Multi-Scale Temporal Imaging: From Micro- and Meso- to Macro-scale-time Nuclear Medicine

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KEYWORDS

• Time • Radiomics • Radiophenomics • Delta radiomics • Multi-scale Temporal Imaging • Longitudinal imaging studies

INTRODUCTION

Living systems are in constant dynamism to keep the "internal milieu" stable despite the variation of external factors. This continuous change at the molecular and cellular levels aims at preventing a change at a large-scale (principle of homeostasis). In a medical context, there are two processes that can cause change at a large-scale: maladies and aging. Aging is a more gradual process that has been less studied.[1] Time provides a common frame of reference by which different processes of change can be related, and thus, time represents our understanding of change.

The human body is a system that is composed of structure on a range of scales from the nanometer size of amino acids, to the micrometer dimension of cells, to the milimeter length of tissues, to the centimeter proportion of organas. Properties of these structures can be measured using different imaging technologies. In the spatial domain, these imaging techniques provide characterization in the form of static or structural imaging. For instance electron density of the structure can be evaluated, and the mapping of this characteristics in the space-domain is achieved by CT images (X-Ray Computed Tomography). By comparing these structural snapshots with an expected norm, anatomical pathologies can be diagnosed and treated. In this way, structure can be captured and described as a multi-scale characterization of the spatial domain.

We capture the function and dynamism of an organ or organism via evaluation of the change in structures (like change in volume of left ventricle to measure function of heart as ejection fraction). Function, like structure, can be described as a multi-scale characterization. However, function

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PET Clin 18 (2023) 135–148
https://doi.org/10.1016/j.cpet.2022.09.008
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could be characterized in the temporal rather than spatial domain:In clinical imaging, time ranges from the seconds of perfusion imaging, to the minutes of ^{18}F-Fluorodeoxyglucose (FDG) kinetics, to the days for ^{177}Lu-PSMA biodistribution, and to the months for tumor growth. If we have dynamic imaging then we can quantify the change to evaluate the function (like glucose metabolism by compartmental modeling in dynamic FDG-PET); however in clinical practice sometimes we only have the temporal snapshots of this dynamism (like static FDG-PET imaging). To interpret the meaning of these snapshots of the function, we have to compare them with the expected status of the dynamic systems at certain times to identify functional pathologies (like 45 second post injection of iodine-based contrast to evaluate arterial perfusion in CT or 60 minutes post injection of 18F-FDG to evaluate metabolic activity in PET).

Change across different time points is a critical factor that is foundational for diagnostic imaging which is the basis of an aphorism in medical imaging community: “the best friend of a radiologist is prior images”. This wisdom emphasizes on the superiority of temporal dynamism over static appearance of structure. In this article, we discuss the interrelatedness of “change” and “time”, the similarities of “imaging of change” regardless of time-scale, and the scale-dependent difference of “temporal imaging”. We first describe the different time scales and the kinds of imaging that take place under those time scales. We then examine the current status of medical imaging literature focused on a macro time scale. We identify strengths and weaknesses of existing evaluations. Finally, we offer some observations and suggestions for future directions of medical imaging research.

TEMPORAL IMAGING AND VARIOUS SCALES OF TIME

The temporal domain can be described over several different time scales. Within the context of medical imaging, we describe three such time scales: micro-, meso-, and macro- time scales.[2] Micro-scale temporal imaging refers to a small temporal window that encompasses a single imaging or acquisition event (session). This can range from the narrow window of beam on-time in a system to repeated scans that occur between when a patient gets on and off the imaging table, including techniques such as dynamic PET and multi-phase CT, or gated imaging. Meso-timescale imaging concerns acquisitions that occur within a short period but as distinct scanning events. Finally, macro-timescale imaging concerns a longer gap between scanning events extending to months or even years. In both the scientific literature and clinical practice, there has been a greater focus and a better understanding of imaging along the micro- and meso- scales. In this section, we describe the micro- and meso-scales in greater detail. The paper then focuses on macro-scale temporal imaging.

Micro-scale temporal imaging

Beyond routine scanning which is considered along micro-scale time, there are multiple established imaging techniques that utilize a series of scans within a single acquisition period to improve understanding of specific biological and metabolic functions. Examples include kinematic and parametric imaging in nuclear medicine[3–5], multiphase CT for renal and liver lesions[6–9], CT angiography[10], perfusion CT and MRI[11–16], and dynamic and diffusion imaging in MRI[17–19], gated cardiac SPECT and PET imaging, and respiratory gated imaging (for motion tracking or compensation). An important development has been 4D medical imaging technologies, where the three spatial dimensions of volumetric imaging modalities are combined with time to precisely observe temporal change and variation.[20] This concept has been investigated with time resolved CT, SPECT, PET, and MRI.

