Article:
Ruddle, RA, Thomas, RG, Randell, R orcid.org/0000-0002-5856-4912 et al. (2 more authors) (2016) The design and evaluation of interfaces for navigating gigapixel images in digital pathology. ACM Transactions on Computer-Human Interaction, 23 (1). 5. ISSN 1073-0516

https://doi.org/10.1145/2834117

The Design and Evaluation of Interfaces for Navigating Gigapixel Images in Digital Pathology

ROY RUDDLE, School of Computing, University of Leeds, UK
RHYS G. THOMAS, School of Computing, University of Leeds, UK
REBECCA RANDELL, School of Healthcare, University of Leeds, UK
PHILIP QUIRKE, Leeds Institute of Cancer and Pathology, University of Leeds, UK
DARREN TREANOR, St James' University Hospital, Leeds, UK, and Leeds Institute of Cancer and Pathology, University of Leeds, UK

This paper describes the design and evaluation of two generations of an interface for navigating datasets of gigapixel images that pathologists use to diagnose cancer. The interface design is innovative because users panned with an overview:detail view scale difference that was up to 57 times larger than established guidelines, and 1 million pixel 'thumbnail' overviews that leveraged the real-estate of high resolution workstation displays. The research involved experts performing real work (pathologists diagnosing cancer), using datasets that were up to 3150 times larger than those used in previous studies that involved navigating images. The evaluation provides evidence about the effectiveness of the interfaces, and characterizes how experts navigate gigapixel images when performing real work. Similar interfaces could be adopted in applications that use other types of high-resolution images (e.g., remote sensing or high-throughput microscopy).

• Interaction design →Interaction design process and methods– Participatory design • Human computer interaction (HCI)→ Empirical studies in HCI • Visualization →Visualization systems and tools.

Additional Key Words and Phrases: Gigapixel images, navigation, pathology, overview+detail, zoomable user interface

ACM Reference Format:

1. INTRODUCTION

In many disciplines, people need to navigate large visualizations to analyze data. Examples include telecommunications and social networks, genomics data where scientists look for mutation patterns in DNA, geographic information systems, and images used in the earth sciences and medicine. A number of styles of user interface have been developed for the navigation of such data [Cockburn et al. 2008], with the most common one often being termed a 'Google Maps interface' (the classic version; Google have since changed their interface). The interface is characterized by twin views showing detail and a smaller-scale overview ('overview+detail'), and allowing users to change the scale of both views by zooming (a zoomable user interface; ZUI [Perlin and Fox 1993]). The overview typically occupies only a small amount of a display, leading to the term 'thumbnail' overview.

Our work focuses on systems for navigating large 2D images, specifically in the medical domain of pathology. Pathologists diagnose diseases such as cancer by

This work is supported by ...

Author's addresses: ....

DOI:http://dx.doi.org/10.1145/0000000.0000000

examining thin sections of tissue under a microscope typically at 25–400× magnification (*note*: this is the true magnification, achieved by combining a 10× eyepiece with objective lenses ranging from 2.5× to 40×; we use the true magnification throughout the present paper). Scanned at 100,000 dots/inch to show diagnostic detail, virtual (digital) slides are several gigapixels in size. However, averaged over a set of case types, diagnosis takes 60% longer with a virtual slide than a conventional microscope [Treanor and Quirke 2007], because the overview+detail interface that commercial virtual slide systems provide is poorly suited to navigating gigapixel images. This negates key advantages of virtual slides (e.g., the ease of obtaining second opinions, which is routine practice for certain cases, and retrieving archived material for comparison) and has impeded the clinical adoption of whole slide imaging technology.

The overall aim of our research is to develop a desktop virtual microscope that allows pathologists to make diagnoses from virtual slides as quickly as they can when examining glass slides with a conventional microscope. It should be noted that diagnosis is overwhelmingly made by human experts – automated diagnosis is currently limited to very specific circumstances [Al-Janabi et al. 2012]. The evaluation of the virtual microscope from a clinical perspective is documented elsewhere [Randell et al. 2013; Randell et al. 2014]. The present article describes the design of novel user interfaces for the navigation of gigapixel images, and evaluations that provide detailed information about how the interfaces were used. Section 4 describes the interface that was designed for the navigation of single gigapixel images, and Section 5 describes the interface for navigating collections of gigapixel images.

The primary contributions of the article are a detailed evaluation of interfaces for navigating individual gigapixel images and collections of such images, and a description of the choices that were made during an iterative design process. The work stands out from previous research because both the design and evaluation involved experts performing real work (pathologists diagnosing cancer), and the images were orders of magnitude larger than those used in previous studies of navigation. The interfaces exploit high-resolution displays (≈10 million pixels) and a gigantic 'thumbnail' overview, and far exceed existing design guidelines for the overview : detail view scale differences [Plaisant et al. 1995; Shneiderman 1998].

2. RELATED WORK

In this section we review approaches to the design of navigation interfaces, interaction techniques and devices that may be used, and interfaces for navigating collections of images rather than just individual images.

2.1 Approaches to Navigation

Four main approaches are used to create navigation interfaces for computer applications: focus+context, zooming, overview+detail, and cue-based. This section summarizes the characteristics of each approach (for a detailed review, see [Cockburn et al. 2008]) and the circumstances under which it is known to be beneficial.

2.1.1. Focus+context. Focus+context interfaces are analogous to inspecting a physical object with a magnifying glass, because users manipulate a magnified (focus) view that is embedded within a view of the whole of an environment to provide context (for a review, see [Tominski et al. 2014]). The focus view has a scale that changes from the center to the edge, so that the overall view is seamless, but the

difference between the maximum and minimum scales is generally modest (e.g., a factor of 12–27 [Appert et al. 2010; Carpendale et al. 2004]).

Research has investigated the design and evaluation of focus+context interfaces for a variety of types of data, including menus, networks and images. For example, with menus participants preferred a focus+context view to a conventional view when browsing but not for goal-directed tasks [Bederson 2000], and participants were significantly faster browsing tree networks to answer questions with a focus+context than a conventional (Windows Explorer-style) file browser [Pirolli et al. 2003]. Some research has aimed to develop versions of focus+context that improve on others (e.g., [Appert et al. 2010]), backed by the implicit assumption that focus+context is superior to non-distorted approaches to navigation (i.e., zooming, and overview+detail). In fact, the parameters used to configure a focus+context interface have to be chosen carefully for a given dataset if users are to navigate faster than with an overview+detail interface [Rooney and Ruddle 2012].

Focus+context has been popularized by the Mac OS X Dock interface for switching between applications, and is provided as a 'magnifier' in the ImageScope virtual slide system to temporarily boost the magnification of a small region of tissue. The primary advantages of focus+context are its aesthetic appeal and that users only have to pan in one view, but the inherently distorted view impedes users' ability to return to parts of a dataset that they have previously viewed [Skopik and Gutwin 2005]. This is one reason to rule out focus+context as the primary navigation approach with virtual slides, because comparing and re-inspecting specific features on a slide is core to the diagnostic process. A second reason is the large size of pathology images, which would necessitate a much larger scale difference than has proved practical with focus+context [Shneiderman 1998].

2.1.2. Zooming. Pure zooming interfaces, like focus+context, present users with a single view of a dataset. However, this view is non-distorted, so the amount of a dataset that is shown depends on the zoom factor at a given moment in time. Users navigate by panning and zooming, either mentally keeping track of their position within the dataset or zooming out to see it.

Zooming interfaces are widely used, and have become the de-facto standard way of navigating on mobile phone and tablet applications, for viewing web pages, documents, photographs, and so forth. Zooming is also the way that pathologists navigate when they use a conventional microscope to inspect physical biopsies on glass slides, although it is worth noting that zooming involves changing fixed magnification lenses and refocusing (this takes approximately 3 s) so pathologists primarily navigate by panning.

The primary advantage of a zoomable interface stems from its simplicity. Users only need to attend to one view, with three controls (panning in XY and zooming), and it is straightforward to design an efficient systems architecture that allows just the visible region to be downloaded at the level of detail that is required and rendered on a display. This is the type of architecture that underpins flight simulators and Google Maps.

The disadvantage of a zoomable interface is that if users need to inspect or compare many different parts of the data then users have to first zoom out until a given part is included within the view, and then pan/zoom in again to inspect the part [Guiard and Beaudouin-Lafon 2004; Guiard et al. 2004], a phenomenon termed *screen thrashing* [Ruddle et al. 2013]. Even if navigation is smooth, with each view rendered in real-time, a substantial *cognitive lag* is introduced by the many panning/zooming actions that users need to make to navigate between items of

interest. That lag, the time delay between users being able to see one item of interest and the next, slows down users' analysis and impedes their ability to comprehend patterns.

2.1.3. Overview+detail. Overview+detail interfaces have two (or more) views, each showing a dataset at a different scale. Normally most of a display is devoted to the detail view so that as much as possible of the dataset is shown magnified. Tools such as DragMag have taken the opposite approach and embedded a small detail view within a larger overview [Ware and Lewis 1995], but that is not suitable for our application because to examine cellular populations pathologists sometimes need to review large amounts of tissue.

From a theoretical perspective, a key distinction is made according to whether the overview shows the data in a *world reference frame* (WRF) or an *ego-centered reference frame* (ERF) [Wickens and Prevett 1995], with both reference frames having position and orientation components. For position, a WRF shows the whole dataset whereas an ERF shows a subset of the data that surround a user, configurations that are sometimes referred to as a *global map* and a *local map*, respectively [Ruddle et al. 1999]. A WRF has a fixed orientation whereas an ERF rotates when a user turns so that the overview is aligned with the dataset, configurations that are termed north-up and forward-up, respectively [Levine et al. 1984]. The optimum reference frame depends on the task that the user is performing, with an ERF superior if the user needs to decide which way to travel next but a WRF superior if the user needs to learn about the environment as a whole [Aretz 1991; Hooper and Coury 1994].

Two key, and interrelated, design decisions concern the *screen-space ratio* and the *scale difference* between the overview and detail view. The screen-space ratio is defined as the proportion of the display area that is occupied by the overview. The larger the overview the more information that it shows (either a given area at a larger scale, or a larger area at a given scale), but the less of the display that is available for the detail view. The scale difference is the scale of the detail view divided by the overview's scale. As the scale difference increases, the overview shows more of a dataset but becomes coarser-grained, which affects a user's ability to identify regions of interest (ROIs) and navigate precisely. It is suggested that additional intermediate views (i.e., local and global maps) are required once the scale difference exceeds 30 [Plaisant et al. 1995; Shneiderman 1998].

Both the screen-space ratio and the scale difference depend on the configuration of a particular system (see Table I). The Google and Bing Maps overviews show the part of the environment that surrounds a user's immediate locality (a local map), which allows the scale difference to be broadly in keeping with guidelines [Plaisant et al. 1995; Shneiderman 1998]. Remote sensing software renders each view into a separate window so users can adjust the size interactively, with some software providing a global map (e.g., ERDAS ER Mapper) and others a local map (e.g., GAMMA).

Table I. View parameters of Web mapping and pathology applications running full-screen on a 1920x1080 pixel display, which is common for PC displays and typical of what is recommended by most virtual slide systems.

Application	**Overview**	**Overview : detail view**	
	Type	**Screen-space ratio**	**Scale difference**
Google Maps	Local	1:101	33
Bing Maps	Local	1:33	16
Aperio ImageScope	Global	1:16	280
Omnyx Pathologist Workstation Philips Pathology Viewing System	Global	1:130	1174

By contrast, commercial pathology virtual slide systems provide a global map overview because it is important for users to be able to see the whole of a slide. Most systems make this overview glass-sized (an overview the same physical size as a glass microscope slide), which causes the scale difference to be extremely large. ImageScope is unusual in that it provides a larger overview, but this still has a scale difference that is an order of magnitude larger than the guidelines. Virtual slide systems also typically provide a 'slide tray' view (so called, because the glass slides for a case are kept together in a physical tray) that lets users select a slide for viewing but is not used for navigation.

