Chapter 2: Data Structures Associated with Biomedical Research

1 Introduction

Our goal in this first chapter is to establish some basic ideas as a precursor to more in-depth analysis, whereas later chapters will examine issues of software engineering and data modeling in greater detail, . We will focus on certain specific data types which emerge from contemporary research methods and clinical/diagnostic data-acquisition modalities (including specialized equipment which itself represents a form of technological breakthrough, such as high-throughput gene sequencing). We will also consider how the goals of "personalized" medicine have motivated the search for data-integration methods working on these data structures emerging from new biomedical technologies.

"Biomedical Technology" is an umbrella term which encompasses many more specific topics and subdisciplines. Different investigative modalities — from genomics to proteomics to bioimaging (to name just a few) — tend to have their own technological ecosystem. Scientists who concentrate on specific fields within the biomedical umbrella therefore become familiar with technology (meaning both computer software and lab equipment) which is used in their area of study. There is less impetus for an overarching expertise that would encompass biomedical software in a more holistic sense, which potentially yields lacunae in biomedical software engineering. There is, in short, relatively little research into design patterns which might be generally applicable to biomedical software as a whole.

At the same time, with the rise of Precision Medicine, Patient-Centered Care, and systems-biologic paradigms which integrate multiple anatomical and biochemical scales (from molecules to cells to tissue and organ systems), biomedical research has become interdisciplinary to an unprecedented degree. One consequence of this (generally positive) trend is that software ecosystems and computational paradigms targeted at specific subdisciplines prove to be suboptimally fragmented. Cross-disciplinary research implies the need to connect hitherto isolated software ecosystems together.

Our goal in this chapter is to make these issues tangible by identifying several specific biomedical subdisciplines and the data structures which they tend to generate. These are the kinds of heterogeneous data models that need to be integrated to provide a computational foundation for multi-disciplinary biomedical research. We are not attempting to develop a comprehensive list of bioinformatic data-types, but merely to describe certain data models which are especially important and recurring in contemporary science. Hopefully these concrete examples can help oriented our analyses when we transition to more abstract discussions about data types, data models, and software-development paradigms.

This chapter will consider "personalized medicine" in the context of Covid-19 (later chapters will address personalized medicine in its more traditional settings, particularly immuno-therapies as promising approaches to cancer care), so we adopt Covid-19 as a lenss for examining the origin and clinical significance of data structures emerging from technologies such as Next-Generation Sequencing and bioimage analysis via Computer Vision. However, data structures characteristic of these technologies are, for the most part, widely used in clinical and diagnostic practice; they are not specific to Covid-19 (here we will not emphasize research which is more narrowly targeted at SARS-CoV-2, such as biophysical analyses of the virus's proteins, or epidemiological studies of the pandemic's origins).

2 Personalized Medicine in the Context of Covid-19

Within just a few months after Covid-19 became a global pandemic, doctors and researchers were developing and experimenting with a diverse range of treatments and remedies against SARS-CoV-2. The treatments which were in some sense tested or adopted include Monoclonal Antibodies, remdesivir, dexamethasone and other steroids, anti-inflamatory drugs (such as tocilizumab and sarilumab), convalescent plasma, baricitinib (a rheumatoid arthritis drug for which Covid-19 is an off-label use), and anti-malarial drugs (specifically chloroquine and hydroxychloroquine).[1] These treatments, that is to say, were either approved (albeit provisionally or "for emergency use") by the United States **FDA** and other government agencies, pending clinical trials, or reported anecdotally to be helpful in combating Covid-19. In either case they were relatively widely adopted in clinical settings. More rigorous attempts to validate claims of any treatments' effectiveness, however, have proven inconclusive (at least as of mid-2021) — certainly no pharmaceutical or clinical intervention has demonstrated success rates comparable to the first wave of vaccines that were approved toward the end of 2020. In short, every well-studied Covid-19 intervention (other than vaccination) appears to be successful in some patients and not others. These mixed results generate questions of their own — what are the biologic mechanisms that cause different treatments to play out differently in distinct patient populations?

Of course, it is possible that associations between treatments and outcomes — at least in the SARS-CoV-2 context — is driven mostly by random chance, or that treatments are correlated to, rather than causative of, outcomes. The Covid-19 mortality rate among hospitalized patients appears on average to be less than 25% (even though over four million people worldwide have died from the pandemic, as of summer 2021). Accordingly, many people even with serious cases of Covid-19 will recover just via statistical distribution. While it is possible that treatments received in hospitals account for some of the recovery rate — the mortality rate amongst hospitalized patients has diminished over time, which implies that hospitals have become more skilled in caring for Covid-19 patients and that treatment plans have become more refined — many patients hospitalized for the disease might well have recovered anyhow (even without additional pharmaceutical or clinical interventions). Given this interpretive uncertainty, it has

[1] See https://www.mayoclinic.org/diseases-conditions/coronavirus/expert-answers/coronavirus-drugs/faq-20485627.

been difficult for researchers to definitively show that particular treatments do in fact improve recipients' chances of recovering from Covid-19. Nevertheless, both observational evidence and clinical trials suggest that a number of Covid-19 treatments do have some positive benefits, even if not for all patients.

This situation then leads to the question of why particular treatments benefit some patients more than others. Such considerations are of scientific interest, of course — clarifying how drugs or other interventions interact with the SARS-CoV-2 virus enhances our knowledge about its infectious mechanisms and the progression of Covid-19 — but more immediately it is of clinical interest, because doctors need guidelines on when to administer which treatment(s) to which individual patients. Because no Covid-19 remedy (apart from vaccination) clearly outperforms others under most circumstances. Many scientists have therefore attempted to study Covid-19 treatments with the goal of giving doctors more detailed information to work with when making these sorts of clinical decisions. The overarching project of a significant subset of Covid-19 research, in short, has been to establish criteria allowing doctors to predict which treatments are most likely to succeed for individual patients, given details of their immunological profile and prior medical history.

In this sense the goals of Covid-19 research overlap with methodologies that have been established in the context of other research areas — notably cancer and AIDS — under the general rubric of "Precision Medicine." As a field of research, Precision Medicine is focused on the correlation between patient-specific biomedical details and the likelihood that particular interventions will have positive effects for particular patients. In contrast to conventional clinical trials, which consider patient-specific details only at a rather coarse level — merely observing obvious datapoints such as age, gender, and ethnicity — precision-medicine research attempts to curate a much more detailed picture of patients' medical and sociodemographic profiles, either as part of formal trials or as observational details in a clinical setting. Ideally, Precision Medicine is motivated by the goal of analyzing patient-profile-to-outcomes correlations not only retroactively (detecting statistical patterns in prior outcomes) but also prognostically. In effect, once a particular sort of treatment has been identified as especially favorable for patients with certain characteristics, it is reasonable to project that future patients with similar characteristics should be given similar treatments. This intuitive and obvious point, however, masks empirical and practical difficulties — in particular, it is not obvious how to quantify the notion that current patients are "similar" to prior ones. Indeed, one of the provisional results of precision-medicine research thus far has been to highlight how statistically significant points of resemblance between patient profiles do not necessarily line up with how we *intuitively* group patients together by visible factors such as age, race, or gender.