Meso-scale temporal Imaging

For meso-scale temporal imaging, common techniques include the notion of pre-op and post-op scans for various surgeries[21–24], dosimetry studies in nuclear medicine, and daily scans during the course of a radiation therapy treatment [25–27]. A specific example is radiopharmaceutical therapy (RPT), for which time is a critical factor. Time is a critical factor in radiopharmaceutical therapy (RPT) effectiveness. After the injection of a radiopharmaceutical into the body, radiation dose is deposited to the tumor and normal organs by an exponential decreasing behavior and with a range of a fraction of seconds to months.[28] In this therapeutic approach, time-dependent mechanisms including radionuclide decay and its clearance from the body, determine the tumor and normal organ dose. Accurate estimation of the dose is a complex task and needs specific methodologies. To do so, longitudinal imaging in terms of single photon emission computed tomography (SPECT) is utilized as a practical approach for dosimetry.[29] SPECT images which are obtained at different time points, are used to assess the therapeutic dose. The images can be acquired at different time points, such as before the first cycle of therapy as single-point dosimetry or between the cycles of therapy as multi-point dosimetry methodologies. Although the dose

obtained using this method suffers from some uncertainties, it can be considered a patient-specific dose and can be directly converted to a biologically effective dose (BED) or other bioeffect doses.[29,30] On the other hand, positron emission tomography (PET) in terms of dynamic imaging is a time-based imaging modality that can be utilized for predictive dosimetry in RPT. Here the time scale has a range of minutes to hours and the obtained data can simulate dose distribution during the RPT. This short-term longitudinal imaging approach, although has a diagnostic time scale, may mimic the large-scale therapeutic time scale of deposited dose in patients who received RPT. Time-activity curve obtained using whole body dynamic PET/CT acquired form first minutes after injection of the radiopharmaceutical to several minutes to hours after that, can predict therapeutic dose, then this multi-time scale imaging modality will be a feasible approach for patient-specific dosimetry.

Macro-scale temporal Imaging

There has commonly been greater emphasis on the micro-scale and meso-scale temporal imaging in both clinical practice and research, with less focus on questions that are at the macro-scale. Macro-scale temporal imaging is the evaluation of changes over months to years with the prototype example of longitudinal imaging of aging.

LONGITUDINAL DATA IN MEDICAL IMAGING RESEARCH

Thinking on the macro-scale is common in clinical care. When interpreting the images of a particular patient, clinicians often invoke earlier imaging studies or other tests. The specific medical history of that patient is then used to inform medical decision-making. When a specific diagnosis is then made, a clinician can also use the natural history and progression of disease to understand the status of that specific diagnosis. With the advent of personalized medicine, the long-term time focus has become even more important in clinical practice.[31,32] Longitudinal imaging information, along with other specific and deep data including genomics, can help improve clinical outcomes.

Beyond the clinic, there has been research along the macro-scale. The first focus of longitudinal studies was on natural change in the form of development.[33–36] Early studies in radiography studied bone growth in children. With the evolution of medical imaging technology and expansion of imaging capability, there has been an increased interest in brain development which has been studied through PET.

Longitudinal studies focused on the long-term benefits of screening, monitoring of different disease processes, and response to treatments are also represented in the literature. These studies can be grouped into two broader classes based on the type of questions they answer: functional imaging studies, which look at various metabolic processes, and structural imaging studies, which seek to gain increased understanding of the physical features of disease.

Tracking Changes in Metabolic Processes

Many functional imaging longitudinal studies in PET research have focused on tracking changes in metabolic processes to evaluate recovery, assess the impact of treatment options, or track the progression of disease. PET has been used to understand which regions of the brain are associated with aphasia due to subcortical lesions following a stroke. Heiss and colleagues[37] performed a study where they used H_2O^{15}-PET activation patterns to identify brain regions that were associated with language performance in patients with poststroke aphasia at 2 and 8 weeks after stroke and compared their performance with healthy controls. They measured flow changes in the eloquent and contralateral homotopic areas over time to determine the differential capacity of the left and right hemispheres. In a later study by de Boissezon and colleagues[38] that focused on subcortical lesions, H_2O^{15}-PET and a word generation task were used to correlate language performance with change in regional cerebral blood flow over a period of 1 year following strokes. Data across patients were pooled and registered to a standard atlas and then used to calculate correlation between longitudinal change in regional cerebral blood flow and longitudinal change with language performance. Such longitudinal PET studies have inspired similar evaluations with other imaging modalities.[39]

