Identifying the third dimension hidden in 2D fluoroscopy – a story of APN Health, LLC

Stephen J. Merrill

Department of Mathematics, Statistics and Computer Science

Marquette University

What this talk is about

- From initial idea and motivation
  to the development of new science
- Role of university professors in
  a company's product development
- Patents and the dichotomy of patents and publishing
- Life history of a startup
- FDA approvals of medical devices

Fluoroscopy

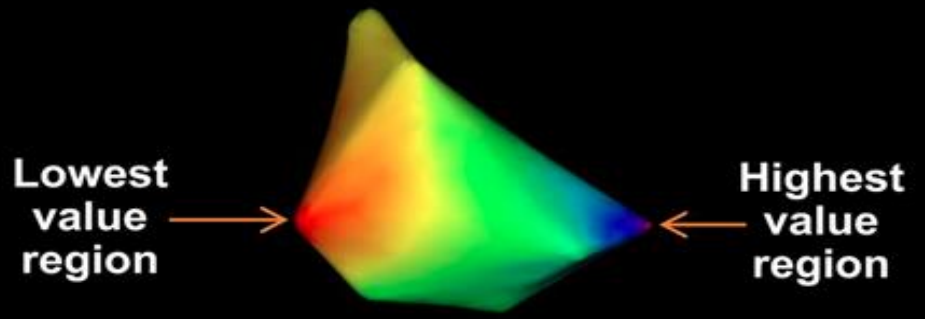
- The fluoroscope is a real-time x-ray based imaging system. We will be discussing its use in interventional cardiology in a electrophysiology (EP) Lab.

GE IGS 730

The EP Lab

- Cardiac mapping – Real-time pictures of the electrical activity in a chamber of interest (atrium or ventricle). Illustrations shown here will be of the left atrium – site of atrial fibrillation (AF).

Figure 9. Reconstruction and depiction of color-coded maps. The scale shows the lowest (earliest LAT) and highest (latest LAT) values, which have been color-coded for ease of view. LAT, local activation time.



- Ablation (RF or cryo)

  over 600,000 in US in 2011 and 240,000 of those were AF.

Clinical motivation – cardiac rhythm management

- The global cardiac rhythm **management** market to be worth $27.8bn by 2021. The market generated $14.6bn in 2010 according to *Cardiac Rhythm Management Devices: World Market Outlook, 2011-2021*, published in December 2011.

  http://www.visiongain.com/Report/728/Cardiac-Rhythm-Management-Devices

  – High growth likely to be in developing countries like China and India

- Limited growth capability especially in developing countries with expensive mapping models such as CARTO 3 System V3.0 (Biosense Webster, Inc., a division of Johnson & Johnson) and EnSite NavX (St. Jude Medical, Inc., a division of Abbott Labs) which require significant infrastructure, upfront cost and highly trained personnel to operate and have catheters and patches with single use capability. Biplane fluoroscopy only available in a few labs only.

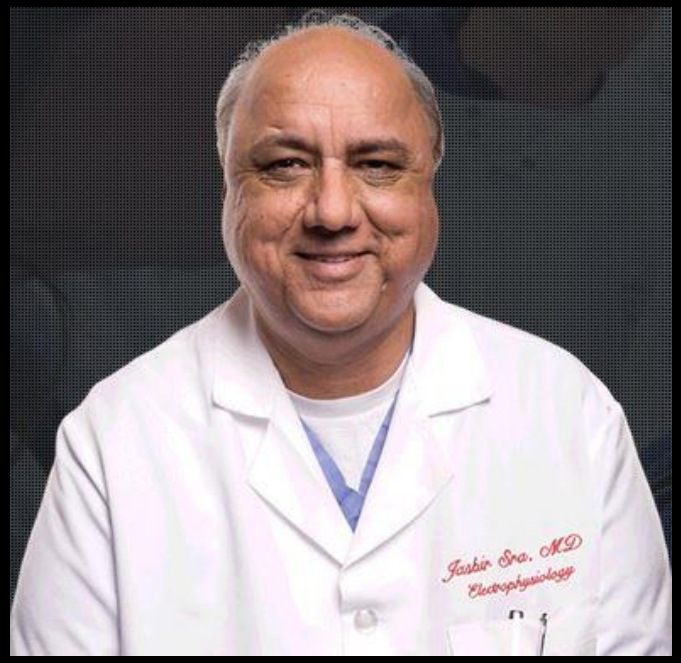
Initial Idea: e-mail of 6/7/2009

Dear Dr Merrill

I am involved in a large project dealing with 3D imaging using 2D fluoroscopy images. I will need some help from you in solving and going over some of the equations etc. Like before I was wondering if it will be possible for you to consult with me on this. I am enclosing some figures for your consideration. If you can spare some time for this please let me know.