In sum, Precision Medicine has been guided by the thesis that compiling detailed patient-centered information can advance clinical medicine by identifying which treatment options are more likely to succeed for individual patients. In the context of Covid-19, both the diversity of legitimate clinical interventions and the failure of any one treatment to show unambiguous success for a broad spectrum of patients point to the potential usefulness of patient-centered approaches. If doctors have detailed information about Covid-19 patients' immunological profiles and clinical history they can — at least in theory — make informed decisions about which treatment options have a higher probability of success. Such predictions would not be a matter of guesswork; instead, statistical analysis of Covid-19 cases in the past, preferably backed by Machine Learning, would detect correlations between patient data and recommended treatments. In effect, the spectrum of possible Covid-19 interventions (antibodies, steroids, convalescent plasma, and so forth) serves as a natural classifier, grouping patients into clusters based on pre-treatment profiles indicating that one or another Covid-19 intervention has, with some probability, a good chance of helping the patient. Researchers have therefore been seeking empirical clues for how to classify patients into categories based on recommended treatment plans.

We will examine in this chapter how the goals of Precision Medicine have spurred scientists to propose more sophisticated data-integration and data management tools in the context of clinical trials and biomedical laboratory investigations. Aside from opening new avenues for empirical research, the *goals* of Precision Medicine have spurred new ways of thinking about the computational ecosystem which supports biomedical research and clinical practice.

2.1 Precision Medicine as a Catalyst for Biomedical Data Sharing

Precision medicine is based on the scientific realization that the effectiveness of a certain clinical intervention — for instance, immunotherapy as a cancer treatment — is dependent on factors that vary significantly between and among patients. In the case of immunotherapy for cancer, assessing the likelihood of favorable outcomes requires genetic, serological, and oncological tests which need to be administered prior to the commencement of treatment. Therefore, analysis of precision-medicine outcomes requires detailed immunoprofiling — building immunological profiles of each patient before (and perhaps during/after) the immunotherapy regimen — alongside an evaluation of how well the patient responds to the treatment, with the best outcome being cancer remission or non-progression.

The contemporary emergence of Precision Medicine is driven, in part, by advances in diagnostic equipment which enable immunological profiles to be much more fine-grained than in previous decades. This level of patient-profiling detail enables granular three-way analysis involving (1) patients' immunology; (2) treatment regimens; and (3) clinical outcomes. This three-way approach has the goal of identifying signals in immunological profiles that indicate which therapeutic interventions are most likely to engender favorable outcomes. As with any statistical analysis, predictive accuracy increases in proportion to the amount of data available. As such, further refinement of precision medicine depends in part on data aggregation: pooling a number of observational studies where patients' immunological profiles are described, in detail, alongside reports on treatment plans and patient outcomes.

Within the scientific research community, organizations such as the Society for Immunotherapy of Cancer (**SITC**) and the Parker Institute for Cancer Immunotherapy (**PICI**) have developed programs and tools to share immunotherapy research data, which join older (but less cutting-edge) projects, such as Cancer Commons or the **RSNA** (Radiological Society of North America) Image Share program. In the Covid-19 population we are similarly presented with multidimensional patient data. Such information traverses molecular testing to identify the virus's genetic material or the unique markers of the pathogen itself; antigen testing (albeit less accurate) to identify specific proteins found on the outer surface of the virus; mapping the genomes of SARS-CoV-2 to learn how it mutates; analyzing blood samples for the presence/absence of antibodies in response to a prior SARS-CoV-2 infection; using high-dimensional flow cytometry to perform taxonomic breakdown of patients into distinct immunotypes related to disease severity and clinical parameters; profiling patients' immunological state prior to the start of treatment and quantifying patients' immunological response once treatment has begun; calculating plasma viscosity (**PV**) for detection of unusually high levels of fibrinogen — leading to atypical blood clots (that are refractory to standard anticoagulant therapy); monitoring cognitive, neurological, or cardiovascular symptoms in "long haulers"; and so forth.

One area where data-integration is significant for Covid-19 research is that of protein biomechanics. For instance, [6] identifies 64 different proteins which are therapeutically relevant to Covid-19. Each of these proteins can be connected to molecular data, bioassay information and, in many cases, to clinical trials that test therapies where the specific protein acts as a target for inhibiting SARS-CoV-2. In combination, aggregating all of this information yields a heterogeneous (but interconnected) data space, characterized by data derived from multiple scientific disciplines and multiple laboratory methods.

Because biomedical diagnostic and investigative laboratories need to use highly specialized software, raw laboratory data is often excluded from data-sharing initiatives. Instead, the information which is shared between hospitals or research centers tends to be a simplified overview — adhering to standards curated by groups such as **OMOP** (Observational Medical Outcomes Partnership) Common Data Model or **CDISC** (Clinical Data Interchange Standards Consortium) — skews more toward succinct summaries of diagnoses, treatments, and/or outcomes. Limitations in sharing more granular diagnostic or prognostic data have been identified as obstacles diminishing the value of data-sharing initiatives. As one example, in a paper discussing research into the sequencing of immunoglobulin repertoires (Ig-seq), [2] comments:

> A major challenge when performing Ig-seq is the production of accurate and high-quality datasets [because] the conversion of mRNA ... into antibody sequencing libraries relies on a number of reagents and amplification steps ... which potentially introduce errors and bias [that] could alter quantitation of critical repertoire features. ... One way to address this is by implementing synthetic control standards, for which the sequence and abundance is known prior to sequencing, thus providing a means to assess quality and accuracy.

The underlying problem in this context is how different laboratories may use different techniques and protocols to achieve similar diagnostic/investigative goals. Consequently, when data is merged from multiple hospitals, it is likely that the raw data derives from different labs, which can lead to situations where protocol variations across each site can introduce errors and bias that contaminate the aggregate data-sharing results.

In the context of Covid-19, Shrestha *et al.* [4] argue for "precision-guided studies" to be prioritized "[r]ather than conducting trials using the conventional trial designs and poor patient selection" (page 1). To accomplish this, the authors recommend "large multicenter trials" which incorporate "predictive enrichment strategies ... to identify and thus target specific phenotypes [patient-profile characteristics], potentially raising the possibility of positive trial outcomes." The underlying problem identified by Shrestha *et al.* is acquiring sufficiently large trial cohorts in contexts where trials are to be targeted at fine-grained patient populations with specific pre-treatment immunological profiles. This problem can be ameliorated by merging prospective patients from multiple institutions, such that concurrent trials spanning multiple health-care settings can be launched as part of a comprehensive approach to comparing treatment options. Such large multicenter trials can produce "large cohorts of patients in a shorter time period" while also steering patients toward more favorable treatment courses.

In short, Shrestha *et al.* explicitly challenge the conventional wisdom which assigns "gold standard" status only to *randomized* trials, arguing that the benefits of larger trial sizes and quicker trial initiations outweigh whatever statistical value is compromised by earmarking patients into trials based on educated guesses as to favorable outcomes (which is warranted by patient-care ethics in any case). The authors also argue for a "robust data infrastructure" which would combine the efforts of clinicians, researchers, and data scientists. In effect, aggressive data-curation would substitute for double-blind trial design as a means of ensuring the scientific value of trial outcomes.