Treatment Response Assessment

Longitudinal PET studies have also been used to assess conditions for certain treatment options and to evaluate the success of those treatments. Tumor hypoxia is an important indicator for the success of radiation therapy treatments as hypoxic cells are more resistant to treatment. As described by Stieb and colleagues,[40] PET is the main clinically validated imaging modality for this purpose and there is an extensive literature base of longitudinal PET studies for tracking the hypoxic status of tumors using a variety of radiotracers. Longitudinal PET studies have also shown potential for monitoring response for metastatic cancers. Hildebrandt and colleagues[41] describe the

potential of FDG-PET/CT for evaluation of response in metastatic breast cancer. They first used retrospective data to define a lesion criteria and found that SUL_{peak} to be a useful biomarker of disease fluctuation. In a follow-up prospective study, patients were monitored using PET/CTs where the contrast-enhanced CT scan was used clinically. When comparing PET and CT for determining which method showed disease progression earlier based on final pathology, PET was able to detect the progression first in 50% of the cases. Thus, functional imaging plays an important role in the long-term treatment and response monitoring of disease.

Serial imaging plays a key role in radiotherapy response evaluation. In recent decade, different imaging modalities such as CT, MRI, SPECT, PET, ultrasound, and optical coherence tomography have been used to assess or predict radiation response of both malignant and healthy tissues. Interestingly, as radiation response is a biological process, these kind of imaging carry very rich spatiotemporal biological information, and a number of them may decode biological mechanisms of treatment and also extract a range of (radio)biological parameters that can be used to set biological-guided radiation therapy approaches. For example, serial ^{99m}Tc-dimercaptosuccinic acid (DMSA) SPECT/CT (pre, during, and post-treatment) provided new details of local radiobiological changes following stereotactic ablative body radiotherapy of renal cell carcinoma.[42] In addition, serial ^{18}F-Fluorothymidine PET/CT was used to analyze pattern and radiation-related changes of cellular proliferation in both tumors and bone marrow in non-small cell lung cancer (NSCLC) patients undergoing radiotherapy.[43]

In a comparative study, serial FLT-PET/CT and FDG-PET/CT were analyzed during radical chemoradiotherapy of NSLC, and it was observed that cellular proliferation imaged by PET/CT during therapy is associated with a patient's outcome (survival). It was suggested that therapy planning has to be changed based on these imaging findings, because tumor cell proliferation may reduce radiation-induced tumor cell killing and has a great impact on clinical outcome.[44] Interestingly, a study showed that serial ^{18}F-Fluorocholine PET/CT during chemotherapy in patients with prostate cancer is correlated with changes in circulating cell-free DNA (cfDNA).[45] It is evident that cfDNA is a useful biomarker for tumor profiling and therapy response evaluation. Recently, several radiobiological parameters were extracted from serial PET/CT images in patients with cancer treated with selective internal radionuclide therapy (SIRT) with yttrium-90 (90Y)-microspheres (^{90}Y-SIRT).[46] In the study, parameters such as cell repopulation time (Tp), kick-off time (Tk), and linear quadratic model parameters (α, α/β) were obtained from serial imaging, dosimetric and clinical data.

Tracking Disease in Neurodegenerative Disorders

Other examples of longitudinal imaging have included studies in neurodegenerative disorders, including normal aging and Alzheimer's disease (amyloid[47] and tau[48] imaging) as well as Parkinson's disease,[49] including both PET and SPECT imaging. These have resulted in publicly available data sets, used extensively for biomarker discovery. Such biomarkers of disease have included disease subtype identification, progression tracking, and predictive modeling.

As an example, functional imaging also plays an important role in monitoring the progression of disease. Li and colleagues[50] describe a longitudinal comparison between two radiotracers, ^{11}C-PE2I and ^{18}F-DOPA, for monitoring Parkinson's disease. In this study, patients were first scanned with each tracer to determine a baseline and then followed up within a period of 2 years. PET findings were correlated with clinical findings quantified as motor severity tests and found that ^{11}C-PE2I showed higher sensitivity to differences in motor severity than ^{18}F-DOPA. In another study looking at aortic dilation in large vessel vasculitis, Muratore and colleagues[51] used FDG-PET/CT to measure the aortic uptake at four different levels at two time points. They found that patients diagnosed with large vessel vasculitis had an increased risk of aortic dilation when compared with controls. Ou and colleagues[52] studied the potential of FDG-PET to be a biomarker for diagnosis of Alzheimer's disease. In this study, a group of patients were recruited, and several biomarkers were tracked over an extended time period. They found that FDG-PET had strong indications for Alzheimer's disease and could be included as an independent biomarker.

