DEEPVOXNET2: YET ANOTHER CNN FRAMEWORK

From pre- to postprocessing and keeping track of the spatial origin of the data

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ABSTRACT

We know that both the CNN mapping function and the sampling scheme are of paramount importance for CNN-based image analysis. It is clear that both functions operate in the same space, with an image axis $I$ and a feature axis $F$. Remarkably, we found that no frameworks existed that unified the two and kept track of the spatial origin of the data automatically. Based on our own practical experience, we found the latter to often result in complex coding and pipelines that are difficult to exchange. This article introduces our framework for 1, 2 or 3D image classification or segmentation: DeepVoxNet2 (DVN2). This article serves as an interactive tutorial, and a pre-compiled version, including the outputs of the code blocks, can be found online in the public DVN2 repository. This tutorial uses data from the multimodal Brain Tumor Image Segmentation Benchmark (BRATS) of 2018 to show an example of a 3D segmentation pipeline.

Keywords  Acute Ischemic Stroke · Core and Penumbra · Medical Imaging · Machine learning · Deconvolution · Convolutional Neural Networks

1 Introduction

Yes, we are introducing yet another CNN framework. However, DVN2 also includes many other essential tools to train and test CNN, but also to process medical images, organize the experiments and analyze the results. This tutorial uses data from the multimodal Brain Tumor Image Segmentation Benchmark (BRATS) of 2018 [4, 1, 2] to show an example of a 3D segmentation pipeline.

1.1 Installation

The DVN2 repository [3] can be installed as a Python library such that all dependencies are also configured correctly. Even when you do not want to use the functionalities of DVN2 explicitly, installing it will provide users with a complete and working Python environment for doing medical image analysis in general. As of now, it is best to add DVN2 to an empty Python 3.9 environment, e.g. using the Anaconda package manager to first create and activate such an environment via:

conda create --name dvn2env python=3.9
conda activate dvn2env
Once you have activated your Python 3.9 environment correctly, there are two options to install \texttt{DVN2} together with all its dependencies, and, as a result, make your environment medical image analysis proof:

- First cloning or downloading the repository and then via:

  ```
  pip install -e /path/to/deepvoxnet2
  ```

- Installing it directly from Github via:

  ```
  pip install git+https://github.com/JeroenBertels/deepvoxnet2
  ```

The first method is helpful if you want to develop and contribute to the \texttt{DVN2} library. To upgrade your installation using the first method, download the latest version and repeat the process or \texttt{git pull} the new version. Repeat the command when using the second method but add the \texttt{-upgrade} flag. You can also install or revert to a specific version of \texttt{DVN2} in that case, append \texttt{@version_tag} (e.g., \texttt{@deepvoxnet-2.12.1}) to the paths in the above commands. Some functions require the SimpleITK and SimpleElastix software to be installed. To install these packages, please append the paths in the above commands with [sitk]. These are not installed by default because they are only available for a limited number of operating systems.

1.2 Schematic overview

The main driver behind the creation of \texttt{DVN2} was that we wanted to make something that gives insights rather than being super efficient or fully self-configuring. To the best of our knowledge, most libraries are oriented towards the latter, and there are no libraries that follow the supervised learning paradigm more closely. In \texttt{DVN2} the focus is on transforming one set of \textit{data pairs} into another. We make no difference between the CNN and sampling function, seeing them as mapping functions that transform one distribution into another, albeit implicitly, and keep track of the spatial aspect of the data. By doing so, the entire pipeline can be constructed in an end-to-end fashion:

\[
\hat{S}^{s''} \xleftarrow{\text{textmap}} \hat{S} \xleftarrow{m} S \xleftarrow{\text{successive}} S' \xleftarrow{\text{CNN}} P(X, Y).
\]

With \(P(X, Y)\), we denote the joint probability distribution of all the \textit{elements} that make up a data pair and is often present only implicitly as the empirical distribution arising from the observed set of data pairs \(S'\). In a straightforward supervised learning setting, a data pair may consist of the input variable \(X\) and output variable \(Y\). However, in \texttt{DVN2} we generalized this concept and made no difference between \(X\) and \(Y\). They can be represented using the same abstraction, i.e. the Sample object (Section\[3\]). Furthermore, a data pair does not necessarily represent a pair but can represent any number of Sample objects. To organize a data pair and the set of data pairs \(S'\) in a structured manner, in \texttt{DVN2} we can use the hierarchical structure of the Mirc, Dataset, Case, Record and Modality objects (Section\[5\]).

In \texttt{DVN2} we represent any transformed set \(S\) implicitly, by implementing the sampling function \(s''\) using the successive application of (i) a Sampler object that can sample a data pair from \(S'\) in the form of an Identifier object (Section\[4.1\]), and (ii) a network of Transformer objects (as a Creator object) that can transform the data pair (Section\[5\]). A crucial design aspect is that the Transformer keeps track of the spatiality of a Sample object, thus keeping track of the voxel-to-world transformation matrix. The combination of this, together with the fact that a Transformer is a generator, allows the construction of complex pipelines end-to-end. This way, we can view a CNN also as a Transformer that converts a data pair into another.