Overview+detail is best combined with a zoomable interface for large datasets [Pietriga et al. 2007]. Any zooming is applied to both views, keeping the scale difference constant. The net result is an interface that is moderately efficient but, even when so-called 'optimal' paths are followed [Van Wijk and Nuij 2003], suffers from screen thrashing when users need to navigate between details that are in separate parts of a dataset.

2.1.4. Cue-based. Cue-based interfaces work by signposting ROIs in a dataset, detected either manually or algorithmically. Cue-based interfaces may be combined with any of the other three approaches and are attracting interest for mobile devices (e.g., see [Burigat and Chittaro 2011]).

2.2 Interaction Techniques and Devices

With all of the above approaches to navigation, usability is affected by details of an interface's implementation. Interaction may utilize common desktop devices (e.g., mouse, keyboard or gamepad), more specialized devices (e.g., isometric and isotonic controllers [Zhai and Milgram 1998]), or be device-free (e.g., bodily movement, gestures or touch [Ball et al. 2007; Beaudouin-Lafon et al. 2014; Nancel et al. 2011]). Each has its advantages, and the present research focused on desktop devices because of their easy availability, familiarity to users and effectiveness.

The relationship between physical movements of a device and on-screen movement of a cursor is dictated by the control-display gain [Casiez et al. 2008]. Today's operating systems increase the gain as users move a device faster (pointer acceleration), because this allows faster pointing than with a constant gain (a linear transfer function) [Casiez and Roussel 2011; Casiez et al. 2008]. Less clutching is required with pointer acceleration than a constant gain, and the amount of clutching also decreases with increasing device operating range (e.g., via use of a large mouse pad) and gain [Beaudouin-Lafon et al. 2014; Casiez et al. 2008]. However, there is a limit to the maximum useful gain, which is dictated by device and screen resolution, the precision of a user's physical movements and the size of on-screen targets [Casiez et al. 2008]. If the gain is too high then objects become difficult, and sometimes impossible, to select (the 'quantization problem' [Appert et al. 2010]).

Irrespective of the transfer function, interfaces need to consider whether panning/zooming involve discrete or continuous navigational changes. Discrete changes are typically executed via a button press or touch gesture. For images, discrete navigation is used to jump to a new position (e.g., by clicking on a particular location in an image) and to zoom by fitting an image to the display or making a step-wise change in the magnification (e.g., <ctrl>+ and <ctrl>− in Photoshop) that is equivalent to changing the objective lens on a microscope.

Continuous pans/zooms may have a magnitude that varies directly with movement of a device (this is termed displacement-based control), or depends on time (velocity- and acceleration-based control). Displacement-based control allows rapid, precise movement [Ruddle and Jones 2001] and is commonly found when an image is

panned with a mouse or zoomed with a scroll wheel (e.g., as in Photoshop and Google Maps; NB: with a scroll wheel the displacement is angular). However, panning a large distance increases the need for clutching. Both velocity- and acceleration-based control allow users to pan/zoom large amounts by making small physical movements with a device, at the expense of lower precision. Velocity-based control provides the steering-type navigation that is found in desktop driving simulators and computer games and, with a gamepad device, proved effective for panning/zooming pathology slides on a high-resolution display-wall in a small-group teaching setting [Randell et al. 2012].

The dragging action that is the de facto standard for panning tablet and phone displays provides hybrid control, because slow pans are displacement-based and faster ones are velocity-based with panning speed increasing with the speed at which a user moves their finger. A similar approach has successfully been applied to display walls (the GlideCursor [Beaudouin-Lafon et al. 2014]). Finally, animated view transitions (e.g., as sometimes implemented for discrete scrolling and zooming movements) are aesthetically pleasing and designed to improve perceptual continuity [Card et al. 1991], but inevitably introduce small time delays.

2.3 Interfaces for Image Collections

The requirement to be able to navigate collections of images is common to applications that range from general purpose (e.g., via Google or Bing image searches), to specialized areas such as photography, surveillance, medicine and biology. Very large image databases depend on sophisticated retrieval algorithms to provide users with a small selection of images, with the algorithms operating on image statistics, feature detection and textual metadata (for a review, see [Datta et al. 2008]). With smaller collections (e.g., an individual's photographs) each image may be manually tagged, to provide textual metadata. Interactive exploration of image collections generally involves search queries, and filtering of the results via either a single attribute such as date or multiple attributes using faceted navigation [Henry et al. 2013]. With all these approaches, thumbnails are generally used to present a collection of images, which users can select individually for detailed viewing.

High-throughput microscopy has led to an explosion in the quantity of image data that is used in biology and medicine [Walter et al. 2010]. Some of the applications used in these domains provide an interface that is similar to those described above – a collection of thumbnails that can be selected for detailed viewing (e.g., OMERO [Moore et al. 2008]). Others allow images to be viewed in the context of quantitative measures, using a tabular layout (e.g., Paramorama [Pretorius et al. 2011]) or embedding thumbnail images within a scatter plot (e.g., iCluster [Hamilton et al. 2009]). Pathology applications provide a 'slide tray' of thumbnails, mimicking the manner in which glass slides are provided, and allow a small number of slides (say, up to six) to be simultaneously viewed in detail in separate windows. None of these bio-medicine applications allow users to pan/zoom collections of large (e.g., gigapixel) images as a single entity.

2.4 Evaluations of Navigation Interfaces

In this section we briefly review the tasks, datasets and metrics that have been used in evaluations of navigation interfaces. The studies may be divided into two sets: perceptual-motor vs. usability. Perceptual-motor studies systematically investigate particular factors that affect an interface, but tend to use low-level tasks (e.g., pointing at a target) and a general-purpose pool of participants (e.g., students). Usability studies are typically application-focused, involving a higher-level

evaluation with tasks that have greater ecological validity and, ideally, domain experts as participants.

Perceptual-motor studies investigate the effect that independent variables such as interaction technique, transfer function, view size, and target distance and width have on participants' ability to acquire explicitly indicated targets. Participants perform many repetitions of simple tasks that are typically graded by the index of difficulty (ID) (e.g., see [Casiez et al. 2008]). In studies where participants move a pointer across a static view, IDs as large as 10 have been investigated (a 1 pixel wide target that is 1163 pixels away [Casiez and Roussel 2011]). Larger IDs have been investigated in studies where participants had to navigate a multi-scale environment, for example, an ID = 17.9 (equivalent to a 1 pixel wide target that is 245,000 pixels away [Guiard and Beaudouin-Lafon 2004]. These studies typically use abstract environments comprising circular or square shapes that are clearly visible against the environment background color (e.g., [Appert et al. 2010; Beaudouin-Lafon et al. 2014; Casiez and Roussel 2011; Guiard and Beaudouin-Lafon 2004; Nancel et al. 2011]). The independent variables are compared using metrics such as movement time, error rate and the number of clutching operations, sometimes complemented by subjective feedback from the participants.

Usability studies involve tasks that are cognitively more demanding than the above, and are classified by terms such as navigate, search/find, compare, and trace/follow [Ball et al. 2007; Jakobsen and Hornbæk 2011; Ruddle et al. 2015; Shupp et al. 2009; Yost et al. 2007]. Navigate tasks involve movement to a clearly identifiable target (similar to the perceptual-motor tasks above). Searching becomes more demanding if the task is open-ended rather than specific (e.g., find the largest vs. find X), more of the environment needs to be covered (e.g., exhaustive vs. regions of interest), and the environment needs to be viewed in greater detail due to the size or saliency of targets. Comparison is affected by the number of items that are involved, and tracing becomes more demanding as it becomes more difficult to discriminate a feature from the background.

Previous usability studies have used a variety of types of dataset, including maps (e.g., [Ball et al. 2007; Hornbæk et al. 2002; Zanella et al. 2002]), documents (e.g., [Baudisch et al. 2004; Cockburn and Savage 2004; Hornbæk and Frøkjær 2003]), graphs (e.g., [Beard and Walker 1990; Nekrasovski et al. 2006; Pirolli et al. 2003]), software structure [Anslow et al. 2010], circuit board layouts [Baudisch et al. 2002], and abstract data [Yost et al. 2007]. Pathology images share more characteristics with maps than the other types of dataset [Ruddle et al. 2015], and in previous usability studies of navigation the largest map was approximately 315 megapixels (a map viewed at up to 20× magnification on a 1024×768 pixel display) [Hornbæk et al. 2002]. In the present study, our virtual slides were up to 45 times larger (14.2 gigapixels vs. 315 megapixels), and the slide collections were 1760 – 3150 times larger.

The most common metrics used in usability studies of navigation are participants' time and accuracy to complete the experiment tasks. Many studies also record behavioral data such as participants' movements [Ball et al. 2007], search strategies [Ruddle et al. 2015], and number of different types of action (e.g., pan vs. zoom) [Hornbæk et al. 2002] to help explain any performance differences that are observed. Some studies also gather subjective feedback, such as perceived ease of use [Javed et al. 2012], preferences [Zanella et al. 2002], and frustration [Shupp et al. 2009].

3. PATHOLOGY

This section provides a background to the medical domain of pathology and virtual slides. For a single patient, a pathologist makes a diagnosis by examining anything from one to more than 200 slides under a microscope, panning and zooming to inspect the tissue at different magnifications. Panning may be discrete (e.g., jumping to another piece of tissue on a slide) or continuous, with the latter typically involving following tissue features. Zooming is discrete, and involves both switching lens and refocusing. Using terminology from human-computer interaction, diagnosis may be divided into the following tasks:

- Overview first [Shneiderman 1996]: A pathologist looks at a slide with the naked eye to note the location of the tissue sections on the glass. Sometimes the pathologist draws a line around small sections with a pen to make them easier to find and search comprehensively. It is impossible to see the whole slide at once under a microscope, because even the lowest commonly used magnification (25×) only shows about 10% of the slide.
- Navigate to another tissue section (these are sometimes widely spaced) or previously identified ROI.
- Search: This may be subdivided into searching for ROIs within a tissue section (typically at 25× – 50×), inspecting a ROI or making a systematic search (both typically at 100× – 400×). Most diagnoses are ROI-based. Only for a minority of case types do pathologists make a systematic search, with examples being following a lawnmower pattern to find asbestos particles in a lung or malignant cells in a cervical smear.
- Compare disparate parts of the tissue on one or more slides, to build up a holistic picture of a tumor.

The amount of time that pathologists take to make a diagnosis depends on the number of slides in a case and, with glass slides, averages 2½ minutes/slide. Viewing slides accounts for 57% of that time, and the remainder is spent on other activities such as reading clinical details and dictating a report [Randell et al. 2012]. However, diagnosis currently takes substantially longer with virtual slides [Treanor and Quirke 2007], and key reasons are:

1) Virtual slides are extremely large images (180,000×100,000 pixels when scanned at a diagnostic resolution of 400× magnification, if the tissue covers the whole of a standard-sized glass slide).
2) A microscope's field size corresponds to 7.2 million pixels on a virtual slide [Randell et al. 2013], but existing virtual slide systems typically only run on FullHD resolution displays (1920 × 1080 pixels). That resolution only provides 29% of a conventional microscope's field (NB: that percentage is the same for all magnifications), and a view that is akin to viewing slides through a keyhole. This makes it more difficult to navigate and search, and increases the number of panning movements that are required.
3) Existing virtual slide systems provide a user interface that is profoundly inefficient for navigating gigapixel images, because:
    a) The overview+detail interfaces provided by these systems typically require pathologists to primarily pan in the detail view, which is time-consuming because of the size of the slides and the distance that pathologists need to pan. It follows that prolonged usage is also likely to cause fatigue, because each pathologist inspects dozens or hundreds of slides per day.

b) The overview : detail view scale difference (see Table 1) means that small ROIs are sometimes only visible in the detail view.
c) The scale difference also slows down navigation to tissue sections and ROIs, because it only allows the approximate location of an ROI to be selected in the overview, and then pathologists have to make adjustments to achieve the desired detail view (view navigation [Guiard et al. 2004]).