Gauging public sentiment, it has been suggested that patients during the Covid-19 pandemic are increasingly reluctant to participate in conventional trials where they run the risk being assigned to a control group where they might lose the opportunity to receive life-saving treatment.[2] In this context Shrestha *et al.*'s approach may be justified as more consistent with patients' wishes for their own care, wishes that should be taken seriously in patient-centered contexts.

Shrestha *et al.* represents only one publication, but their philosophy of trial design perhaps portends a paradigm-shift away from individual, controlled studies and toward nonrandomized, concurrent trials. In lieu of single investigations comparing an

[2] See, for instance, [5], or `https://www.pharmacytoday.org/drugs/drugs-2020-04-22-story4`. Also [1] is an interesting discussion about the merits of double-blind trials (and in particular the idea of "unblinding" follow-up studies), albeit well before Covid.

Figure 1: Table Outlining Several Data Formats and the Contexts where they are Acquired

Immunological Profile Dimension	Lab/Clinical Method	File Format
Sociodemographic	Scan Patient Records	CSV, SQL
Medical History	Scan Patient Records	CDISC, OMOP, PCOR
Immune Repertoire	NGS	FASTA, FASTQ
Cell Type Classification	Flow/Mass Cytometry	FCS
Immune/Tumor Microenvironment	Confocal Microscopy	DICOM, OME-TIFF, CoCo

experimental group with a control group, concurrent trials allow the results of different studies to be compared against one another; each trial serves as a *de facto* control vis-à-vis each concurrent trial. Integrative data-modeling tools thereby steers patients into different trials based on personalized data packages (which may include immunological, cardiovascular, neurological and other general medical-history data) obtained for each patient prior to their involvement in a trial, and likewise made available for subsequent analysis.

While some of the data related to immunological profiles may be sociodemographic or part of a patient's medical history (fitting nicely within conventional Clinical Research Network models), contemporary immunoprofiling is powered by highly specialized diagnostic equipment and methods — which require special-purpose file formats and software. For instance, one dimension of immunological profiling is "immune repertoire"; the more robust a person's repertoire, the wider variety of antibodies they can produce to fight off pathogens. Immune repertoire is often measured by studying genetic diversity in B-cells; in recent years, this has been done using "Next Generation Sequencing" (**NGS**), which produces files in formats such as **FASTQ**. Another dimension of immunological profiling is quantifying the proportions of different sorts of blood cells in a patient's blood sample, which is typically done via Flow Cytometry or Mass Cytometry, yielding **FCS** (Flow Cytometry Standard) files. The immunological evaluations which are the goal of these methods are sometimes called Cell-Type Classification or "Automated Cell-type Discovery and Classification" (**ACDC**). Yet another dimension of immunological profiling in the context of cancer treatments is the Immune Environment, or "Tumor Microenvironment," which concerns the interplay between a tumor and surrounding cells, such as blood/lymph vessels.

With respect to immunological profiling of the tumor microenvironment, this environment is sometimes surveyed using high-powered contemporary bioimaging techniques, such as "Confocal Microscopy" — a kind of layered imaging that acquires **2D** scans at different depths, creating a **3D**-like model. Image analysis is necessary to derive oncological findings from these images, looking not only for "Distinguished Regions" but also for linear paths and patterns (e.g., connective tissues or blood vessels). As a result, Confocal Microscopy data involves both raw images and image-annotations that summarize image-analysis/Computer Vision results. **DICOM** and **OME/TIFF** are examples of common bioimaging formats.[3]

As outlined in the above table (Figure 1), immunological profiles draw on a diversity of data formats and lab/data-acquisition modalities (this table is not intended to be a complete list of criteria or file formats, but rather to indicate the range of diagnostic technologies and data formats which are relevant to immunoprofiling). This table hopefully indicates how immuno-oncology data sharing is inherently more complex when compared to data-sharing initiatives which focus primarily on clinical outcomes — such as **OMOP**, **CDISC**, or the Patient-Centered Outcomes Research Network (**PCORnet**).

Formats such as the **OMOP** Common Data Model (**CDM**), the **PCORnet CDM**, or the **CDISC** specifications promote data sharing primarily through **SQL**-style tables, where data analysis and extraction can be achieved via conventional **SQL** queries. The situation is very different, however, when the data that must be exchanged derives from specialized hardware and software, which demands special-purpose file formats, parsers, and query engines. This problem-space is accentuated when preparing multi-site sharing that can span dozens of hospitals, research centers, and/or laboratories. Problems of cross-institutional data integration will be analyzed further at the end of this chapter.

Prior to that discussion, the following section will examine in detail the file formats and data structures which were briefly mentioned thus far in this chapter. Our goal in this discussion is to document the kinds of data which are endemic to different branches of biomedical research. A separate analysis — one which to some extent depends on first describing the data formats involved — concerns how to fuse multiple data formats into a common overarching format, such as a "Common Data Model of Everything." One recurring theme we will encounter in the subsequent discussion is the goal of merging certain data profiles into others (e.g., **FCS** into **DICOM**), or else adopting common interchange formats (such as **XML**) in lieu of domain-specific binary formats which demand special-purpose parsers. We will examine both the strengths and weaknesses of proposals for adopting common formats rather than idiosyncratic "legacy" formats that are tied to particular laboratory methodologies for historical reasons. However, our main purpose in the current discussion is to establish basic facts about data formats in current use. Later chapters will analyze problems connected to the integration of these formats into common data models.

Note also that the following inventory of biomedical data for-

[3] Robust image-annotation formats are not particularly well standardized (at least to a degree comparable to **FCS** or **FASTQ**), though some annotations can be expressed via formats such as **DICOM** Presentations, **COCO** (Common Objects in Context), **VOC** (Visual Object Classes), or Annotation and Image Markup (the latter will be emphasized in later chapters).

mats is by no means exclusive. In particular, we have largely neglected antigen tests, biochemical assays, and many other lab techniques which rely on chemical reactions to obtain lab/diagnostic findings. Our discussion here is oriented more toward methodologies which require relatively complex intermediate computational processing to arrive at clinically useful findings.

3 A Review of Certain Commonly-Used Biomedical Data Formats

Because a major focus of this book is the goal of *integrating* disparate data structures into a common format, it is an important preliminary step to examine the data formats which need integration to begin with. For reasons explained above, this list is by no means exhaustive or comprehensive; nevertheless, the data profiles considered here constitute a representative spectrum of structures which are important to contemporary bioinformatics.

Note in addition that some of these data formats are demonstrated in computer code which we have prepared to accompany this book. The authors have republished and/or modified open-source libraries used to parse data in the formats discussed in this section, and we provide examples to demonstrate how these file formats are used in real-world contexts. For each format there is an accompanying code project (associated with a **Qt** **.pro** file) which can be opened in the **Qt** Creator **IDE** and compiled. The resulting executable will load a sample file and use parsers endemic to the file format being discussed. The details of each format may accordingly be studied by looking at the computer code for parsing the files and/or by running the demo programs through a debugger. More information about how to use these demonstration code libraries for pedagogical purposes is provided along with the code samples themselves.

