Virtual Clinical Trials for the Assessment of Novel Breast Screening Modalities

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Abstract. Validation of any imaging system is challenging due to the huge number of system parameters that should be evaluated. The ultimate metric of system performance is a clinical trial. However, the use of clinical trials is limited by cost and duration. We are strong proponents of a preclinical alternative, in the form of Virtual Clinical Trials (VCT), which model human anatomy, image acquisition, display and processing, and image analysis and interpretation. A complete VCT pipeline was envisioned by combining the breast anatomy and image acquisition simulation pipeline developed at the University of Pennsylvania, with the MeVIC image display and observation pipeline developed by researchers at Barco. Today an integrated virtual clinical trial design program, *VCTdesigner*, and a virtual clinical trial management program, *VCTmanager*, are freely available (www.VCTworld.org). The pipeline design is flexible and extensible, making it possible to add functionality easily and rapidly. It is our hope that by freely distributing the VCTmanager software, our field can standardize on this platform for running VCT.

Keywords: Virtual clinical trials, observer models, anatomy models, imaging simulations, breast cancer, imaging.

1 Introduction

Validation of any imaging system is challenging due to the huge number of system parameters that should be evaluated. The ultimate metric of system performance is a clinical trial. However, the use of clinical trials is limited by cost and duration. In addition, trials involving ionizing radiation require repeated irradiation of volunteers, which may be impractical. In particular, breast-screening trials have a low incidence of disease; therefore, radiation must be used judiciously. We are, therefore, strong proponents of a preclinical alternative, in the form of *Virtual Clinical Trials* (VCT), which model human anatomy, image acquisition, display and processing, and image analysis and interpretation.

We coined the phrase "Virtual Clinical Trials" in 2009, in anticipation of the growing abilities of anatomy and imaging system simulations, together with innovations in observer models. A complete VCT pipeline (Fig. 1) was envisioned by combining the breast anatomy and image acquisition simulation pipeline developed at the University of Pennsylvania, with the MeVIC image display and observation pipeline developed

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by researchers at Barco, Inc. Today an integrated virtual clinical trial design program, *VCTdesigner*, and a virtual clinical trial management program, *VCTmanager*, are freely available (www.VCTworld.org).

We believe that VCTs have at least two significant roles: quantitative and objective assessment of system performance in the design of novel imaging methods; and, validation of clinical trial designs prior to execution of real clinical trials. Traditionally, novel imaging methods (whether acquisition systems, display systems or image processing solutions) are evaluated with simple test objects (uniform fields, edges, etc.) and limited clinical data sets. Similarly, clinical trials are restricted to volunteers meeting specific entry criteria, such as age or absence of prior disease, to simplify study design and data analysis. These traditional evaluation methods provide tractable results that allow one to grade or rank systems in terms of superiority *vis-a-vis* that specific test or that particular patient group; however, these tests do not necessarily predict clinical performance in the full clinical population.

By contrast, a VCT is cast in terms of close surrogates of real clinical tasks, such as the detection or classification of calcifications or masses in the breast, or the estimation of breast density or parenchymal properties. Thus, it is expected that rankings obtained by a VCT would closely match clinical performance. We also expect that results of a VCT can act as a guide for the design of actual clinical trials, by allowing clinical researchers to simulate various trial designs *a priori* and to calculate the effect and power more accurately when designing clinical trials. VCTs can also extend the results of a clinical trial by simulating patients otherwise excluded (e.g., detection of multifocal disease in women with surgical clips).

While we have concentrated, to date, on VCT for x-ray imaging of the breast, the methods presented here are general and thus are applicable to imaging other body parts with a variety of image modalities. In addition, while we explicitly discuss the use of observer models as surrogates for human observers, it is also relevant to consider VCT for quantitative measurement systems, such as computer-aided diagnosis (CAD) systems and systems designed to estimate breast density or breast cancer risk.