Different Modalities Toward Improved Assessments

Longitudinal studies in structural imaging have spanned several different modalities. CT has been used for early detection and characterization of different types of tumors. The National Lung Screening Trial found that periodic CT studies are the imaging modality of choice for identifying the early emergence of lung cancer over time.[53] Similarly, the Response Evaluation Criteria in Solid Tumors (RECIST) use CT.[54] The RECIST criteria were developed to quantitatively assess changes in tumor burden over time. CT is considered one

of the most reliable modalities for applying RECIST criteria. RECIST criteria have been applied extensively in clinical trials as a means to define and measure treatment response, and quantify progression-free survival.[55] However, there is need for further demonstrations of machine learning or high-dimensional radiomic analysis as applied to the interpretation of CT changes over time. As an example, in a study by Xu and colleagues[56] on patients experiencing locally advanced NSCLC, a neural network-based model was trained on CT imaging data obtained pretreatment, and 1-, 3-, and 6-month post-radiotherapy treatment. This study is an example of how we can incorporate pretreatment and posttreatment data over multiple time points when training predictive or evaluative algorithms.

Longitudinal studies and clinical standards are also common in radiographic imaging. The Radiographic Assessment of Lung Edema (RALE) score was designed to quantitatively evaluate alveolar opacities on chest radiographs specifically related to pulmonary edema in acure respiratory distress syndrome.[57] It has been shown to have excellent diagnostic performance. An increased RALE score was correlated with worse survival and became adopted as both a prognostic measure and a means of tracking physiologic changes over time that then guide clinical decision-making, such as conservative fluid administration.[58] Another example is mammograms, which are often used for screening for breast cancer. Longitudinal studies of mammographic data have found a connection between breast density and breast cancer risk. Earlier studies were more qualitative in nature, looking at breast imaging reporting & data system (BI-RADS) classifications to assign breast density classifications.[59] More recent works have been more quantitative as they have had an increased emphasis on volumetric classifications.[60]

DEXA scans are the standard for evaluating bone density and hip fracture risk. However, individualized extrapolation of bone densitometry timelines is rarely performed. Instead, an individual's bone density is compared with age- and sex-matched population statistics by a Z-score rather than evaluating how an individual's bone density is changing over time. We are not aware of any scoring methods which evaluate an individual's bone density change over time, yet there are several studies which exemplify individual variations in bone mineralization through space and time perturbations. DEXA scans sensitively evaluate both spatial and temporal changes in bone density. A small study by Iida and colleagues[61] showed that 3 months after hip fracture, greater and lesser trochanteric bone density increased; contrarily, 3 years postfracture, the greater trochanteric bone density decreased. In another work by Hong and colleagues,[62] a radiomics-based scoring system was correlated with increased risk of hip fracture incidence. These studies exemplify how DEXA scans are capable of both measuring and predicting dynamic changes in physiologic states over space and time.

MR imaging is one of our greatest tools to study the human brain. The human brain is highly dynamic and constantly remodels throughout the course of our growth, development, and later years. MR imaging allows interrogation of the underlying pathologic changes in diseases of cognitive impairment such as dementia. In a study by Smith and colleagues,[63] brain MR imaging with a median comparison time of 5.8 years, the change velocity of specific brain structures/regions was determined and correlated with either healthy or pathologic aging. A recent study led by Cambridge and the University of Pennsylvania aggregated 123,984 MR imaging scans from 101,457 unique people across almost the entire human lifespan. This study sketches a trajectory for brain development over time and proposes a model by which outside images can be compared with the developmental timeline, similar to a pediatric growth chart.[64] However, they explicitly state that the current "brain chart" does not yet support the scoring of a single patient's image as would be desired in a clinical medicine context. Ultimately, we see great potential in the future of quantitative tools for time-series MR imaging analysis especially with regard to understanding brain structure.

Delta Radiomics

The concept of delta radiomics has been introduced to quantify changes typically due to therapies.[65] This information could be extracted from pre-, intra- and post-treatment images.[66] Recently, Shayesteh and colleagues[67] compared treatment response prediction power of MR imaging-based pre-, post-, and delta-radiomic features in locally advanced rectal cancer treated by neoadjuvant chemoradiation therapy. They included 53 patients from two different centers and developed different machine learning algorithms based on these features. They reported that the best performance was achieved by delta-radiomic features which significantly outperformed standalone pre- and post-treatment images-based models, thus confirming that longitudinal changes during treatment sessions could serve as a predictive model. Van Timmeren and

colleagues[68] investigated the added value of longitudinal radiomic features in cone-beam CT for prognostic modeling in NSCLC patients. They included patients with at least four imaging sessions and evaluated models on three external data sets and built models using the Cox proportional hazards model using radiomic and clinical features for overall survival and locoregional recurrence prediction. They concluded that longitudinal radiomic features do not improve prognostication in NSCLC.