3.1 DICOM (Digital Imaging and Communications in Medicine)

The **DICOM** format is closely associated with the **PACS** (Picture Archiving and Communications System) standard for sharing biomedical images; both formats together constitute the *de facto* standard for bioimaging in clinical and diagnostic settings. A **PACS** workstation is guaranteed to have certain capabilities with respect to the diversity of image-formats the software can receive and process from outside sources. This level of standardization is important because biomedical images are commonly shared amongst disparate institutions; for example, radiographic images generated in a hospital may be sent to a laboratory for diagnostic processing. The **DICOM** and **PACS** standards guarantee that recipients of images will be able to view and share them properly, assuming that the images are provided in certain canonical formats and with certain basic metadata (it is worth noting that, in the absence of metadata, it may be impossible for software to display images because of ambiguities in color depth, color format, image dimensions, and other details which determine how binary image data is translated to visual pixel renderings). These standards eliminate the sorts of delays which might otherwise be caused when a lab, for example, is unable to view images sent by a hospital or doctor's office.

Although the primary purpose of **DICOM** is to facilitate image transfer, a close second in importance is properly associating the images with relevant clinical metadata. Images are typically grouped into series, which are associated with specific patients and specific diagnostic goals (often diagnostic codes described via fixed vocabularies, such as the "Radiographic Lexicon," also known as RadLex). In the Covid-19 context, for example, lung x-rays may be requested to support a SARS-CoV-2 diagnosis and/or to test how far the disease has progressed into the patient's lungs. At a minimum, them, all images generated for that diagnostic purpose need to be grouped together in the current clinical context (specifically that this image-series results from a possible Covid-19 diagnosis and has a specific clinical/diagnostic purpose) and associated with a specific patient (usually identified by some sort of anonymizing code). This residual non-image information needs to be tracked via metadata, typically represented within **DICOM** "headers."

Given that **DICOM** thereby serves as a forum for exchanging general patient info, not only images themselves, the **DICOM** standard was designed to be flexible and extensible. This has led the scope of **DICOM** to expand of the years, encompassing a greater diversity of graphics data (**3D** images, audio, video, ultrasound, etc.) and also non-image content (such recommended treatment plans, image annotations, or diagnostic comments). The **DICOM** system is oriented to enabling these scope-extensions without breaking backward compatibility with older **DICOM** standards.

All **DICOM** data is associated with classificatory "tags," which indicate the type of information asserted by a given data-point and how it is encoded. Each tag is assigned a "group number" and an "element number"; this two-layer organization allows tags to be grouped together which serve a similar purpose or derive from a similar clinical or diagnostic context (the pairing of group numbers and element numbers may be roughly compared to **XML** namespaces and element names). Different **DICOM** group numbers are used to group tags into those specific to, for example, image data (e.g. image dimensions and color model), series/study data (date, patient **ID**, accession number, etc.), patient-specific information (birth date, gender, native language, and many other data-points), and numerous additional group numbers specific to different kinds of images (or other graphics content, such as video) which may be present in a **DICOM** series. Officially recognized **DICOM** groups are each assigned *even* group numbers. The *odd* **DICOM** group numbers can be used for non-standard **DICOM** extensions, but **DICOM** clients are not required to parse or recognize tags with odd group numbers. In effect, organizations are free to use odd **DICOM** groups to encode any information they believe is relevant, but there is no guarantee that third parties accessing their data will be able to interpret these non-standard codes.

Another important detail pertinent to the **DICOM** data model is that **DICOM** files freely combine binary and textual data. Most data in **DICOM** tags such as those just described is textual data, encoding character-based details such as a patient's name or date of birth. Of course, **DICOM** also has to encode binary image data as well.

In this context, note that many "file formats" are actually *zipped* files which are unpacked into *folders* behind-the-scenes (so that they are actually "folder formats").[4] Programmers familiar with formats based on zipped folders might instinctively feel that the natural way to fuse textual and binary content is to create folders wherein the two sorts of content are spread across different individual files. For example, an **XML** file could encode textual data such as that present in most **DICOM** tag-groups, whereas a series of image files could store the individual series images.

However, the **DICOM** standard embraces a much different architecture, where **DICOM** tags introduce data streams that may be either textual or binary; the tag itself (in fields immediately following the group and element numbers) asserts the number of bytes need to encode information belonging to that tag, and those bytes may be interpreted either as character-streams or as binary sequences holding (in particular) image data. Whereas file formats that expand to unzipped folders are "file-based" (in that, once the unzip step is completed, information is spread across multiple files), **DICOM** is "stream-based" — all **DICOM** data, from an identifier tag which requires only one or two bytes to be encoded to a video asset that may run into megabytes of size, is inserted into a sequence of tagged byte-streams which collectively span a **DICOM** file.[5]

The mixture of binary and textual data in **DICOM** tags — together with idiosyncratic features such as numeric group/element tag identifiers rather than character-based entity/field names — sets **DICOM** apart from most serialization formats, which makes it difficult to contemplate re-encoding **DICOM** data in other systems, such as **XML**. As a result, **XML** processing algorithms or Semantic Web query formats cannot be readily applied to **DICOM** data; instead, any application wanting to query or examine **DICOM** data streams needs to use **DICOM**-specific code libraries, such as **DCMTK** (this library is reproduced in the code accompanying the present book). **DICOM**'s opacity to modern query languages has sometimes been a source of frustration for programmers, and has led to the development of proposals such as "Semantic **DICOM**" which involve extracting different sorts of data from **DICOM** series and warehousing this extracted information in databases that are amenable to analytic techniques which are not **DICOM**-specific. In so-called "Semantic" **DICOM**, textual header data is placed in **NoSQL** databases of various sorts whereas image data is marshaled into individual files, or stashed in an image database. The rationale for this "deconstruction" of **DICOM** data is both to analyze **DICOM** data using non-**DICOM**-specific algorithms and to merge **DICOM** information with data having other profiles. We will examine Semantic **DICOM** proposals in greater detail in a later chapter.

3.2 Next Generation Sequencing and other Genomics Formats

At the core of all genomics data is the four "letters" (**ACTG**, or Adenine, Cytosine, Guanine, and Thymine) which are the building-blocks of **DNA** and **RNA** (for **RNA**, Thymine is replaced by Uracil, marked with a letter **U**). However, genetic data is much more complex than merely strings of letters drawn from four choices, because genomics files also represent groupings of these elements (and also, in some contexts, points of divergence amongst two or more genetic sequences). Genomics data structures differ in how these groupings and comparisons are described.

An early and simple example of a genomics file type is **FASTA** (this name derives from the term "FAST-All," and originates in a software program which extended an earlier "FAST-Protein" application). The **FASTA** format is used for encoding amino acid sequences as well as nucleotides, so numerous letters may be used in addition to **ACTG**/**ACUG**. Each letter represents either a single nucleotide or a single amino acid, and sequences are represented by strings of the corresponding letters.

The other structuring elements of **FASTA** files are "comment lines," which precede sequence notations and provide context explaining the source of the sequences. While in theory the comments are human-readable explanations which are not formally part of the **FASTA** format, in practice certain structural norms have been adopted in the construction of **FASTA** comment lines, so that these conventions serve as a *de facto* extension to the **FASTA** standard. In particular, **FASTA** comments often employ references to databases from which sequences are obtained, using the "pipe" (i.e., vertical-line) character (**|**, Latin-1 code 124) as a field-delimiter. A more recent variation on **FASTA**, called **FASTQ**, supplements this sort of contextual information with "quality scores" which measure the probability that a sequence has been read accurately by the physical equipment used for the gene sequencing operations that yielded the data being presented.