Thanks

Dr. Jasbir S. Sra, MD, FACC, FHRS
Clinical Professor of Medicine, Univ. of Wisconsin
Director Electrophysiology -Aurora Cardiovascular Services



Note 1: From 2006 – 2008, Dr. Sra was a co-advisor of my doctoral student Shivani (Ratnakumar) Kohut who worked on CT-fluoroscope registration of cardiac images.
Note 2: APN Health was incorporated in May of 2007

Some progress – this leads to a patent application

- In a message dated 9/17/2009 8:33:36 A.M. Central Daylight Time, stevem@mscs.mu.edu writes:
- Dr. Sra,
  Just wanted to let you know that I recently made progress on your problem. I think it can be done if one more piece of information is available, the rate of movement of the catheter. It could be monitored an any place. As the x-y position can be noted, the x-y component of the rate of movement can be computed and subtracted from the total rate (the Pythagorean theorem gives the z coordinate). The direction in the z direction is given by knowing x-y position relative to the midline.

  steve merrill

Patents and Publishing

- **Patent First, Publish Later**
- The U.S. patent system bestows legal rights upon those who disclose their inventions to the U.S. Patent and Trademark Office (USPTO) in the form of a patent application. The date of application is important.
- According to U.S. law, a patent cannot be obtained if an invention was previously known or used by other people in the U.S., or was already patented or published anywhere in the world ("prior art") including in a thesis or dissertation – or a poster! Furthermore, publicly using (demonstrating) or selling an invention more than 1 year prior to filing a patent application completely bars you from ever winning a patent on that invention.

Steps for getting a patent – That first idea from 2009

- https://www.uspto.gov/patents-getting-started/patent-process-overview
- Patent applications are written in a language not commonly used
  For an example, look at https://patents.justia.com/patent/8634896
  filed in 2010 and granted in 2014.

3D model creation of anatomic structures using single-plane fluoroscopy

Patent number: 8634896

Abstract: A method for 3D reconstruction of the positions of a catheter as it is moved within a human body, comprising: (a) ascertaining the 3D position of a point on a catheter for insertion into the body; (b) acquiring fixed-angle, single-plane fluoroscopic image data of the body and catheter; (c) transferring the image data and catheter-point position to a computer; (d) determining 2D image coordinates of the point on the catheter; (e) changing the insertion length of catheter by a measured amount; (f) acquiring additional single-plane fluoroscopic image data of the body and catheter from the same angle, transferring the length change and image data to the computer, and determining image coordinates of the point on the catheter; (g) computing the 3D position of the catheter point; and (h) repeating steps e-g. A 3D model is constructed by assembling the plural 3D positions of the catheter point.

Type: Grant

Filed: September 20, 2010

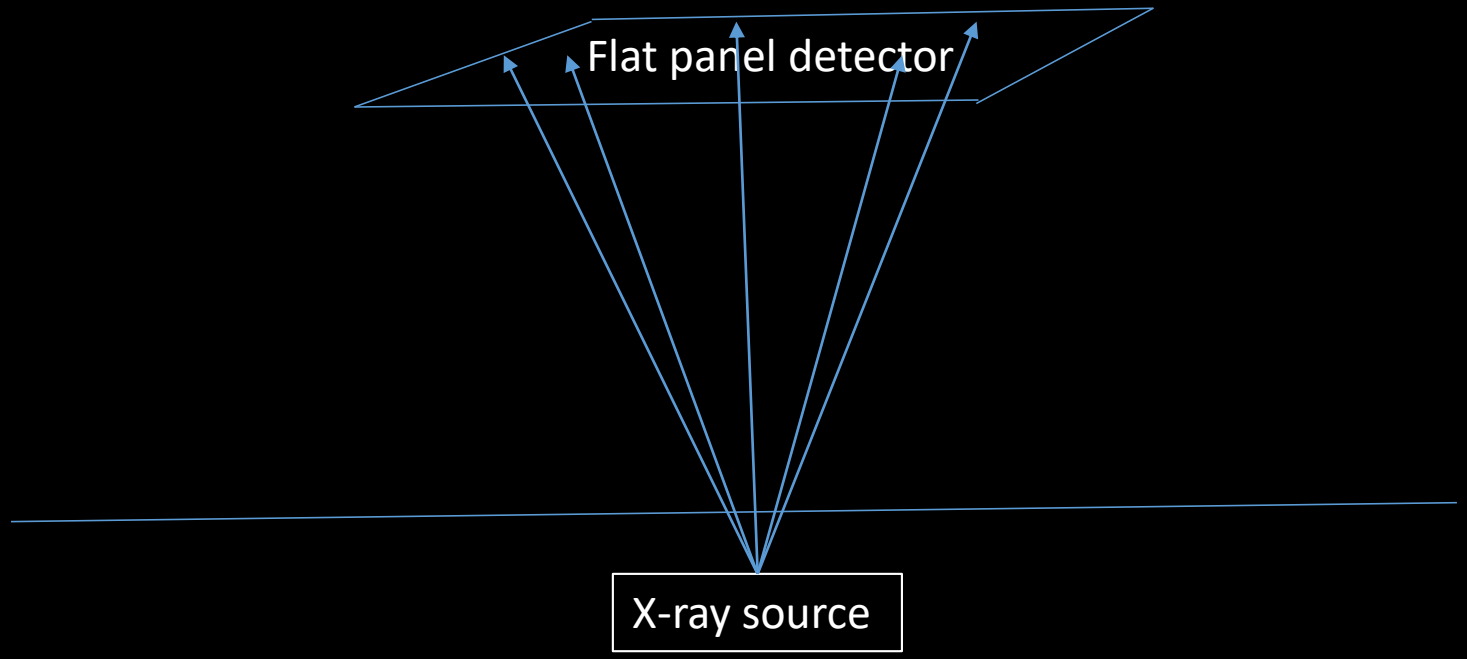
Date of Patent: January 21, 2014

Assignee: APN Health, LLC

Inventors: Jasbir Sra, Stephen J. Merrill

After testing, new ideas were needed

- The science of how the fluoroscopic image is created.