2 VCTworld

The *VCTmanager* simulation pipeline is implemented in an extensible C++ and OpenCL software platform. The structure of the pipeline is illustrated in Fig. 1. Synthetic breast images are generated using the breast anatomy and imaging simulation methods developed at the University of Pennsylvania (UPenn) over the last two decades [1-5]. Normal breast anatomy is simulated with a recursive partitioning algorithm using octrees [5]. Lesions can be included automatically based upon a configurable set of rules [6]. Phantom deformation due to clinical breast positioning and compression is simulated using a finite element (FE) model and rapid post-FE software [7]. DBT image acquisition is currently simulated by ray tracing projections through the phantoms, assuming a polyenergetic x-ray beam without scatter, and an ideal detector model. Processed or reconstructed images are obtained using the Real-Time Tomography, LLC (RTT) image reconstruction and processing software [8]. Other imaging modalities are

also supported, although not yet fully integrated, including dedicated breast CT, magnetic resonance imaging, and ultrasound imaging.

The display and virtual observer simulation is based upon MeVIC (Medical Virtual Imaging Chain) [9-11] developed at Barco. Datasets (volumes of interest) of projection images or tomographic image stacks, with and without simulated lesions, are input to the display and virtual observer portion of the simulation pipeline. Each stack is first decomposed into spatiotemporal frequency components using a 3D fast Fourier transform (FFT). Various elements of the human visual system (HVS) are simulated in the Fourier domain. Then, a 3D inverse FFT is applied to the perceived amplitudes to transform the perceived image(s) back into the space-time domain. Finally, the results are input to a multi-slice channelized Hotelling observer (msCHO) developed by Platiša *et al* [12]. Further details of the simulation have been provided previously [11].

The simulation modules in the pipeline are interconnected using an XML-based dynamic parsimonious data representation, offering a high level of control for the simulations. The data are structured at two levels. At a high-level, the clinical trial is defined in terms of the research arms (e.g., defining the modalities or modality parameters to be tested, and the patient population). At the next level, *virtual patient* or *virtual imaging study* data are defined that parallel the DICOM metadata for an equivalent imaging procedure on the system(s) being simulated together with such demographic data as can be simulated. For example, this information can include a unique name and numerical identifier; study information such as modality, date and time; series and image information including acquisition parameters and desired display state (for presentation/for processing); and demographic data including breast size, breast density, etc. These data both guide the simulation and serve as the source of the DICOM metadata for the image files that are created.

An example of the simulation is shown in Fig. 2. A single slice from the breast anatomy model containing a calcification cluster is shown in Fig. 2A. The actual model consists of a 450 mL breast compressed to 5 cm with isotropic voxels of dimension (200 μm) [3]. The choice of voxel size is modality and task dependent. Each voxel is assigned a unique tissue type (adipose, fibroglandular, calcification, etc.) that is indicated by the grayscale in the figure. A projection mammogram is shown in Fig. 2B, simulating a Selenia Dimensions (Hologic, Bedford MA) 2D acquisition, and processed with Adara™ (RTT, Villanova PA). A magnified region is inset. Finally, a tomosynthesis reconstruction in shown in Fig 2C, simulated with a 3D Selenia Dimensions acquisition geometry, and reconstructed with Briona™ (RTT).

Trial design is performed using the matching *VCTdesigner* software. At the current time, we use simulations of full calcification clusters and complex breast masses for human observer trials; while for the virtual clinical trials, we typically simulate a single calcification or a simple mass. Typical VCT trials can involve 3,000-30,000 image datasets per condition, depending upon the desired statistics. The vast majority of the *VCTworld* software is optimized to run on the GPU allowing us to simulate a single image (breast generation through observer simulation) in less than a minute, and thus simulate complete VCT in less than a day.

