Visual Exploration, Analysis, and Communication of Physiological Processes

L. A. Garrison[1,2,3,4] and S. Bruckner[1,2,3,5]

[1]Univ. Bergen, Norway, [2]Mohn Medical Imaging & Visualization Centre, Norway, [3]Center for Data Science, Univ. Bergen, Norway [4]Bouvet ASA, Norway [5]Univ. Rostock, Germany

Abstract

Describing the myriad biological processes occurring in living beings over time, the science of physiology is complex and critical to our understanding of how life works. Physiology spans many spatio-temporal scales to combine and bridge from the basic sciences (biology, physics, and chemistry) to medicine. Recent years have seen an explosion of new and finer-grained experimental and acquisition methods to characterize these data. The volume and complexity of these data necessitate effective visualizations to complement standard analysis practice. Visualization approaches must carefully consider and be adaptable to the user's main task, be it exploratory, analytical, or communication-oriented. This research contributes to the areas of theory, empirical findings, methods, applications, and research replicability in visualizing physiology. Our overarching theme is the cross-disciplinary application of medical illustration and visualization techniques to address challenges in exploring, analyzing, and communicating aspects of human physiology to audiences with differing expertise.

CCS Concepts

• ***Human-centered computing*** → ***Visualization application domains; Visualization design and evaluation methods; Visualization techniques;***

1. Introduction

Physiology describes the millions of interconnected biochemical processes that sustain life [HG11]. Unifying the basic disciplines of biology, chemistry, and physics with medicine and numerous connecting disciplines, such as systems biology, human physiology is dynamic, complex, and multifaceted. Human physiology requires a careful balancing act, known as homeostasis, of multitudes of biochemical processes occurring over a broad span of time and space, as summarized in Fig. 1. Cascading effects may occur when processes fall out of balance. For instance, an uncontrolled signalling pathway at the molecular scale can affect or precipitate numerous full-body scale events, such as cancerous tumor formation and migration. In spite of human physiology's overwhelming complexity, deeper understanding of our bodily processes can lead to, e.g., improved communication between experts and lay audiences, promote more targeted and effective drug development, and advance the quality of healthcare and individual health management.

Myriad data types and sources describe aspects of physiology. Advances in hardware and software have led to new imaging paradigms at higher resolution, more sophisticated simulations, and new experimental methods enabling researchers to map the spatio-temporal organization of the body and dynamic behaviors of molecules, cells, tissues, and organs in unprecedented detail. With the range of available data, it is now possible to model human physiology across multiple scales, with the grand challenge of linking these data sources to ultimately model a complete physiological human [ABBC05, Hun06, FBC*08, TCA*11, VH16]. Consequently, the time has come to discuss visualization for multiscale

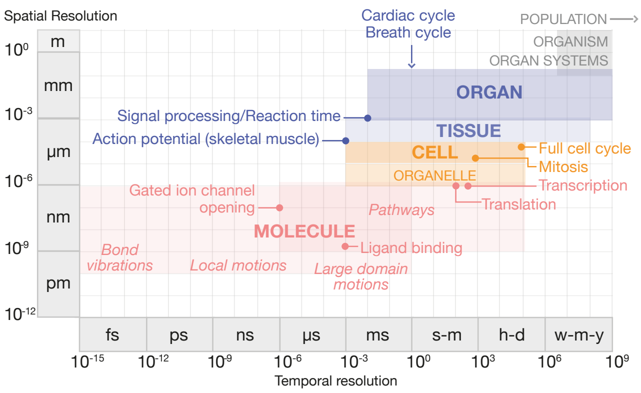

Figure 1: *Human physiology is multiscale, integrating the functions of molecules from nanometers to a whole organism in size, and temporally from femtoseconds to years, i.e., an organism's lifespan [HG11, GKV*22].*

