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Authors

Forsch, Nickolas
Govil, Sachin
Perry, James
et al.

Publication Date

2021-05-01

DOI

10.1016/j.jocs.2020.101211

Peer reviewed

HHS Public Access

Author manuscript

J Comput Sci. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

J Comput Sci. 2021 May ; 52: . doi:10.1016/j.jocs.2020.101211.

Computational analysis of cardiac structure and function in congenital heart disease: Translating discoveries to clinical strategies

Nickolas Forsch[1], **Sachin Govil**[1], **James C Perry**[1,2], **Sanjeet Hegde**[2], **Alistair A Young**[3,4], **Jeffrey H Omens**[1,5], **Andrew D McCulloch**[1,5]

[1]Department of Bioengineering, University of California San Diego, La Jolla, CA, USA

[2]Department of Pediatrics, University of California San Diego, La Jolla, CA, USA

[3]Department of Biomedical Engineering, King's College London, London, UK

[4]Department of Anatomy and Medical Imaging, University of Auckland, Auckland, NZ

[5]Deparment of Medicine, University of California San Diego, La Jolla, CA, USA

Abstract

Increased availability and access to medical image data has enabled more quantitative approaches to clinical diagnosis, prognosis, and treatment planning for congenital heart disease. Here we present an overview of long-term clinical management of tetralogy of Fallot (TOF) and its intersection with novel computational and data science approaches to discovering biomarkers of functional and prognostic importance. Efforts in translational medicine that seek to address the clinical challenges associated with cardiovascular diseases using personalized and precision-based approaches are then discussed. The considerations and challenges of translational cardiovascular medicine are reviewed, and examples of digital platforms with collaborative, cloud-based, and scalable design are provided.

Corresponding Author: Nickolas Forsch, MS, Department of Bioengineering, University of California San Diego, Address: 9500 Gilman Drive, MC 0412, La Jolla, CA 92093-0412, nforsch@eng.ucsd.edu, Telephone: +1 734-585-4450.

Author Contributions

Nickolas Forsch: Conceptualization, Writing- Original draft preparation, Writing- Review and Editing, Visualization; **Sachin Govil:** Conceptualization, Writing- Original draft preparation, Writing- Review and Editing; **James C. Perry:** Conceptualization, Writing- Review and Editing; **Sanjeet Hegde:** Conceptualization, Writing- Review and Editing; **Alistair A. Young:** Conceptualization, Writing- Review and Editing; **Jeffrey H. Omens:** Conceptualization, Writing- Review and Editing; **Andrew D. McCulloch:** Conceptualization, Writing- Review and Editing.

Conflict of Interest Statements

A.D.M. and J.H.O. are co-founders of and have an equity interest in Insilicomed, and A.D.M. has an equity interest in Vektor Medical. A.D.M. and J.H.O. serve on the scientific advisory board of Insilicomed, and A.D.M. as scientific advisor to both companies. Some of their research grants have been identified for conflict of interest management based on the overall scope of the project and its potential benefit to these companies. The authors are required to disclose this relationship in publications acknowledging the grant support; however, the research subject and findings reported in this study did not involve the companies in any way and have no specific relationship with the business activities or scientific interests of either company. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies. A.A.Y. has provided consultancy to Siemens Healthineers, Erlangen, Germany.

Keywords

cardiac magnetic resonance; statistical shape atlases; congenital heart disease; translational medicine; cardiovascular medicine

I. Introduction

The wide-scale availability of large, heterogeneous patient datasets brings new opportunities and challenges to addressing complex problems in clinical medicine. In the field of cardiology, advances in cardiovascular imaging have the potential to enable more quantitative approaches to diagnosis, surgical planning and medical therapies, but much of the information in clinical cardiac imaging data goes under-utilized by routine clinical image assessment methods. In diagnostics, cardiac magnetic resonance (CMR) imaging is not routine in acquired heart diseases but is common in congenital heart disease (CHD), where patients are often very young and repeated exposure to ionizing radiation is contraindicated. Improved availability of clinical datasets for research is accelerating the intersection of medicine and computational science, fostering collaborations within and between the biomedical science, computational science, and clinical communities. Anecdotal and empirical clinical practice is evolving towards evidence-based precision medicine. New innovations and discoveries arising from interdisciplinary collaborations on research that aims to translate from bench to bedside involve technical, regulatory, and ethical hurdles. In this article, we discuss the breadth of clinical challenges, research strategies, processes, and impact of translational computational science in the context of clinical management in CHD.

