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Methoden des maschinellen Lernens für die Tracerkinetische Modellierung

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ABSTRACT

Tracer kinetic modelling based on dynamic PET is an important field of Nuclear Medicine for quantitative functional imaging. Yet, its implementation in clinical routine has been constrained by its complexity and computational costs. Machine learning poses an opportunity to improve modelling processes in terms of arterial input function prediction, the prediction of kinetic modelling parameters and model selection in both clinical and preclinical studies while reducing processing time. Moreover, it can help improving kinetic modelling data used in downstream tasks such as tumor detection. In this review, we introduce the basics of tracer kinetic modelling and present a literature review of original works and conference papers using machine learning methods in this field.

ZUSAMMENFASSUNG

Die Modellierung der Kinetik von Tracern auf der Grundlage der dynamischen PET ist ein wichtiger Bereich der quantitativen funktionellen Bildgebung in der Nuklearmedizin. Ihre Umsetzung in der klinischen Routine wird jedoch durch ihre Komplexität und ihre Rechenkosten eingeschränkt. Das maschinelle Lernen bietet die Möglichkeit, die Modellierungsprozesse im Hinblick auf die Vorhersage der arteriellen Eingangsfunktion, die Berechnung der kinetischen Modellierungsparameter und die Modellauswahl sowohl in klinischen als auch in präklinischen Studien zu verbessern und gleichzeitig die Verarbeitungszeit zu verkürzen. Darüber hinaus kann sie dazu beitragen, den Nutzen von kinetischen Modellierungsdaten bei nachgelagerten Aufgaben, wie z. B. der Tumorerkennung, zu verbessern. In dieser Übersicht stellen wir die Grundlagen der kinetischen Modellierung von Tracern vor und präsentieren eine Literaturübersicht über Originalarbeiten und Konferenzbeiträge, die Methoden des maschinellen Lernens in diesem Bereich verwenden.

Introduction

In dynamic PET studies, mathematical models are commonly used to describe the relationship between the measured temporal data and the kinetic physiological parameters that determine the uptake of a radiotracer and its clearance. The class of models most commonly used in this context are compartmental models that are described by ordinary differential equations. Standard estimation procedures such as nonlinear least squares estimation can be used to estimate the model parameters from the measured data [1]. Depending on the properties and errors of the measured data, model-based methods can be developed that are generally simpler than full parameter models but use additional assumptions about physiological parameters [2, 3].

Machine learning is used at various points in data processing, which is relevant for kinetic modelling of tracers. It addresses data correction (e. g., motion correction, attenuation correction, and scatter correction), image reconstruction (e. g., improvement of image resolution and noise behaviour) and image analysis (e. g., tissue segmentation). The improvement of image properties and more precise definition of volumes-of-interest influences the precision of the kinetic parameters. However, machine learning methods are also used directly in modelling, namely for estimating kinetic parameters and for model selection. The machine learning algorithms used for kinetic modelling applications are largely based on convolutional or recursive neural network architectures. However, algorithms such as generative adversarial networks and their variations are also used in medical image analysis, e. g., in reconstructions, and thus have an influence on the quality of the kinetic outcome parameters. An overview of the commonly used algorithms is given in Hellwig et al. within this issue. The majority of applications in literature relate to clinical rather than to preclinical applications.

The aim of this article is first to review the basics of tracer kinetic modelling and then to present papers that address arterial input function prediction, the prediction of kinetic modelling parameters and model selection in both clinical and preclinical studies using machine learning. Furthermore, we elucidate the impact of machine learning methods on auxiliary and downstream tasks related to kinetic modelling.

The literature search was carried out via PubMed (U.S. National Institutes of Health's National Library of Medicine (NIH/NLM)) on July 10th, 2023. Our search strategy included the following keywords: (PET OR “positron emission tomography”) AND (“kinetic modelling” OR “kinetic modeling” OR “tracer kinetic modelling” OR “tracer kinetic modeling” OR “parametric image”) AND (“artificial intelligence” OR “machine learning” OR “deep learning”). In total 20 matching publications were found in PubMed. Additionally, the authors included eleven research papers not found in the PubMed search that matched the same criteria in Google Scholar.