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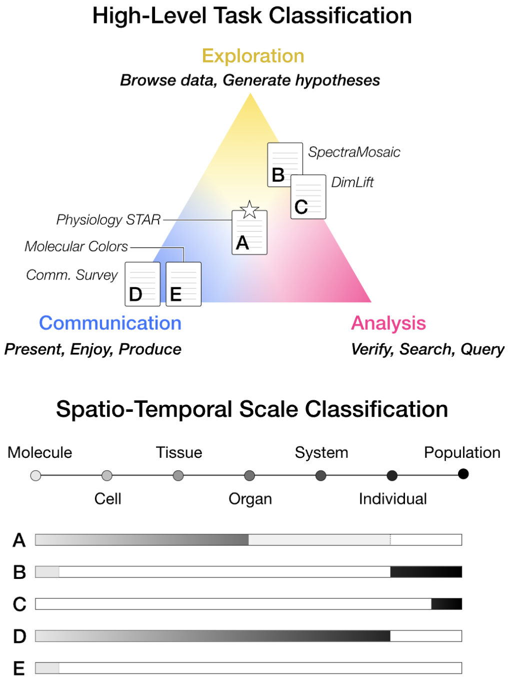

Figure 2: *Body of work classified according to the high-level task(s) and the spatio-temporal scale(s) which they address:* ***(A)*** *Trends & Opportunities in Visualization for Physiology: A Multiscale Overview [GKV*22],* ***(B)*** *Interactive Visual Exploration of Metabolite Ratios in MR Spectroscopy Studies [GVC*20],* ***(C)*** *DimLift: Interactive Hierarchical Data Exploration through Dimensional Bundling [GMS*21],* ***(D)*** *An Exploration of Practice and Preferences for the Visual Communication of Biomedical Processes [GMF*21], and* ***(E)*** *Considering Best Practices in Color Palettes for Molecular Visualizations [GB22].*

physiology. The volume and complexity of these data introduce numerous challenges, including expert **discovery** of relevant patterns and features of interest, scaling discovery from the individual to the cohort level, and retaining semantic connections to the source data throughout the discovery process. However, the challenges do not end with expert discovery. Findings must be **communicated** to relevant stakeholders from different disciplines and degrees of health literacy.

Visualization is a powerful means to help address these challenges, allowing recognition of patterns, trends, outliers that are otherwise difficult to detect. Biomedical illustration, a related field to Visualization, is typically employed for visually communicating physiology. With a greater focus on concepts rather than strictly data, biomedical illustration techniques can fill gaps where data are unavailable, and abstract information to an audience-appropriate degree.

The research detailed in this application is based on the first author's PhD thesis and consists of five publications (Papers A–E in Fig. 2) contributing to the areas of theory, empirical findings, method, and application. The overarching theme of this research is the **cross-disciplinary application of visualization and biomedical illustration** techniques to address challenges in exploring, analyzing, and communicating aspects of physiology to audiences and users with different degrees of expertise. This perspective is partly enabled by the increased recognition of physiology as a multidisciplinary field of study. Additionally, the advent of COVID-19 and greater daily exposure to health data have led to increased societal demands for compelling and understandable visualizations describing physiology. Crafting such visualizations requires new methods spanning across disciplines. Our research **scope** is restricted to visualization primarily for the field of human physiology. The **actors** on which we focus include: domain experts, i.e., individuals with deep knowledge of the particular biochemical process being visualized, and non-experts, i.e., individuals lacking expert-degree knowledge of the process in question, which can include the general public. Our **cases** emphasize high-level user tasks, predominately (1) visual exploratory analysis or (2) visual communication of physiology. Taken together, our work spans the molecular scale up to population (cohort) scale, which we frame in the context of high-level user tasks, adapted from Brehmer & Munzner's multi-level task typology [BM13]: (exploration, analysis, and communication), illustrated in Fig. 2.