By viewing the CNN as just another Transformer, we were able to create the holistic CNN framework that \texttt{DVN2} is (Section\[6\]). If, for example, \(S'\) operates in the original image space and the set \(S\) uses image crops, you can extend the Transformer network straightforwardly. For example, first resulting in a set \(\hat{S}\) after application of the CNN, e.g., as the sampling function \(m\), and then putting back the patches such that \(\hat{S}'\) operates again in the original image space. As a result, we can build one large Transformer network and select which outputs are used for training the CNN.

Furthermore, \texttt{DVN2} contains functions to construct U-Net and DeepMedic CNN architectures and gives insights about crucial design aspects such as the RF and the possible output sizes. It also contains various metrics and losses that consistently work and give results in 3D. Other functionalities are related to analyses (e.g. statistical testing), conversions (e.g. image I/O such as dicom reading), transformations (e.g. registration, resampling) and plotting (Section\[7\]).

2 The Sample object

One of the core objects of \texttt{DVN2} is the Sample object. In line with the definitions of \(X\) and \(Y\) from the previous chapter, the Sample represents an array with a batch axis \(B\), a spatial axis \(I\) and a feature axis \(F\). The spatial axis itself is 3D,
hence the Sample object is a 5D array of size $B \times I_0 \times I_1 \times I_2 \times F$. Different from the standard Numpy array, the Sample object also has an affine attribute. This affine attribute stores the voxel-to-world transformation matrix for each batch element. As a result, the affine is a 3D array of size $B \times 4 \times 4$, thus assuming the same voxel-to-world transformation for each feature $f$ given a batch element $b$.

```python
from deepvoxnet2.components.sample import Sample

array_of_ones = np.ones((2, 100, 100, 3))
sample_of_ones = Sample(array_of_ones, affine=None)
print(sample_of_ones.shape)
print(sample_of_ones.affine)
```

It should be clear that, upon creation, the Sample object ensures the underlying array is 5D and that an affine attribute is specified. Therefore, be careful and specific. It is best practice always to provide the entire 5D array and affine attribute yourself to avoid unexpected behavior. In that sense, when working with only two spatial dimensions, it would be straightforward to set the fourth dimension of the Sample object as the singleton dimension.

```python
default_affine = np.eye(4)
sample_of_ones = Sample(array_of_ones[:,:, :, None, :], affine=np.stack([default_affine] * 2, axis=0))
print(sample_of_ones.shape)
print(sample_of_ones.affine)
```

You may have a medical image, for example, in Nifti format, and you want to convert this into a Sample object. In this case, you can load the image and use the internal data and affine attribute to create the Sample. Below we do this for the FLAIR image and the ground truth, here, the whole tumor segmentation of the first subject. It should not be surprising that both the FLAIR and ground truth are equal in size and have the same voxel-to-word transformation.

```python
import nibabel as nib
from deepvoxnet2 import DEMO_DIR

flair_path = os.path.join(DEMO_DIR, "brats_2018", "case_0", "FLAIR.nii.gz")
flair_image = nib.load(flair_path)
print(flair_image.shape)
print(flair_image.affine)
flair_sample = Sample(flair_image.get_fdata()[None, ..., None], affine=flair_image.affine[None, ...])
print(flair_sample.shape)
print(flair_sample.affine)
```

It should be clear that a Sample object is not so different from a Numpy array. If you do not care about the spatiality of the data, you can always use the default affine and ignore it. Let us already define a visualization function that will become handy later on in this tutorial. For a list of Sample objects, it will simply depict the first batch element and first feature the middle slice of each Sample in the list.

```python
from matplotlib import pyplot as plt

def visualize_list_of_samples(list_of_samples):
    n_cols = len(list_of_samples)
    ```
file: fig, axs = plt.subplots(1, n_cols, figsize=(n_cols * 3 * list_of_samples[0].shape[1] / 240, 3 * list_of_samples[0].shape[1] / 240))
axs = [axs] if n_cols == 1 else axs
for i, sample in enumerate(list_of_samples):
    axs[i].imshow(sample[0, :, :, sample.shape[3] // 2, 0].T, cmap="gray"), axs[i].axis("off")
plt.subplots_adjust(wspace=0, hspace=0)
plt.show()
visualize_list_of_samples((flair_sample, gt_sample))

3 Organizing the data

Now that we have defined the Sample object, which can represent any $x$ or $y$, we could potentially start constructing multiple sets of data pairs, e.g. $S'$, $S''$, etc. We could do so by simply having a list of lists of Sample objects. If we only had one data pair, this would look as follows:

```python
[]: simple_set = [(flair_sample, gt_sample)]
```

However, such a representation is neither valid nor feasible for various reasons. Remember that the set $S'$ represents pairs of native data, e.g. samples drawn from the distribution $P(X, Y)$. It would become impossible to load everything into memory at once for large datasets or large data. Furthermore, the subsequently derived sets $S''$, etc., are in fact (practically) infinite, e.g. data augmentation, and thus impossible to represent with a simple list. We, therefore, chose to organize the native data only, i.e. the set $S'$, in a more structured manner. The other sets are represented implicitly by defining the sampling functions $s''$, etc (see Section 4 and 5).

To organize our data, we have created a hierarchical structure of dictionaries: Mirc > Dataset > Case > Record > Modality. When creating instantiations of a Dataset, Case, Record or Modality, we need to specify an “ID”. As a result, each dictionary consists of key-value pairs, with the keys corresponding to the lower-level object’s IDs. The purpose of the Mirc object is to group multiple Dataset objects and provide the user with higher-level functionalities, of which we will explain a few at the end of this section.

3.1 The Modality object

Starting from the lowest level, a Modality is simply something that returns a Sample object when `load()` is called. This is useful because when having a large dataset, it is impossible to load every image simultaneously; thus, the method provides a way to only create a Sample object from it when needed. Note that the Modality is an abstract class, and to use the feature above, we should e.g. use the NiftiFileModality. When the dataset is small, or for e.g. metadata such as age, it could be more efficient or appropriate to load everything to disk and use the NiftiModality or ArrayModality instead. Other Modality subtypes that are readily available are ImageFileModality and ImageFileMultiModality. These use the Image library to load 2D images from disk (e.g. PNG, JPG) and convert them to 5D correctly (setting the fourth dimension as the singleton dimension as mentioned before).