The remainder of this article describes the design and evaluation of novel user interfaces for single (§4) and collections of gigapixel images (§5). The evaluations were performed by consultant and trainee pathologists, diagnosing real but archived patient cases (for practical reasons, it was not possible to use 'live' cases).

4. INDIVIDUAL GIGAPIXEL IMAGES

As noted above, the overview+detail interface of commercial virtual slide systems is poorly suited to navigating gigapixel images, causing pathologists to take considerably longer to make a diagnosis than when using a conventional microscope. The following section describes the design of our virtual microscope for viewing and navigating individual virtual slides, followed by an evaluation of how doctors used our interface to make diagnoses. The focus of the present paper is on the navigation interface, and for details of the evaluation from a clinical perspective the reader is referred to [Randell et al. 2013].

The interface was designed and implemented during a six-month long iterative process. During this, we used pathologists' feedback to investigate variants of the interface details (see below), while two core aspects of the design remained unchanged: (a) a display resolution providing a greater field than a conventional microscope (11 vs. an equivalent of 7 million pixels; [Randell et al. 2013]), and (b) using a ≈1 million pixel overview.

4.1 Design

The core project team comprised two human-computer interaction specialists, one software engineer, and a consultant pathologist. The design process involved discussions by the core team, with diagnosis walkthroughs for nine types of case led by the pathologist, video analysis of how three other pathologists navigated slides when diagnosing with a conventional microscope, the implementation of a range of interface options, and their evaluation with a total of nine pathologists. The majority of this design work took place during a concentrated six-month period.

Our design was informed by four years usage of a wall-sized (3.0×1.3m; 54 million pixels) virtual microscope that we developed and which enabled pathologists to rapidly make diagnoses by panning/zooming with a gamepad device [Treanor et al. 2009]. For virtual microscopes to be practical for routine diagnosis they need to have a much smaller footprint than our wall-sized system – they need one that is similar to that of a desktop workstation. However, existing desktop virtual slide systems have two key deficiencies: they show only a small amount of what a pathologist sees through a conventional microscope at a given magnification, and they provide a user interface that is profoundly inefficient for navigating gigapixel images (see §3). We addressed these deficiencies by designing a virtual microscope that: (1) renders gigapixel images in real-time on a display that provides a greater field than a conventional microscope (see Figure 1), and (2) allows users to pan slides quickly and precisely by moving the cursor in a gigantic (≈1 million pixels) "thumbnail" overview. Although such overviews have been used in some previous research [Jakobsen and

Hornbæk 2011; Treanor et al. 2009], they are not provided by commercial virtual slide systems. The size of a virtual slide means that, even with a 1 million pixel overview, the overview : detail view scale difference breaks established guidelines [Plaisant et al. 1995; Shneiderman 1998]. The remainder of this section describes the interface options that were investigated, separating them into the two main interface requirements: zooming and panning.

4.1.1. Zooming. Use of a conventional microscope involves discretely changing magnification by switching lenses. Of the four zooming interfaces that we investigated, the first mimicked a conventional microscope by using one key to zoom in and another to zoom out. In both cases, the magnification changed by a factor of two, consistent with the step size of microscope lenses (400×, 200×, etc.). The second used the mouse scroll wheel to provide zooming, and with the third users double clicked the left/right mouse buttons to discretely zoom in/out by a factor of two. The fourth was a variant that worked with all of the other zooming interfaces and, like Google Maps, made the center of the zoom the cursor position, not the middle of the detail view.

The final interface provided keys and the scroll wheel to zoom, both devices changing the magnification discretely in steps that had a factor of two to be consistent with microscope lenses. Keys encouraged two-handed interaction (non-dominant hand for zooming with keys; dominant hand for panning with the mouse) but the scroll wheel allowed all interaction to be performed with a single device. A third key was added to fit a virtual slide to the detail view. The keys invoked a fast (250ms) animated zoom rather than an instant change of magnification, in response to pathologists' feedback. They also preferred to zoom on the middle of the detail view, not the cursor position.

Fig 1. The virtual microscope showing a GI biopsy slide at 400× magnification.

4.1.2. Panning. Four styles of panning were investigated. One provided a steering interface (velocity-based control), with the direction and speed of panning dictated by the cursor's offset from a dead zone in the center of the detail view. Although this made it straightforward to pan along tissue features, velocity-based control is slow for precise movements and the pathologists preferred displacement-based control. A second allowed pathologists to incrementally pan by clicking in the detail view, which caused the tissue under the click to move to the center of the view in an animated pan. The advantage was that only small physical mouse movements were needed to inspect a localized region of tissue (if the cursor position was kept constant then every pan was an identical distance and direction), but navigating to other parts of a slide required large movements.

The third style used displacement-based control, which allowed pathologists to click-and-drag to easily make small pans in the detail view (e.g., following a tissue feature) and large pans in the overview (e.g., to another part of a slide). The disadvantages were that pathologists had to make large physical mouse movements to switch between panning in the overview and detail view (this is a consequence of using high-resolution displays), meaning that in practice pathologists almost exclusively used the detail view and for large pans made a multitude of panning/zooming movements (screen thrashing [Ruddle et al. 2013]).

The fourth style also involved displacement-based control, and was the style that was used in the evaluation. The cursor was locked into the overview, meaning that pathologists only had to move the mouse to pan (a 'click-less pan'), rather than performing a click-and-drag action. Initially the click-less pan was disliked by some users, probably a consequence of their familiarity with Google Maps and other similar interfaces. However, after having the benefits explained and some practice the pathologists quickly became comfortable with the click-less pan style. The overview was 1440 pixels wide (the width of one of the monitors; see Figure 1) and had a height that depended on the aspect ratio of a given virtual slide. The overview averaged 1440×877 pixels for the slides used in the evaluation, allowing pathologists to see and move directly to diagnostic details that are invisible on conventionally sized thumbnails. Slow cursor movements (≤ 4 pixels/s) were averaged across the five graphics frames to smooth the panning. After 30 minutes of training, participants were able to navigate proficiently.

4.2 Evaluation Method

A total of 16 pathologists participated in the evaluation (8 consultants with 6–28 years experience of pathology, and 8 specialist trainees who were qualified doctors with 0.5 – 5.5 years experience of pathology). Each pathologist took part on two occasions, first to learn how to use the virtual microscope and then to diagnose 12 single-slide patient cases, half with a conventional microscope and half with the virtual microscope.

A one-line, written clinical history was provided for each diagnosis (e.g., "Female, 49 years, skin lesion on nose, excised"). Participants treated each diagnosis as if it was part of their everyday work, recording their diagnosis in writing in a box on an answer sheet.

The virtual microscope consisted of three Dell UltraSharp U2713HM 27-inch monitors, arranged with a curved form factor (see Figure 1), as investigated in some previous research (e.g., [Shupp et al. 2009]). Each monitor had a resolution of 2650×1440 pixels (0.23 mm pixel pitch), and was oriented in portrait mode to give a total resolution of 4320×2650 pixels. The PC had two dual-output NVIDIA Quadro

FX1800 graphics cards. All interaction was performed using a standard keyboard and a SteelSeries Xai high-resolution gaming mouse (SteelSeries ApS, Valby, Denmark).

The slides were from two of the most common types of pathology case (GI biopsies and skin specimens; see Figure 2), and scanned at 400× magnification (see Figure 3). Skin specimens occupy a much smaller region on a microscope slide than GI biopsies, making the virtual slides correspondingly lower in resolution and reducing the scale difference between the overview and detail view (see Table II).

Table II. Descriptive statistics for the skin specimen and GI biopsy virtual slides and the slide overview used in the individual image evaluation. The scale difference is calculated for when a slide was displayed at native resolution (400× magnification) in the detail view.

Case type	Slide			Overview : detail view	
	Area (gigapixels)	Mean width (pixels)	Mean height (pixels)	Mean screen-space ratio	Mean scale difference
Skin specimen	0.6 - 3.0	45,920	35,184	1:6	32
GI biopsy	5.1 - 9.8	143,520	55,471	1:14	100

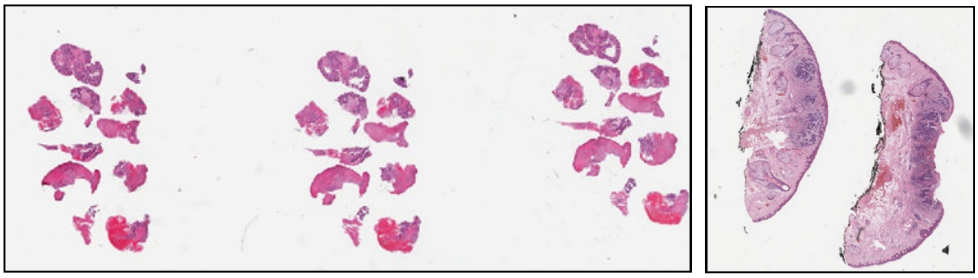

Fig 2. Virtual slides of a GI biopsy (left) and skin specimen (right). The slides may be viewed online at http://slides.virtualpathology.leeds.ac.uk/Research_4/Slide_Library/TOCHI_Examples/TOCHI_Example_1.svs and http://slides.virtualpathology.leeds.ac.uk/Research_4/Slide_Library/TOCHI_Examples/TOCHI_Example_2.svs respectively.

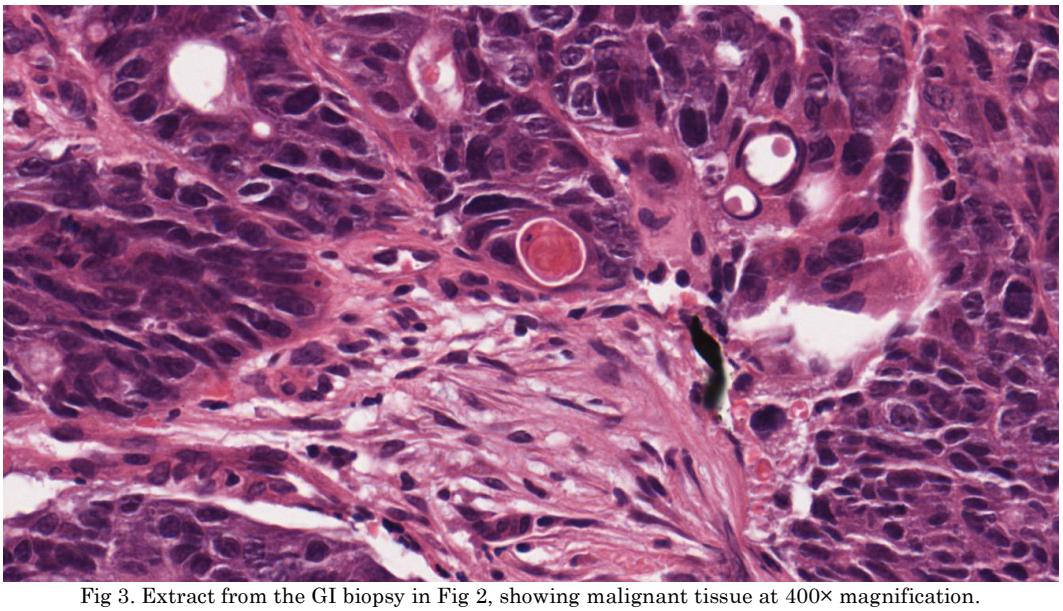

Fig 3. Extract from the GI biopsy in Fig 2, showing malignant tissue at 400× magnification.