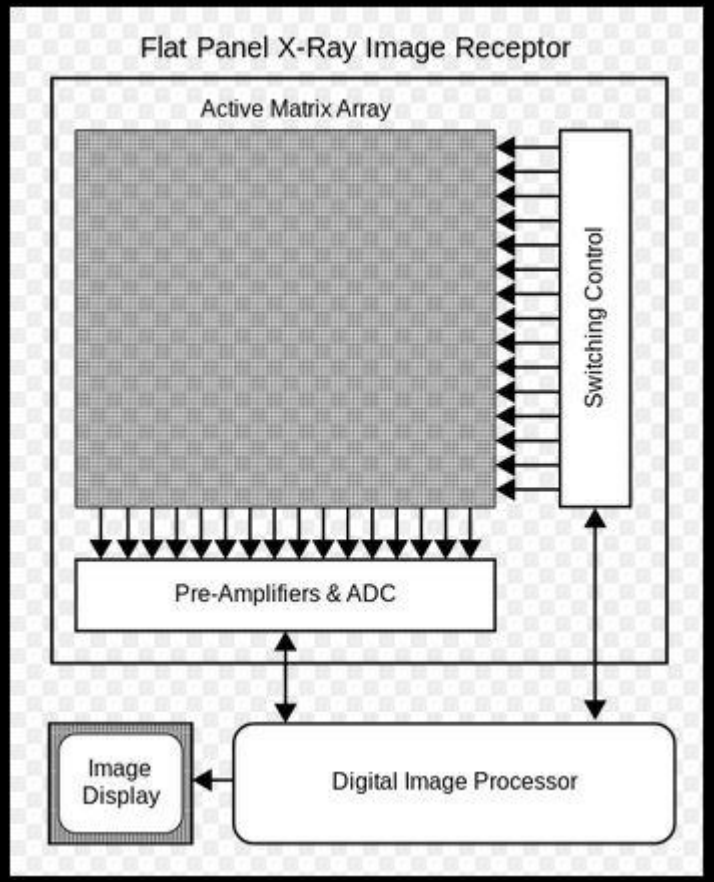
The flat panel detector

Pixellated detector

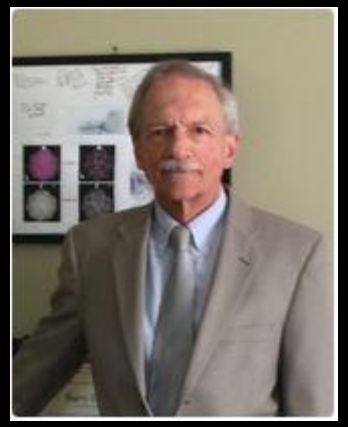
– Array of light sensitive detectors covered by light emitting phosphor (indirect detection)

– Light generated by X-rays is converted into charge within detector

– resolution is limited by the pixelation, binning that necessarily is used, and scatter and other noise present.