2. Contributions

We frame our contributions within our state-of-the-art report offering a broad, multiscale overview of the challenges and opportunities in visualization for physiology (Fig. 2A [GKV*22]). Amongst the findings of this report, we identify two open opportunities: (1) exploratory analysis of multifaceted physiology data for expert users (Fig. 2B [GVC*20] and 2C [GMS*21]), and (2) visual communication to experts and non-experts (Fig. 2D [GMF*21] and 2E [GB22]). Our contributions in exploratory analysis focus on the identification of biomarkers that can lead to early diagnosis and assessment of numerous diseases and disorders of the central nervous system. Going beyond a standard approach to medical visualization, our work encompasses non-spatial visual analysis of different types of complex cohort data. Since the scientific investigation pipeline is only complete when results are shared, we follow with select challenges for the visual communication of physiology to stakeholders with different levels of expertise on a range of physiological processes. All application code, study artifacts, and empirical data are open-sourced and available for analysis and reuse. In the following, we briefly summarize the motivation, challenges, and results of these contributions. For additional information, we refer the committee to supplementary material.

Exploratory Analysis of Multifaceted Data. Our investigation of multifaceted physiology data takes place over two studies [GVC*20, GMS*21] targeting processes occurring at different spatio-temporal scales.

SpectraMosaic. A brain tumor prognosis is among the worst of all malignancies, and early detection is key to an improved prognosis. This push for early detection has inspired clinical research into acquisition modalities such as magnetic resonance spectroscopy (MRS), a non-invasive technique used to estimate concentrations of certain biomolecules (metabolites) in living tissue [BSD15]. Most clinical tools to quantify spectral data produce rudimen-

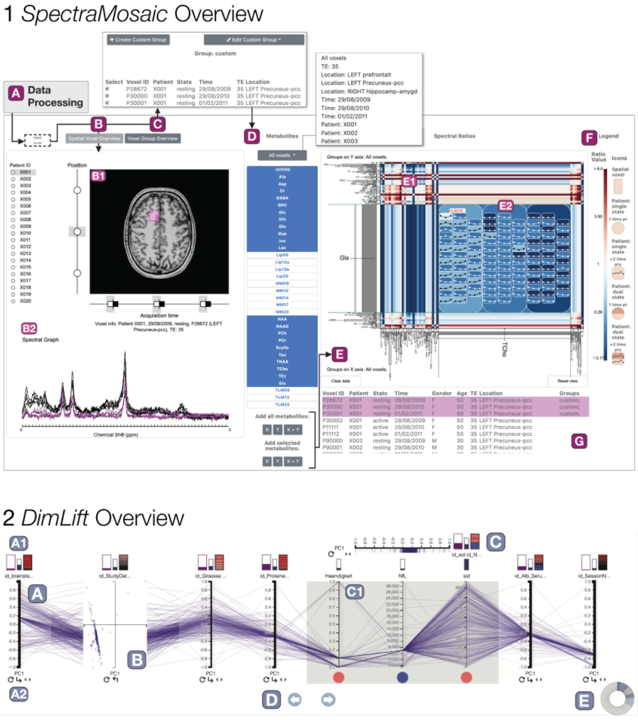

Figure 3: *Contributions for exploratory analysis of multifaceted data:* ***(1) SpectraMosaic*** *application overview [GVC*20] and* ***(2) DimLift*** *mixed-initiative visual approach [GMS*21].*

tary graphical visual output that is challenging to interpret in isolation. However, metabolites are most useful when presented as ratios. Standard domain tools often present these as basic tables [Pro01, CON13], which does little to facilitate interpretation or comparison. Translation from these acquired metabolite signals into clinically-useful biomarkers is an open challenge with limited attention from the visualization community [NLK*14]. With MRS data we see a clear opportunity to leverage visualization in a uniquely non-spatial manner to identify molecular-scale patterns of disease.

We developed *SpectraMosaic* [GVG*19a, GVC*20] in a year-long collaboration alongside cognitive neuroscientists, MR physicists, and MR engineers at Univ. of Bergen and Haukeland Univ. Hospital (Norway). Our participation in the spectroscopy research group weekly meetings provided numerous opportunities for discussion and feedback, including time with, and in the scanner, to better understand the modality and its idiosyncrasies. Shown in Fig. 3.1, our novel visual approach enables exploration of any permutation of metabolites in ratio form for an entire cohort, by sample region, individual, acquisition time, or brain activity, i.e., active task or no task during the acquisition. We encode ratios first in a heatmap overview, with a detail view using a system of glyphs encoding all possible case combinations. We additionally include linked relevant patient information to relate ratios to the original spectral output and sample region. Data may be arranged in customizable groups for comparison, and we incorporate uncertainty visualization at key points of the exploratory pipeline [TD20]. Performing multiple iterations of evaluations alongside domain experts in a "think-aloud" protocol, we found that *SpectraMosaic* supports insights in patterns of metabolite concentrations that are more immediately detectable than with standard exploratory approaches. An early version of this work [GVG*19b] was recognized with the the EuroVis Best Poster Award in 2019.