When a slide was opened it was automatically fitted to the display. The participant then navigated the slide to make their diagnosis, and recorded this on an answer sheet. Participants' actions were recorded using a log file and by videoing the display, for subsequent analysis.

4.3 Evaluation Results

This section reports how participants used the interface. We start by comparing diagnosis time and accuracy for the virtual microscope vs. a conventional microscope. Then we describe the process used to divide interaction into sequences of meta-actions, and then analyze how participants interacted with the virtual microscope by considering four generic visualization tasks (see §3): overview first, navigate, search, and compare.

4.3.1. Diagnosis time, confidence and accuracy. The amount of time that pathologists spend making a diagnosis varies considerably, both between cases and from one pathologist to another [Velez et al. 2008], and in the present evaluation there was a similar variation with participants taking from 41 to 372 seconds to make a diagnosis (M = 136.0 s; SD = 72.5). On average participants were 18% slower making diagnoses with the virtual microscope than a conventional microscope, but the difference was not statistically significant (for details, see [Randell et al. 2013]) and this represents a considerable improvement on the time taken with other virtual slide systems [Treanor and Quirke 2007].

Pathology diagnosis is highly subjective. Participants were confident in the diagnoses that they made with both devices, but more so with the conventional microscope (M = 5.8 vs. 5.3, on a 7-point Likert scale). After review by a consultant pathologist, two 'errors' were identified that had possible consequences for patient care. Both errors involved the same skin case and the virtual microscope. Further investigation indicated that possible causes were image quality (due to the scanning process, or use of ordinary rather than medical-grade monitors), and today's pathologists' general lack of familiarity with virtual slides (for further detail, see [Randell et al. 2013]). In terms of the effect on the data reported in this evaluation, any uncertainty that led to the errors is likely to have increased the amount of panning/zooming that participants performed, rather than decreased it.

4.3.2. Meta-actions. The amount of time that participants spent panning or zooming was significantly correlated with the diagnosis time, $r(95) = .94$, $p < .01$, and accounted for 49% (SD = 12) of the diagnosis time, with the detail view stationary for the other 51%. Participants performed this panning/zooming in many short movements, some separated by as little as one sixtieth of a second (the graphics frame rate) and others by longer. Cognitively speaking, it is likely that participants considered that many of these actions were part of a single larger 'meta' action, and this was certainly the case when the detail view was only momentarily stationary. Therefore, we investigated different thresholds for grouping actions into meta-actions (see Table III), reviewed video recordings of participants' physical interaction behavior during the trials, and chose a threshold for 0.5 seconds for the subsequent data analysis.

Table III. Rate at which actions and meta-actions were performed (the number of actions or meta-actions, divided by the trial time). Actions separated by less than the threshold were grouped into meta-actions.

Statistic	Actions/min	Meta-action rate (/min), for given threshold			
		0.25s	0.5s	0.75s	1.0s
Mean	124.2	18.9	11.1	7.4	5.0
SD	30.5	5.9	3.9	2.9	2.2

We analyzed the meta-actions using a combination of Excel pivot tables, Tableau, and Paramorama2 [Pretorius et al. 2015]. Tableau Gantt charts were useful for analyzing the timeline of meta-actions within a trial, and Paramorama2 is unique in its capability for allowing objective measures to be analyzed in the context of subjective data. We used nine objective measures for each meta-action (the type, duration, distance panned, panning rate, path straightness, bounding box, magnification, and amount of zooming in and out) and images showing the navigation path on a slide, and plots of pan distance vs. time (pan-only meta-actions) or distance panned vs. magnification (zooming meta-actions). From this analysis, we categorized the meta-actions in the ways described below.

Pan-only meta-actions were the most common (see Table IV), and were subdivided into the panning that participants performed to navigate (see §4.3.4) and search the slides (see §4.3.5). To be classified as a navigate movement, a meta-action had to involve discrete panning – panning that was both straight (the distance panned divided by the length of the diagonal of the detail view bounding box was ≤ 1.1) and fast (> 1000 pixels/second; this threshold was chosen by analyzing the speed distribution of all straight pans). It follows that the search meta-actions involved more meandering and/or slower panning. Most of the remaining meta-actions involved both panning and zooming, with zoom-only meta-actions being the least common. Participants predominantly used the mouse scroll wheel to zoom, rather than the keys.

Table IV. Percentage of meta-actions, navigation time, and distance panned in detail view coordinates for different categories of meta-action.

Metric	Mean/SD	Pan-only		Pan & zoom	Zoom-only
		Navigate	Search		
% meta-actions	*M*	18.9	44.3	29.9	6.9
	SD	13.4	17.7	17.8	8.1
% navigation time	*M*	6.0	48.1	45.0	0.9
	SD	6.0	23.7	24.5	1.2
% distance panned	*M*	9.5	50.9	39.5	-
	SD	10.7	25.2	26.9	-

In each trial, participants panned an average of 152,000 pixels (*SD* = 124,000) in detail view coordinates, at a rate of 1050 pixels/second (*SD* = 678), and zoomed by an amount that was equivalent to doubling or halving the magnification every seven seconds. Zooming was almost instantaneous with the virtual microscope. However, with the conventional microscope each magnification step (e.g., 25× to 50×) took an average of 2.8 seconds (*SD* = 1.2) because participants had to change lens, adjust the condenser and refocus the microscope. Zooming in by a large amount needed to be performed in discrete steps to avoid breaking the slide glass because lens length increases with magnification.

Two examples of participants' tracks across a slide and timelines of the meta-actions they performed are shown in Figure 4. The examples are from different participants, and are the GI and skin trials that, overall, were closest to median performance in terms of the trial duration, number of meta-actions, distance panned and amount of zooming.

4.3.3. Overview first. The only way that pathologists can see the whole of a glass slide is to look at it with the naked eye. This means that they typically start a diagnosis by navigating and searching a glass slide at a low magnification (25× or 50×). By contrast, when a virtual slide was fitted to the detail view the image was displayed at a magnification of 10× – 50× (the magnification depended on the

dimensions of the image). In other words, the virtual microscope allowed participants to see at a glance a low-magnification view of the whole slide. As a result they switched to a higher magnification sooner with the virtual microscope than a conventional microscope.

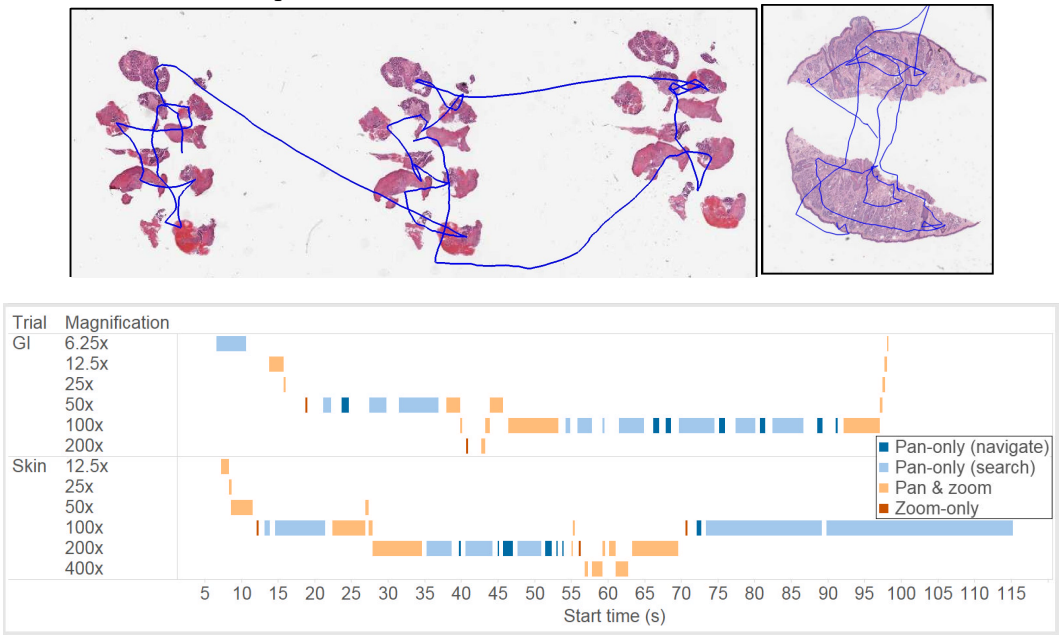

Fig 4. The path taken by participants in typical GI (top left) and skin (top right) trials. The Gantt charts show the timeline of the meta-actions for each trial.

To further investigate, the average time that each participant spent viewing a slide at the beginning of a trial at magnification ≤ 50× was calculated for each combination of microscope (conventional vs. virtual) and case type (skin vs. GI). The average times were analyzed using an analysis of variance (ANOVA) that had two repeated measures (microscope × case type). Participants spent significantly less time with the virtual microscope than a conventional microscope, $F(1, 15) = 38.37$, $p < .001$, and less time with skin than GI cases, $F(1, 15) = 4.81$, $p < .05$. There was also a significant microscope × case type interaction, $F(1, 15) = 4.85$, $p < .05$ (see Figure 5). The interaction is likely to have occurred because the skin specimens covered a substantially smaller area of a glass slide than did the GI biopsies. With a conventional microscope, this substantially reduced the number of separate views that were needed to inspect the whole slide, and hence the time that was required. With the virtual microscope, a slide was initially fitted to the detail view so that the whole slide could be inspected. Participants then typically zoomed in a little and panned (see Figure 4), so the ≈ 20 seconds mean time shown in Figure 5 may represent a low bound for the low-magnification inspection of a slide.

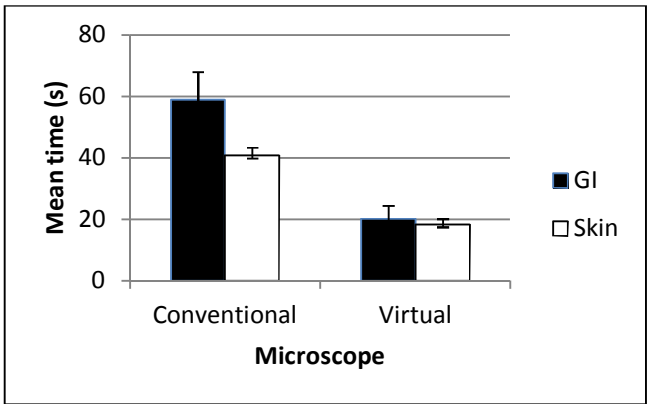

Fig 5. Mean time spent viewing a slide at the beginning of a trial at magnification ≤ 50× for each combination of microscope and case type (GI vs. skin). Error bars show standard error of the mean.

4.3.4. Navigate. A key navigational action during diagnosis is to make discrete movements to another tissue section or ROI. Our interface was designed to speed up this navigation by allowing participants to pan directly between sections and ROIs at any magnification. Of the distance that participants performed in straight, fast pans, 43% took place during a local maximum of magnification (i.e., between zooms in and out) and another 52% took place during a period of panning when participants kept the magnification constant for at least seven seconds (i.e., more than four times the median meta-action duration of 1.6s). Performing this panning in the overview rather than the detail view substantially reduced the amount that participants moved the cursor (67% of the panning involved a scale difference > 30, and 7% involved a scale difference > 100).