II. Background

Clinical management of CHD, characterized by the presence of cardiac malformations at birth, has transformed greatly over the past few decades. Clinical innovations for complex CHD over several decades have resulted in a shift to more definitive treatment strategies that have increased early survival rates and extended life expectancy into adulthood. Complete surgical repair of complex cardiac malformations in diseases such as tetralogy of Fallot (TOF) has resulted in twenty-five-year survival of upwards of 95% [35]. In spite of the abundance of successful outcomes after complete repair, patients with TOF are commonly burdened with chronic pulmonary valve insufficiency and right ventricle (RV) volume overload owing to residual structural and electromechanical malformations [36]. Interventions such as pulmonary valve replacement (PVR) can help alleviate pulmonary insufficiency, but surgical procedures carry risk, and long-term outcomes after PVR remain inconsistent [4,15,30,39]. To closely monitor the long-term sequelae in TOF, clinical management depends on the routine use of non-invasive medical imaging, including echocardiography and CMR [18]. Imaging enables the quantitative assessment of regional and global cardiac structure and function, and with its greater accessibility and use in practice, measurable indices with prognostic value have been derived and used to assess adverse remodeling of the heart and guide therapy [19,22].

In spite of the wealth of information available from a single CMR image dataset, its value towards clinical decision-making has limitations. Assessment of medical image data requires specialized technical personnel, accurate and reliable software to analyze images, and time to perform the analysis and interpret the results. Additionally, current standards for the quantitative assessment of cardiac structure and function have been under-utilized for prognostic purposes. It is clear that clinical practice surrounding the treatment and management of CHD could benefit from the translation of computational tools that: 1) accelerate the process of extracting relevant information from image data; 2) condense complex cardiac features into interpretable and quantifiable measures; and 3) provide new insight into disease mechanisms and clinical outcome predictors.

Various computational techniques exist to extract three-dimensional (3D) measurements of cardiac anatomy and morphology from medical images commonly by image segmentation. These techniques can be entirely manual, requiring a human analyst to trace features of interest from a set of images, semi-automated, such as guide-point modeling, or entirely automated, such as via deep learning-based algorithms. Fully manual techniques are time-consuming but can be highly accurate depending on the training of the analyst, whereas fully automated techniques are faster but are prone to error depending on the training of the algorithm. Compared with fully automated techniques, manual or semi-automated segmentation methods often require significant local expert knowledge to achieve an acceptable accuracy; in clinical practice, this translates to extra costs and time. In contrast, once a reliable automated algorithm has been trained and validated, its use can support local expertise and can be scaled up for widespread deployment.

CMR imaging is highly suitable for quantitative cardiac analysis and many advances in semi-automated and fully automated segmentation have been based on data from this imaging modality due to its widespread use [17]. Previously, semi-automated techniques such as guide-point modeling relied on the interactive placement of “guide-points” to anatomical landmarks or features of an image to constrain the alignment of a 3D model to a patient-specific anatomy [40]. More recent efforts have focused on cardiac image segmentation using deep learning, enabled by more advanced computer hardware and the increased availability of training data. Deep learning-based models typically use artificial neural networks (e.g., CNNs, FCNs, Unets, and RNNs) to develop a general-purpose learning procedure in end-to-end fashion [10]. However, the accuracy and reliability of deep learning models is contingent on access to a large image dataset that is representative of the clinical cohort of interest. Rigorous validation methods are essential for the translation of machine learning for cardiac image analysis into clinical practice, and significant coordinated effort has been made. For example, Bhuva *et al.* [8] compared the precision of machine learning and humans across multiple diseases, institutions, scanner manufacturers, and scanner types. Additionally, while automated and semi-automated segmentation methods have already reached clinical CMR analysis software programs, validation is still in-progress for anatomically challenging regions of the heart, such as the RV and atria, but recent studies have made strong advances [3,5,31]. These segmentation methods are even more limited in the analysis of complex CHD anatomies, such as dextro-transposition of the great arteries where the RV is the system ventricle. Development of large databases of both anatomically normal and abnormal hearts will help solve these challenges

by providing training and validation data for deep learning models. Segmentation and analysis methods have been successfully developed using large pre-clinical epidemiological studies including the Multi-Ethnic Study of Atherosclerosis and the UK Biobank [20,28]. In order to translate these methods to specific clinical cohorts, some adaptation and retraining is required to cope with the altered geometry and function seen in CHD patients.