Genomics file formats have evolved alongside gene-sequencing technology. Genetics has been revolutionized in particular by "Next-Generation Sequencing," where many small **DNA** sequences are extracted in parallel and then assembled together with the aid of computer software. **NGS** has made it cost-effective to perform gene sequencing on a much larger scale (e.g., a human genome can be extracted in a single day), which has greatly expanded the quantity of genomics data available to research, while also generating a larger quantity of intermediate data (because **NGS** requires a computational infrastructure to derive complete results).

Both of these trends have affected the software ecosystem supporting genomics; a window onto this evolution can be gleaned by considering new file formats which have emerged to encode **NGS**-related data. For example, the Sequence Alignment Map (**SAM**) and Variant Call Format (**VCF**) are employed to notate both alignment/commonalities among gene sequences and their points of divergence.

In the case of **VCF**, data structures do not represent nucleotide

[4] For example, **e-book** files are merely zipped files encoding entire book directories, which generally include different files for individual chapters, images and other non-textual content, and metadata in formats such as **XML**.

[5] As an aside, **DICOM** tag-sequences can be nested in other tags, so technically **DICOM** files are hierarchical by analogy to **XML** or **JSON**; however, this hierarchical structure is much less common in the **DICOM** context than in other encoding schemes. It is reasonable to consider the **DICOM** format as first and foremost a string of sibling tags rather than as a hierarchical document structure, for most purposes.

or amino acid sequences directly, but instead notate the variation present in one sequence when compared against a reference sequence (such as the transposition, deletion, or insertion of individual nucleotides). The **VCF** format is column-based, where one column marks a position in the respective sequences where a variation occurs (i.e., the sequences have different letters, or one sequence has no corresponding letter at all) and other columns provide contextual information, including the type of variation and the origin of the divergent sample. The columns present in a given **VCF** file are labeled by a line preceded by a single "pound" character (**#**, or Latin-1 code 35), immediately before the raw data. Prior to this information are "header" lines which begin with a double-**#** and provide information *about* the column fields, including their identification codes and data types (such as strings, booleans, or floating-point numbers).

The **SAM** format is also primarily column-based, with an "alignment" section comprised of individual lines encoding 11 canonical fields as well as potentially other optional fields. The 11 mandatory fields correspond to technical details concerning how alignments between distinct sequences are discerned (the number 0 or the asterisk character are used to represent missing values). One of these fields, treated as a single integer, is actually the binary encoding of a bitset — in other words, a string of boolean values, so the corresponding column actually represents a collection of roughly 12 individual true/false data-points. Optional fields, after the 11 canonical columns, are grouped according to two-character tags, accompanied by single-character encodings of types (there are only a few recognized types in this context, such as signed integers or single-precision floating-point decimals). In addition to alignment data, each **SAM** file has header lines, marked by an initial "at" character (**@**, Latin-1 code 64) and a two-letter code indicating the header record type. Each header line then has a sequence of tab-delimited fields which in turn have their own two-letter identifiers. Note that the vocabulary for fields across the **SAM** format is fixed — every tag or field descriptor has (only) a two-letter code, and the set of codes recognized in each context is defined by the **SAM** standard.

When notating alignments, **SAM** identifies a *reference* sequence against which other sequences may be compared (i.e., aligned). In this context, **SAM** distinguishes between *padded* and *unpadded* reference sequences. The explanation for this distinction derives from the nature of sequence variation — one way that a variant sequence may differ from a reference sequence is in the *insertion* of a nucleotide or amino acid in a position where no corresponding element exists in the reference sequence. In these situations, the most straightforward way to notate the variation is to mark a gap in the *reference* sequence (typically via an asterisk). The potential problem with this notation is that it conceptually distorts the relation between the reference and the variation — the reference constitutes a basis against which a variation (or multiple variations) may be defined, so it is counter-intuitive to *modify* the reference-sequence in light of how variations diverge from it. A further complication is that modifying the reference propagates to modifying all variant sequences which do *not* have an insertion at the relevant position. In any case, some applications call for the use of "unpadded" reference sequences, which have no modifications (forcing insertions to be notated with more complex representations), whereas others are facilitated by "padding" the reference base with gaps where one or another variant possesses an inserted letter.

The preceding overview of genomic file formats has only considered structures that encode raw sequence data and its alignments or variants; this discussion has overlooked any of the tools or notations which build a coherent narrative on the basis of sequencing, such as observing how a genomic profile has emerged over time. For example, data visualization tools may be used to study genetic variations — including the mutations which have led to divergent strains of SARS-CoV-2 — by picturing them as trees, where branches separate at the point of variation on a specific genomic site. In SARS-CoV-2, for instance, one can model the temporal evolution of viral variants via data structures identifying when a particular strain emerged, from which prior strain, and the genomic site where a mutation forms the basis of the variant's specificity. These data structures, however, are different in form and visualizations than the underlying genomic data itself.

3.3 The Flow Cytometry Standard (FCS) File Format

Flow Cytometry uses a combination of lasers and fluorochromes to investigate the properties of blood cells, proteins, and other cell-scale entities which may be present in blood samples or other tissue samples. Flow Cytometers are machines which reduce blood samples (or other fluid samples) to single-cell streams and then probe the samples with laser beams. Depending on the size and shape of the cell (or other particle of interest) some light will be diffracted around the cell (this is referred to as "forward scatter") while other light will reflect off the cell (yielding "side scatter"). The combination of forward and side scatter provides information about any one particular cell; in general, larger cells produce greater forward scatter, and more complex cells (complexity in this context is often referred to as "granularity," measuring the geometric intricacy of the surfaces within or around cells which would scatter light waves in different directions) produce greater side scatter.

Note that these two dimensions are independent in general; cells can be both relatively large and relatively complex, so that greater forward scatter does not imply lesser side scatter, or vice-versa. In addition to laser probes, modern-day Flow Cytometry machines often use a diverse range of fluorochromes to mark cells or materials that may be present inside or on the surface of cells, which then emit fluorescent light signals that can be absorbed by detectors that are placed parallel to the photodiodes and photomultipliers which measure forward/side scatter. Collectively, the scatter signals and fluorochromes are called "channels." The data produced by modern Flow Cytometry instruments may have as many as 12 to 14 channels. Computationally, the end result is a data structure which is notated as a matrix, where each row corresponds to a single cell (referred to in coding as an "event") and each column represents one channel.

The canonical format for representing Flow Cytometry data is **FCS** (Flow Cytometry Standard). Each **FCS** file encodes the "event matrix" (essentially a table marking the observations for each cell according to each channel; this data has no relation to matrices in the linear-algebraic sense except that code libraries designed for matrix arithmetic are convenient tools for representing the relatively large tables that emerge from **FCS** data).