Longitudinal Imaging in Animal Studies

Longitudinal imaging in animal studies is considered as an important approach to have a deeper look in several diseases as well as aging.[69] Animal models, especially mice, because of similar anatomy and physiology to humans, are a main component of preclinical research. Several animal studies have used longitudinal imaging to study disease such as Alzheimer's, Parkinson's, atherosclerosis, osteoporosis, bone metastasis, lung, and liver cancers. In these studies, special imaging techniques such as micro-CT, micro-MR, PET, SPECT, optical, and microscopy imaging have been used.[69] Furthermore, due to the increasing number of transgenic and disease models available, such imaging approaches enable researchers to test and discover most optimized therapy toward personalized ones. In the realm of nuclear medicine, it is observed that a longitudinal mouse-PET imaging is a reliable method for estimating binding parameters without a reference region or blood sampling.[70] Moreover, longitudinal imaging using PET has a brilliant history in animal studies. For example, micro-FDPA-714 PET was shown as a feasible method to assess translocator protein expression longitudinally in a mouse model of epilepsy with hippocampal sclerosis.[71] Interestingly, longitudinal animal imaging using PET is recruited by several researchers to capture biological information such as cellular growth,[72] apoptosis,[73] activation,[71] and immunologic response.[74]

The natural history of disease offers a final point for the importance of macroscale thinking. As patients are followed over time, change can be contextualized by what was previously observed. As diagnoses have been encountered before and at different stages of disease progression, clinicians are able to refer to these prior documentations or experience to better understand specific diseases and assess treatment options. Natural history for chronic disease is more direct as a particular time point can be compared against the known arc of development for such a disease. For acute diseases, we have a different understanding of change based on the status of that disease. Both longitudinal and cross-sectional approaches have been used to study disease with this understanding of disease progression and related changes in health over a macroscale time frame.

In the 2022, Cassen Award lecture addressed to the Society for Nuclear Medicine and Molecular Imaging, Simon Cherry advocated for using the temporal domain to our advantage. He describes the human body as a dynamic state of organ-based constituents where many processes go unobserved with modern clinical imaging. Particularly, whole-body PET imaging exemplifies a method which can capture processes within the entire body at the same time point. Furthermore, with improved detector sensitivity, processes occurring at both short (100 ms) and intermediate (days) time scales can now be observed with low radiation exposure. Ultimately, proper leveraging of the temporal domain through dynamic imaging will enable single subject research, that is, personalized medicine.

FOUR CHALLENGES IN QUANTIFYING TIME INTERVAL CHANGES

Different studies of macroscale time in the medical imaging literature were described in the previous section. There are some challenges to expanding the scope and application of these types of studies in the near future. In this section, we identify four challenges, specifically related to (i) data collection, (ii) algorithmic developments, (iii) performance metrics, and (iv) ethical considerations and discuss the need for addressing the key concerns.

The first major challenge is the issue of data. The volume of data that could be used for longitudinal studies is constantly increasing as medical imaging procedures are occurring more often than ever before. For many applications, well curated and extensive data sets are required for the development of algorithms and techniques. Further, the diversity of these data sets is critical to reduce bias in algorithms across all possible patient populations, imaging devices, and acquisition and processing protocols. Increasing access to data is critical for long-term development of techniques and furthering of studies on the macro-scale.

An additional concern with data is the issue of data sparsity. Often, data acquired at different time points and at different institutions do not have perfect concordance with one another. There can be many causes for this across longitudinal studies including technological evolution over time, difference in standards across institutions, variable time points between tests, multicentric

data acquisition, missing sessions or specific imaging modality, and only repetition of some imaging tasks. The cumulative effect leads to data sets where certain data points are incomplete. One potential method to address time series data with uneven sampling called the Lomb–Scargle periodogram has already been applied to personalized omics studies and continues to provide quality-controlled insights into temporally relevant biomedical processes.[75,76] The robustness of algorithms to account for this factor is key to the success of long-term studies on the macroscale.

The second major challenge concerns the need for the development of better algorithms. Faster and more efficient algorithms will be needed to handle increasingly larger and more complex data sets. Robustness is important to minimize bias and enable accurate and precise characterization. Currently, there are performance constraints due to both hardware and software challenges. Adding time to current algorithms increases the complexity of the problems being analyzed. Although the development of technologies, such as application specific integrated circuits and various algorithms enable faster processing and handling of larger volumes of data, this problem will continue to require consideration. From the algorithmic perspective, development of future algorithms for longitudinal studies should be done in a way that is specific for the temporal domain and optimized for the analysis of longitudinal data. Time series models which analyze sequence of data points across a period of time by recurrent neural network concepts such as long short-term memory could be used as a tool for the analysis of longitudinal data set.