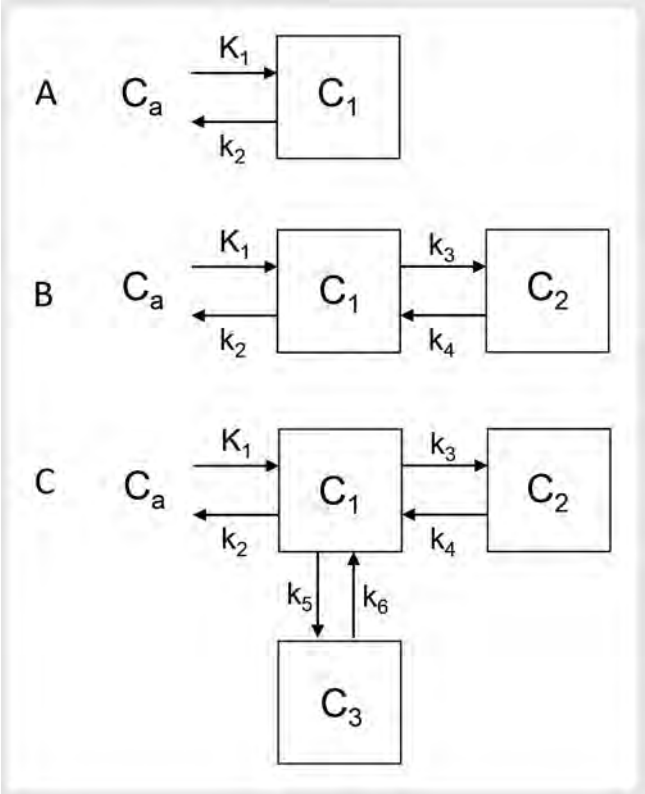
Out of the 20 PubMed matches, five were discarded as they did not include machine learning approaches and two as they were review articles, not original works. All other 13 PubMed matches, as well as the additional eleven papers selected from the Google Scholar search, are discussed below.

Basics of tracer kinetic modelling in PET

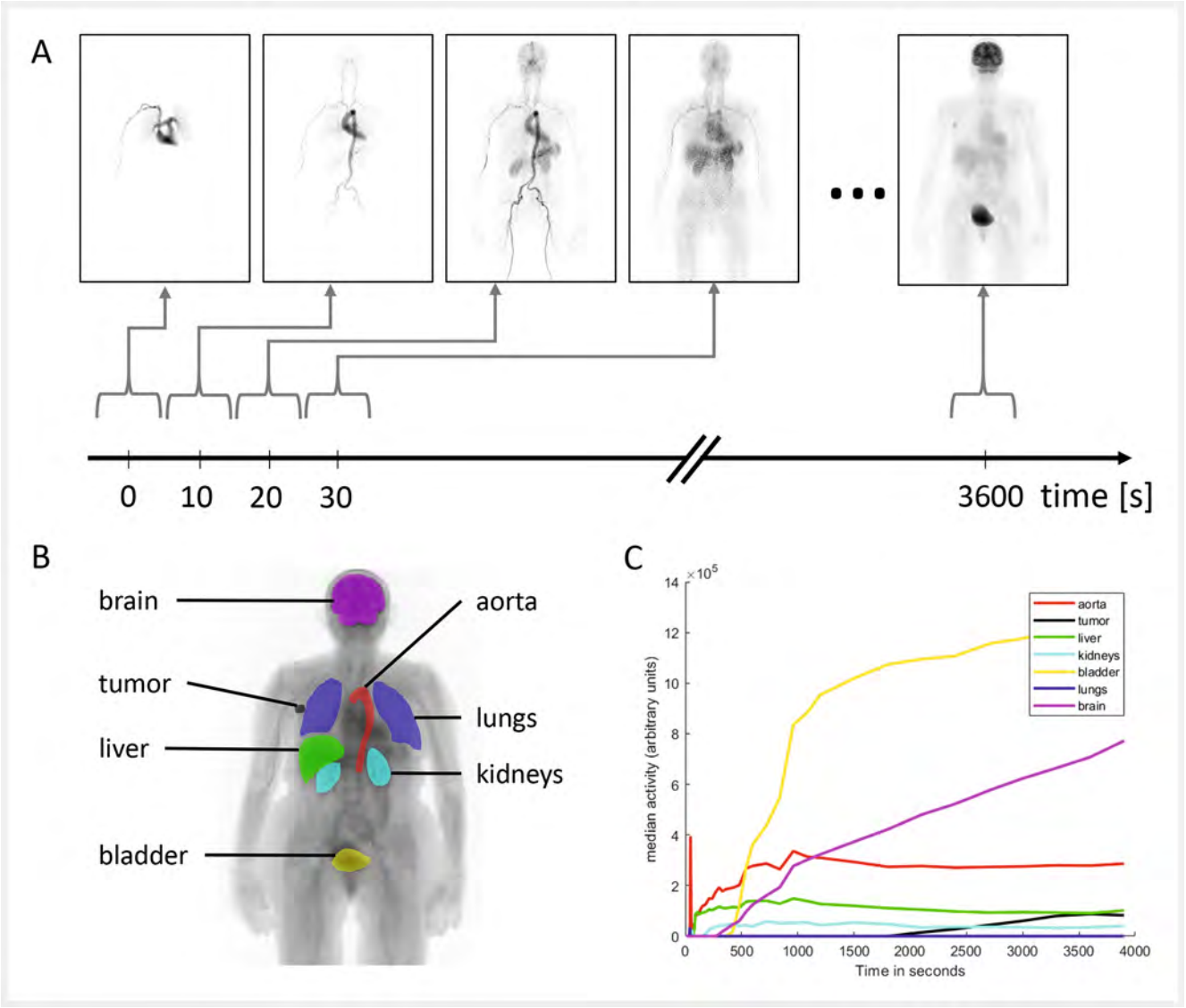
In the following, we present the concepts and assumptions commonly used for tracer kinetic modelling (also known as physiologically-based pharmacokinetic (PBPK) modelling) in dynamic PET.