Another way of navigating is to zoom out until a given section/ROI is included within the view and then pan/zoom in again to inspect the section/ROI, and this is how both a conventional zooming interface [Guiard and Beaudouin-Lafon 2004; Guiard et al. 2004] and conventional microscopes are used. However, out of the distance panned during pan-zoom meta-actions, 30% was during a local maximum of magnification and another 35% took place when participants kept the magnification constant for at least seven seconds, both types of panning that are more consistent with search (see §4.3.5) than navigate. It was only the remaining 35% that was typical of a conventional zooming interface, occurring when participants performed brief pans either after having zoomed out or while making a series of zooms in/out. Four trials accounted for a quarter of the distance that participants panned with zooming interface movements (see Figure 6).

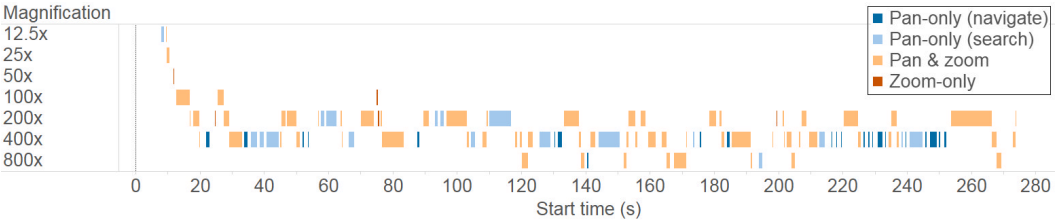

Fig 6. The timeline of meta-actions in the trial that contained the most interaction that was like usage of a conventional zooming interface.

4.3.5. Search. As well as making discrete movements between sections of tissue, participants made many smaller movements to search and inspect areas of tissue for

important features. Some of this involved pan-zoom meta-actions that were reported above (see §4.3.4). The remainder involved panning-only.

Of the pan-only search, 83% covered a larger area than the detail view, and would have required clutched panning movements with a conventional interface. By panning in the overview, participants made physical movements that were substantially smaller than if panning had been performed in the detail view (60% of 'search' panning involved an overview : detail view scale difference > 30, and 3% involved a scale difference > 100).

There was a risk that the scale difference made it difficult for participants to control their panning. The difficulty would be greatest when participants attempted to make the finest movements of the cursor, so we investigated meta-actions where participants made very small cursor movements (termed 'micro' meta-actions, and defined as when the cursor moved within a 10×10 pixel bounding box in the overview). There were 451 micro meta-actions, out of a total of 2587 meta-actions.

Ten trials (all GI cases) accounted for 227 of the micro meta-actions. For each of these trials, we reviewed the video of the workstation display. The videos showed that 44% of the micro meta-actions took place when participants were inspecting details on a slide by making a sequence of pans, with some of the pans involving micro movement and others macro movement. Another 44% took place when participants were inspecting a slide by making a sequence of pans and zooms. The other 12% of micro meta-actions were divided equally between occasions when participants were adjusting the position of a slide (e.g., so monitor bezels did not cross a tissue feature) and occasions when participants appeared to have difficulty controlling panning of a slide.

4.3.6. Compare. Pathologists sometimes revisit parts of a slide to make comparisons during diagnosis (see §3). In the evaluation, revisiting was not analyzed for the conventional microscope trials because of the difficulty of ascertaining which part of a slide is being viewed from video filmed through a second eyepiece. However, revisiting was straightforward to determine for the virtual microscope trials, by superimposing paths recorded in the log files onto the relevant slide (see Figure 4) and counting the number of times that a path moved from one tissue section to another.

At the start of each trial the cursor was centered on a slide, so in the GI cases participants tended to start by panning from the central tissue section to the section that was on the left or right hand side of the slide. Thus, revisiting was defined as occurring when the path moved more than three times between tissue sections, which occurred in 14 of the 48 GI trials (29%). The skin cases had two tissue sections, so revisiting was defined as occurring when the path moved more than twice between tissue sections, which occurred in 19 of the 48 trials (40%).

4.4 Discussion

Compared with conventional microscopes, current virtual slide systems are much slower for diagnosis, with key causes being the substantially smaller field and panning being performed predominantly in the detail view. We addressed these causes by designing a novel virtual microscope that provides a larger field than a conventional microscope, and a gigantic overview (≈ 1 million pixels). The field of the detail view benefited diagnosis by allowing pathologists to view the whole of a slide at low magnification. The overview is unusually large in both absolute terms and the proportion of screen space that it occupies (10× more than Google Maps). The overview leveraged the real estate of a high resolution display to allow pathologists to identify and navigate directly between ROIs at a high magnifications, and search

tissue with single rather than clutched mouse movements. The evaluation stands out from previous studies because it involved domain experts doing 'real' work (diagnosing archived patient cases), navigating images that were orders of magnitude higher in resolution that those used in previous studies (e.g., [Ball et al. 2007; Jakobsen and Hornbæk 2011]).

The navigation data reported in the present paper characterize how pathologists used the interface and provide evidence about its effectiveness. The remainder of this section discusses the findings in the context of four generic visualization tasks: overview first, navigate, search and compare.

4.4.1. Overview first. The high resolution of the detail view allowed participants to view the whole of a slide at a low magnification, which is impossible with a conventional microscope. This resulted in a change of behavior, with participants only using a low magnification (≤ 50×) for a brief period and then navigating/searching at a higher magnification. By contrast, with a conventional microscope participants spent an average of two (skin specimens) to three (GI biopsies) times longer initially viewing a slide at low magnification.

4.4.2. Navigate. Participants used two approaches to navigate discretely between sections of tissue and ROIs. Sometimes participants navigated in a manner found with conventional zooming interfaces (zoom out until one's desired destination is within the view, pan to it, and then zoom in; see Figure 6). However, more typically participants used our interface in the manner intended by its design, panning directly between parts of a slide at a given magnification (see Figure 4). Overall, 95% of pan-only navigation was performed in this way, speeding up navigation and reducing context switching, because participants did not have to change from high magnification to low and then high again to start searching a new region of the tissue or compare previously seen features of interest.

Direct navigation benefits from a large, high-resolution overview and detail view. The size of the overview meant that slides were displayed at a magnification of 4× – 19×. In other words, the large overview displayed a slide at a size that sometimes approached the lowest power magnification (25×) that pathologists use to make a diagnosis with a conventional microscope. It follows that, in the evaluation, the large overview helped participants to identify the exact position within a ROI to which they wished to navigate.

Having identified where they wished to navigate, the high resolution of the overview allowed participants to select that position more accurately than would be possible with a traditionally sized overview. This was because one pixel in the overview corresponded to 21 – 111 pixels of a slide at the native scan resolution (400×), whereas with most commercial virtual slide systems the scale difference is more than 1000 (see Table 1).

Multi-scale navigation may be thought of as involving both view pointing (moving a view so a target is visible) and cursor pointing (selecting the target) [Guiard et al. 2004], though in our application the cursor pointing was implicit (a participant changed the view so that they could look at a tissue feature rather than actually select it). The high-resolution detail view substantially reduced the precision with which participants needed to perform view pointing, because even at 400× a position only had to be selected with 23 pixel accuracy in the overview to be visible within the detail view. By contrast, single pixel accuracy is required with most commercial virtual slide systems. In previous research, selecting a one pixel rather than a nine pixel target caused the error rate to increase four-fold and the time taken to double

[Casiez and Roussel 2011], and the difference between one and 23 pixel target areas would be substantially greater.

4.4.3 Search. When searching a piece of tissue, participants need to both decide where to go and control their movement. Decisions were facilitated by the high-resolution detail view because, unlike most other virtual slide systems, it showed an area of tissue that was comparable with the field of a conventional microscope (see §3). A large field decreases the number of separate views that are needed to see the whole of a slide, and increases the ease with which users can control panning movements because there is more 'peripheral' information about parts of the slide that are about to come into the center of a user's view.

Most pan-only searches covered a larger area than the detail view. Panning in the overview meant that participants were able to conduct these searches in a single movement, rather than having to make clutched panning movements in the detail view. Overview panning also substantially reduced the amount that users needed to physically move the interaction device during panning, which in day-to-day usage would considerably reduce fatigue.

The majority of these searches involved an overview : detail view scale difference that exceeded established guidelines of 20 [Plaisant et al. 1995] or 30 [Shneiderman 1998]. However, on only a small percentage of occasions did the scale difference cause difficulty to participants for controlling panning during a search.

4.4.4 Compare. In approximately one third of trials, participants revisited a tissue section, which was behavior indicative of pathologists making comparisons between parts of the tissue or checking their diagnosis. The overview panning allowed participants to perform these revisits by navigating in a single, rapid movement. The ease of conducting this navigation may have increased its frequency, which is arguably beneficial because repeat views could help pathologists to increase the certainty of their diagnosis. Generalizing to other analysis scenarios, as data become more complex then users are likely to need to make more comparisons, meaning that our overview panning approach would become progressively more beneficial.

5. GIGAPIXEL IMAGE COLLECTIONS

The second version of the virtual microscope was purpose-designed for the viewing and navigation of collections of gigapixel images, to provide pathologists with a tool for the diagnosis of large clinical cases. In our regional cancer center, 50% of slides occur in cases with at least 11 slides. The evaluation described below involved cases with 12–25 slides, and for details from a clinical perspective the reader is referred to [Randell et al. 2014]. The evaluation was preceded by a series of design iterations over a 16-month period, and feedback from seven pathologists.

5.1 Design

The design process involved brainstorming by the core project team (this generated 35 pages of ideas in 1½ hours), the creation of mock-ups in Photoshop, displaying the mock-ups life-size on a 11 megapixel workstation to storyboard the ways that pathologists would interact to diagnose large cases, and then iterations of implementation and formative evaluation. The design (see Figure 7) is innovative because:

1) The whole case is displayed as a seamless world of slides, which pathologists can pan through in a continuous fashion, as well as jump directly to any place in that world (e.g., a specific feature on a particular slide).
2) Navigation is aided by two large overviews on a dedicated 3.1 megapixel monitor (32% of the total display area). One overview shows a single slide (a

'local map' of the world) and the other shows every slide in the case (a 'global map').

3) A 6.7 megapixel medical-grade monitor provides a bezel-free detail view, to avoid situations where pathologists need to adjust the position of a slide because a tissue feature was crossing monitor bezels (see §4.3.5).

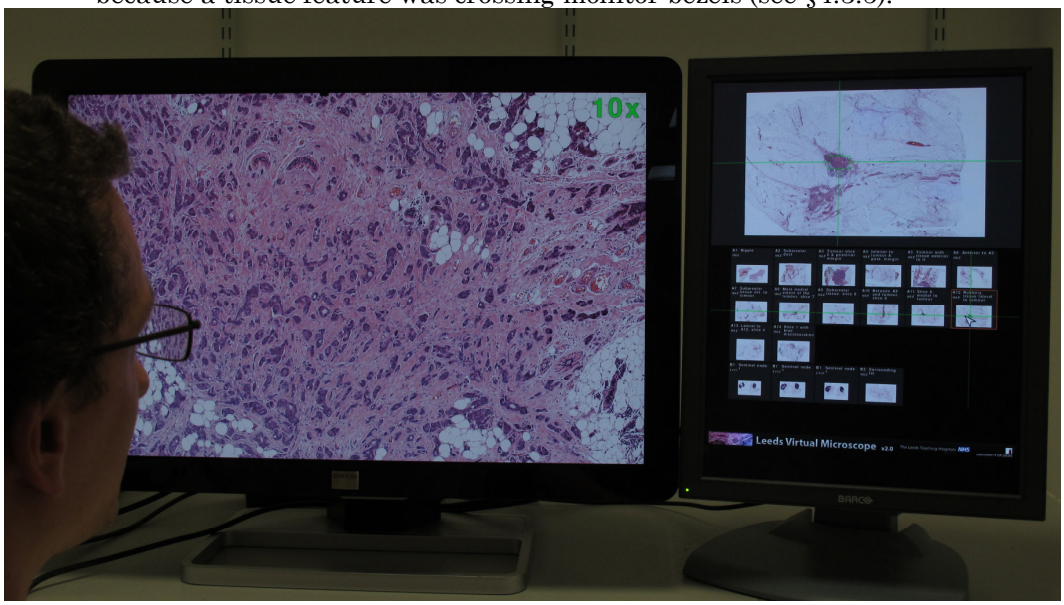

Fig 7. An 18-slide breast case shown on the virtual microscope. The detail view is shown on the left-hand monitor (a Barco Coronis Fusion 6MP DL). The true magnification is 100×, but it is shown as 10× because pathologists' terminology only refers to a microscope's objective lens, not the additional 10× eyepiece. The slide (top) and case overviews (bottom) are shown on the right-hand monitor (a Barco Nio Color 3MP).