Quantitative analysis in the longitudinal time frame requires unique solutions. In creating quantitative metrics to represent longitudinal changes, normal and abnormal needs to be distinguished. Both physiologic and pathologic processes display an extraordinary range of temporal behaviors and structural patterns that transcend comprehension based on linear dynamics. In the context of medical imaging, image registration is used to bring images acquired at different times or across modalities into the same frame of reference. Two important characteristics of a registration method for longitudinal data are its robustness and stability (**Fig. 1**). A registration is robust when its performance is not drastically altered by deviations of the input image from the prior knowledge. For example, the algorithm must be able to withstand the presence of imaging artifacts as well as the advent of new imaging discoveries such as new pathologies. A registration is stable when changes in the input data results in changes in the outcome of registration. Stability is important for longitudinal studies to measure differences that are attributed to temporal anatomic changes.[78] For nonrigid registration algorithms, changes in region/volume of interest due to the registration method should be considered, and using segmentation information for registration is recommended for precise registration.

The third major challenge is the development of performance metrics for algorithms, and the need for the correct metrics to be chosen for each task. With the development of task forces such as the Quantitative Imaging Biomarkers Alliance, standardization and reliability of metrics has taken on a more important role in medical imaging research. Reproducibility along the temporal domain is a particular concern as the change in a metric over time needs to be attributed to the result of change in disease state or a natural process, rather than a difference in acquisition condition or similar factors. In addition, metrics need to be chosen in a task-specific way. The figure of merit for a given task must be selected to reflect the scientific question in mind.

The fourth major challenge is ethical consideration in terms of patient convenience, privacy, and safety. Longitudinal imaging imposes a heavy burden on patients. In addition to time and costs, consecutive imaging exposes patients to a higher level of radiation which increases the chance of cancer risk. However, low dose protocol studies with advanced image reconstruction methods are an advanced solution for imaging centers to reduce the radiation dose effectively.

RECOMMENDATIONS

Information derived from changes over time is central to our understanding of normal physiologic processes, such as development and aging and pathophysiology of diseases. Although medical imaging in both clinical use and research has been focused on localized change, by better understanding the relationship between change and time, we are able to expand our scope. Although most of the longitudinal imaging studies have observations with two or more time points to capture and characterize change over time, methods for investigating time interval changes in medical imaging remain subjective or limited to primitive quantitative techniques. In this section, we outline five main considerations for how medical imaging research can better incorporate ideas of time and change. We offer suggestions for some broader concepts that affect how we think about and understand time as well as some specific

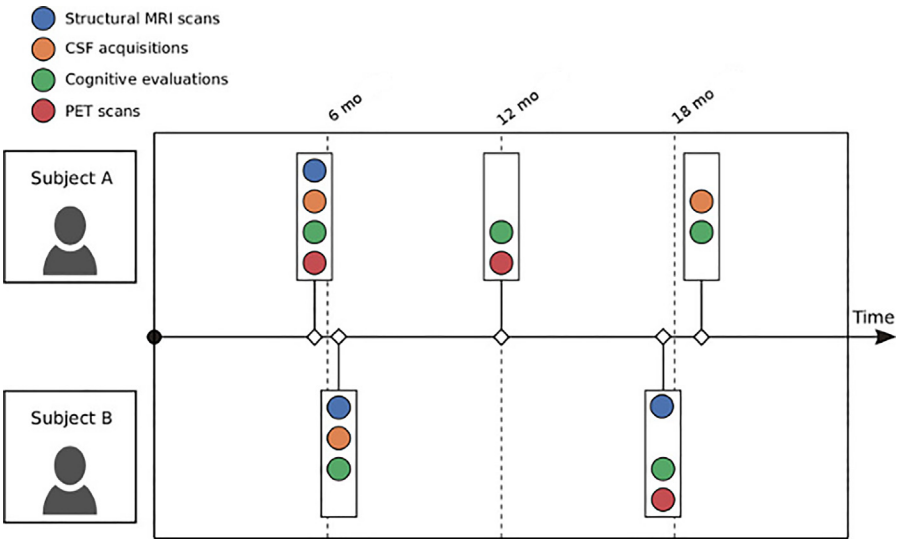

Fig. 1. shows an example of a longitudinal study for two subjects, with multiple data modalities, over a fixed span of time. It illustrates some of the challenges that can appear in a longitudinal, multimodal data study:

1. Each subject can have a different number of acquisitions, leading to an unbalanced data problem. In the figure, Patient B missed the 12th month acquisition for some reasons.
2. There can be missing data due to missing acquisitions from some modalities. In the figure, only patient A at the 6-month follow-up has all the acquisitions.
3. Data are not necessarily acquired at the same time point for different subjects.
4. Time spacing between follow-ups can be variable, even within a single subject.