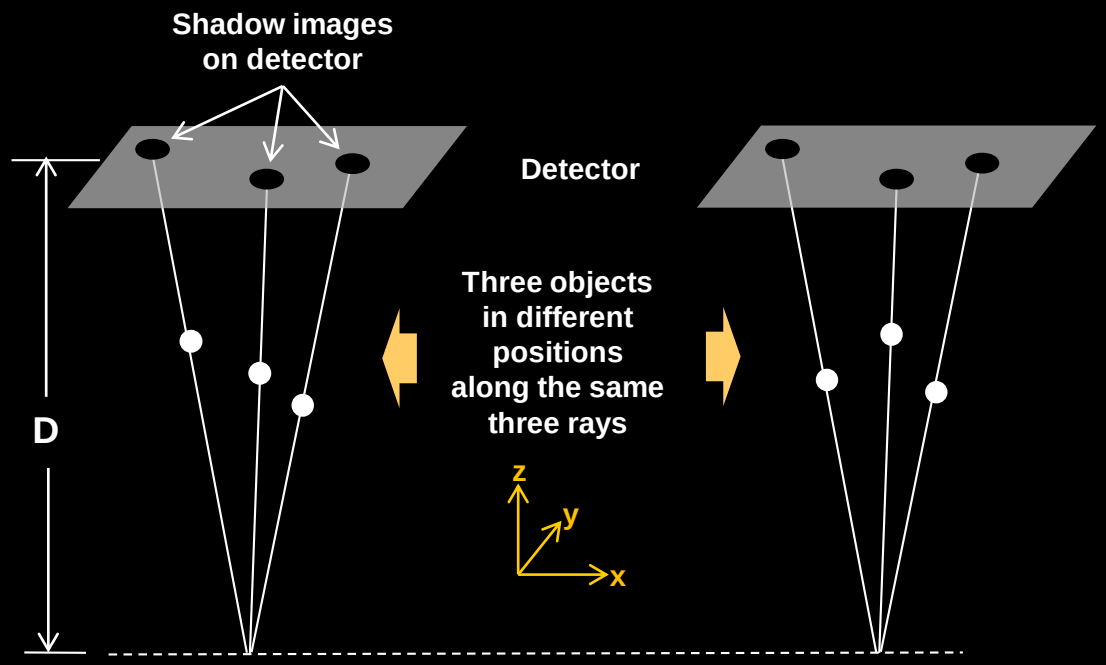


Key idea
Use conical projection to determine depth



Barry Belanger is a medical imaging scientist and engineer with 33 years of experience at GE Healthcare, primarily involving fluoroscopic x-ray systems for interventional cardiovascular applications. His roles included systems engineering, chief engineer, engineering management, and clinical applications development. He holds a BS in Electrical Engineering from Worcester Polytechnic Institute, MS degrees in Biomedical and Electrical & Computer Engineering from the University of Michigan, and a PhD in Biophysics from the Medical College of Wisconsin. He has authored and co-authored numerous scientific publications and patents, and is an emeritus member of the American Association of Physicists in Medicine.

Just knowing the (x-y) position on the detector does not give you the depth (z)

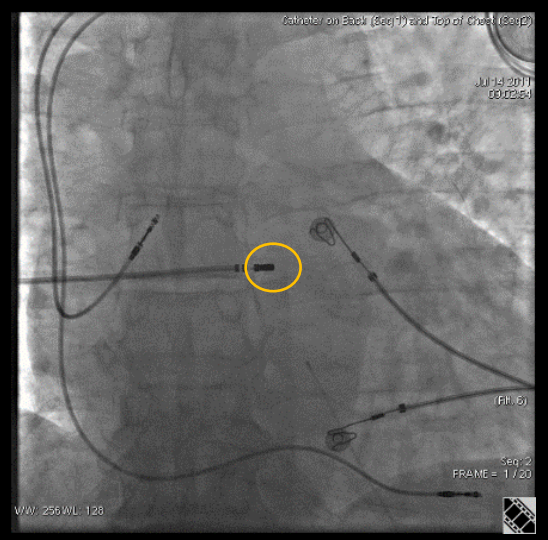


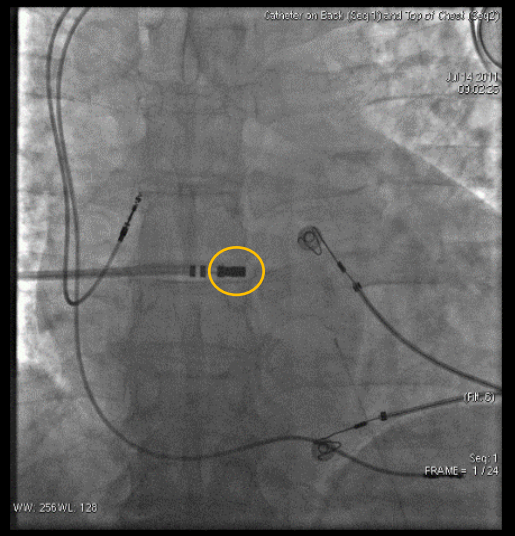
In the absence of additional information, the 2D locations of the shadow images on the detector do not provide unique 3D locations for the three objects.

Additional information needed.

Effect of radial geometry

Effective Size: Objects of a given size appear smaller when closer to the detector, and larger when farther away.





Note the difference in apparent size of the catheter electrode, a radio-opaque platinum tip, in the two images.

The difference in apparent size can be subtle (dependent on difference in depth), but it is observable and measurable. The next step is to find accurate ways to measure the effective size and relate that to depth.