Compartmental models

For applications in PET, compartment models are usually used to describe the uptake, metabolism and clearance of radiotracers in tissue (▶ **Fig. 1**) or cells [4]. A compartment describes a possible physical and/or chemical state of the radiotracer, often combining and describing several possible states in a single compartment. Here, blood is not counted as a compartment. Compartment models also describe the rate of change at which a radiotracer transitions from one state to another. The meaning of the rate constants depends on the interpretation of the source and target compartments. All modelling approaches aim to estimate one or more rate constants (or a ratio of them) from measurements of the radioactivity concentration in tissue and blood. A detailed and comprehensive description, also of the following aspects, can be found in [5].



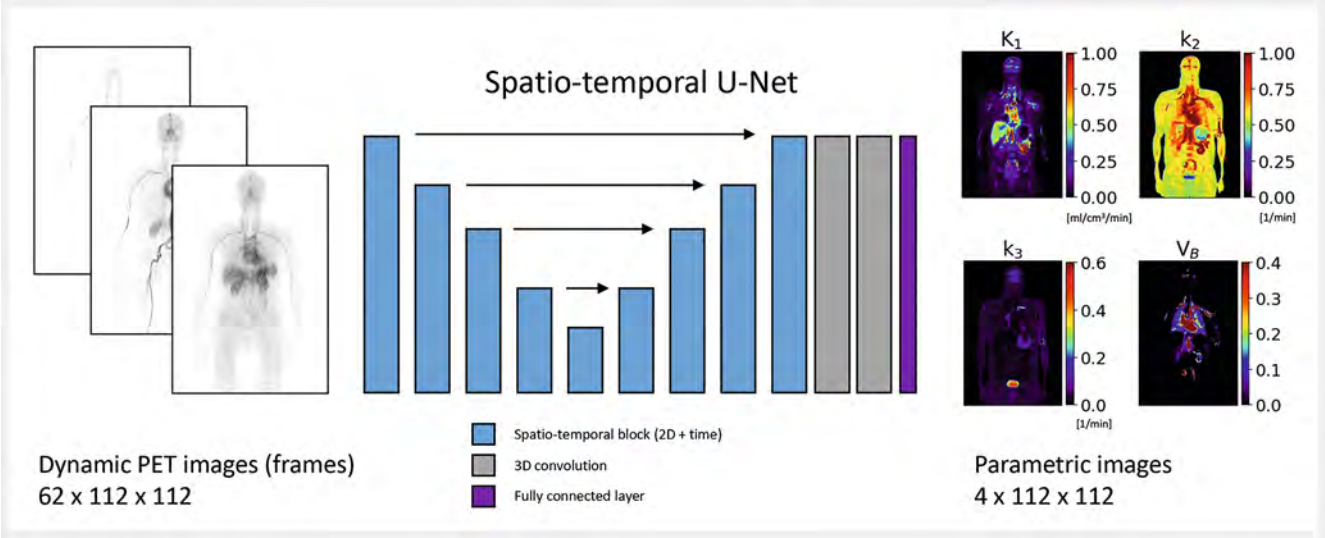
▶ **Fig. 1** Examples of compartmental model configurations. C_a: tracer concentration in arterial blood; C_1, C_2, C_3: tracer concentrations in compartments 1–3; K_1, k_2, k_n: rate constants describing the movement between compartments 1–3. **A** One tissue compartment model for e. g., a blood flow tracer; **B** Two tissue compartment model for e. g., [^{18}F]FDG; **C** Three tissue compartment model for a receptor-binding ligand.