Large enough collections of cardiac image segmentations can be used to generate statistical atlases of morphological and functional variations within a population using unsupervised machine learning methods such as principal component analysis (PCA). PCA, when used on anatomically co-registered models of cardiac shape, can reduce thousands of input variables into a much smaller set by decomposing the variability of the data into a set of orthogonal components ranked by the amount of variance explained. As a result, a collection of models from a patient population is characterized by a reduced set of orthogonal components and their associated variance. In turn, each patient's cardiac shape can be represented by a condensed set of measures (e.g., Z-scores) that each quantify the distance from the population mean and individually represent the variation of hundreds of input variables. This process has advantages from a clinical, technical, and physiological perspective: the simplification of complex, multi-dimensional data from CMR images into interpretable features allows for more quantitative assessment of potentially important markers of patient status and outcomes while providing qualitative representations of biological phenomena that may contain mechanistic insight. Furthermore, patient-specific measures derived from statistical atlases of cardiac structure and function allow for inter- and intra-cohort comparisons that can assess how abnormal an individual is relative to a healthy population and any differences from patients with the same disease and similar interventions. Technically, databases can be composed of much smaller files with numeric data type rather than hundreds to thousands of gigabytes of image data.

Patient-specific metrics quantified from statistical cardiac atlases can also be used to discriminate other relevant clinical factors, such as global ventricular function, specific disease phenotypes, and differences in treatment strategies using unsupervised learning algorithms, including K-means clustering and partial least squares regression (see Figure 1 for an overview). These analyses can provide the foundation by which new hypotheses are generated and can be used to discover valuable predictors of clinical outcomes that can be validated using supervised learning methods, such as regularized kernel learning algorithms [33,34]. All of the aforementioned machine learning tools can be easily implemented using Python bindings to well-known machine learning libraries, e.g. Tensorflow (https://www.tensorflow.org) and PyTorch (https://pytorch.org). In practice, cardiac atlases of ventricular geometry have been used in healthy, CHD, and cardiovascular disease populations to associate shape and structure with cardiovascular risk factors [2,13,20,27,28]. In studies of TOF, statistical atlases have been used to investigate the 3D shape of the RV and predict ventricular remodeling [23,25].

The statistical atlas-based approach is just one of many being undertaken in the field of computational cardiac modeling. Multi-scale models of biomechanics and electrophysiology can build on the information gained from statistical atlases to further test for relationships between observable features of cardiac structure and function from imaging and intrinsic

myocardial material properties and electrical activation patterns, which can otherwise only be measured invasively [21]. This analysis enables the exploration of the mechanisms that give rise to differences in patient outcomes that are either resultant or independent from easily measurable markers. The “Your Personal Virtual Fleart” project takes another approach that aims to employ patient-specific computational models rather than population-based models to improve ventricular tachycardia risk stratification in TOF patients via simulated electrophysiological pacing studies [32,37]. Others are modeling the great vessels and adjacent vasculature rather than the heart itself using computational fluid dynamics with fluid-structure interactions to quantify how hemodynamics are altered as a result of surgical interventions, such as a Fontan procedure or placement of a shunt, in a variety of CHD patient cohorts [26]. These models are made with the open-source software package SimVascular, which provides a complete pipeline from image segmentation to patient-specific blood flow simulation and analysis [38]. Strategies such as the “digital twin” that synergize mechanistic and statistical approaches have the potential to accelerate the translation of discovery to precision medicine in the clinic [11].

III. Translation Process

An overview of the translation process in cardiovascular medicine is shown in Figure 2. Data acquisition and hosting are at the core of computational research and have several additional requirements in the context of translational medicine. These requirements primarily involve the security and privacy of any collected human subject data, e.g. medical images, medical reports, lab reports, and omics data. The Health Insurance Portability and Accountability Act (HIPAA) maintains that all patient data must be anonymized such that original patient data is unlinked to data presented in research. Accomplishing this requires significant resources particularly when accounting for the numerous data types involved, each of which have their own data format and associated metadata that may also vary between medical institutions [1,9]. Additionally, re-identification of patient data may be necessary to relate any discoveries back to the patient, which poses its own challenges [6]. There are several publicly available tools to remove identifying information from patient datasets (e.g., electronic medical records) such as Google’s Cloud Healthcare API (https://cloud.google.com) and the Anonymization toward De-identification (deid) Python module (https://pypi.org); however, the lack of a single tool endorsed at the community level makes it difficult to maintain a consistent standard for anonymization between research groups and clinical institutions around the world. In addition to data acquisition, several cloud-based platforms with HIPAA-compliant, data-sharing capabilities and collaborative code generation are being developed to accelerate the discovery and dissemination of landmark findings from computational studies. Platforms such as iDASH (integrating data for analysis, anonymization, and sharing), previously supported by the NIH National Center for Biomedical Computing, aim to provide computational biomedical researchers access to data, software, and a high-performance computing environment for studies that focus on various health conditions spanning multiscale biology [29]. Another such platform funded by the American Heart Association Precision Medicine Platform is the Cardiac Atlas Project (https://www.cardiacatlas.org), which is a large-scale database of cardiac images and associated clinical data that facilitates collaborative statistical analysis of regional