```python
[]: from deepvnxnet2.components.mirc import NiftiFileModality, NiftiModality, ArrayModality
flair_modality = NiftiFileModality("flair", file_path=flair_path)
flair_modality_ = NiftiModality("flair", nifty=flair_image)
flair_modality__ = ArrayModality("flair", array=flair_image.get_fdata(), affine=flair_image.affine)
assert np.array_equal(flair_modality.load(), flair_modality_.load())
assert np.array_equal(flair_modality.load(), flair_modality__.load())
print(flair_modality.load().shape)
print(flair_modality.load().affine)
gt_modality = NiftiFileModality("gt", file_path=flair_path)
metadata_modality = ArrayModality("age", array=45) # just an example how we could make a metadata Sample, e.g. of age
```
Notice that we have created a “flair” Modality in three ways but that the final Sample objects are, in fact, the same. As such, always think of what is the most efficient way to represent a particular data type and Sample object in your specific situation.

3.2 The Record, Case and Dataset objects

To create “pairs” of data, we should group multiple Modality objects under a so-called Record. Multiple Record objects need to be grouped under a Case object. The idea of the existence of both a Case and a Record is that there might be multiple records (e.g. observations) for a certain case (e.g. a subject). Imagine having multiple experts annotating the same subject or having multiple parts of the body scanned separately. Finally, cases should be grouped under a Dataset object. Let us construct two tumor datasets based on data from BRATS 2018 below.

```python
from deepvoxnet2.components.mirc import Dataset, Case, Record
def get_tumor_dataset(dataset_id, case_indices):
    tumor_dataset = Dataset(dataset_id)
    for i in case_indices:
        subject = Case(f"subject_{i}"
        for j in range(1):  # we only have a single observation for each subject here
            observation = Record(f"observation_{j}"
            flair_modality = NiftiFileModality("flair", file_path=os.path.join(DEMO_DIR, "brats_2018", f"case_{i}", "FLAIR.nii.gz"))
            gt_modality = NiftiFileModality("gt", file_path=os.path.join(DEMO_DIR, "brats_2018", f"case_{i}", "GT_W.nii.gz"))
            age_modality = ArrayModality("age", np.random.randint(20, 80))
            observation.add(flair_modality)
            observation.add(gt_modality)
            observation.add(age_modality)
            subject.add(observation)
        tumor_dataset.add(subject)
    return tumor_dataset

train_tumor_dataset = get_tumor_dataset("train_dataset", range(0, 8))
val_tumor_dataset = get_tumor_dataset("val_dataset", range(8, 10))

for tumor_dataset in [train_tumor_dataset, val_tumor_dataset]:
    print(f"{tumor_dataset.dataset_id} contains {len(tumor_dataset)} cases:")
    for case_id in tumor_dataset:
        print(f"\t{case_id} contains {len(tumor_dataset[case_id])} records:")
        for record_id in tumor_dataset[case_id]:
            print(f"\t\t{record_id} contains {len(tumor_dataset[case_id][record_id])} modalities:")
            for modality_id in tumor_dataset[case_id][record_id]:
                print(f"\t\t\t{modality_id}"

3.3 The Mirc object

When we have built our dataset, we can group it, optionally with other datasets, into a Mirc object. The Mirc object is a powerful tool for getting a complete overview of all your data. Calling get_dataset_ids(), get_case_ids(), get_record_ids() or get_modality_ids() you can get a quick overview on what data is available in your Mirc object. You can also calculate the mean and standard deviation for a particular modality by using the mean_and_std method. The inspect method is particularly useful to check multiple modalities for spatial consistency within a certain Record and get an overview of the distribution of voxel sizes and other spatial characteristics of your data. Using
the get_df method, it is possible to acquire a Pandas DataFrame such that you could do other types of analyses or inspections. This is particularly useful if you want to inspect distributions of non-imaging data, such as age.

```python
from deepvoxnet2.components.mirc import Mirc

my_mirc = Mirc(train_tumor_dataset, val_tumor_dataset)
print(my_mirc.get_dataset_ids())
print(my_mirc.get_case_ids())
print(my_mirc.get_record_ids())
print(my_mirc.get_modality_ids())
print(my_mirc.mean_and_std("flair", n=2))  # computing the mean and standard deviation
  using all your images might be too expensive, therefore limit the number of images
  used setting the n option
print(my_mirc.inspect(["flair", "gt"], ns=[2, 2]))
print(my_mirc.get_df("age"))
```