Ultimately, the purpose of **FCS** representation is to cluster events (that is, individual cells) into groups and then count the relative size of each group, which can give information about the sample being analyzed — for instance, a blood sample can be examined to measure the ratio of monocytes to lymphocytes. Such classification does not emerge automatically from the raw event data; instead, a series of mathematical and geometrical transformations is often necessary to transform event matrices into scatter-plots where event classification becomes visually obvious. The process of clustering events subsequent to these transformations is called "gating." As a result, a complete description of **FCS** analysis requires the raw **FCS** data to be paired with representations of transforms which are applied to individual channels and with descriptions of gates applied to the resulting two-dimensional spaces (each space being a side-by-side comparison of two channels). Flow Cytometry data is also presented sometimes as a histogram, visualizing individual transformed channels on their own.

Note that this discussion has largely equated cells with events, given that historically and in practice the most common application of cytometry is to quantify the sorts of cells observed in a biological sample; however, cytometry can also be used to probe other submicroscopic (roughly cellular-scale) entities, such as microbes (which may be multi-cellular) or extra-cellular vessicles (particles that are released from cells). Flow Cytometry can also indirectly examine entities which are too small to generate discrete events in the raw data; for instance, side-scatter and/or fluorescent channels can be used to quantify proteins or biomarkers occurring on the exterior of cells.

Preliminary to raw event data, **FCS** files also contain "headers" which present information about the individual channels and about the experimental setup (e.g., the make and model of the machine used for the actual cytometry). Headers in **FCS** are preceded by dollar-sign characters (**$**, or Latin-1 code 36). Some headers provide information about the overall experiment, while others are specific to individual channels. These latter header fields have a specific internal structure encoded in the tag name: in general they contain the letter **P** (for "parameter"), followed by a number representing the channel, and then an additional letter representing which specific piece of information is being presented about that channel. For example, the code **$P9F** would be used as a tag marking a string value representing the name of the optical filter applied to the 9th channel. The **FCS** standard also allows for post-processing information, such as channel transformations and gating, to be recorded in **FCS** headers fields, although such information is often instead presented in separate files, with formats such as **GatingML**.

There are a variety of mathematical transforms which may be applied to channels prior to gating, including various logarithmic transforms, and bi-exponential calculations (such as transforms based on hyperbolic sines and inverse hyperbolic signs). Considering an overall Flow Cytometry workflow, there are in totality, then, at least four different stages of observation/analysis which must be recorded: machine setup and overall experimental properties (encoded via **FCS** header data); event matrices themselves; transform functions which have been applied to various channels; and gating steps, or the geometry of regions applied to cross-channel scatter plots that classify events based on cell types.

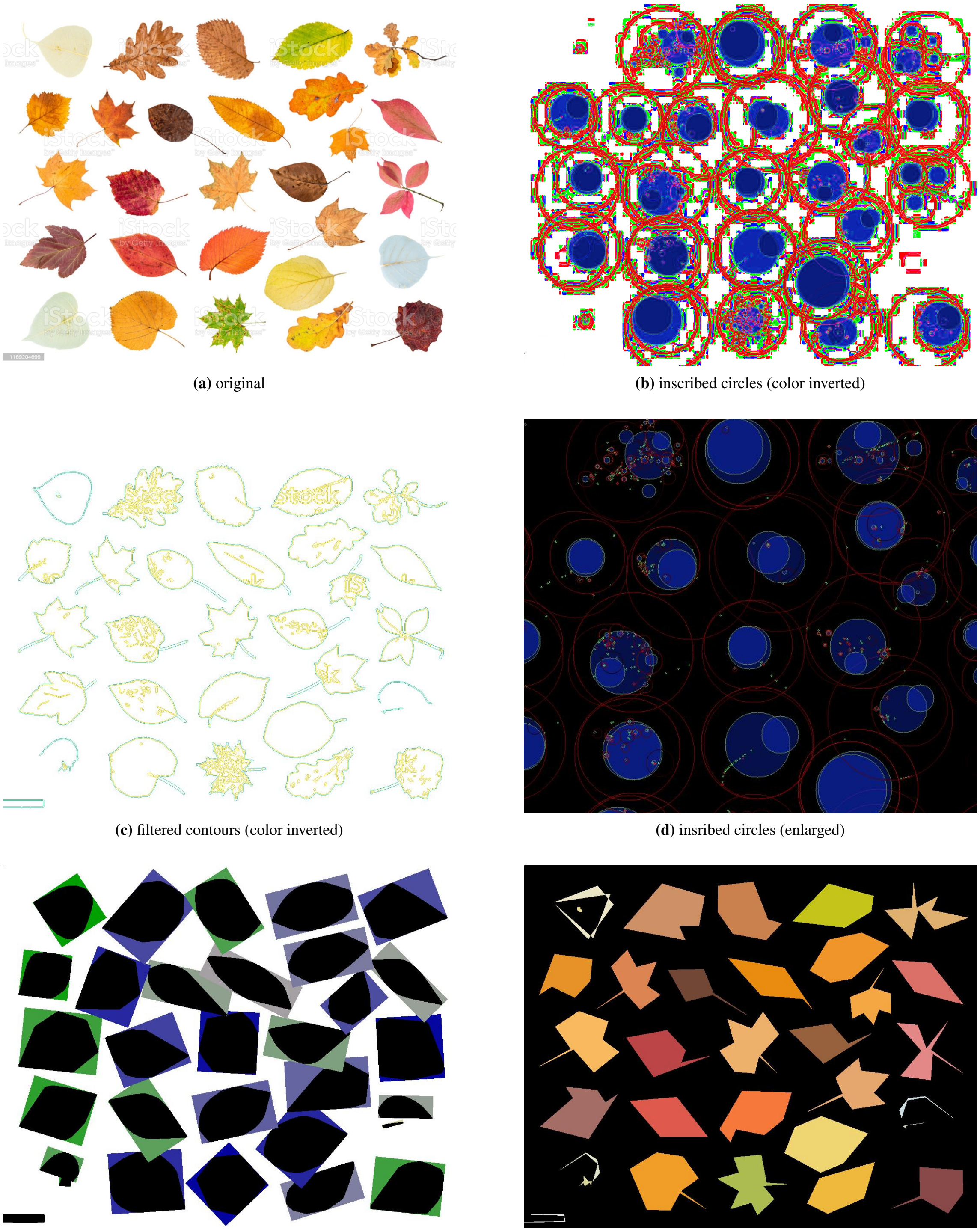
These different kinds of data have generally given rise to several different file formats, as well as to proposals to unify these formats into an overarching common vocabulary, potentially replacing **FCS** (as we will cite specifically in later chapters). One proposal is to encode **FCS** within **DICOM**; other suggestions are oriented around **XML**. The rationale for merging **FCS** within the overall **DICOM** infrastructure derives in part from the conceptual similarities between "gating" applied to **FCS** scatter-plots and "segmentation" of biomedical image data — although **FCS** plots are not images *per se*, they are akin to bioimages in that they are obtained through optical instruments and can (with suitable mathematical transformation) take on a visual form where clusters of related events (evincing a common cell-type) are geometrically circumscribed — roughly analogous to how discrete objects form distinguished regions within photographs. These conceptual similarities have yielded calls to record **FCS** data according to annotations and terminologies associated with image data, which is the subject of the next subsection.