JCI Insight 2016;1(21):e90453

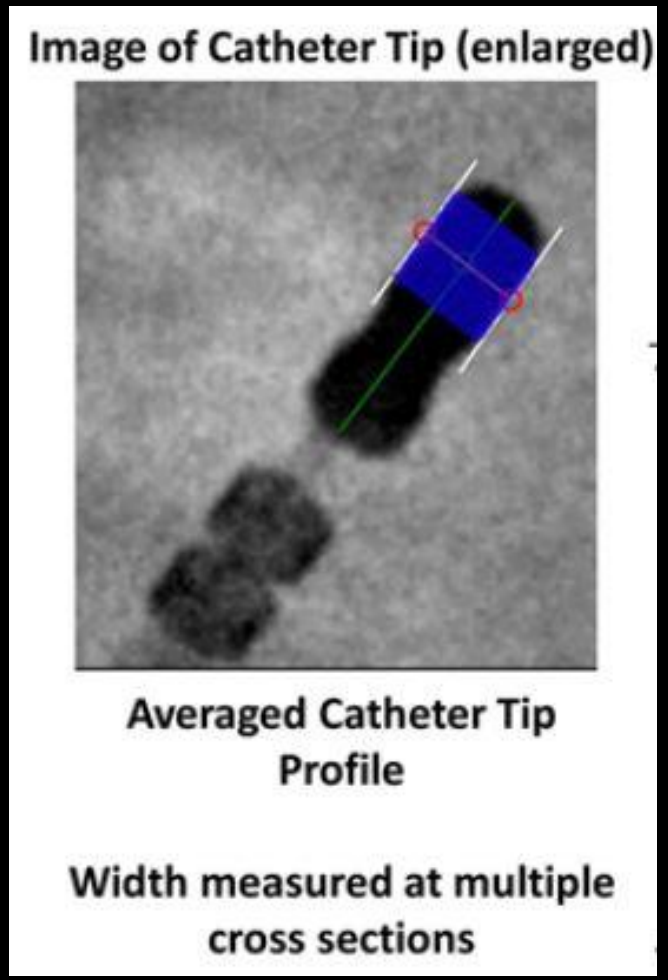
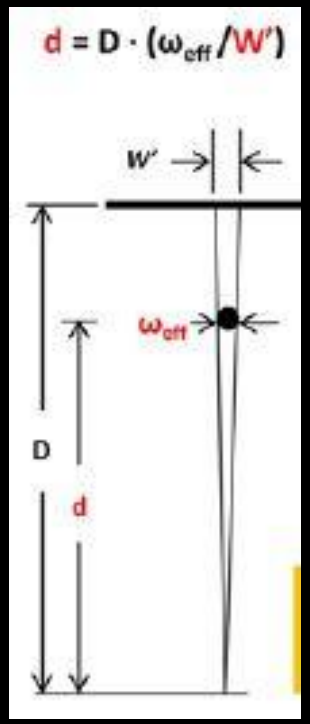
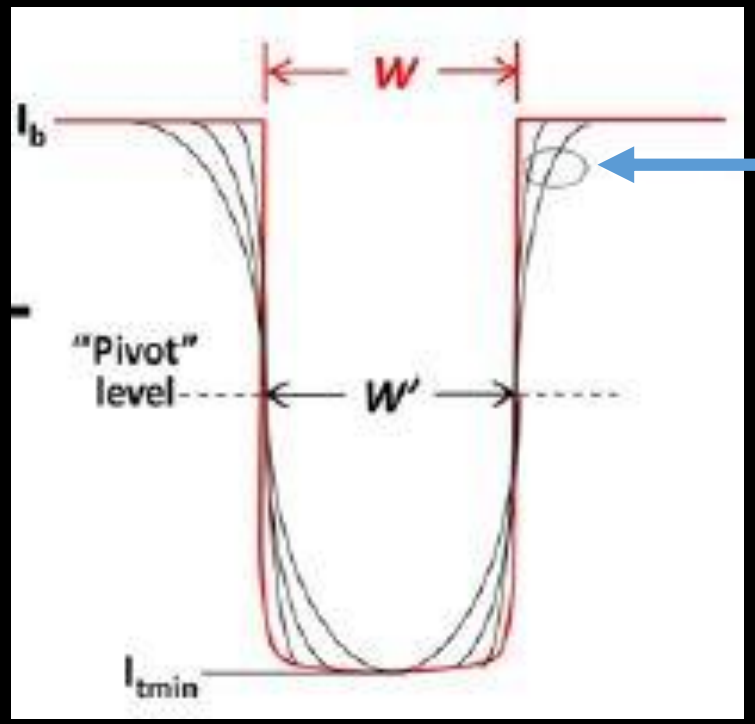


Figure 7. Accurate catheter width and depth measurement. Taking multiple cross sections perpendicular to the center line (left image in blue) greatly improves the accuracy of the effective width (ω_{eff}) measurement of a catheter tip. This information is then used to identify the depth of the catheter tip by the equation depicted here.





X-ray intensity profiles showing three different degrees of edge softening, due to focal spot penumbra, lateral movement of catheter tip, and photon scattering in x-ray detector.

Example of Prior Art

Hindawi Publishing Corporation
International Journal of Biomedical Imaging
Volume 2010, Article ID 631264, 13 pages
doi:10.1155/2010/631264

Research Article

Is Single-View Fluoroscopy Sufficient in Guiding Cardiac Ablation Procedures?

Pascal Fallavollita

School of Computing, 557 Goodwin Hall, Queen's University, Kingston, ON, Canada K7L 3N6