heart shape and wall motion for normal and pathological patient populations [14]. The Cardiac Atlas Project database also promotes public standards for data anonymization by providing tools for de-identification of DICOM, the standard file format of medical images. Merging data repositories and tools for CMR image analysis, cloud-based platform Arterys allows for rapid analysis of image data using advanced computational algorithms. Using the cloud-based platform and computing resources, clinicians are able to quantitatively analyze four-dimensional blood flow in approximately ten minutes (https://arterys.com). In order to establish these digital platforms, privacy-protecting analytics and secure data-sharing methods must be implemented such that all data contributed and accessed have a minimal risk of disclosure of sensitive information. One of the biggest limitations in scaling up these endeavors, however, is that all collaborating institutions have to ensure that any contributed or accessed data is approved by each local IRB and other institutional guidelines, and conforms to the standards set by the platform.

Successful implementation of new initiatives for knowledge discovery and datadriven decision-making inevitably improves the clinical understanding of disease outcomes and associated risk factors while also illuminating the mechanisms of disease progression. Altogether, these platforms contribute to precision medicine, an approach that relies on scientifically-derived biomarkers via machine learning techniques applied to large-scale datasets, rather than classical diagnostic markers. The integration of these platforms and associated workflows in the clinic, however, is a more complicated endeavor. Typically, big-data population studies in translational computational science are conducted with retrospective data, often resulting in heterogeneous datasets. While any novel discoveries or insights from these studies may be scientifically validated, they need to be clinically validated through prospective clinical studies to ensure that patient outcomes are significantly improved. Consenting and enrolling patients at scale to assess the effectiveness of novel biomarkers requires significant resources both in time, as the follow-up time period for these patients could be several years, and funding, to cover the costs of intermittent exams during this period [7,12]. After demonstrating success in small clinical studies, these software-based workflows may be subject to FDA approval via the Software as a Medical Device (SaMD) pathway prior to widespread use (https://www.fda.gov). Only after passing all of these regulatory hurdles can the discoveries and insights from these platforms be integrated with clinical workflows and hospital-side technologies, such as the electronic medical record and PACS (photo archiving and communication system) information systems. This integration will also require significant community effort in order to ensure that distributed systems are able to interact with each other efficiently while maintaining HIPAA-compliance. The effort will also require the development of extensive documentation and training seminars to educate clinicians on how to use platform tools, interpret results, and communicate results back to patients in a comprehensible way.

IV. Impacts and Lessons Learned

The impact of this work on the fields of biomedical engineering and computational sciences is traditionally measured by the number of high-impact publications, adoption of methods by other research groups and institutions, and the securing of funding by national agencies to continue improving the technology towards shareable industry standards [16]. In the context

of translational medicine, however, there are additional ways to measure impact that are clinically motivated, including impact on patient management and outcomes, changes to the gold standard of care, and widespread adoption of these tools and techniques across hospital networks [24]. In the case of platform technologies such as Arterys and the Cardiac Atlas Project, impact can also be measured by overall size of the data repositories, the number and variety of data contributors and users, and the robustness of software-based tools and documentation.

One of the main challenges when it comes to performing translational research is that its two primary components – the development of technology in the lab and the implementation of that technology in the locale – are often considered in isolation rather than as a single, complete strategy. Typically, scientific funding sources for the development of technology is provided to answer important questions with novel approaches, while funding for its implementation and continual support is typically left out. This is partially influenced by the difference in timelines and incentives of these two components of translational computational science. The timeline for technology development is often much shorter and has a more immediate observed impact by way of publications and conferencing within the scientific community. The timeline for the implementation of the technology, however, can take much longer and requires significantly more resources for expansion and continual support, such as web-based hosting fees in the case of platform technologies. Furthermore, the measurable impact on health and healthcare is far more drawn out considering the regulatory hurdles that have to be crossed prior to adoption at the bedside. One way to encourage the implementation of a technology alongside its development with the potential to generate sustainable revenue is by funding agencies prioritizing research projects that have a high potential to generate and protect intellectual property, such as via patenting, and ensure that the funding agency retains exclusive licensing rights to the technology. In this manner, the successful implementation of the technology in a healthcare system can be financially sustainable and has potential to generate revenue for supporting similar endeavors. The key to the success of this approach is an emphasis on observed impact both scientifically and medically.