The design iterations principally focused on the overviews and the panning interface. These and other aspects of the interface are described below.

5.1.1. Overviews. The first design provided two overview modes, to conceptually separate gaining an overview of the whole case from inspecting each slide in detail. The former involves panning across all slides at a low magnification and is impossible with a conventional microscope, whereas the latter involves viewing each slide in turn at a medium-high magnification, as is the case when diagnosis is made with glass slides. In the first mode only the case overview was shown, whereas both the case and the slide overview were shown in the second mode. To change mode pathologists pressed a key, but in usage this was felt to unnecessarily slow down diagnosis so we changed to a single mode design, which always showed both overviews.

Initially in the single-mode design all three views were tightly coupled, meaning that the center of each view corresponded to the same position within the world of slides. However, this meant that the slide overview generally showed part of several slides, and not the whole of the slide upon which a pathologist's attention was focused. We addressed this by implementing loosely coupled views, so that the slide overview showed the whole of whichever slide was in the center of the detail view. This meant that the slide overview changed suddenly if a pathologist panned continuously from one slide to another, which provided feedback that the slide had been changed.

The slide overview (1526 × 853 pixels) used a fixed magnification, which was calculated from the size of a glass slide. This meant that the size of a given diagnostic

feature was constant across slides, and each slide occupied an amount of the overview that corresponded to the area of glass covered by the tissue. The case overview showed each slide life-sized, so the overview area depended on the number of slides. A maximum of 30 slides could be shown life-sized on the system. With the 2% of cases that contain more than 30 slides, a user may either fit the case to the case overview so each slide is smaller than life-sized, or display the slides life-sized and pan the case overview by holding down a key and moving the cursor.

5.1.2. Panning. Building on the successful evaluation of the first generation of our interface (see above), the cursor was constrained so that it could only move within the region occupied by the case overview. This ensured that panning was efficient in terms of the physical distance that pathologists needed to move the mouse.

To make a discrete pan a pathologist clicked on a position in the case overview, which caused the detail view to change so that it was centered on that position. The cursor speed was dictated by the PC's system preferences, which default to give a non-linear transfer function with a maximum gain of approximately 11 [Casiez and Roussel 2011]. Continuous pans were performed by moving the mouse with the left button held down, applying an additional transfer function to scale the slide movement by an amount that increased linearly with the zoom level (the amount that the slide was zoomed out from native resolution; 1.0 for 400×, 2.0 for 200×, and so on). This provided an effective solution to the quantization problem [Appert et al. 2010], even though the overview : detail view scale difference was sometimes as large as 1704 (this occurred at 800× magnification of a virtual slide; users could zoom to twice the native image resolution).

5.1.3. Other functionality. The slides are organized in a clinically relevant layout, which follows user-definable rules. For the evaluation described below, the rules started each tissue part on a new row. The tissue part (A, B, etc.), tissue block (1, 2, etc), histochemical stain (H&E, etc) and brief textual details were included as metadata for each slide that was visible in all of the views. The cursor keys allowed pathologists to move left/right/up/down between slides in the case overview, and two other keys allowed them to move to the next/previous slide in the case.

Zooming was performed using keys to zoom in/out and the scroll wheel, as for the first generation interface. When a case was opened the detail view was centered on the first slide, at a magnification that showed the whole of that slide and part of its neighbors in the case. When a pathologist selected another slide its initial magnification was the same as the previous slide's last magnification, but double clicking on a slide changed the magnification to fit it to the detail view.

5.2 Evaluation Method

Twelve consultant pathologists participated in the evaluation. There were four consultants from each of three specialisms (breast, GI and gynecology), and they had 16–25 years of experience of pathology. Each pathologist took part on two occasions, first to learn how to use the virtual microscope (30–60 minutes) and then to diagnose two patient cases in their specialty (45–60 minutes in total). Each participant diagnosed one case with a conventional microscope and another with the virtual microscope, counterbalanced across participants.

For each case, participants were provided with clinical details (e.g., "Carcinoma right breast. Macroscopically involved lymph nodes up to level II.") and a macroscopic description of the tissue. Participants treated each case as if it was part of their everyday work, recording their diagnosis on a proforma that captured standard information that would have to be recorded when reporting such a case.

The virtual microscope consisted of a Barco Coronis Fusion 6MP DL (3280×2048 pixels; 0.1995 mm pixel pitch) and a Barco Nio Color 3MP (2048×1536 pixels; 0.207 mm pixel pitch) monitor (see Figure 7). The PC had two dual-output NVIDIA Quadro FX1800 graphics cards. All interaction was performed using a standard keyboard and a SteelSeries Xai high-resolution gaming mouse (SteelSeries ApS, Valby, Denmark).

The cases were typical of routine diagnostic work. All of the slides were scanned at 400× magnification, and the slide overview and case overview used constant scale differences (see Table V) so that diagnostic features had a consistent size between slides. Participants' actions were recorded using a log file and by videoing the display.

Table V. Descriptive statistics for each type of case in the image collections evaluations. The overview scale differences were identical for all case types, and were calculated for when a slide was displayed at native resolution (400× magnification) in the detail view.

Measure		**Case type**		
		Breast	**GI**	**Gynaecology**
Slide	Area (gigapixels)	2.2 – 13.6	4.4 – 13.7	3.2 – 14.2
	Mean width (pixels)	117,195	114,092	108,866
	Mean height (pixels)	82,974	80,364	77,090
Case A	Number of slides	18	12	18
	Area (gigapixels)	739	554	554
Case B	Number of slides	19	12	25
	Area (gigapixels)	739	554	926
Screen-space ratio	Both overviews together	1:3		
Scale difference	Slide overview : detail	121		
	Case overview : detail	852		

5.3 Evaluation Results

This section reports how participants used the interface. The results are divided into the same sections as the individual gigapixel image evaluation.

5.3.1. Diagnosis time, confidence and accuracy. There was negligible difference between the time that participants took to make diagnoses with the conventional and virtual microscopes (on average the latter was 2% slower). For details see [Randell et al. 2014].

Participants had similar confidence in the diagnoses that they made with the conventional and virtual microscopes (M = 6.6 vs. 6.2, on a 7-point Likert scale). To assess accuracy, all of participants' diagnoses were reviewed by a consultant pathologist. A discrepancy was defined as a difference in the assessment of an important diagnostic feature (tumor stage, grade or type, or node stage), compared to a reference diagnosis. The reference diagnosis was taken as the majority opinion of all four pathologists viewing that case (of which there were two on glass and two on the LVM for all cases). When no majority opinion was available (e.g. a 2:2 split between the four opinions, or a wider spread of opinions), the original clinical diagnosis was used as the reference diagnosis. In total there were four discrepancies with a conventional microscope and five discrepancies with the virtual microscope. All of the discrepancies were considered to be within the usual variability seen in histopathology diagnosis. However, the detection of subtle differences would require a full-scale clinical trial.

5.3.2. Meta-actions. As in Section 4, a 0.5 second threshold was used to define meta-actions, which participants performed at an average rate of 16.1 meta-actions/minute (SD = 4.1). The amount of time that participants spent panning or zooming was significantly correlated with the diagnosis time, $r(11) = .85$, $p < .01$, and on average participants spent 23% (SD = 8) of the diagnosis time panning/zooming, with the detail view stationary for the other 77%. In each trial, participants panned

an average of 1,710,000 pixels (*SD* = 679,000) in detail view coordinates, at a rate of 1770 pixels/second (*SD* = 635), and zoomed by an amount that was equivalent to doubling or halving the magnification every six seconds. A summary of the different types of meta-action is shown in Table VI.

Table VI. Percentage of meta-actions, navigation time, and distance panned in detail view coordinates for different categories of meta-action.

Metric	Mean/SD	Between slides	Within a slide			
			Pan-only		Pan & zoom	Zoom-only
			Navigate	Search		
% meta-actions	*M*	9.6	17.5	36.7	3.5	32.6
	SD	4.2	7.1	4.8	2.8	6.2
% navigation time	*M*	1.4	11.3	76.0	7.2	4.1
	SD	2.5	8.1	8.3	6.2	2.9
% distance panned	*M*	57.1	7.5	32.6	2.8	-
	SD	19.2	5.3	16.6	3.2	-

5.*3.3 Overview first*. In a multi-slide case, pathologists need to inspect every slide, some in detail but for others a low magnification suffices. 'Overview' time was calculated as the time that participants spent viewing a slide before using a magnification that was > 50× or moving to another slide, and return visits to a slide were not included. With the virtual microscope, overview time averaged 19.0 seconds (*SD* = 26.5) for each slide, which was similar to the single-slide cases (see §4.3.3). However, the time varied widely – for 3% of slides a static overview was sufficient (participants did not pan or zoom), whereas the overview time was zero for 25% of slides (participants sometimes chose to navigate between slides at a magnification > 50×). With the conventional microscope, the video data only allowed overview times to be reliably calculated for eight participants. The data showed that they initially viewed each slide at a magnification of ≤ 50× for an average of 35.1 seconds (*SD* = 27.0).

5.3.4. Navigate. Participants made discrete navigational movements both between slides and within a slide. Between-slide navigation accounted for the majority of the distance that participants panned (see Table VI). Participants made 44% of the slide changes when the case overview : detail view scale difference was greater than 100. Nine participants principally clicked with the mouse, two used the cursor keys and one by a combination of the two methods. A small percentage (3%) of slide changes occurred when participants panned continuously from one slide to another. Slide changes were almost instantaneous when participants clicked or used a cursor key. However, analysis of the video data showed that when using the conventional microscope participants took an average of 5.3 seconds (*SD* = 3.8) to change a slide, because they had to physically remove one piece of glass, insert another and, often, refocus the microscope.

For the within-slide meta-actions that were classified as navigate (fast and straight panning; see criteria in §4.3.2), participants panned 44% of the distance during a local maximum of magnification (i.e., between zooms in and out) and another 45% during a period when the magnification was constant for at least seven seconds. The navigate panning took place at scale differences of 7 – 1704, with the vast majority involving a scale difference that was greater than 100.

A small amount of panning took place during pan & zoom meta-actions (see Table VI). The vast majority (71%) of this took place when participants kept the magnification constant for at least seven seconds, and another 10% took place during a local maximum of magnification. Both behaviors are more consistent with a search

task (see §5.3.5) than a navigate task. Only the remaining 20% was typical of a conventional zooming interface (see Figure 8), occurring when participants performed brief pans either after having zoomed out or while making a series of zooms in/out.