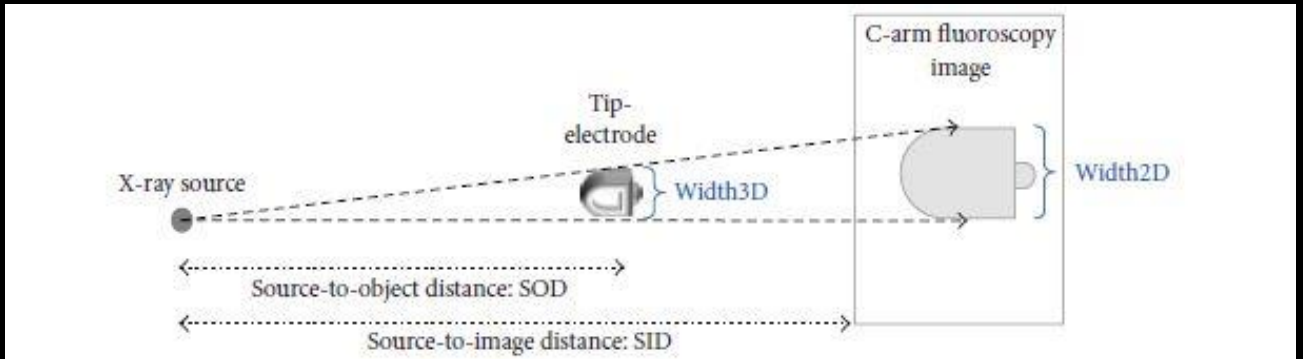
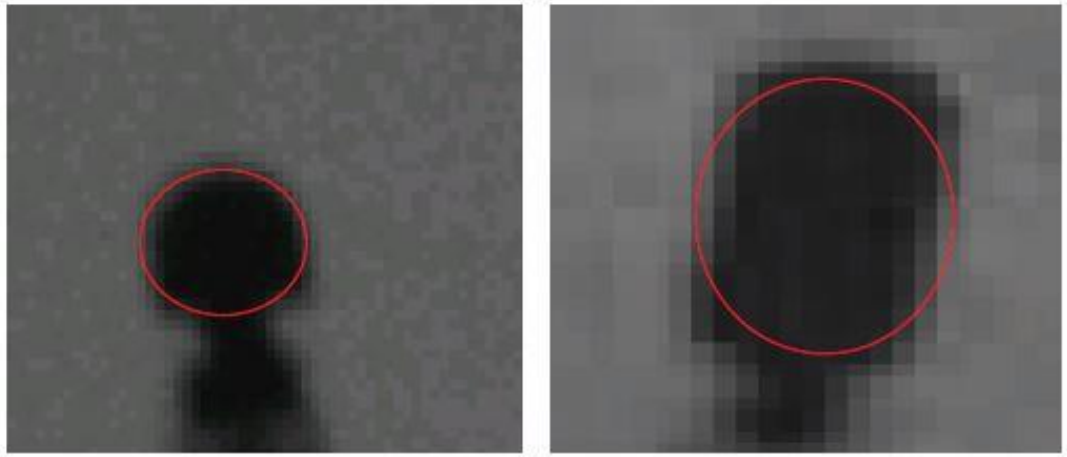


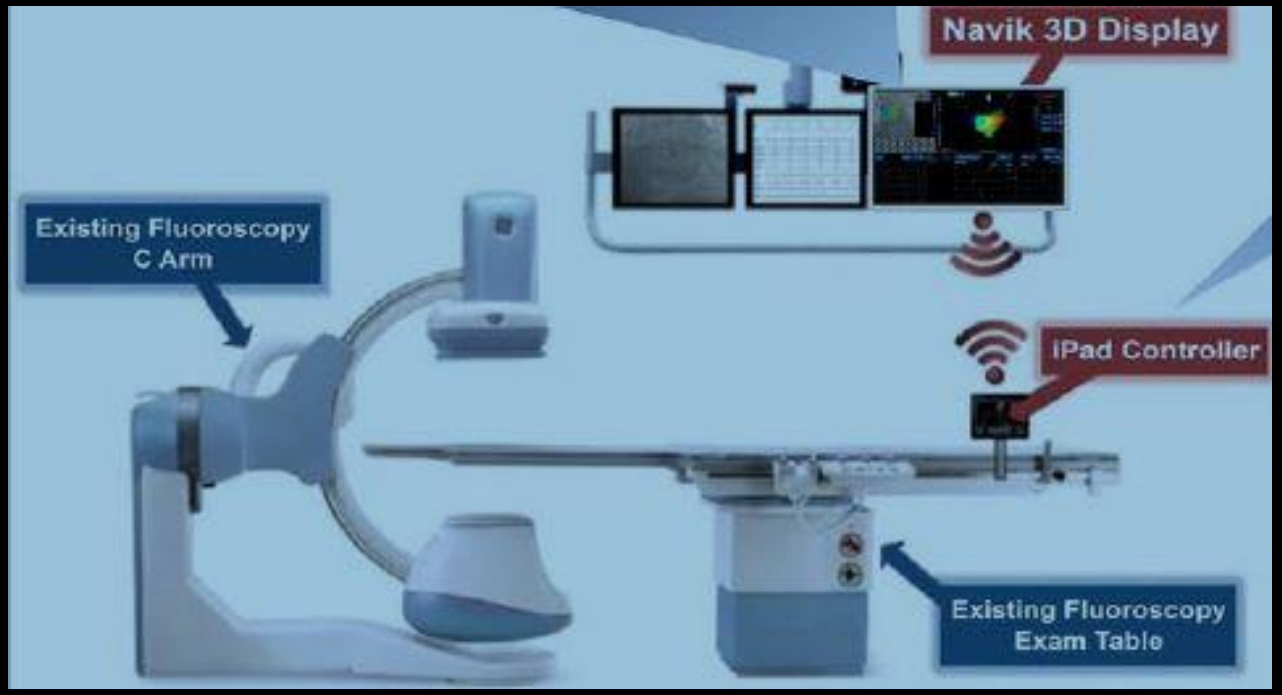
FIGURE 3: Geometric model relating the size of the electrode projection and the distance from the C-arm source.



… In conclusion, this paper describes our achievements and shortfalls in developing an affordable fluoroscopic navigation system to guide RF catheter ablation of cardiac arrhythmias

APN Health goal

- Combine fluoroscopy technology, which is available in all interventional labs, with proprietary APN Health-Navik 3D software imaging and data collection techniques to produce 3D visualization and mapping for catheter placement and ablation.
- June 2014 Working Navik 3D prototype established with real-time data acquisition, processing, and information rendering.