▶ **Fig. 2** **A** Example for dynamic PET data for a large field-of-view PET scanner. The example shows [^{18}F]FDG coronal maximum intensity projections of several PET frames over time. **B** Segmentation mask for several organs overlaid over the integrated PET image for the same patient. **C** Organ-based time-activity curves per organ obtained averaging the activity concentration of all frames of **A** over the respective segmentation masks of **B**.

a) Model implementation

Kinetic modelling of tracers requires measurements of the radioactivity concentration in tissue and in arterial plasma over time. The radioactivity concentration in tissue is determined by positron emission tomography and the time course of the radioactivity, i. e., the time-activity curve, is given by definition of volumes-of-interest on reconstructed PET images or on a voxel-by-voxel level (▶ **Fig. 2**). The radioactivity concentration in arterial blood is usually obtained from a radial artery, manually or with an online detection system for continuous sampling. From these blood samples, the concentration of radiotracer in plasma and whole blood and the proportion of metabolites are assessed. However, the experimental determination of an arterial plasma input function has some disadvantages as it is invasive and labour intensive and with regard to tracer kinetic modelling, errors in the measured input function can lead to increased uncertainty in the estimated parameters of the assumed model. Also, for organs like the lungs or the liver, where blood flow is not purely arterial, other input functions such as portal vein have to be considered. For these reasons, a number of alternatives have been proposed, such as the determination of image-derived input functions, population-based input functions or approaches that estimate the input function and kinetic parameters simultaneously. A detailed description of the limitations of these approaches is given in [6]. If the ligand forms a significant proportion of metabolites, the arterial plasma input function must be corrected. For this purpose, a mono- or bi-exponential function is fitted to the proportion of the intact tracer and multiplied by the total plasma curve.



▶ **Fig. 3** Spatio-temporal U-Net used by our team to directly estimate micro-parameters of an irreversible two-compartment model from 62 dynamic PET frames. The input of the network is a series of 62 2 D slices of the patient (one per dynamic PET frame, size 112 × 112 with 2.5 mm squared pixels). The resulting 3 D images of all four micro-parameters K_1, k_2, k_3 and V_B are generated thus slice by slice and compounded. The architecture included skip connections within the spatio-temporal U-Net part. Additionally, two 3 D convolution layers and a fully connected layer were added do obtain the four desired channels (one per micro-parameter).

The description of compartment models is done by ordinary differential equations (ODEs), the derivation of which is described in detail in [5]. The individual parameters of such models are commonly called micro-parameters (▶ **Fig. 1, 3**). ▶ **Fig. 1A** shows a one-tissue compartment model used to represent tracers showing reversible tissue uptake. In such case, the rate of change of the tissue concentration in compartment C_1, the following applies:

$$\frac{dC_1}{dt} = K_1 C_a(t) - k_2 C_1(t)$$

▶ **Fig. 1B** shows a model with two tissue compartments used to describe a tracer that is either metabolized and trapped in the tissue (represented by compartment 2) or returns to the blood (represented by compartment 1). Then, the rate of change of the tissue concentrations in compartments C_1 and C_2 is:

$$\frac{dC_1}{dt} = K_1 C_a(t) - k_2 C_1(t) - k_3 C_1(t) + k_4 C_2(t)$$

$$\frac{dC_2}{dt} = k_3 C_1(t) - k_4 C_2(t)$$

The solutions of the differential equations can be found in [5]. It can be assumed that the measured tissue activity will be the sum in both compartments, so that the model prediction is $C_1(t) + C_2(t)$. In order to model the fact that radioactivity is also present freely in the blood, a further micro-parameter is commonly used, namely the blood volume, V_B, describing the percentage of blood in a given voxel, region of interest or organ.

That is, given knowledge of the input function, the model configuration and its rate constants, the tissue concentration can be mathematically predicted at any time point. However, in an experimental setup with PET, the opposite mathematical problem arises: given measurements of radioactivity in the tissue, the input function and a proposed model configuration, the goal is to estimate the underlying rate constants. Various methods are available for parameter estimation, depending on the model and the sample size and statistical quality of the data. Nonlinear least squares estimation is a commonly used method for parameter estimation in the context of compartmental models, which are, however, prone to noise and require high computational effort. To determine which model configuration best describes the measurement data, statistical tests such as the F-test [7, 8], the Akaike information criterion [9] or the Schwarz criterion [10] are commonly used. In addition, the standard errors of the fitted parameters as well as their correlation provide information about their uncertainty. Also the patterns of the residual sums of squares of the model fit, which is expected to be randomly distributed around zero, show the goodness-of-fit.

For reversible tracers, the ratio of estimated rate constants equals selected distribution volumes. V_T, which is considered here, is defined as the ratio of the concentration of tracer in a region of tissue to that in blood plasma at equilibrium [3, 11]. For irreversible tracers, such as [^{18}F]FDG, the net uptake of the tracer into tissue is assessed [2].

b) Model-based methods

In addition to compartmental models, there are model-based methods that are generally simpler than full parameter models and that use additional assumptions on physiological parameters. Nevertheless, they can provide accurate and reliable estimates.