In the usage of the Mirc object example mentioned above, we have grouped both our training and our validation set under one Mirc object. Keep in mind that this was just for illustration purposes. It is always a good idea to keep the two separate.

```python
my_train_mirc = Mirc(train_tumor_dataset)
my_val_mirc = Mirc(val_tumor_dataset)
```

## 4 Data sampling

Once we have defined the set $S'$, e.g. by means of a Mirc object containing Record objects at its lowest level or simply a list of lists of Sample objects, we can start thinking about the sampling functions, e.g. the function $s''$ that produces the set $S''$ from $S'$ (Equation 1). It turns out that we can often view any sampling function that goes from one set of data pairs to another as something that first samples a data pair and then applies some form of data transformation to it creating zero, one or more transformed data pairs. In this section, we will discuss the first part of the sampling function, more specifically, the Sampler object. For now, you can view the Sampler object as having an internal list of objects that we can index to retrieve the object. While the retrieved object could be a Record object or a list of Sample objects, we chose to define it as a new object, i.e. the Identifier object.

### 4.1 The Identifier object

Let us start by saying that the Identifier object could be any object since we could define the word sampling as retrieving something from a list. In our specific use case, the returned Identifier object will be used by the data transformation function (see Section 5), and thus should contain all information necessary to do the transformation. Letting the Identifier represent a list of Samples or a Record would be sufficient in that case. However, if representing a Record, the Identifier has no notion from which Dataset or Case it was from. For this purpose, if we want to keep track of this additional information, we could wrap a Record as a MircIdentifier.

```python
from deepvoxnet2.components.sampler import MircIdentifier

record_identifier = MircIdentifier(my_mirc, dataset_id="train_dataset",
  case_id="subject_0", record_id="observation_0")
print(record_identifier())
for modality_id in record_identifier.mirc[record_identifier.
  dataset_id][record_identifier.case_id][record_identifier.record_id]:
  print(modality_id)
```

### 4.2 The Sampler object

As mentioned before, we defined a Sampler as a rather simple object, specifically a list of Identifier objects, but with some additional functionalities. An important functionality is the ability to shuffle its internal list of Identifier objects by calling randomize(). Whether this call will do anything depends on the value of the shuffle option when
you create the Sampler, which defaults to False. The shuffling itself is a new permutation of the list of Identifiers, potentially with replacement according to the probability density if specified using the weights option. In DeepVoxNet2, you can use the MircSampler to convert a Mirc object to a Sampler of MircIdentifiers. Depending on the mode option, either "per_case" or "per_record", the internal list of MircIdentifiers and its shuffling will be different. Using mode="per_case", the list size will be the number of Case objects in the Mirc object, thus with Record objects selected uniformly across all Case objects. Using mode="per_record", the list size will be the number of Record objects in the Mirc object, thus with Records selected uniformly across all Record objects.

```python
from deepvoxnet2.components.sampler import Sampler, MircSampler

a_simple_sampler = Sampler([1, 2, 3, 4, 5], shuffle=True, weights=[1, 1, 10, 1, 1])
for i in range(5):
    print(f"a_simple_sampler at iteration {i}: ", [a_simple_sampler[j] for j in range(len(a_simple_sampler))])
    a_simple_sampler.randomize()

my_train_sampler = MircSampler(my_train_mirc, mode="per_case", shuffle=True)  # shuffle=True typically for training
my_val_sampler = MircSampler(my_val_mirc, mode="per_case", shuffle=False)  # shuffle=False typically for validation
for i in range(5):
    print(f"my_train_sampler at iteration {i}: ", [my_train_sampler[j].case_id for j in range(len(my_train_sampler))])
    my_train_sampler.randomize()
    my_val_sampler.randomize()
```

It might look strange that a Sampler has a finite internal list and is not just something that generates Identifier objects indefinitely or until completion. However, using this abstraction, it is easier to keep track of having seen all data pairs at least once before shuffling (without weights specified), etc.

## 5 Data transformation

Now that we have selected a data pair from our set \( S' \), e.g. as a MircIdentifier using a MircSampler constructed from a Mirc object, we want to transform this data pair into zero, one or more transformed data pairs. To do so, DeepVoxNet2 uses Transformer objects. To achieve complex transformations, a network of Transformer objects can be constructed and wrapped as a Creator object to unlock higher-level functionalities.

To start, we can view a Transformer object as having an input and an output using the most straightforward representation of a data pair, i.e. a list of Sample objects. Furthermore, from its input, it can generate zero, one or more (potentially infinite) outputs. What transformation and how many strictly depends on the type of Transformer and what options you specify. Typically, the input of one Transformer is the output of another.

### 5.1 The InputTransformer object

While all Transformers work as input-to-output and use a list-of-Sample-objects representation, one type of Transformer is slightly different: the InputTransformer. In a sense, the InputTransformer has no input and thus cannot be connected to the output of another Transformer. They serve as the start of your Transformer network and exist to convert any type of Identifier into a list of Sample objects. It is this property that makes it possible to work with a more structured form of your dataset, using any type of Identifier produced by the Sampler. The sole thing that must be foreseen is a dedicated InputTransformer that knows how to convert the Identifier to a list of Sample objects that it will present at its output. When making use of MircIdentifiers, we can use the MircInput InputTransformer. When using a list of Sample objects already, we should use the SampleInput InputTransformer. Typically for any InputTransformer is that we need to load the Identifier into the Transformer manually by using its load method.

```python
from deepvoxnet2.components.transformers import _MircInput
```
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mirc_input = _MircInput(["flair", "gt"], n=1)  # the use of _MircInput(...) is for
  # illustrative purposes only
mirc_input.load(my_val_sampler[1])  # here we do this manually, but usually we use the
  # higher-level Creator, which we can also use for debugging
x_y = mirc_input()  # normally we will use MircInput(...) instead, which does
  # _MircInput(...)() in one go

def visualize_transformer_output(transformer_output):
    for i in range(100):
        try:
            transformer_output_i = transformer_output.eval()
            print(f"Evaluation {i}:")
            visualize_list_of_samples(transformer_output_i)
        except StopIteration:
            print(f"Generation stopped after n={i} evaluations")
            break
visualize_transformer_output(x_y)