3.4 Image Segmentation, Contours, and Regions of Interest

Many image-processing use-cases in biology and medicine involve isolating particular "foreground" regions from within diagnostic or laboratory images (e.g., individual cells from within a tissue sample magnified via microscopy; tumors within a radiographic image intended to diagnose solid-tumor cancer; or patterns of ground-glass opacity which suggest the presence of SARS-CoV-2 in lung scans). The process of isolating particular regions within images is sometimes discussed via the generic term "segmentation," although technically segmentation involves a complete partition of the image, wherein every point of the image is assigned to exactly one segment. The goal of image-analysis is often less about segmenting extraneous "background" material, but rather demarcating *Regions of Interest* which are conceptually more important than the rest of the image.

This overall theme applies outside of biology as well; image tagging refers to the process of classifying images according to their most prominent features or objects. If a photograph is classified as an image of a car, for example, the most important "Region of Interest" is the area which demarcates the car itself, considered as a foreground, from other background content (perhaps the street or driveway where the car is parked). Similarly, if a microscopic image reveals three blood cells, the Regions of Interest are the cells themselves.

In contrast to other discussions in this section, our examination of image-annotation will not focus on specific file formats so much



(a) original

(b) inscribed circles (color inverted)

(c) filtered contours (color inverted)

(d) insribed circles (enlarged)

(e) convex hull with bounding rectangles

(f) interior-contour color average

Figure 2: Visualizing Contour Feature-Vectors
(note that in (e) the colors are inverted, and the gap between the convex hull and bounding rectangle is shaded to visualize the angle of the rectangle to external image borders)

as on how regions of interest may be characterized. To prepare this discussion, it is useful to consider a concrete example of how Regions of Interest may be isolated from images using image-processing algorithms. Readers may wish to consult the code accompanying book, which contains a demonstration of image analysis using the **OpenCV** Computer Vision library. This code sample demonstrates a common image-analysis workflow. The most crucial step is probably that of finding contours (via the **OpenCV** **findContours** procedure) which yields a set of pixel-sequences that (with some likelihood) mark boundaries between disparate objects in the source image. Usually contour-extraction is preceded by a preliminary step involving a "morphological operator," which has the effect of simplifying the image somewhat and reducing the chance that spurious boundaries will be discerned that are in fact effects of light or of inconsistent coloration.

After images have been transformed morphologically, boundaries are identified by searching for consistent color-patches on either side of an apparent boundary-line. The actual methodology for isolating apparent boundaries depends on the image-processing algorithm used. Most algorithms work with matrix-based "kernels" which calculate color divergence one step away from an individual pixel. A given pixel, for instance, will in general be surrounded by eight other pixels (including those which are diagonally as well as orthogonally adjacent). In each of these directions, the adjacent pixel will diverge from the current pixel (at the center of the matrix) by some vector of quantities, depending on the color model. For example, in a conventional **RGB** (or **BGR**) color-space two pixels may be compared in the red, green, and blue channels, so the contrast between adjacent pixels may be split into a vector of three magnitudes.

Such comparisons can then be repeated over each of the eight pixels surrounding a central point, yielding a 3-by-3 matrix each of whose entries contains three quantities (for red, green, and blue offsets). These matrices are typically reworked by applying some mathematical function to the matrix cells, often resulting in a single real-valued matrix (instead of a matrix of color vectors). The preferred calculation is then repeated at every point in the image, yielding a space of matrices which can be statistically analyzed; the end result of that analysis, at least in the context of boundary-detection algorithms, is a tracing of lines which appear to demarcate borders between distinct regions of an image, where "region" in this context refers to pixels grouped together by virtue of emanating from a common real-world object depicted via the image. Within image-analysis tools such as **OpenCV**, such boundary-lines are referred to as "contours."

Once contours are extracted, **OpenCV** has a variety of tools that may be used to characterize the regions thereby delineated. These include the dimensions of the bounding rectangle (the smallest rectangle with sides parallel to those of the image overall that fully contains the contour) as well as dimensions and angles of the bounding rotated rectangle (the smallest rectangle containing the contours when the rectangle's sides are not restricted to being parallel with the external image boundaries).

Other metrics involve inscribed circles (the largest circle wholly contained within the contour) or circumscribing circles (the smallest circle wholly containing the contour) where either may be measured both at the center of gravity of the contour's internal region (that is, the circles are fixed at that point) or allowing the circle center to vary; one then looks for the the largest inscribing circle, or smallest circumscribing circle, where the center point can be anywhere within or even (in the latter case) outside the contour's interior. Metrics based on circles may be generalized to ellipses, yielding further details based on the ellipses' eccentricity and the angle of their major axis.

Separate and apart from these morphological analyses — which approximate the contour with canonical shapes such as rectangles, circles, or ellipses — other methods quantify the degree of "convexity" evinced by a contour (how much it deviates from its convex hull), the color-average inside the contour, the contour's area or perimeter, as well as relationships between contours (notably whether contours enclose other contours in their interior). The demo code shows calculations based on each of these measures. Via analyses such as these, every contour may be associated with space of at least 12-15 features, which in turn may be used to classify the regions bounded by each contour. Not every contour is in fact the boundary of a bonafide image region; a principal goal of image-analysis is to isolate those contours which are likely to be statistically significant (in the sense of bounding a region of interest) as opposed to background "noise."

All of these metrics classify regions only on basic mathematical levels; none of this quantitative data suffices to discern whether contour-delimited regions correspond to cells, cars, or any other kind of real-world objects. Nevertheless, region feature-vectors are the starting point for statistical calculations which lead to more sophisticated image-tagging. This is roughly a two-step process, first identifying regions which seem likely to correspond to real-world objects and then classifying those objects themselves. In the biomedical context, image-tagging involves classifying regions which are biologically and/or diagnostically significant. An image-processing algorithm might attempt to isolate a solid-tumor mass, for example; such an algorithm may be able to correctly demarcate the region of an image where a tumor is visible. For diagnostic purposes further details would then need to be added, classifying tumors into categories such as "sarcomas larger than 5cm." Such classifications may or may not be possible with automated tools; traditionally these details are added by radiologists or pathologists who manually examine radiographic images, although image-analysis tools could be used to expedite this process (e.g., to select the most diagnostically valuable images from a **DICOM** image-series).

The end result of biomedical image-analysis is of course these diagnostic or investigative annotations, such as labeling an image-region as a particular kind of tumor, with a particular size and characteristics — these are the details generally recorded in an annotated imaging database or notated via **DICOM** extensions such as Treatment Plans or Structured Reports. Data of a more quantitative sort, such as the feature-vectors characterizing image contours, is important only as an intermediary processing step. Nevertheless, there are several reasons why intermediate image-analysis data may continue to be important even after the higher-level and more "semantic" (as opposed to purely quantitative) analytic steps have occurred.

For one thing, it is inconvenient for pathologists/radiologists to manually mark off image regions in the course of reporting their diagnostic findings. As such, machine-segmented Regions of Interest (or some subspace derived from them, such as a polygonal frame enclosing their convex hull) can be integrated into diagnostic reports, which means that techniques must be applied to incorporate mathematically extracted contours/regions into image annotations. Moreover, there are scenarios where behind-the-scenes image process data may need to be retained for subsequent research; this data may be relevant for holistic statistical analysis of large-scale data-sets and/or for revisiting diagnoses over time. For instance, a software component may try to measure the progression of a tumor by comparing automatically-extracted image regions taken at two different times, assuming that the corresponding regions depicting "the same" tumor can be isolated and then mathematically compared.