Those include invasive and non-invasive data-driven methods that do not require *a priori* hypotheses about the underlying model structure. Examples for data-driven methods are graphical methods of Patlak and Logan [2, 3]. These methods transform the data in such a way that, after a suitable time, certain kinetic modelling parameters (called often macro-parameters, which are functions of micro-parameters) can be calculated using a linear regression of the transformed data, making parameter estimation more efficient and less prone to noise compared to non-linear estimation techniques. These methods are suitable for generating parametric images, which means that a time activity curve is derived from each voxel in the image, from which kinetic parameters are derived and then stored in the corresponding voxel in that image. The Patlak representation applies to tracers with irreversible trapping, such as [^{18}F]FDG, and in this case allows the calculation of parametric images of the rate of net influx, K_i [2]. For tracers with reversible binding, the Logan representation allows the calculation of parametric images of the distribution volume V_T [3], as for [^{18}F]flumazenil [12].

Applications for tracer kinetic modelling

Machine learning methods have been applied to different data processing steps for tracer kinetic modelling. In this section, we refer to publications that address the prediction of the arterial input function, the kinetic modelling parameters and the model selection, both in clinical and preclinical studies.

a) Prediction of the arterial input function

Most tracer kinetic models take for granted that the arterial input function is known. As discussed above, this curve is not necessarily known, yet extracting it from the image data is a promising front for machine learning applications.

In a clinical [^{15}O]H_2O brain PET study, which included both baseline scans and scans after a pharmacological intervention, the goal was to investigate whether an arterial input function can be accurately predicted by machine learning. Kuttner et al. [6] used a prediction method based on a Gaussian process for this purpose, which followed on from their initial preclinical method with mice [13]. Different image-derived time activity curves of the carotid artery were used as training datasets, both scans at baseline and scans after pharmacological intervention. The prediction method was evaluated by comparing measured arterial blood samples and machine learning-based blood curves. Furthermore, the kinetic modelling parameters (values of cerebral blood flow in the whole brain grey matter) derived from experimental and machine learning-based input functions were compared. The results showed good agreement of the input functions and a strong correlation between methods. Baseline data and data after pharmacological intervention could be successfully distinguished.

Wang L et al. [14] proposed a deep convolutional neural network to directly deriving the arterial input function from the dynamic PET frames. They trained and evaluated their approach with two datasets, one with 35 patients injected with [^{18}F]FDG, and one with 26 patients within a brain PET study using [^{11}C]DPA-713. They evaluated two models and compared the model results with the manually extracted image-derived input function yielding qualitatively satisfactory results. They further used the obtained input function to estimate the macro-parameter K_i yielding an acceptable root mean square error with respect to the manual method.

Ding et al. [15] proposed a dual-tracer dynamic PET protocol for patients with neuroendocrine tumors, using the tracers [^{18}F]FDG and [^{68}Ga]Ga-DOTATATE. Their clinical study included a machine learning algorithm (namely, recurrent extreme gradient boosting) in order to automatically separate the arterial input function of both tracers and as such enable derivation of the kinetic micro-parameters for both tracers separately. They evaluated their approach in 12 patients concluding that the use of the machine learning approach enables separation of the kinetic information in the given dual tracer setup by separating the injection of both radiopharmaceuticals by only 5 min.

In all reviewed works, it could be shown that machine learning methods can be successfully used in human and animal studies to non-invasively estimate the arterial input function. However, a broad clinical and preclinical application is pending. With regard to the estimation of the arterial input function, further applications of machine learning methods could e. g. lie in the correction of the time delay of the input function and the dispersion of the radiotracer in the blood. When taking arterial blood samples, delay and dispersion effects occur in relation to the radiotracer in the arterial blood in the brain tissue and the corresponding blood sample. These effects play a role especially in whole-body PET and must be taken into account, conventionally by including a delay and blood volume term in the model equations. Furthermore, machine learning methods could prove useful for correcting for radiotracer metabolites. This means that further development of approaches is imperative, as the use of machine learning methods in determining/predicting the arterial input function avoids the disadvantages of invasive arterial blood sampling and or other, image-based approaches (e. g. partial volume effects, predefined assumptions about the model function). In preclinical research, there is also the fact that longitudinal studies are only possible without arterial cannulation. Machine learning methods offer the possibility to circumvent these disadvantages and to non-invasively assess the arterial input function.

b) Prediction of kinetic parameters

Deriving kinetic parameters, either micro- or macro-parameters, requires non-linear optimization, a task that is often dealt with using machine learning tools. As a result, applying such methods directly on dynamic images for parameter estimation is a straightforward option.

In a human [^{18}F]FDG study, Pan et al. [16] developed a kinetic modelling method that uses a support vector machine algorithm, or to be precisely, support vector regression, for prediction of kinetic modelling parameters. The method uses a predefined reference database of tumor data and specifically addresses the fitting of noisy data. The parameters of the kinetic modelling were compared with those obtained with the conventional iterative fitting. Statistical analysis revealed that the machine learning based method is a robust method, which is also reproducible and user-independent.