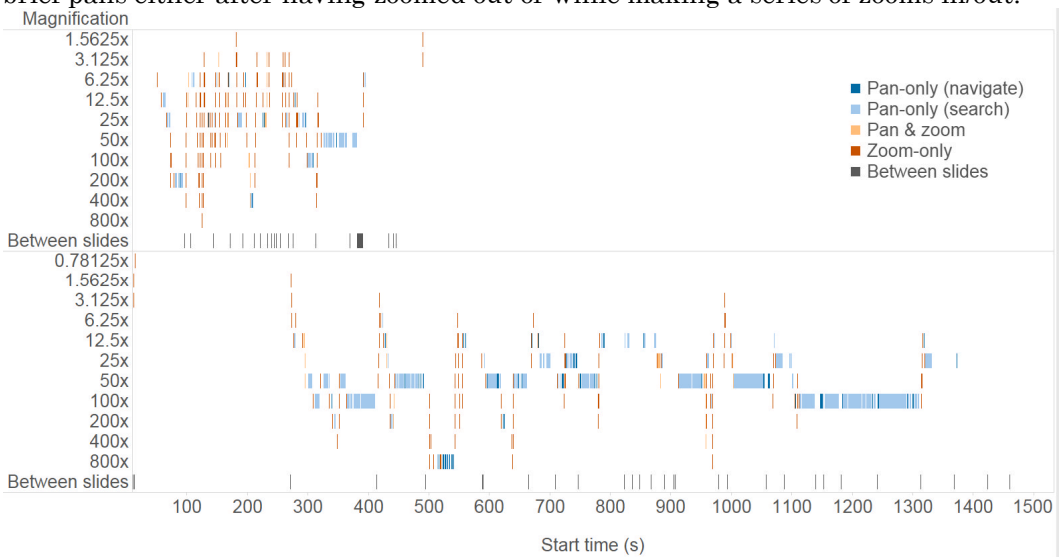

Fig 8. The timelines of meta-actions from the same breast case, showing trials where pathologists adopted substantially different navigation strategies. One pathologist predominantly used the interface as intended (top), but the other performed one third of the within-slide panning in a manner similar to a conventional zooming interface (bottom).

5.3.5. Search. Some of the search meta-actions combined panning and zooming, and are reported above (see §5.3.4). However, the majority were pan-only. Of these, 81% covered a larger area than the detail view (3280 × 2048 pixels) and, therefore, would have required clutched panning movements with a conventional interface. By panning in the overview, participants made physical movements that were substantially smaller than if panning had been performed in the detail view, with 80% of search panning involving a case overview : detail view scale difference that was greater than 100.

The large scale difference increased the likelihood that participants would find it difficult to control panning movements, particularly in micro meta-actions where participants made small cursor movements (i.e., moved the cursor within a 10×10 pixel bounding box in the case overview). There were 415 micro meta-actions, out of a total of 3259 meta-actions. To investigate the micro meta-actions, we reviewed videos of the workstation display for 11 participants (a recording error meant that video was not recorded for the other participant). The micro meta-actions typically took place when participants made a sequence of pans to inspect a region of interest, with the majority taking place in a sequence that contained at least five pan-only meta-actions, and the longest sequence containing 18 pans. For only 1% of the micro-pans did the videos indicate that a participant may have had difficulty with the interface (e.g., panning a small amount back-and-forth).

5.3.6. Compare. It takes five seconds to change slides on a conventional microscope (see §5.3.4), whereas the virtual microscope allowed the same operation to be performed with a single click or key press. Therefore, it is no surprise that participants revisited slides considerably (seven times) more often with the virtual microscope than a conventional microscope. With the virtual microscope, participants

clicked to perform 87% of the revisits, 45% of those being to revisit a slide that was not adjacent to the present slide in the case overview.

5.4 Discussion

The image collections interface provided a step change improvement in the speed with which pathologists could make diagnoses, and there was negligible (2%) difference between our system and a conventional microscope. The interface provided a number of benefits: the detail view resolution allowed pathologists to view the whole of a slide at low magnification, the overviews helped pathologists to identify and navigate directly to ROIs both within- and between-slides, and the panning method allowed pathologists to search tissue without making clutched mouse movements. These benefits would be expected to make diagnosis faster with our system than a conventional microscope but, instead, there was parity in the time taken. This was due to pathologists revisiting slides much more often, perhaps to confirm aspects of a diagnosis. A much larger study would be needed to determine whether this revisiting improved the quality of diagnosis. The remainder of this section discusses the findings in the context of the four generic visualization tasks.

5.4.1. Overview first. The high resolution of the detail view allowed participants to view the whole of a slide at a low magnification, and this sometimes allowed them to complete their assessment of a particular slide without panning or zooming at all. As with single-slide cases (see §4), the net result was that participants spent considerably less time viewing slides at a low magnification with the virtual microscope than with the conventional microscope. However, these data need to be interpreted with some caution because, with both microscopes, the nature of diagnosis means that the timings include periods when participants were looking at slides as well as performing other tasks such as reading the case notes.

5.4.2. Navigate. Discrete navigational movements between slides accounted for more than half of the total distance that participants panned, in detail view coordinates. Participants performed the majority of these movements by clicking with the mouse, providing a substantial time advantage over a conventional microscope for which changing slide takes five seconds. Unlike changing slide with the cursor keys, clicking allowed participants to navigate directly to a specific point of a slide. The high resolution of the detail view meant that, even at 400× magnification, view pointing [Guiard et al. 2004] only needed to be accurate to a 2×3 pixel region for the point that was clicked in the case overview to lie within the detail view. The bezel-free detail view meant that participants did not have to make adjustments that sometimes took place with the single-slide interface.

5.4.3. Search. Participants searched without difficulty for the vast majority of the time, with the micro-panning data showing that difficulties occurred only very occasionally and were minor in nature. This is notable because the vast majority of the search panning was performed using a scale difference that far exceeded established guidelines [Plaisant et al. 1995; Shneiderman 1998].

A large proportion of the search meta-actions involved panning over a wide area, so participants would have had to make clutching movements with conventional overview+detail interfaces, whereas our interface allowed participants to pan in a single movement that also involved considerably less physical movement. This sped up diagnosis and, with prolonged usage, is likely to considerably reduce fatigue.

5.4.4 Compare. The large amount of display real estate (≈1.5 million pixels) that was devoted to the case overview allowed participants to simultaneously see every slide in the cases at life-size and with a single click, select a particular location on a specific slide to revisit. Allowing empty cells in the grid layout meant that slides

could be organized in a clinically relevant manner, which is likely to have improved the ease with which participants could recognize slides that they wished to revisit.

The ease with which participants could switch between slides led to a seven-fold increase in the number of times that they revisited slides with the virtual microscope, compared with a conventional microscope. In other words, with the virtual microscope participants relied less on knowledge in the head and more on knowledge in the world [Gray and Fu 2001], which is clearly beneficial.

6. CONCLUSIONS

This paper describes the design and evaluation of user interfaces that allow gigapixel images to be navigated effectively. The evaluations involved domain experts (consultant and trainee pathologists) performing real work, and datasets that were up to 3150 times larger than those used in any previous research that investigated the details of navigating images. The effectiveness of our interfaces was demonstrated by the time that the pathologists took to make diagnoses, compared with the gold standard of a conventional light microscope (the device that pathologists have used for over 100 years), and detailed analysis of their navigational behavior.

The interfaces combined zooming with the overview+detail approach [Cockburn et al. 2008], as popularized by Google Maps, but were innovative in the following key ways. First, the interfaces rewrite established guidelines for the maximum recommended overview:detail view scale difference, because our design allowed users to pan quickly and precisely with scale differences that were considerably larger than established guidelines (our maximum scale difference was 1702, compared with guidelines of 20 [Plaisant et al. 1995] or 30 [Shneiderman 1998]). Second, we allocated an unusually large proportion of the real estate to the overviews (a screen-space ratio of 1:3, exceeding the 1:7 of [Treanor et al. 2009] and 1:10 ratios of [Jakobsen and Hornbæk 2011]), which allowed all of the slides in a collection to be shown life-sized and a 1 megapixel overview to be shown of the current slide. As the size of an overview increases the scale difference decreases, making it easier for users to identify ROIs in the overview, lowering the precision required for view pointing [Guiard et al. 2004], and generally facilitating panning. However, as the image collections interface indicates (see §5), a thumbnail overview could be used to effectively navigate a single gigapixel image on an ordinary desktop display. Third, the high resolution of the detail view was advantageous for providing a quick overview of each image.

If pathology 'goes digital' then hospitals and health services could make considerable cost savings and quality improvements, particularly from streamlining workflows and in the seeking of secondary opinions, which is routine for some cancers (e.g., see [Al - Janabi et al. 2012; Randell et al. 2012]). Validation and regulatory approval for whole slide imaging, and a substantial investment in computing infrastructure (storage, network bandwidth, systems integration, etc) would be needed, but these are not insurmountable. However, a show-stopper is the time pathologists take to make diagnoses with existing virtual slide systems [Treanor and Quirke 2007]. Our research shows how diagnosis time can be addressed, removing a barrier for widespread adoption of digital pathology. Diagnosis is likely to be further speeded up as pathologists become more experienced with virtual slides.

Finally, although our interfaces were purpose-designed for a specific application, their design could be generalized to other applications. The interfaces have already been used in informal settings to navigate an astronomy sky survey (the whole

UKIDSS Galactic Plane Survey; a 7.0 gigapixel image) and a large geographic map (19.2 gigapixels; a 1:50000 scale Ordnance Survey map of the whole of the UK). Remote sensing datasets are similar in scale, with LANDSAT 7 scenes (28.5m horizontal resolution) of the whole of the Amazon rainforest (7 million sq km) producing a combined image that is 8.6 gigapixels – approximately the size of one pathology slide. Other application areas could include those involving high-throughput microscopy, providing users with the ability to seamlessly navigate collections of large numbers of images that have modest resolution [Walter et al. 2010].

PRIOR PUBLICATION

We have previously published papers that evaluated the individual [Randell et al. 2013] and image collection interfaces [Randell et al. 2014] from a clinical perspective. This work described in the present paper is almost entirely new. Only a few details (high-level design concepts, and headline data about diagnosis time, confidence and accuracy for our interfaces vs. a conventional microscope) are duplicated.

ACKNOWLEDGMENTS

This research was supported by the National Institute for Health Research (NEAT L004), Engineering and Physical Sciences Research Council (EP/K503836/1; EP/J017620/1) and Medical Research Council (MR/L01629X/1). The data used for this research are openly available from the University of Leeds data archive at http://doi.org/10.5518/17.

REFERENCES

AL-JANABI, S., HUISMAN, A. AND VAN DIEST, P.J. 2012. Digital pathology: Current status and future perspectives. *Histopathology 61*, 1-9.

ANSLOW, C., MARSHALL, S., NOBLE, J., TEMPERO, E. AND BIDDLE, R. 2010. User evaluation of polymetric views using a large visualization wall. In *Proceedings of the 5th international symposium on Software visualization* ACM, New York, 25-34.

APPERT, C., CHAPUIS, O. AND PIETRIGA, E. 2010. High-precision magnification lenses. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 273-282.

ARETZ, A. 1991. The design of electronic map displays. *Human Factors 33*, 85-101.

BALL, R., NORTH, C. AND BOWMAN, D.A. 2007. Move to improve: Promoting physical navigation to increase user performance with large displays. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 191-200.

BAUDISCH, P., GOOD, N., BELLOTTI, V. AND SCHRAEDLEY, P. 2002. Keeping things in context: a comparative evaluation of focus plus context screens, overviews, and zooming. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 259-266.

BAUDISCH, P., LEE, B. AND HANNA, L. 2004. Fishnet, a fisheye web browser with search term popouts: a comparative evaluation with overview and linear view. In *Proceedings of the working conference on Advanced visual interfaces (AVI)* ACM, New York, 133-140.

BEARD, D.V. AND WALKER, J.Q. 1990. Navigational techniques to improve the display of large two-dimensional spaces. *Behaviour & Information Technology 9*, 451-466.