DimLift*.* Clinical investigation of biomarkers for early disease diagnosis often requires extensive analysis of multifaceted cohort data beyond a single data source. Analysis of these data can be overwhelming. The data are heterogeneous, high-dimensional, with many missing items. While visual analysis approaches incorporating dimensionality reduction methods can make analysis more manageable, they risk losing subtle, interesting relationships. To solve this issue, we build on prior work exploring dimensional subspaces and subsets, the interplay of these dimensional spaces with items space [TFH11, YRWG13], and the exploration of these spaces in mixed-type data [MGS*21] to provide a means to identify less strong, but semantically meaningful, dimensional relationships.

Our *DimLift* approach [GMS*21], shown in Fig. 3.2, is a mixed-initiative, iterative dimensionality reduction technique enabling identification of subtle but interesting patterns and relationships through *dimensional bundles*. These *bundles* are subsets of dimensions contributing similarly to the overall variance of the dataset. Rather than a conventional monolithic treatment, our approach produces hierarchical *bundles* of dimensions which retain the expressitivity of the original dataset. Key to this method is the user's ability to steer the dimensionality reduction process. This work results from an international and interdisciplinary collaboration between clinical and visualization researchers from Univ. Bergen, Otto-von-Guericke Univ. (Germany), and the Center for Behavioral Brain Science (Germany). While our approach is by design broadly applicable, one of our primary motivations was to support efforts investigating biomarkers for cerebral small vessel disease (CSVD), a disorder associated with abnormalities of small blood vessels in the brain [PC20]. This disease is responsible for one in five strokes worldwide and is the most common cause of vascular cognitive impairment in the elderly. Our collaborators' typical investigation necessitates a hypothesis confirmation approach, with many time-consuming analysis iterations in SPSS. Conversely, our method supports an exploratory hypothesis *generation* approach. With *DimLift*, clinical researchers can augment their existing analysis pipeline in SPSS by first exploring their data for subtle interesting patterns and relationships that otherwise may take hours to uncover or be overlooked entirely. We received a Melzer Grant from Univ. of Bergen in support of this work, and have since received interest from researchers in Haukeland Univ. Hospital for use of *DimLift* to analyze clinical aging data.

Visual Communication of Physiology. The research process does not end with expert analysis. Experts' findings must be shared with stakeholders in other domains with different expertise to carry findings from the lab bench into policy. It is natural to expect that experts in a topic may have different preferences and criteria to evaluate a visual communication relative to a non-expert audience. This impacts the success of an image in communicating a given scenario. Our goal in this study was to gain insights into how visualization

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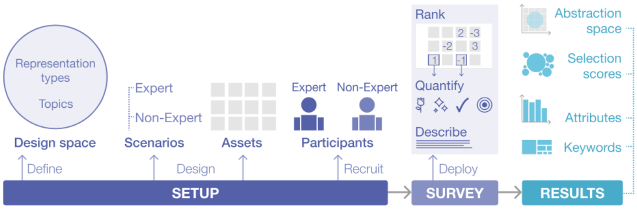

Figure 4: *Three-phase study pipeline.* ***Setup****: define design space, create scenarios & assets, and recruit participants;* ***Survey****: participants rank, quantify, and describe top & bottom selections per scenario;* ***Results****: analyze abstraction space, scores, attribute rankings, and keywords [GMF*21].*

and biomedical illustration techniques are used and assessed for visual communication by different audience groups. Designed over a series of expert interviews and focus groups with professional biomedical illustrators and visualization researchers across Europe and North America, our interdisciplinary study with researchers from Univ. Bergen, Otto-von-Guericke Univ. (Germany), and Johns Hopkins Univ. (USA) [GMF*21] focuses on common communication scenarios of five well-known physiological processes and their standard visual representations. Feeding into these scenarios is a set of visual assets that we developed to capture the range of standard practices by biomedical illustrators and visualization researchers to depict a process, e.g., blood flow. We framed these scenarios in a survey with participant self-rated expertise on the physiological process spanning from minimal to expert knowledge of a given topic. We summarize our process in Fig. 4.