Golish et al. [17] proposed using a neural network to estimate kinetic parameters directly from time-activity-curves. They evaluated this in a simulation study as well as in four canine experiments with [^{13}N]ammonia. The simulation analysis showed that the error of the neural network was comparable with the conventional Patlak method and with a weighted non-linear regression, while in the canine study (where no ground truth was available) the correlation of the methods showed differences below 10 %.

Recently, a simulation study for human brain [^{18}F]FDG and [^{11}C]flumazenil data aimed to estimate kinetic modelling parameters without an arterial input function. Wang B et al. [18] used deep neural networks to predict parametric images of modelling macro-parameters, such as K_i and V_T. They considered the macro-parameters as nonlinear functions of the activity concentration of the tracer and used deep learning to determine this nonlinear function to obtain the macro-parameters directly from dynamic PET data. The results demonstrated superior performance of deep neural networks as compared to Patlak and Logan analyses in terms of robustness and accuracy.

In a study by Wang R et al. [19], deep learning methods were used to predict [^{11}C]UCB-J PET images from [^{18}F]FDG images using U-Net models. Quantitative and semi-quantitative parameters, using the cerebellum as reference region, were calculated. Four models were trained and tested: 1) [^{18}F]FDG SUV ratio (SUVR) to [^{11}C]UCB-J SUVR, 2) [^{18}F]FDG K_i ratio to [^{11}C]UCB-J SUVR, 3) [^{18}F]FDG SUVR to [^{11}C]UCB-J distribution volume ratio (DVR), and 4) [^{18}F]FDG K_i ratio to [^{11}C]UCB-J DVR and also a [^{18F}]FDG SUVR to [^{11}C]PiB SUVR network was trained and tested for [^{11}C]PiB image prediction. The results showed that synthetic [^{11}C]UCB-J PET images from [^{18}F]FDG images can be calculated with reasonable prediction accuracy whereas predicting [^{11}C]PiB SUVR images from [^{18}F]FDG images, requires additional diagnostic information.

In a brain [^{11}C]DASB-PET study, Cui et al. [20] examined an unsupervised deep learning-based denoising method, i. e., conditional deep image prior (CDIP), for calculation of parametric images using Logan graphical analysis (reference tissue model [21]). Anatomical information based on the patient's computed tomography (CT) or magnetic resonance (MR) image was used as network input. Compared with the conventional method, the proposed method generated parametric images with more detailed structures, as shown in simulated and patient data, and improved contrast-to-noise ratios.

In a [^{11}C]raclopride simulation study for rat brain data, Fuller et al. [22] examined a number of machine learning algorithms to detect and classify transient changes in voxel-based time-activity curves. Those included support vector machine classifiers, shallow feedforward neural networks, convolutional neural networks and long short-term memory networks. For the analysis, simulated [^{11}C]racloprid data, covering a wide range of known noise levels and activation response magnitudes, were used to train and test the machine learning algorithms. At all noise levels tested, the use of machine learning algorithms resulted in an improvement in specificity, and no decrease in sensitivity, compared to the linear parametric neurotransmitter PET method [23], with which the method was compared.

From our own team, De Benetti et al. [24] lately introduced a spatio-temporal deep neural network to derive the micro-parameters of a two-compartment model for [^{18}F]FDG in an unsupervised way. They evaluated it in a dataset with 23 patients having 62 frames of variable duration acquired with a long field-of-view scanner over a full hour immediately after injection. The network, based on a U-Net architecture, predicted directly a 4-channel 3 D volume, namely, a K_1, k_2, k_3 and V_B. They assumed k_4 to be zero and compared their results with a curve-fitting approach at voxel-level and the previous literature yielding comparable metrics and qualitatively match the expected distribution (▶ **Fig. 3**).

In a whole body [^{18}F]FDG PET study, Huang et al. [25] investigated the feasibility of generating parametric PET images directly from static PET scans using deep learning, enabling significant reduction in scanning time. The proposed approach yields qualitatively and quantitatively consistent results with reference images, holding promise for enhancing patient comfort and efficiency in clinical settings, although further research is needed to validate clinical applications and interpret the network models.

Wang H et al. [26] presented a deep learning approach that utilizes static PET images to synthesize highly correlated and consistent dynamic parametric images, as shown for images from patients with lung cancer diagnosis. The method outperformed existing networks in terms of image quality, correlation, and clinical evaluation, providing a valuable quantitative diagnostic reference for clinicians seeking enhanced cancer detection and quantification.