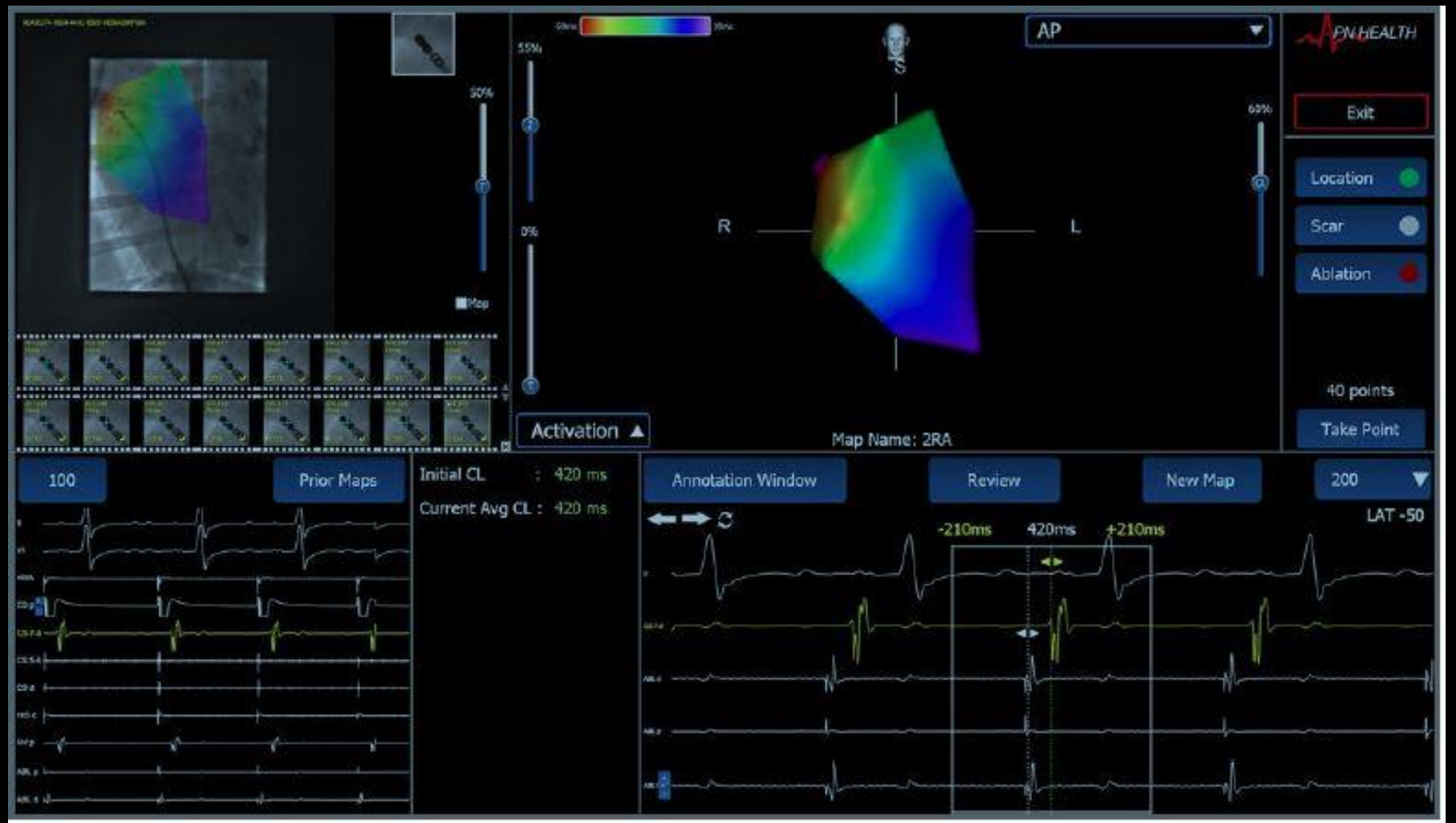


Figure 2. Screenshot of Navik 3D user interface and a right atrial map created during the experiments. The 3D map (top, center) also can be projected in 2D on the fluoroscopy screen (top left). Red indicates the earliest or lowest value region of the map, blue the last or highest value. The colors in the 3D maps above represent: purple = late activation time, blue/green/yellow = intermediate activation time, and red = early activation time. AP, anteroposterior; CL, cycle length; LAT, local activation time.

Next Step – FDA approvals

- The average cost for the development to approval of a device is $23,000,000.
- This presents a major barrier to startups.
- The nature of the application that is needed is determined by “preapplications” which allow the applicant to communicate with the FDA about what is required in a complete application.
- The application will be required to contain both bench (phantom) results as well as animal experiments.

FDA Campus
Silver Spring, MD

CDRH (devices) in Bldg 62 (Bio and Chem Labs), Bldg 64 (Engineering and Physics), and Bldg 66 (administration and reviewers)

OFEMS
Office of Facilities, Engineering and Mission Support Services

Regulation of Medical Devices – FDA Center for Devices and Radiological Health (CDRH)

- A medical device is any product that does not achieve its purposes by chemical action or metabolism (those are regulated by CDER (drugs) and CBER (biologics)).
- Examples: tongue depressor, bandages

and

Robotic surgery systems, MRI machines

Classification

- Classification determines extent of regulatory control (risk-based)
- Regulatory Control increases from
  Class I – Low Risk (adhesive bandages, I.V. stand, sunglasses)
  Class II – Moderate Risk (powered wheelchair, surgical mask)
  Class III – High Risk (heart valves, implanted joints)
- Includes intended use (labeling and instructions) for the device

