manual and mental work, which makes hard the identification of variabilities and relations in the data, since it requires from them to go through the multiple slices of all the parameter maps. Instead, the Cocoon is versatile in showing all the multiple dimensions in one view and in aiding their investigation. Thus, it enables them to see the consequences of each modeling choice, to perform and analyze selections and see their exact relation to the anatomy.

Although the first results of the evaluation are promising, they also exposed some limitations. The iCoCooN is a tool that needs training and time to learn. This is also supported by the statements of the test subjects in the previous phases of the evaluation. They agreed that once the user becomes familiar with the visual mapping of the dimensions, the exploration and analysis is faster and easier than with current practice. In order to improve this further, semi-automation of the data exploration and analysis would be required. Moreover, iCoCooN misses the functionality for the inspection of the related enhancement curves, in order to quantitatively see the absorption of the contrast agent in the tissue. This would give additional information on the physical meaning of the visualized data and their patterns.

5.2. Usability and Effectiveness Evaluation

Our application is built for a specific target group and we are just able to conduct user studies with a limited amount of experts. In order to strengthen our evaluation, we decided to perform a controlled study with non-experts, specifically for the usability and effectiveness of the Cocoon, compared to independent multiples. For this, we translated the clinical tasks of Section 2 to two domains more accessible to general users, i.e. airlines and climate measurements. The tasks are described in Table 4. As we are outside the clinical domain, linking to the anatomy, which was already positively judged by clinical researchers, is not tested here. For the other tasks, we created two synthetic, but realistically sized datasets using the PCDC tool [BHvLF12]. Since we focus on evaluating the Cocoon for our concrete application, we use similar dimensions to the ones of our case. Exploring the limits of scalability of the representation is not expected to be of interest in our application. Therefore, it was considered out of the scope of this paper and was not tested further.

We had 15 test subjects: 8 females and 7 males, between 23 and 44 years old. All of them had normal vision, with or without glasses and none of them was colorblind. Their background included electrical engineering (4), computer sciences (3), biomedical engineering (2), mechanical engineering (2), chemistry (2), hydraulics engineering (1), and mathematics (1). They described their computer expertise as medium (9) to high (6). Only two test subjects had experience with PCPs and CCs. First, we gave them a small **introduction** to explain the reasoning behind the study and to present notions such as PCPs, CCs and the Cocoon. Secondly, we demonstrated basic **functionality**. Thirdly, we did some **first exercises**, until the test subjects were confident with the visualizations. Fourthly, we conducted two **experiments** with the synthetic datasets. For each one of the experiments, the test subjects needed to perform the five tasks given in Table 4 as fast and accurate as possible, once using only the independent multiples and once only the Cocoon. We exchanged the order of the two representations both between the experiments and across users, to avoid bias. For all tasks, we measured completion times and correctness of answers, which were known to us. Finally, we asked the test

Table 5: Evaluation results: (Left) Mean and standard deviation of completion times (s) and task correctness (0=wrong to 1=correct) for the two experiments. (Right) Mean and standard deviation of gradings (1-5) and the overall rankings (1-10) for the two representations. Bold indicates lower time and higher correctness, while color relates to statistically significant difference ($p < 0.01$, $p < 0.05$, $p > 0.05$).

	Cocoon				Independent Multiples			
Airlines	μ_t	σ_t	μ_{cor}	σ_{cor}	μ_t	σ_t	μ_{cor}	σ_{cor}
Variability	55.67	31.35	1.00	0.00	31.47	26.26	0.97	0.13
Relations	46.80	30.9	1.00	0.00	46.87	30.01	1.00	0.00
Behaviors	61.60	25.04	0.87	0.35	56.00	35.99	0.40	0.51
Patterns	93.67	39.52	0.73	0.46	82.73	45.14	0.33	0.49
Exploration	66.47	26.95	0.97	0.13	79.27	36.59	0.73	0.32
Climates	μ_t	σ_t	μ_{cor}	σ_{cor}	μ_t	σ_t	μ_{cor}	σ_{cor}
Variability	24.60	9.92	1.00	0.00	23.60	9.68	0.80	0.17
Relations	46.87	27.22	0.93	0.26	38.60	30.67	0.93	0.26
Behaviors	41.60	14.21	1.00	0.00	45.20	25.51	0.73	0.46
Patterns	77.73	34.29	0.93	0.27	77.00	33.47	0.67	0.49
Exploration	38.53	17.18	1.00	0.00	44.40	27.49	0.87	0.23