BEAUDOUIN-LAFON, M., HUOT, S., OLAFSDOTTIR, H. AND DRAGICEVIC, P. 2014. GlideCursor: Pointing with an inertial cursor. In *Proceedings of the 2014 International Working Conference on Advanced Visual Interfaces (AVI)* ACM, New York, 49-56.

BEDERSON, B. 2000. Fisheye menus. In *Proceedings of the 13th Annual ACM Symposium on User Interface Software and Technology* ACM, New York, 217-225.

BURIGAT, S. AND CHITTARO, L. 2011. Visualizing references to off-screen content on mobile devices: A comparison of Arrows, Wedge, and Overview+Detail. *Interacting with Computers 23*, 156-166.

CARD, S.K., ROBERTSON, G.G. AND MACKINLAY, J.D. 1991. The information visualizer, an information workspace. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 181-186.

CARPENDALE, S., LIGH, J. AND PATTISON, E. 2004. Achieving higher magnification in context. In *Proceedings of the 17th annual ACM symposium on User interface software and technology (UIST)* ACM, New York, 71-80.

CASIEZ, G. AND ROUSSEL, N. 2011. No more bricolage!: Methods and tools to characterize, replicate and

compare pointing transfer functions. In *Proceedings of the 24th annual ACM symposium on User interface software and technology (UIST)* ACM, New York, 603-614.
CASIEZ, G., VOGEL, D., BALAKRISHNAN, R. AND COCKBURN, A. 2008. The impact of control-display gain on user performance in pointing tasks. *Human–Computer Interaction 23*, 215-250.
COCKBURN, A., KARLSON, A. AND BEDERSON, B.B. 2008. A review of overview+detail, zooming, and focus+context interfaces. *ACM Computing Surveys 41*, Article 2 (December 2008).
COCKBURN, A. AND SAVAGE, J. 2004. Comparing speed-dependent automatic zooming with traditional scroll, pan and zoom methods. In *People and Computers XVII — Designing for Society* Springer, 87-102.
DATTA, R., JOSHI, D., LI, J. AND WANG, J.Z. 2008. Image retrieval: Ideas, influences, and trends of the new age. *ACM Computing Surveys 40*, Article 5 (May 2008).
GRAY, W. AND FU, W. 2001. Ignoring perfect knowledge in-the-world for imperfect knowledge in-the-head: Implications of rational analysis for interface design. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 112-119.
GUIARD, Y. AND BEAUDOUIN-LAFON, M. 2004. Target acquisition in multiscale electronic worlds. *International Journal of Human-Computer Studies 61*, 875-905.
GUIARD, Y., BEAUDOUIN-LAFON, M., BASTIN, J., PASVEER, D. AND ZHAI, S. 2004. View size and pointing difficulty in multi-scale navigation. In *Proceedings of the working conference on Advanced visual interfaces (AVI)* ACM, New York, 117-124.
HAMILTON, N.A., WANG, J.T., KERR, M.C. AND TEASDALE, R.D. 2009. Statistical and visual differentiation of subcellular imaging. *BMC bioinformatics 10*, 94.
HENRY, M.J., HAMPTON, S., ENDERT, A., ROBERTS, I. AND PAYNE, D. 2013. MultiFacet: A faceted interface for browsing large multimedia collections. In *IEEE International Symposium on Multimedia (ISM)* IEEE, Los Alamitos, CA, 347-350.
HOOPER, E. AND COURY, B. 1994. Graphical displays for orientation information. *Human Factors 36*, 62-78.
HORNBÆK, K., BEDERSON, B.B. AND PLAISANT, C. 2002. Navigation patterns and usability of zoomable user interfaces with and without an overview. *ACM Transactions on Computer-Human Interaction 9*, 362-389.
HORNBÆK, K. AND FRØKJÆR, E. 2003. Reading patterns and usability in visualizations of electronic documents. *ACM Transactions on Computer-Human Interaction 10*, 119-149.
JAKOBSEN, M.R. AND HORNBÆK, K. 2011. Sizing up visualizations: effects of display size in focus+context, overview+detail, and zooming interfaces. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 1451-1460.
JAVED, W., GHANI, S. AND ELMQVIST, N. 2012. Polyzoom: multiscale and multifocus exploration in 2d visual spaces. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 287-296.
LEVINE, M., MARCHON, I. AND HANLEY, G. 1984. The placement and misplacement of you-are-here maps. *Environment and Behavior 16*, 139-157.
MOORE, J., ALLAN, C., BUREL, J.-M., LORANGER, B., MACDONALD, D., MONK, J. AND SWEDLOW, J.R. 2008. Open tools for storage and management of quantitative image data. *Methods in Cell Biology 85*, 555-570.
NANCEL, M., WAGNER, J., PIETRIGA, E., CHAPUIS, O. AND MACKAY, W. 2011. Mid-air pan-and-zoom on wall-sized displays. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 177-186.
NEKRASOVSKI, D., BODNAR, A., MCGRENERE, J., GUIMBRETIÈRE, F. AND MUNZNER, T. 2006. An evaluation of pan & zoom and rubber sheet navigation with and without an overview. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 11-20.
PERLIN, K. AND FOX, D. 1993. Pad: An alternative approach to the computer interface. In *Proceedings of the 20th annual conference on Computer graphics and interactive techniques* ACM, New York, 57-64.
PIETRIGA, E., APPERT, C. AND BEAUDOUIN-LAFON, M. 2007. Pointing and beyond: an operationalization and preliminary evaluation of multi-scale searching. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 1215-1224.
PIROLLI, P., CARD, S.K. AND VAN DER WEGE, M.M. 2003. The effects of information scent on visual search in the hyperbolic tree browser. *ACM Transactions on Computer-Human Interaction 10*, 20-53.
PLAISANT, C., CARR, D. AND SHNEIDERMAN, B. 1995. Image-browser taxonomy and guidelines for designers. *IEEE Software 12*, 21-32.
PRETORIUS, A., ZHOU, Y. AND RUDDLE, R. 2015. Visual parameter optimisation for biomedical image processing. *BMC bioinformatics 16 (Suppl. 11)*, S9.
PRETORIUS, A.J., BRAY, M.P., CARPENTER, A.E. AND RUDDLE, R.A. 2011. Visualization of parameter space for image analysis. *IEEE Transactions on Visualization and Computer Graphics 17*, 2402-2411.
RANDELL, R., HUTCHINS, G., SANDARS, J., AMBEPITIYA, T., TREANOR, D., THOMAS, R. AND RUDDLE, R.A. 2012. Using a high-resolution wall-sized virtual microscope to teach undergraduate

medical students. In *CHI '12 Extended Abstracts on Human Factors in Computing Systems* ACM, New York, 2435-2440.
RANDELL, R., RUDDLE, R.A., MELLO-THOMS, C., THOMAS, R.G., QUIRKE, P. AND TREANOR, D. 2013. Virtual reality microscope versus conventional microscope on time to diagnosis: an experimental study. *Histopathology 62*, 351-358.
RANDELL, R., RUDDLE, R.A., QUIRKE, P., THOMAS, R.G. AND TREANOR, D. 2012. Working at the microscope: Analysis of the activities involved in diagnostic pathology. *Histopathology 60*, 504-510.
RANDELL, R., RUDDLE, R.A., THOMAS, R.G., MELLO-THOMS, C. AND TREANOR, D. 2014. Diagnosis of major cancer resection specimens with virtual slides: Impact of a novel digital pathology workstation. *Human Pathology 45*, 2101-2106.
ROONEY, C. AND RUDDLE, R.A. 2012. Improving window manipulation and content interaction on high resolution, wall-sized displays. *International Journal of Human-Computer Interaction 28*, 423-432.
RUDDLE, R.A., FATEEN, W., TREANOR, D., SONDERGELD, P. AND QUIRKE, P. 2013. Leveraging wall-sized high-resolution displays for comparative genomics analyses of copy number variation. In *Proceedings of the 3rd IEEE Symposium on Biological Data Visualization* IEEE, Los Alamitos, CA, 89-96.
RUDDLE, R.A. AND JONES, D.M. 2001. Movement in cluttered virtual environments. *Presence: Teleoperators and Virtual Environments 10*, 511-524.
RUDDLE, R.A., PAYNE, S.J. AND JONES, D.M. 1999. The effects of maps on navigation and search strategies in very-large-scale virtual environments. *Journal of Experimental Psychology: Applied 5*, 54-75.
RUDDLE, R.A., THOMAS, R.G., RANDELL, R.S., QUIRKE, P. AND TREANOR, D. 2015. Performance and interaction behaviour during visual search on large, high-resolution displays. *Information Visualization 14*, 137-147.
SHNEIDERMAN, B. 1996. The eyes have it: A task by data type taxonomy for information visualizations. In *IEEE Symposium on Visual Languages* IEEE, Los Alamitos, CA, 336-343.
SHNEIDERMAN, B. 1998. *Designing the user interface: Strategies for effective human-computer interaction*. Addison-Wesley, Reading, MA.
SHUPP, L., ANDREWS, C., DICKEY-KURDZIOLEK, M., YOST, B. AND NORTH, C. 2009. Shaping the display of the future: The effects of display size and curvature. *Human-Computer Interaction 24*, 230-272.
SKOPIK, A. AND GUTWIN, C. 2005. Improving revisitation in fisheye views with visit wear. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 771-780.
TOMINSKI, C., GLADISCH, S., KISTER, U., DACHSELT, R. AND SCHUMANN, H. 2014. A survey on interactive lenses in visualization. *EuroVis State-of-the-Art Reports*, 43-62.
TREANOR, D., JORDAN OWERS, N., HODRIEN, J., QUIRKE, P. AND RUDDLE, R.A. 2009. Virtual reality Powerwall versus conventional microscope for viewing pathology slides: an experimental comparison. *Histopathology 5*, 294-300.
TREANOR, D. AND QUIRKE, P. 2007. The virtual slide and conventional microscope – a direct comparison of their diagnostic efficiency. In *Proceedings of the Annual Meeting of the Pathological Society of Great Britain and Ireland*, Glasgow. 2007.
VAN WIJK, J.J. AND NUIJ, W.A. 2003. Smooth and efficient zooming and panning. In *IEEE Symposium on Information Visualization* IEEE, Los Alamitos, CA, 15-23.
VELEZ, N., JUKIC, D. AND HO, J. 2008. Evaluation of 2 whole-slide imaging applications in dermatopathology. *Human Pathology 39*, 1341-1349.
WALTER, T., SHATTUCK, D.W., BALDOCK, R., BASTIN, M.E., CARPENTER, A.E., DUCE, S., ELLENBERG, J., FRASER, A., HAMILTON, N. AND PIEPER, S. 2010. Visualization of image data from cells to organisms. *Nature Methods 7*, S26-S41.
WARE, C. AND LEWIS, M. 1995. The DragMag image magnifier. In *Conference companion on Human factors in computing systems* ACM, New York, 407-408.
WICKENS, C. AND PREVETT, T. 1995. Exploring the dimensions of egocentricity in aircraft navigation displays. *Journal of Experimental Psychology: Applied 1*, 110-135.
YOST, B., HACIAHMETOGLU, Y. AND NORTH, C. 2007. Beyond visual acuity: The perceptual scalability of information visualizations for large displays. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 101-110.
ZANELLA, A., CARPENDALE, M.S.T. AND ROUNDING, M. 2002. On the effects of viewing cues in comprehending distortions. In *Proceedings of the second Nordic conference on Human-computer interaction* ACM, New York, 119-128.
ZHAI, S. AND MILGRAM, P. 1998. Quantifying coordination in multiple DOF movement and its application to evaluating 6 DOF input devices. In *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* ACM, New York, 320-327.