In the above example, the InputTransformer ran out of generating new data pairs after one iteration. In fact, by setting the n option differently (n=1 by default for most Transformers), you can let the Transformer generate n outputs from one input.

5.2 The Creator object

Suppose we not only want to load the Identifier but also want to transform it, such that in combination with the Sampler, we create an implicit new set of data pairs. For this purpose, the returned output of any Transformer, e.g. x_y in the above code snippet, is a Connection object that can be connected to the input of another Transformer. Without going into too much detail, it is simply a reference to a list of Sample objects at a certain output index (a Transformer can have multiple inputs and outputs; see later) of a certain Transformer. It is this abstraction that allows us to build a network of Transformers. Suppose we want to create a new set in which we remove the Y and only keep X, or vice versa:

```python
x = Split(indices=(0,), n=1)(x_y)
visualize_transformer_output(x)
y = Split(indices=(1,), n=1)(x_y)
visualize_transformer_output(y)
```

Even though we ask to produce a total of N=1*1=1 transformed data pairs (for each new identifier), the generation stops immediately. This is because we already ran that same MircInput object (i.e. mirc_input) until completion in the previous code snippet. As soon as the Split Transformer wants to read the output of mirc_input, the latter will tell it has already been depleted. To overcome this burden, e.g. when debugging or when the Transformer network has run until completion for Identifier A, but we want to reuse it and run it for Identifier B, we can use the Creator object. The Creator object has a higher-level view of the Transformer network. For example, it can find all InputTransformer objects in the Transformer network and can reset the state of all Transformer objects. Below, let us first rebuild the Transformer network from above and then wrap it as a Creator.

```python
from deepvoxnet2.components.transformers import Split
x = Split(indices=(0,), n=1)(x_y)
visualize_transformer_output(x)
y = Split(indices=(1,), n=1)(x_y)
visualize_transformer_output(y)
```

```python
from deepvoxnet2.components.transformers import MircInput
from deepvoxnet2.components.creator import Creator
x_y = MircInput(["flair", "gt"], n=1, output_shapes=[[1, 240, 240, None, 1], (1, 240, None, 1)])
x = Split(indices=(0,), n=1)(x_y)
y = Split(indices=(1,), n=1)(x_y)
x_creator = Creator(outputs=[x])
y_creator = Creator(outputs=[y])
```
x_y_creator = Creator(outputs=[x, y])

def visualize_creator_outputs(creator, identifier):
    i = 0
    for creator_outputs_i in creator.eval(identifier):
        print(f"Evaluation {i}:")
        for j, transformer_output_i in enumerate(creator_outputs_i):
            print(f"\tOutput of Transformer {j}:")
            visualize_list_of_samples(transformer_output_i)
        i += 1
    print(f"Generation stopped after n={i} evaluations")

visualize_creator_outputs(x_creator, my_val_sampler[1])
visualize_creator_outputs(y_creator, my_val_sampler[1])
visualize_creator_outputs(x_y_creator, my_val_sampler[1])

Notice how the Creator object has the potential to evaluate the output of multiple Transformer objects at once (we give it a list of Transformer outputs upon creation). Evaluating the Creator is somewhat different from evaluating a Transformer output as we did before. When we evaluated a Transformer output, we would have first needed to make sure that all InputTransformer objects had loaded the Identifier manually. Then, using .eval() we updated that particular output of that particular Transformer. However, when using .eval(identifier) of the Creator object, the Creator will first reset all Transformer objects and then load the specified Identifier into all InputTransformer objects it can find in its Transformer network. Finally, this will return a proper generator object that you can run until completion (i.e. as soon as at least one InputTransformer is depleted).

Another useful, higher-level functionality of the Creator object is that it traces back which Transformer objects are needed to compute the requested Transformer outputs. As a result, it will simplify the Transformer network internally. Furthermore, we can save the entire Creator as an object and load it for later use using its static save_creator and load_creator methods. Last but not least, it will give names to the Transformers, and you will be able to summarize the network in a printout. Note that we also specified some input shapes in the code snippet above. This is optional, but the summary will become more informative when doing so, and you can keep better track of the shapes.

[ ]: import tempfile
tmp_dir = tempfile.TemporaryDirectory()
tmp_file = os.path.join(tmp_dir.name, "x_y_creator.pkl")
Creator.save_creator(x_y_creator, file_path=tmp_file)  # or x_y_creator.save(tmp_file)
x_y_creator = Creator.load_creator(tmp_file)
x_y_creator.summary()
tmp_dir.cleanup()

Be careful with saving and loading Creator objects as soon as you have KerasModel Transformer objects in your network of Transformer objects (see later in Section 6.1). The Keras models will be cleared before saving; thus, you should manually save, load and set them using the set_keras_models method. As soon as you use a DvnModel (Section 6.3) and use its own save and load methods, this will be taken care of for you.