In summary, the applications of machine learning methods are manifold and relate to the shortening of data acquisition and the handling of noise in measurement data by means of (modified) support vector machines; furthermore, applications lie in the field of parametric imaging, even without an arterial input function, using neural networks. Further applications of machine learning methods with regard to kinetic parameter prediction could be found, for example, in dealing with multi-bed dynamic PET acquisitions, or modelling not only arterial, but also venous tracer input. Machine learning techniques have proven to be suitable in terms of good statistical performance, low computational cost and general applicability for parametric imaging.

c) Support in parametric image reconstruction

In contrast to estimation from reconstructed images, parametric images can be also estimated directly from raw measurements, such as sinograms. The combination of reconstruction and parametric image estimation is called parametric image reconstruction [27]. It has the advantage of avoiding amplification of noise in two-step estimation and improving the quality of parametric images. However, direct parametric image reconstruction increases methodological complexity, to which machine learning or deep learning can additionally contribute.

For [^{18}F]FDG and [^{11}C]PIB PET data sets, Gong et al. [28] introduced an unsupervised deep learning approach for direct parametric reconstruction from dynamic sinograms. By incorporating patient anatomical information and a kernel layer for denoising, along with an embedded linear kinetic model, the framework

shows improved performance over conventional and kernel-based methods on various tracer datasets.

In a [^{18}F]FDG study, using a PET scanner with a long axial field-of-view, Li Y et al. [29] presented a deep learning framework that reconstructs high-quality Patlak K_i parametric images from limited-frame sinograms without the need for an input function. Their results demonstrated the method's potential to address challenges related to long scan times and input function dependency, offering improved efficiency and accuracy for dynamic PET imaging in a clinical context.

d) Kinetic model selection

For different tissue types, e. g. in the brain or whole body, the kinetics of a given tracer may underlie different model structures. Therefore, data-driven methods that can be generalised to any number of compartments and allow the estimation of macro-parameters are particularly suitable for parametric imaging. For the selection of the underlying model structure, statistical tests such as the F-test, the Akaike information criterion or the Schwarz criterion are conventionally used; recently, approaches based on machine learning methods have been proposed.

In a [^{11}C]racloprid study, using real human imaging data and simulation data, Klyuzhin et al. [30] examined a number of machine learning algorithms for selection of the underlying model structure as assessed by the linear parametric neurotransmitter PET method [23]. Machine learning algorithms included a number of artificial neural networks and, in addition, the use of “personalized” artificial neural networks, i. e. that operate on a data set of a particular subject and scan. The training of the personalized artificial neural networks was carried out using simulated image data, taking into account the signal and noise properties of the “real world” measurement data. The performances of the algorithms were compared with the results of the F-tests on the residuals of the model fits (which resulted from the application of the linear parametric neurotransmitter method). In this work, the applicability and superiority of the artificial neural networks could be shown on simulated as well as “real world” data, compared to the conventionally used F-test. This is in line with the [^{11}C]raclopride simulation study for rat brain data by Fuller et al. [22]. Also in this work, machine learning algorithms showed better performance as compared to statistical F-tests (combined with cluster size analysis).

In general, these studies demonstrated that machine learning is superior to conventional methods, such as the statistical F-test, in selecting the model underlying the kinetics of the tracer.

e) Auxiliary and downstream tasks

Machine-learning approaches do not only need to target the major tasks of tracer kinetic modelling, but also can deal with auxiliary tasks that improve the dynamic PET data, and as result can facilitate or help obtain higher quality kinetic models. Also, downstream tasks after obtaining kinetic parameters can also profit from machine learning. Such downstream tasks can be, for instance, the detection of tumor tissue or anomalies in the kinetic behaviour.

Spuhler et al. [31] introduced a convolutional neural network to generate patient-specific transmission maps from T1-weighted images of the brain, which served for MR-based attenuation correction of the PET data. They evaluated their approach on a dataset with 11 patients scanned with [^{11}C]WAY-100 635 and 10 others with [^{11}C]DASB. Static and dynamic PET data were reconstructed using synthesized and ^{68}Ge-transmission data with filtered backprojection. As metrics they used the quality of the PET images, but also the quality of the derived kinetic parameters. Overall, they claim the generated transmission maps produce comparable images with deviations to the state-of-art in the range of less than 2 %.

In a brain study, Klyuzhin et al. [32] used machine learning for denoising dynamic [^{11}C]raclopride PET images. They proposed a denoising autoencoder neural network and compared it with conventional denoising methods. The denoised images were then used to derive kinetic parameters. They used simulated dynamic PET images such that quantitative evaluations were possible. The machine learning denoised images enabled to calculate kinetic parameters with higher uniformity, lower coefficient of variation of voxel values and higher structural similarity index.