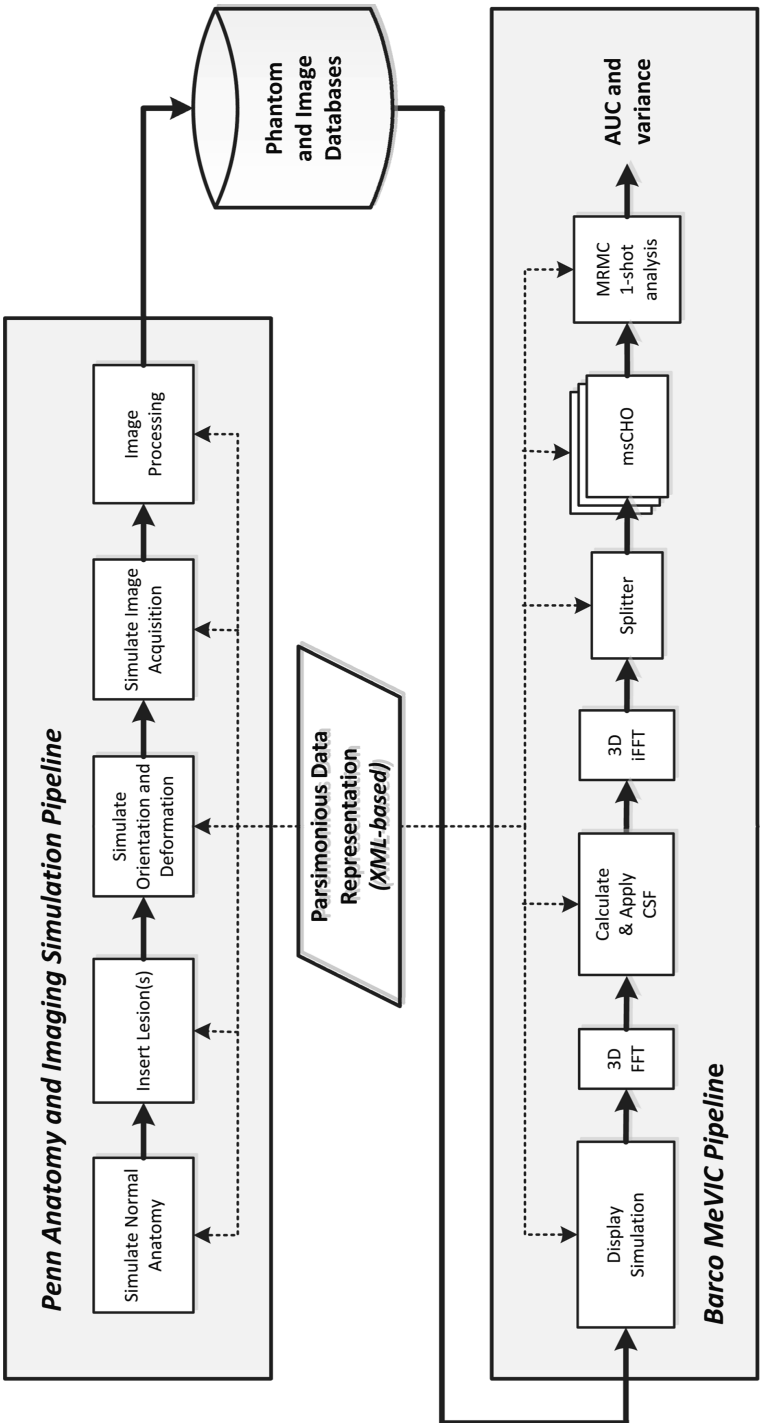

Fig. 1. Flow chart of the VCTmanager pipeline for simulation of breast anatomy, image acquisition, display and observation