For these kinds of scenarios, it is reasonable to assume that at least some intermediate image-processing data should be retained for subsequent analysis, which then raises the question of how image-feature vectors should optimally be represented in a database context. We will address this question in a later chapter.

Similar comments apply also to audio feature-vectors, such as those derived from Fast Fourier Transforms (**FFT**) or Mel-Frequency Cepstral Coefficients (**MFCC**), which in bioinformatics may classify **EKG**s, sonograms, and other biologically useful audio resources; [3] summarize that for EKG signals "[m]orphological features include the coefficients of the Hermite transform, the wavelet transform or the discrete cosine transform ... that aim to model the ECG beat instead of extracting features from the raw data" (page 2). Because machine-learning and other statistical analytic techniques operate on **EKG** feature vectors, these vectors serve as intermediate representations of **EKG** waveforms from which diagnostic findings are derived. The process of extracting feature-vectors from audio waveforms bears some mathematical similarities to that of extracting feature-vectors from Distinguished Regions of bioimages (reflected in the extension of **DICOM** to encompass audio assets), which will be emphasized in later chapters.

3.5 Common Data Models for Clinical Research

Other biomedically important data structures derive from initiatives to share or pool clinical data for research purposes. A good example of such an initiative is the **OMOP** partnership mentioned earlier. The **OMOP** format prioritizes data-integration according to largely conventional **SQL** paradigms; in the **OMOP** context most information is held in relational databases, and data integration involves merging disparate database tables. Toward that end, the Common Data Model standardizes those specific tables which should be present among compliant data sets and the columns within each of these tables, where the various columns are given a canonical name and data type. For example, specific tables include ones for personal (patient) information, data about a specific visit made by a patient to a health-care provider, data about one specific procedure administered to a patient, information about a specific occasion when a patient received a drug/pharmaceutical, data about the costs of either drugs or procedures (or other "medical events"), and so forth. The point is not that health care providers' software would internally store information with this precise configuration of tables, but rather that biomedical data (in whatever format internally used) can be shared by distributing each data field into the specific collection of tables and columns mandated by the **OMOP CDM**. The key data-integration step in this case is then whichever algorithms each individual institution uses to initialize **OMOP** tables from local information.

Readers who would like to examine the specific tables and columns which constitute the **OMOP** Common Data Model may consult the source code accompanying this book (see the **omop** project). This code implements **C++** classes corresponding to **OMOP CDM** tables. The project is not an **OMOP** client as such — there is no logic for populating the tables from a database instance — but it serves as a reference illustrating the fields and structures which are endemic to **OMOP** data representations.

The accompanying code similarly has a **pcor** project which demonstrates the **PCORnet** Common Data Model. Similar to the **OMOP CDM**, this standard (developed by the National Patient-Centered Clinical Research Initiative) promotes data integration by specifying that shared data be distributed into a collection of tables with fixed roles and column-sets. The various tables include a "Demographic" specification with essential personal patient info, a table representing patients' enrollment in a clinical trial, a "Dispensing" table noting medicines dispensed by a pharmacy to a patient, and tables for diagnoses, lab results, "vital signs," and so forth. It is interesting to contrast the **OMOP** and **PCORnet** Common Data Models, which can be readily compared because they are structurally similar; the fact that they nonetheless recognize fairly different table and column sets point to the specific interests of Observational Medicine and of patient-centered advocacy, respectively.

In contrast to the table-based and **SQL**-inspired formats for **OMOP** and **PCORnet**, parts of the **CDISC** standard lean more toward Semantic Web information structures (as with the **BRIDG** — Biomedical Research Integrated Domain Group — specification which is one of several **CDISC** standard models). The contrast between table-oriented and Semantic Web notions of a "controlled vocabulary" embody alternative theories of the role of semantic normalization in technology. For table-oriented environments, Controlled Vocabularies specifically address the organization of digital resources; for example, table names, column names, and in some cases the values asserted within columns are required to have identifiers drawn from a restricted class of terms. This restriction applies to individual values when those values are neither numeric nor string types (such as a person's name, which for obvious reasons cannot be tied to a list of accepted values) but rather to columns whose data may reasonably restricted to a given enumeration. For instance, the state where a patient resides must be one of the fifty US states (assuming a patient is an American citizen and excluding, for sake of argument, territories such as the District of Columbia). It is possible to write or abbreviate state names in different ways, but a Controlled Vocabulary could reasonably stipulate that all conformant data sets use identical terms for the same state name.

This discussion uses terminology associated with relational database tables; for general discussion of data-integration it makes sense however to adopt more type-theoretic language, so that we can consider the names of data types, the names of the fields which data types contain, and (in some cases) the values which are spanned by those fields. In lieu of restricting names to data types themselves, a system may instead assign names to *interfaces*, or in effect to prototypes and specifications which data types need to put into operation. A protocol may specify a collection of interfaces, and a software component which implements the protocol will provide one data data for each interface that the protocol outlines. Controlled Vocabularies therefore specifies the names of interfaces, as well as the names of data fields accessed through the values which instantiate data types implementing each interface. Controlled Vocabularies would also specify the range of nominal values assigned to enumerative types, in the case of data types whose values derive from a specified list (e.g., the set of US states).

In the case of Semantic Web data, by contrast, Controlled Vocabularies (typically called "Ontologies" in this context) serve a more generic role, typically connecting data types not only to particular software implementations but also to more abstract concepts. For example, cancer is classified (according to histological criteria) into one of six groups (Carcinoma, Sarcoma, Myeloma, Leukemia, Lymphoma and Mixed). A data-representation standard could reasonably stipulate that any tumor — that is, any data structure describing the characteristics of a tumor — include a data field classifying the tumor into one of the six groups (at least those whose cancers present as tumors that can be detected via bioimaging). In this sense the six groups (and canonical names associated with them) constrain the range of values spanned by a cancer-type (and by extension tumor-type) data field. Such a formal stipulation can be defined both as a restriction on table data and as part of a Semantic Web Ontology; in short, semantic standardization at this level is common to both paradigms. However, an Ontology may further model "philosophical" traits associated with a tumor; for instance, the fact that a tumor is a form of biological tissue, and more generally a biological entity, which in turn is a physical thing, possessing characteristics such as size and volume. These more general concepts do not fit within type systems themselves — there is rarely a data type modeling "physical things" in general — so the purpose of Standardized Vocabularies in contexts such as the Semantic Web is not merely to serve as a guideline for implementing code libraries (e.g., those that would export data in the **OMOP** or **PCORNET** Common Data Models) but as a basis for Artificial Intelligence. In this sense the values which are represented within Semantic Web data structures may in some cases be associated with specific computational data types, but they are also modeled in terms of networks of concepts that are designed to serve as a foundation for **AI** reasoning.

Later in the book we will return to the role of Ontologies and other meta-models in data-integration contexts. Before engaging these more theoretical discussions, however, we will try to develop a more substantial concrete picture of how data-integration problems arise. This discussion will be the focus of the following chapter, beginning with further investigation of the overlap between data-integration challenges and Precision Medicine.

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