From Martí-Juan G, Sanroma-Guell G, Piella G. A survey on machine and statistical learning for longitudinal analysis of neuroimaging data in Alzheimer's disease. Comput Methods Programs Biomed. 2020;189:105348.[77]

avenues that require further research and development efforts.

i. *Multiscalar framework*: The development of a multiscalar framework is important for our understanding of change in time. Such a framework would allow us to understand how discoveries in a micro- or meso-scale would affect processes along the macro-scale and vice versa. In physics, multiscalar frameworks are important to understand the relationships between different fundamental forces across a range of size, from the scale of quantum mechanics to cosmological interactions. In biology, we have an understanding of the effects that certain drugs or biological processes have in the microtime or mesotime scales but are only beginning to understand their long-term impacts on the macro-scale. Similarly, we can use medical imaging to study changes in the micro- or meso-scale and relate those to the long-term implications on the macro scale (**Fig. 2**).

Quantitative image analysis of time interval changes can benefit from data of high spatial granularity. Studying population averages, such as averaging voxel values within a lesion, can be misleading due to masking of association between variables that can occur by combining data, a statistical phenomenon known as the Simpson's paradox.[79] Analyzing voxel level data allows for generation of high-resolution landscape information for more accurate characterization of complex biological phenomena. Most of the longitudinal quantitative image analysis research uses voxel-level information to evaluate how experimental variables affect individual voxel engagement. Researchers can explore dispersed patterns of signal activation across several voxels in relation to experimental factors using supervoxel pattern analysis.[80] By increasing spatial resolution for measurement of change, we are able to better characterize disease patterns.

ii. *Backward and forward time*: Time reconstruction is a technique that investigates the fingerprint of change over time by reconstructing the prior conditions of an imaged object of interest. One example can be found in clinical oncology. Cancer cells can evolve over time and adapt to the environment to overcome threats and take advantage of opportunities. Substantial variation

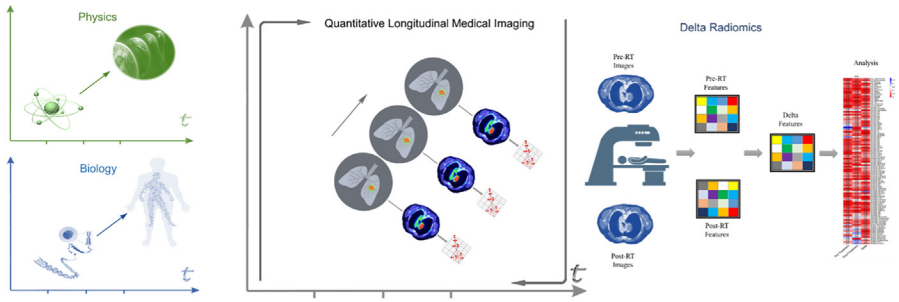

Fig. 2. Time scales in physics and biology have been studied well. In medical imaging, longitudinal imaging would be able to provide more information for personalized medicine. Delta radiomics is an example of quantitative longitudinal imaging.

in gene mutation status and biomarker expression between primary and metastatic lesions limits the successful implementation of personalized cancer therapies.[81] Within a tumor microenvironment, local Darwinian dynamics characteristically produce molecular variations between cells in the same tumor. Regional heterogeneity in molecular features of cancer cells within a tumor or between tumors is known to be induced by branching clonal evolution of cells driven by accumulating mutations. The knowledge of these changes over time can have significant implications in tumor response to treatment and patients outcomes.