V. Conclusions

The emergence of translational computational science in the field of cardiology can transform clinical decision-making. Computational modeling of individual or population-wide cardiac structure and function has allowed us to capture more relevant and quantifiable information from routinely-collected health data that is normally unrecognized. While technological and scientific validation is ubiquitous in the laboratory, significant resources and effort are required to interface new technology within the medical community, gain acceptance, and integrate with clinical practice. Research planning with a clear strategy and pathway to translation can help focus efforts across scientific and medical communities towards the common goal of redirecting and improving medical practice.

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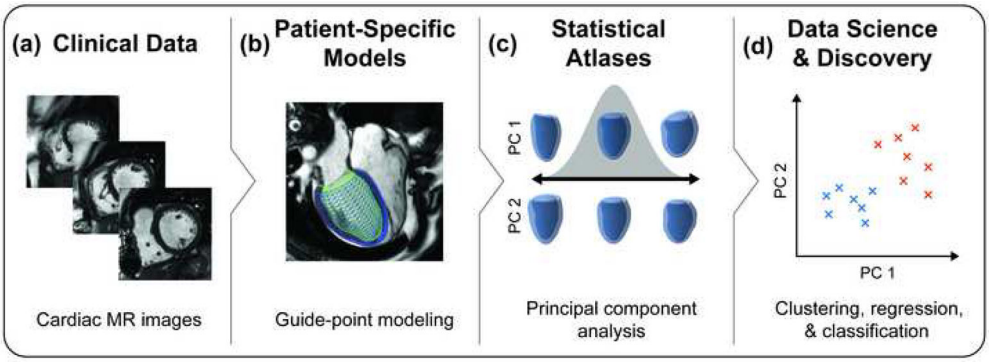

Figure 1.

Overview of the process of discovering novel predictors of clinical outcome from routinely acquired image data. (a) Cardiac MRI datasets are used to generate (b) patient-specific models of ventricular shape and function via guide-point modeling or automated image segmentation techniques. (c) Principal component analysis can be used to quantify the statistical variation of cardiac shape in a patient population and derive novel markers of remodeling. (d) Machine learning methods can be used to discover associations of atlas-derived markers with patient outcomes and support clinical decision-making. MR, magnetic resonance.

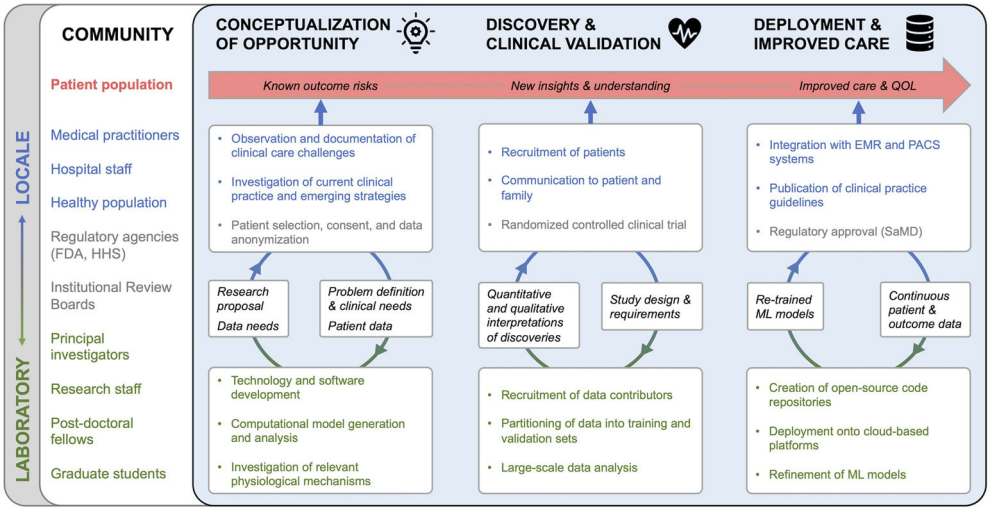

Figure 2.

Translational process of computational cardiology highlighting the interplay between the laboratory (e.g., research facility and computing resources) and the locale (point of care). EMR, electronic medical record; PACS, picture archiving and communication system; SaMD, Software as a Medical Device; ML, machine learning.