### 5.3 More complex Transformer networks

The beauty of the Transformer network is that the transformation can become arbitrarily complex, while the construction of it remains relatively simple. Without describing the functioning of all available Transformer objects, there are a couple of intricacies that are still useful to explain.

The first thing has to do with the data pair, i.e. a list of Sample objects, and was already part of the above example code. To be clear, it is important to not view a data pair as a pair but rather as a list containing one or more Sample objects. This pair does not need to remain intact when flowing through the Transformer network. As a result, the resulting set may look entirely different when applying a sampling function (i.e. combination of the Sampler and Transformer network). After the use of the Split Transformer, we could use the Group Transformer to group again, resulting in a set identical to the original (depending on the Sampler, of course).
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from deepvoxnet2.components.transformers import Group

x, y = Group()([x, y])
x_y_creator = Creator(outputs=[x_y])
visualize_creator_outputs(x_y_creator, my_val_sampler[1])

Also, note that you can use multiple InputTransformers and that they will see the same Identifier. This can be useful since it allows you to build one network and wrap different parts of it in different Creator objects. Since the Creator simplifies the underlying Transformer network, it is possible that not all InputTransformers are used and thus, you could evaluate certain parts with an Identifier lacking certain information. Just as an example how we could use two InputTransformer objects instead:

x = x_input = MircInput(['flair'], n=1, output_shapes=[(1, 240, 240, None, 1)])
y = y_input = MircInput(['gt'], n=1, output_shapes=[(1, 240, 240, None, 1)])
x, y = Group()([x, y])
x_y_creator = Creator(outputs=[x, y])
visualize_creator_outputs(x_y_creator, my_val_sampler[1])

Second, some Transformer objects need a reference Transformer to calculate their internal transformation. For example, if we want to deform the Samples using an affine transformation, we want first to compute the affine transform based on a reference Sample. Similarly, if we want to produce some crops, we might want those to originate from non-zero portions of a particular Sample. For this purpose, it is always a good idea to have the reference output be a list of only one Sample, such that there is no ambiguity in which Sample is used as a reference.

from deepvoxnet2.components.transformers import AffineDeformation, RandomCrop

x_y_affine = AffineDeformation(x, rotation_window_width=(1, 0, 0), translation_window_width=(10, 10, 0))(x_y)
x_y_flip = Flip(flip_probabilities=(0.5, 0, 0), n=2)(x_y_affine)
x_flip = Split(indices=(0,))(x_y_flip)
mask_flip = Threshold(lower_threshold=0)(x_flip)
x_y_crop = RandomCrop(mask_flip, (85, 85, 85), nonzero=True, n=4)(x_y_flip)
x_y_crop_creator = Creator(outputs=[x_y_crop])
visualize_creator_outputs(x_y_crop_creator, my_val_sampler[1])

Notice how x_y_crop_creator generates \(N=1*1*1*1*2*4=8\) crops while the x_y_crop_creator_ only generates a single crop. This is because the x_y_crop_creator_ also generates the output of the AffineDeformation Transformer, and requesting it to generate an output the second time will deplete the underlying InputTransformer objects already (\(n=1\) for most Transformer objects by default). So be careful with the so-called shortcut connections.

Third, remember that we said that the input and output of a Transformer is a list of Sample objects. In fact, this is only partly true and this has to do with the concept that a Transformer is applying the same random transformation to all Sample objects it can find at its input. A Transformer can be connected to multiple inputs, resulting in multiple outputs, meaning that a Transformer may transform multiple data pairs that are connected to the Transformer. As such, we could have constructed the Transformer network from above in many different ways, so always choose the most efficient route. Try to find some differences in the below code:

affine_transformer = AffineDeformation(x, rotation_window_width=(1, 0, 0), translation_window_width=(10, 10, 0))
x_affine, y_affine = affine_transformer(x_input, y_input)

flip_transformer = Flip(flip_probabilities=(0.5, 0, 0), n=2)
x_flip = flip_transformer(x_affine)
y_flip = flip_transformer(y_affine)

mask_flip = Threshold(lower_threshold=0)(x_flip)
x_crops, y_crops = RandomCrop(mask_flip, (85, 85, 85), nonzero=True, n=4)(x_flip, y_flip)
x_y_crops = Group()([x_crops, y_crops])
Again, notice how the above Transformer network can generate 8 transformed data pairs starting from a particular identifier. As soon as the network gets more complex, it is always a good idea if the generated number corresponds to what you had in mind. It is possible that an InputTransformer triggers to stop the generation too soon due to unwanted shortcuts in your network, e.g. your network contains parallel paths with one path generating more than the other.

Finally, the most remarkable thing about the Transformer network is that it works with Sample objects, hence it always has a notion of where the Sample is located in the world. We could use the Put Transformer to put back all the image crops into a reference Sample space of choice.

```
x_buffer = Buffer(buffer_size=None)(x_crop)
x_put = Put(reference_connection=x_input)(x_buffer)
x_put_creator = Creator(outputs=[x_put])
visualize_creator_outputs(x_put_creator, my_val_sampler[1])
```

As an exercise, you can explore what would happen with the reconstructed image if you would take more crops (increase n of RandomCrop). Alternatively, what happens if you use the GridCrop instead of the RandomCrop using the default n=None option?