In a [^{18}F]FDG brain PET/MRI study in humans, the goal was to develop an approach for motion correction that is based on conditional generative adversarial networks with specific regard to image-derived arterial input functions. In the work of Shiyam Sundar et al. [33] the subject's motion during the PET measurement was determined from contemporaneously acquired MR navigators for six degrees of freedom (translations, rotations) and used to correct the training data set. These data set were augmented by means of rotation, translation, shearing, additive gaussian noise, brightness, contrast, which yielded synthetic data sets and mappings were calculated between individual frames and a reference frame (55–60 min after injection). With regard to the determination of the arterial input function, experimentally collected blood samples served as reference. The input function derived from the image as calculated by conditional generative adversarial networks was compared with the experimentally determined arterial input function based on the areas under the curves and the calculated average cerebral metabolic rates of glucose levels in the grey matter. It was shown that the conditional generative adversarial network methodology is suitable for motion correction of brain PET/MRI data and allows the determination of an image-based input function through the correction.

Feng et al. [34] proposed the use of deep learning to improve the quality of the estimation of Patlak macro-parameters from dynamic [^{18}F]FDG PET images. They used a convolutional neural network trained on pairs of Patlak images obtained by direct Patlak reconstruction (i. e., direct reconstruction of the Patlak macro-parameters from PET sinograms) and indirect reconstruction (i. e., derivation of Patlak parameters from reconstructed direct images). The evaluation and training was performed on a multi-bed dynamic PET dataset with 10 patients. A population-based input function was assumed. The root mean square difference was dropped by half between both direct and indirect reconstructions pointing at the value of using deep learning to improved indirect Patlak reconstructions.

Xie et al. [35] introduced a similar deep learning approach as Feng et al., but they included motion-correction for the direct Patlak reconstruction. The results of 15 patients undergoing dynamic [^{18}F]FDG PET of the brain produced significantly lower contrast-to-noise ratios for the machine learning approach when compared to conventional denoising methods such as Gaussian, nonlocal mean and BM4 D denoising.

A machine learning method for automatically detecting prostate tumors at voxel-level from dynamic PET data from [^{11}C]choline patients was proposed by Rubinstein et al. [36]. They evaluated their approach using data of 24 patients and using a deep autoencoder to extract features which were combined with kinetic parameters extracted with conventional methods and handcrafted radiomics to detect anomalous voxels. Their best algorithm offered a high area under the receiver operating characteristics curve (AUC-ROC) above 0.8 which is a promising result for the type of data used.

In a clinical study with 11 non-small cell lung cancer patients undergoing dynamic PET/MRI using [^{18}F]FDG, Besson et al. [37] showed that machine learning classification yielded a tumor detection accuracy of 97 % if given hand-crafted features obtained from the dynamic PET/MRI including the kinetic micro-parameters k_2 and k_3, as well as dynamic contrast-enhanced MRI perfusion (DCE) parameters.

Finally, Abazari et al. [38] used generative adversarial networks and biomathematical models to introduce a framework for generating synthetic PET images for different tumor scenarios. The resulting simulations are compared with published data showing very similar behaviour both quantitatively and qualitatively. This work is purely in-silico but bears significant value to validate kinetic modelling tools.

Overall, the research shows that kinetic information bears relevant information for multiple downstream tasks in the pipeline of dynamic PET image analysis. Machine learning approaches enable the combination of kinetic parameters with additional data in order to extract more information out of the images.

Steps into clinical practice

The research works presented here show the potential of machine learning for tracer kinetic modelling, yet the answer remains, how this can help pushing it into clinical practice. To the best of our knowledge, medical device companies have not yet released machine learning tools for tracer kinetic modelling, yet in particular the producers of large field-of-view PET devices are actively working on such tools. Additionally, some of the research papers presented offer the implemented code as open source, enabling other researchers and clinicians to deploy it in their own setup. We believe that within the next few years these developments could accelerate the use of tracer kinetic modelling in research and possibly also in routine clinical works. Yet, the path thereto is not short and both market needs and the regulatory frame will control the speed of this development.

Conclusion

Tracer kinetic modelling despite its potential has not made it to clinical practice. Yet, machine learning works have shown that several of its aspects such as derivation of the (arterial) input function, estimation of kinetic parameters, or selection of models, can strongly profit from it. Moreover, machine learning has been shown to be helpful in several downstream tasks such as automatic generation of attenuation maps, image denoising, motion-correction or tumor detection. With the rapid developments in the field of artificial intelligence more advantages are to be expected and possibly a breakthrough in the clinical use of dynamic PET information.

Statements and Declarations

Author Contributions

IM created the initial draft, ▶ **Fig. 1** and overall structure. TW critically reviewed and extended all sections completing the draft including ▶ **Fig. 2, 3**. KS extended some sections and reviewed the completed version of the article.

Conflict of Interest

IM and TW declare that no conflicts of interest exist. KS received research grants from Siemens Healthineers and Novartis and conference sponsorships from United Imaging, Siemens Healthineers, Novartis and Subtle Medical.

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