Medical Software is regulated by CDRH

- Classification depends on intended use – Class III if it supports or sustains human life. Failure of such a system causes great harm.

  example – software associated with an automated defibrillator

- Monitoring software and devices which advise a physician tends to be Class II.

  example – fitbit

September 28, 2017:

- The Food and Drug Administration announced a new program that offers a "fast track" for nine technology companies to gain approval for features in their devices.
- The announcement includes Apple, Samsung Electronics, Fitbit, Verily Life Science (an arm of Google), Johnson & Johnson, and Roche Holding AG.
- Called the "Pre-Cert for Software Pilot," the move is meant to allow companies to develop technologies more rapidly, while still maintaining some government oversight over those projects. The affected companies will be able to get their products pre-cleared going forward, rather than going through the FDA's standard application and approval process.

510(k) Clearances – Class II devices

- Section 510(k) of the Food, Drug and Cosmetic Act requires device manufacturers who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification - also called PMN or 510(k). This allows FDA to determine whether the device is substantially equivalent to a device already placed into one of the three classification categories (a predicate device)
- APN needed to demonstrate that it was substantially equivalent to the CARTO predicate device.

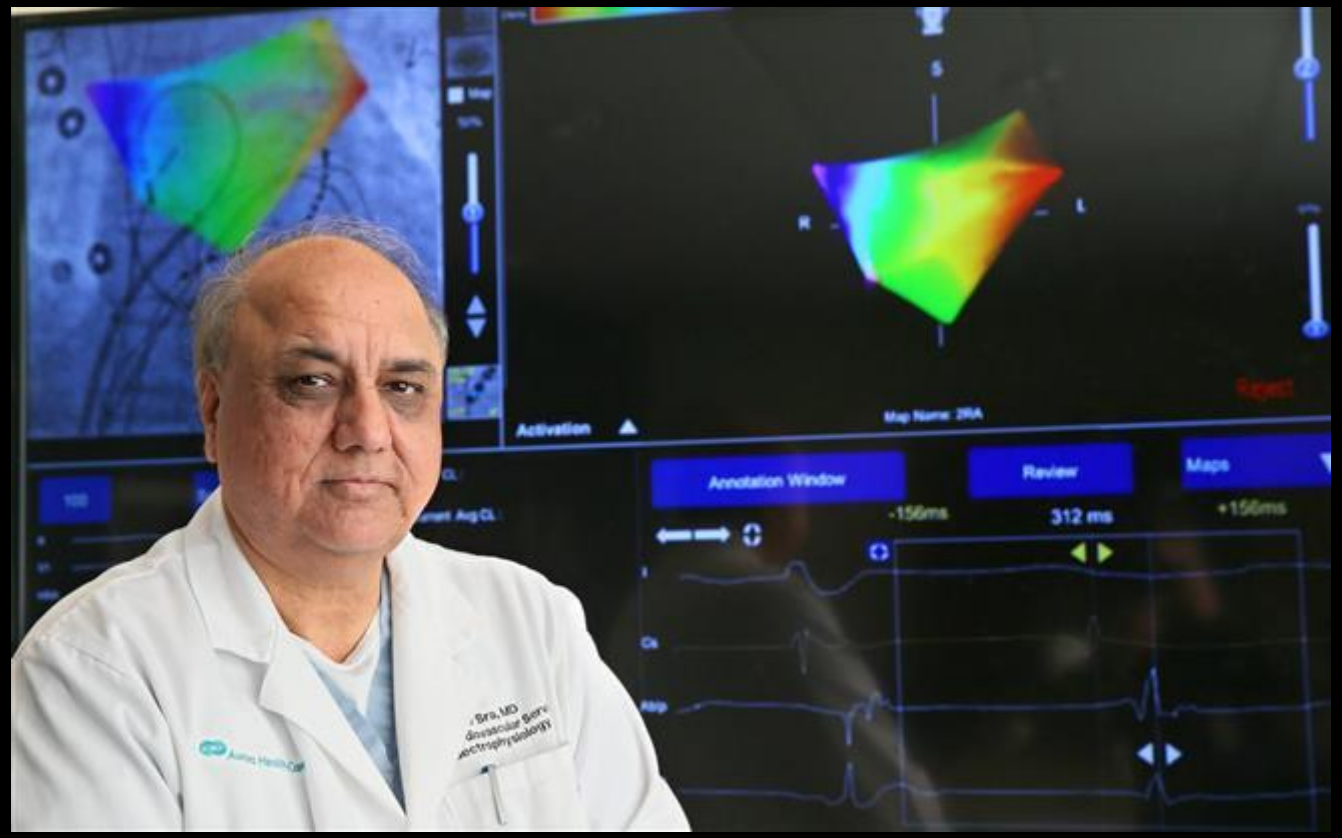
FDA clearance – 510(k) process

- July 2015 FDA 510(k) application filed – roughly 3000 pages
  “predicate device” is CARTO XP
- January 2016 FDA clearance to market the Navik 3D product.

MILWAUKEE-WISCONSIN JOURNAL SENTINEL

March 30, 2016

Aurora doctor forms company to create less-costly arrhythmia treatment



- http://www.apnhealth.com/