### 6 DVN2 for CNN-based applications

At this point, we can generate, albeit still implicitly, a wide variety of sets, e.g. $S''$, starting from the set $S'$. Using the suggested DVN2 way, we could operate as follows:

- organize the set of data pairs $S'$ as Record objects in a Mirc object;
- create a MircSampler from the Mirc object to sample MircIdentifiers;
- make a Transformer network (as a Creator) that starts from a MircIdentifier and generates new data pairs.

As a result, we have a powerful tool at our disposal that we can use to make CNN-based application pipelines. In order to effectively use it, in DVN2 we linked with the Tensorflow library, particularly Keras. Nevertheless, until this point, everything was coded in Python independently of the deep learning framework. The following functions can be adapted when desired to use other deep learning frameworks such as Pytorch.

#### 6.1 The KerasModel Transformer

First of all, in DVN2 we have provided functions to create a DeepMedic- or U-Net-like CNN architecture as a Keras model. It provides a variety of options, such as different types of layer normalizations, residual connections, siam networks, padding, etc. Furthermore, it provides the user with plenty of information, for example, the RF and possible output sizes, and even an estimated memory usage. When using the default settings, it will create the No-New Net variant of the standard U-Net:

```
no_new_net_model = create_generalized_unet_v2_model()
```

We can see that the model performs internal padding because both the output and input size is 128 x 128 x 128 voxels$^3$. We also see that the RF size is 185 x 185 x 185 voxels$^3$. Besides plenty of other information, the summary provides us with potential alternative output and input sizes. Suppose we want to create a simple U-Net-like CNN that transforms a single input patch of size 85 x 85 x 85 voxels$^3$ into an output patch of 53 x 53 x 53 voxels$^3$, representing the predicted segmentation. To do so, we could modify some of the default options like below:

```
my_own_unet_model = create_generalized_unet_v2_model(
    number_input_features=1,
    subsample_factors_per_pathway=(
```
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In order to proceed, it is important to understand that a CNN can be seen as a Transformer. The standard view of a CNN is that it transforms inputs into outputs, specifically, a list of arrays into another list of arrays. Or, sometimes viewed as transforming a specific (joint) distribution into another (joint) distribution. Unique to DVN2 is that we keep this view on CNNs but add the spatiality to it, thus transforming a specific list of Sample objects into another. To do so, DVN2 provides the KerasModel Transformer, which wraps a CNN as a Transformer that you can use in your Transformer network. Using the default options, it assumes the output Sample objects have the same scale as the first input Sample object and are spatially centered. If this is not the case, you can use the output_affines and output_to_input options to specify the affine transformations from output to input and the input reference for each output, respectively.

```python
from deepvoxnet2.components.transformers import KerasModel
x_crop_pred = KerasModel(my_own_unet_model)(x_crop)
x_buffer = Buffer(buffer_size=None)(x_crop_pred)
x_put = Put(reference_connection=x_input)(x_buffer)
x_put_creator = Creator(outputs=[x_put])
visualize_creator_outputs(x_put_creator, my_val_sampler[1])
```

Note how we have reconstructed a prediction by letting the crop flow through the CNN and putting it back in the original image space. At this point, the CNN is not trained and the weights are still random. How can we tune these weights?

### 6.2 Tensorflow Dataset wrapper

We only need to define the set of data pairs that contain learning pairs that can be used to train the CNN. We can identify the proper Transformer objects, put them in a Creator and make a true set of data pairs together with a Sampler. The Tensorflow Dataset is used for this purpose, which is just another representation for a set of data pairs. The combination of a Creator and a Sampler has all information that is necessary to construct a Tensorflow Dataset.

```python
import time
from deepvoxnet2.components.transformers import Crop
from deepvoxnet2.components.model import TfDataset
y_crop_true = Crop(y_crop, (53, 53, 53))(y_crop)
learning_set_creator = Creator([x_crop, y_crop_true])
my_tf_train_dataset = TfDataset(learning_set_creator, my_train_sampler, batch_size=1)
count = 0
prev_time = time.time()
for element in my_tf_train_dataset:
    print("Generation took {:.2f} s".format(time.time() - prev_time), [[sample.shape/uni2423 for sample in transformer_output] for transformer_output in element])
count += 1
prev_time = time.time()
```
Using the standard options, it iterates through `my_train_sampler` only once. Before going to the next Identifier in the Sampler, it will ask the underlying Transformer network in the Creator to run until completion. This is the reason why a total of N=8*8 elements were produced, and that it seemed to go in blocks of 8. Looking at the structure and shape of an element, this is precisely what we would expect from our `learning_set_creator`. We could use this dataset to train the CNN. With a batch size of 1, each epoch would contain 64 updates, which we could define here as one loop through the entire new set of transformed data pairs. In order to better shuffle across subjects (Identifiers, actually) and make the generation quicker, we could play around with some options.

```python
my_tf_train_dataset = TfDataset(learning_set_creator, my_train_sampler, batch_size=16, shuffle_samples=64, prefetch_size=64)
count = 0
prev_time = time.time()
for element in my_tf_train_dataset:
    print("Generation took {:.2f} s".format(time.time() - prev_time), [sample.shape for sample in transformer_output] for transformer_output in element)
count += 1
prev_time = time.time()
print(f"The entire my_tf_train_dataset contains {count} elements")
```

It is possible to use the native Keras routines from this point onwards to train the CNN.

```python
from deepvoxnet2.keras.optimizers import SGD
from deepvoxnet2.keras.losses import get_loss
my_own_unet_model.compile(optimizer=SGD(learning_rate=1e-3, momentum=0.9, nesterov=True), loss=get_loss("dice_loss", reduce_along_batch=True))
my_own_unet_model.fit(my_tf_train_dataset, epochs=10)
visualize_creator_outputs(x_put_creator, my_val_sampler[1])
```

However, how to now have your creator for training, predictions, etc., in one place? We created the DvnModel for simplicity and to allow for a more holistic way of defining and training or testing the complete pipeline.