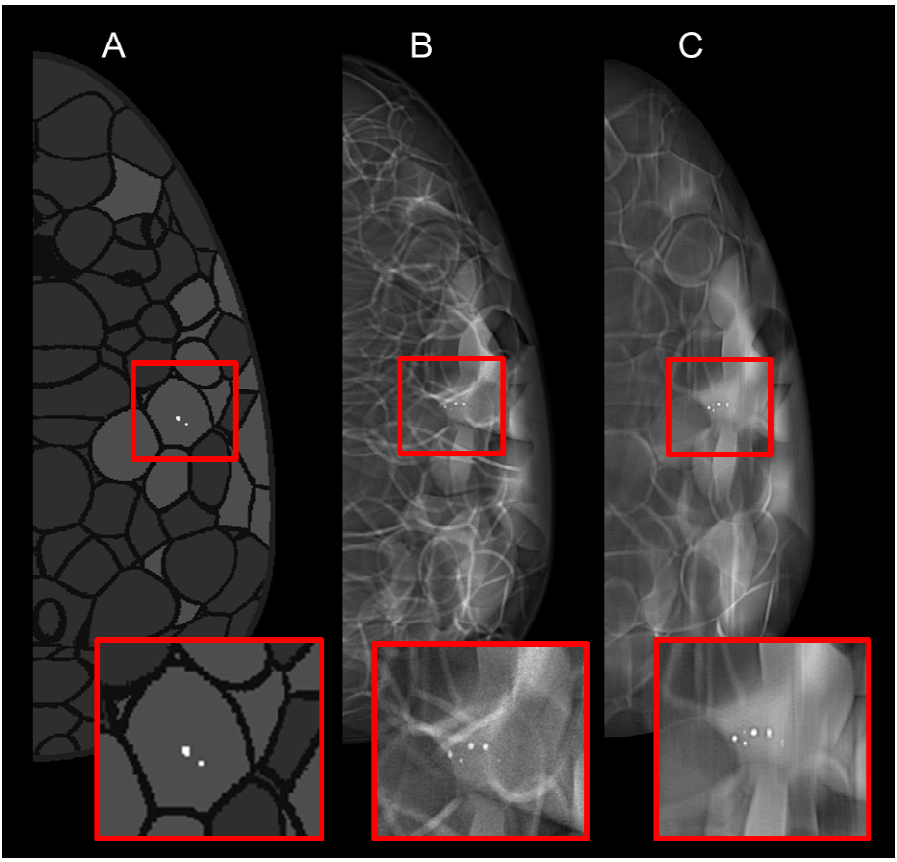

Fig. 2. Example of a breast model with calcifications in cross-section (A), together with the resulting mammogram (B), and DBT slice (C). A magnified image is inset

3 VCT Validation

It is essential that all VCT software be extensively validated. Without such validation, the results are unlikely to have clinical value. The vast majority of our efforts in the last two decades have been on validating our VCT pipeline and constituent software. We have two basic validation approaches. First, we attempt to validate the simulation results against the task being tested. For example, in early testing of our anatomy simulation, we compared texture measures of our simulated images against similar measures of clinical mammograms [1]. In this evaluation, we determined whether the distribution of texture values of an individual simulated breast was consistent with that of a real breast, and whether the distribution of the set of all simulated breasts matched a large set of real breasts. In this way, we concluded that we were able to simulate virtually any breast that might be seen clinically.

The VCT pipeline has been validated for a variety of applications, including the validation and optimization of digital breast tomosynthesis (DBT) reconstruction methods [13-15], DBT image denoising methods [16], ultrasound tomography (UST) reconstruction and segmentation methods [17], analysis of power spectra descriptors in simulated phantom DBT images [18], analysis of texture properties in digital mammography (DM) and DBT images [19, 20], analysis of tumor detectability in DBT [21, 22], and breast imaging dosimetry [23].

Next, once we develop a validation method, we attempt to automate the process. This allows for *regression testing* of future software generations. Given the complexity of the simulation software, regression testing allows us to determine whether prospective changes to the software alter the fundamental operation of the pipeline. These tests are hierarchical, allowing testing from individual components to the entire pipeline. As functionality is added to the pipeline, more extensive testing with human observers or machine observers is periodically necessary; when applicable, these new tests are added to the regression test set.

Finally, physical versions of the 3D anthropomorphic phantom have also been produced and used to validate various applications [24, 25]. This phantom provides the ultimate validation of the acquisition simulation method, as it is possible to compare the simulated and real images of the phantom directly. The addition of simulated lesions to the phantom provide further opportunities for validation, as it is then possible to compare human and machine detection directly.

4 The Future of VCTs

In the last five years, the term "Virtual Clinical Trials" has entered into routine use in our field. There is substantial research on the topic, both by our collaborators and by other labs. It is our hope that by freely distributing the *VCTworld* software, our field can standardize on this platform for running VCT. The pipeline design is flexible and extensible, making it possible to add functionality easily and rapidly.

There is an increasing demand for features, as the use of VCTs increase. We need to create models with increased realism and of all body parts, to extend the use of VCT. Similarly, we need observer models that better match human observers in terms of the tasks that are to be evaluated. Observer models that involve search and models that can detect complex lesions are required; for example, support of calcification clusters having a variety of sizes and numbers of calcifications, or models that can detect masses with a variety of shapes and sizes, or models that can detect lesions with both calcifications and masses. Ultimately, we will need to create general observers; observers that can read medical images of any body part or disease.

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