Although time reconstruction enables a backwards look at change, the opposite is also possible by looking at *expected* change. Using the known natural history of different diseases, a predictive expectation of disease change can be generated from imaging at a single time point after diagnosis. One application of this concept is using quantitative changes between two imaging studies to train models for predicting future outcomes for improved treatment and surveillance strategies. In a study of renal cell carcinoma in patients with von Hippel–Lindau, Farhadi and colleagues[82] used tumor doubling time based on two CT time points to estimate renal tumor growth rate from baseline MR imaging markers to optimize frequency of imaging for patients on active surveillance. As such, forward projection of time based on a diagnosis can be used for improvement of disease treatment.

iii. *Advanced methods of mapping time relationships*: Another area for improvement is the implementation of new techniques that provide a more nuanced mathematical understanding of time relationships. Recent developments in manifold learning, such as the uniform manifold approximation and projection (UMAP) technique,[83] could enable more complex processing of medical imaging data. Dimensionality reduction in biological data has been developed and implemented extensively for single-cell multiparametric data analysis. Manifold transformations are commonly used with a method called K-nearest neighbor clustering, where cells are clustered based on their distance from each other in multidimensional space, and then projected onto a lower dimensional space (usually 2D or 3D space). The global architecture of the low-dimensional projection becomes a fingerprint-like representation of cellular qualities in high-dimensional space. Furthermore, cells close in the low-dimensional projection most likely have similar parameters in high-dimensional space, meaning that cell types often self-segregate distinctly.

An example of K-nearest neighbor clustering applied to biological data shows the heterogeneity of leukemic cells within individuals.[84] Furthermore, progression through time in the form of cellular development has been inferred by a similarly based technique termed "Wanderlust."[85] By repeatedly wayfinding between nodes in the graph and then creating an average path, the Wanderlust algorithm produced a trajectory that represented the B cell developmental timeline. Wanderlust extrapolates where a cell sample would be on that timeline without time information being strictly provided. The SCONIFY technique by Burns and colleagues added to dimensionality reduction methods by building the ability to compare differences between biological samples while preserving single-cell resolution.[86] In this case, they compared biological conditions related to cell signaling states. Newer efforts have investigated cell spatial relationships and aimed to compare changes in cell biology over time.[87,88] With advances in computer vision and high-dimensional radiomic analysis of clinical images, we draw an analogy between single cell multiparametric data

and superpixels or supervoxels. In this fashion, we propose that existing analytical techniques can be translated to radiologic data where differences in biological states are to be compared, namely the progression through time. Manifold transformations are already being used to approximate a person's progression through biological states and their position along a disease timeline. In a study by Bazzego and colleagues[89], the investigators show a reconstruction of head and neck cancer timelines by PET/CT. Each person's radiomic profile underwent dimensionality reduction and was then annotated by tumor size (TNM staging criteria). The investigators were then able to approximate a trajectory through progression of tumor stage.

iv. *Harmonization techniques*: Different challenges in longitudinal studies could be addressed through new techniques and methodologies. In each center, scanners may change over time as well as acquisition and reconstruction protocols. These changes may lead to variability in image quality and quantitative image-derived metrics. Harmonization techniques could be applied on the images or quantitative indices to tackle these issues. Image-based harmonization using for instance unpaired adversarial neural networks could be used to harmonize images across different scanner and acquisition/reconstruction settings. In addition, for machine learning and deep learning-based models, transfer learning techniques could be applied to adapt developed diagnostic and prognostic models for new settings.

v. *Missing or limited data:* Other issues such as missing sessions or specific imaging modalities for longitudinal studies could potentially be addressed by artificial intelligence-based techniques. Different, deep learning-based models were proposed for image-to-image translation, including MR imaging to CT, MR imaging /CT to PET (and vice versa), and converting different MR imaging sequences to each other. These models could be potentially applied in real clinical situations to generate missing sessions or imaging modality in longitudinal studies. Another issue in longitudinal studies is that a high volume of images might be available collectively in different centers; yet, sharing data between different centers is not straightforward, owing to ethical, legal, and privacy issues. In this context, federated learning frameworks, aiming to develop machine and deep learning models across different centers without sharing data between different centers, could potentially address this challenge for longitudinal studies.

SUMMARY

In medicine, time plays an important role in how we understand the progression of disease and development. Imaging provides a method to characterize this change, and with a focus on different time scales, we are able to contextualize that change and understand the implications for better medical outcomes. The present work focuses on methods and applications beyond only micro- and meso-scales. We discussed strengths and limitations of existing macro-scale (longitudinal) imaging and made recommendation for future advanced imaging efforts integrating this important time scale.

CLINICS CARE POINTS

- Ability to measure change across different time points is critical for diagnostic imaging
- There has commonly been greater emphasis on the micro and meso-scale temporal imaging in both clinical practice and research, than macro-scale.
- Techniques used for quantification of change in one temporal scale can be used in and integrated with other temporal scales (toward multi-scale temporal imaging).
- Challenges associated with longitudinal studies include the need for improved data collection, limitations of current algorithms and performance metrics for studying temporal changes, and ethical considerations.

DISCLOSURE

This research was supported, in part, by the Intramural Research Program of the National Institutes of Health Clinical Center. The opinions expressed in this publication are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government. The authors declare no conflicts of interest.

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