### 6.3 The DvnModel object

It should be clear that the set of data pairs used for training differs from the set we are interested in, represented by the `x_put_creator`. However, this may not fully suffice, e.g. we do not yet have a prediction for our entire image. This is because usually, even more different sets of pairs are used. In order to group an arbitrary number of data pairs, together with training information such as loss functions and many more, we first create the most holistic Transformer pipeline and then create a DvnModel.

```python
from deepvoxnet2.components.model import DvnModel
# training part of the Transformer network
x_affine, y_affine = AffineDeformation(x, rotation_window_width=(1, 0, 0), translation_window_width=(10, 10, 0))(x_input, y_input)
x_flip, y_flip = Flip(flip_probabilities=(0.5, 0, 0), n=2)(x_affine, y_affine)
mix_flip = MixProbabilisticFlip(flip_probabilities=(0.5, 0, 0), n=2)(x_flip, y_flip)
mix_flip_crop = RandomCrop(mix_flip, [(85, 85, 85), (53, 53, 53)], nonzero=True, n=4)(x_flip, y_flip) # notice how we can take differently sized crops around the same coordinate
y_train_pred, y_train = KerasModel(my_own_unet_model)(x_flip_crop), y_flip_crop
# validation and testing part of the Transformer network
mask = Threshold(lower_threshold=0)(x_input)
```
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```python
x_crop, y_crop = RandomCrop(mask, [(85, 85, 85), (53, 53, 53)], nonzero=True, n=100)(x_input, y_input)  # notice that n is much larger now
y_val_pred, y_val = KerasModel(my_own_unet_model)(x_crop), y_crop
y_val_pred_buffer = Buffer(buffer_size=None)(y_val_pred)
y_full_val_pred, y_full_val = Put(reference_connection=x_input)(y_val_pred_buffer), y_input
# creating a single DvnModel of the complete pipeline, typically in a [y_pred, y_true, sample_weights] order, similar to keras, but substituted x by y_pred
my_super_cool_dvnmodel = DvnModel(
    outputs={
        "train": [y_train_pred, y_train],
        "full_val": [y_full_val_pred, y_full_val],
        "full_test": [y_full_val_pred]
    }
)
```

The DvnModel can be used to call the training routines directly, without the need to create Creator objects and TfDataset objects. Furthermore, the DvnModel can be saved, storing all the Creator objects and the KerasModel. We advise users to have a careful look at the DvnModel class for all its use cases and how compile, fit, predict methods, etc, can be used similar to the Keras API.

7 Other functionalities in DVN2

The main contribution of DVN2 is the intuitive way of implementing preprocessing, sampling and postprocessing and providing a way to store everything under one single object. However, there are other unexplored fruits available.

7.1 Utilities

Under deepvoxnet.utilities there are many useful utility functions available:

- **conversions.py** Here, you can find many useful loading and conversion functions. For example, reading a Dicom file (including time series such as CTP data) from disk, conversions between Nifti, SimpleITK and Dicom.

- **transformations.py** Perfect for resampling, registration, etc., mainly starting from Nifti files. This is unlike many other libraries that require SimpleITK file formats or you need to use via the Terminal.

- **drawing.py** Some cool functions to draw overlays.

7.2 Analysis

Under deepvoxnet.analysis we can find several handy tools to:

- **data.py** The Data class can be viewed as a single-column Pandas Dataframe with additional functionalities, specifically to work with data that has MultiIndex structure as Dataset > Case > Record. We could group or compute statistics across either of these indices.

- **analysis.py** The Analysis class can be viewed as a multi-column Pandas Dataframe with additional functionalities. For example, when having two columns, we can apply a metric function to each row such that a Data object is returned.

- **plotting.py** This library uses the Figure class for plotting such that you can draw figures using an absolute scale. Furthermore, since typical plotting libraries cannot handle NaNs, we have the Series, SeriesGroup and GroupedSeries objects that compute statistics and can be used to plot, even if they contain NaNs.

8 Conclusion

We have provided a novel CNN framework that can be used to design end-to-end CNN pipelines for either 1D, 2D or 3D segmentation or classification. Some of the key design aspects of DVN2 are that it stays close to the supervised learning paradigm and keeps track of the spatial aspects of data pairs. While potentially memory and computationally
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hungry, DeepVoxNet2 provides users with a multitude of intuitive abstractions meant to increase the awareness of some of the underlying mechanisms of CNNs. On top of this, DeepVoxNet2 provides other useful utility and analysis functions for medical image analysis, such as functions related to image I/O, registration, statistical analysis and visualization.

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