Our results show frequent overlap in abstraction preferences between expert and non-expert audiences, although experts and non-experts express different criteria to define ineffective visualizations. We also found that some illustrative conventions, e.g., glows, are ambiguous in meaning, and unexpected preferences for biomedical illustrations in place of data-driven visualizations in some scenarios. Our findings suggest numerous opportunities for the continued convergence of visualization and biomedical illustration techniques for targeted visual communication of physiology. Awarded an Honorable Mention for Best Paper (VCBM 2021), this study has sparked research in molecular storytelling by colleagues at Masaryk Univ., and a new branch of investigation with colleagues from Otto-von-Guericke Univ. on narrative medical visualization.

An opportunity that we discuss in greater depth in this research is a case for the development of semantically-consistent guidelines according to aesthetics, interpretability, and effectiveness for the coloring of molecular scenes [GB22]. The intent of such guidelines is to elevate the scientific literacy of non-expert audiences in the context of molecular visualization, which is particularly relevant to public health communication. This work has sparked further collaborations and discussions in the systems biology domain.

Research Replicability. To support open science, our application code is certified through the Graphics Stamp Replicability Initiative for *SpectraMosaic* [GVC*20] and *DimLift* [GMS*21]. We created publicly-available data packages for our empirical work [GKV*22, GMF*21, GB22]. We refer to our supplementary material for code and data package repository information.

3. Discussion & Outlook

The myriad interconnected biochemical processes contributing to physiology are complex, yet necessary, to understanding life. Data-driven research has introduced a new paradigm where researchers first acquire physiological data in ever-increasing resolution and volume and then try to ask questions of the data. Increasingly multidisciplinary teams are necessary to solve challenges in exploring, analyzing, and communicating these data. Visualization plays an integral role in identifying and solving these challenges.

This body of work is enriched for its numerous multidisciplinary, multi-institutional collaborations. However, we note some limitations. Our work is not comprehensive in its coverage and discussion of visualization for physiology. To do so within a manageable scope would have been impossible. Instead, we rely on representative topics and gaps identified from our state-of-the-art report [GKV*22]. The studies we conducted are predominately qualitative with small sample sizes. While the results are sufficient to draw preliminary conclusions, we hope to build on these studies with larger and more demographically-varied cohorts. The methods that we developed for exploratory analysis of physiology data target experts in a research setting. However, our ultimate goal, shared by many who develop visual methods for medical data, is to see our work realized in clinical routine where clinicians and patients can see an immediate, positive health impact.

Some data acquisition methods and modalities have received little attention from the visualization community to-date, e.g., nascent chain tracking [DDM17]. This will continue to be the case as hardware and software advances continue to yield new paradigms for data acquisition. Processes occurring over broad ranges of space and time present ongoing challenges in balancing insights with complexity. This is true for most molecular pathways, which are the basis for processes at larger scales. Dimensionality reduction strategies are common with physiology data. Continued research linking insights to source data is crucial for expert trust and adoption. Semi-automated systems allowing the user the flexibility to steer their inquiries may be effective for experts with mainly analytical goals, but are often too abstract for non-expert users. This introduces a delay in the sharing of information that might be critical to public health. Our field needs to consider how our bespoke, often expert-curated approaches can be adapted and shared with other stakeholders. Community-driven approaches to visual communication are imperative for advancing public health and health literacy in our global society. Our research provides a valuable foundation for developing visual methods for exploratory analysis and communication of multifaceted physiological data.

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