Gradings	Cocoon		Indep. Multiples	
Characteristics	μ_{gC}	σ_{gC}	μ_{gIM}	σ_{gIM}
Easy to Use	3.87	0.74	4.33	0.62
Easy to Understand	3.73	0.80	4.13	0.74
Useful	4.13	0.74	3.87	0.74
Suit. for Variability	4.13	0.83	4.20	0.68
Suit. for Relations	4.20	0.68	3.73	0.70
Suit. for Behaviors	4.47	0.74	3.87	0.99
Suit. for Patterns	4.27	0.70	3.53	0.83
Suit. for Explor.	4.73	0.59	2.73	1.03
Not Overloading	4.27	0.70	2.27	1.03
Overall Ranking	8.13	1.36	6.47	0.99

subjects to complete a small **survey**, consisting of a grading scale (1-5), an overall ranking (1-10) and open questions.

5.2.1. Evaluation Results

The completion times and correctness for the five tasks of the two experiments, as well as the gradings of the test subjects are summarized in Table 5, together with their color-encoded statistically significant difference, as it resulted from t-tests analysis. For the more demanding tasks, i.e. comparison of behaviors, detection of patterns and exploration, the observations from the Cocoon were more **correct** than the independent multiples in both experiments ($p < 0.05$). The **time** difference was in favor of the independent multiples, but not statistically significant between the two representations ($p > 0.05$), except for the variability task in the airlines experiment. Additionally, there is a statistically significant difference between the **gradings** in the two representations in favor of the Cocoon, which was judged more suitable for the more demanding tasks and for the identification of relations task ($p < 0.05$). Also, it was considered less overloading than the independent multiples ($p \ll 0.01$). Both representations, were considered comparably useful, easy to use and understand ($p > 0.05$). In the **overall ranking**, the Cocoon comes first with a difference of 1.67 points ($p = 0.0012$), while only two test subjects ranked the independent multiples higher. Nine test subjects commented that they would not need the independent multiples at all, on top or instead of the Cocoon. The rest commented that the independent multiples could be useful and faster in certain instances; i.e. for simple tasks, for comparison of few parameters or for beginners.

In their **general comments**, the test subjects stated that when higher dimensionality is involved in the tasks, they preferred the Cocoon, because they could check everything in a single, compact view ("The Cocoon offers compact information giving a more intuitive understanding of complex relations. With the independent multiples, I had to compile all the information from multiple windows in my mind first"). They also stated that Cocoon made them more attentive, efficient and eventually more accurate ("I felt that I could be faster with PCPs. However, I realized that I was jumping

easily to conclusions and making more mistakes, because I was not paying attention to the multiple relations that affected my observations"). Yet, choosing the most effective view is time demanding and requires training ("I needed to think and learn which was the most effective view. Getting the correct view of the Cocoon takes time", "The Cocoon has a higher learning curve, but can provide more information at a glance with adequate training").

6. Conclusions and Future Work

In this paper, we presented iCoCooN: a visualization tool that aids clinical researchers to explore and analyze how different choices in modeling affect the parameter space derived from modeling DCE-MRI data. The contribution of our work lies within the design of the Cocoon that allows users to explore the required DCE-MRI data aspects in a single combined view, while its interactive features facilitate the exploration and interpretation of the data and, especially, the correspondence to anatomy. The value of iCoCooN for our application was confirmed by an evaluation with clinical experts. An additional evaluation with general users indicated that the Cocoon produces more accurate results compared to the independent PCPs and CCs, especially for more complex tasks. At any case, adequate training of the users is essential. The evaluations also provided feedback towards future work. The tool can still improve by reducing interaction workload and time for adjusting the view; also, by reducing clutter in the Cocoon with lines illumination or bundling [HVV10]. Finally, although the tool can be extended to other similar applications, scalability needs to be examined by additional evaluations. First indications show that iCoCooN has good potential of use for the easier exploration and analysis of model-induced variations in DCE-MRI data.

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