Introduction to Fiducial Registration for Medical Applications

J. Michael Fitzpatrick

VISE Instructional Workshop
Summer Seminar Series

Tuesday & Wednesday, August 11 &12, 2015
5326 Stevenson Center, Vanderbilt University

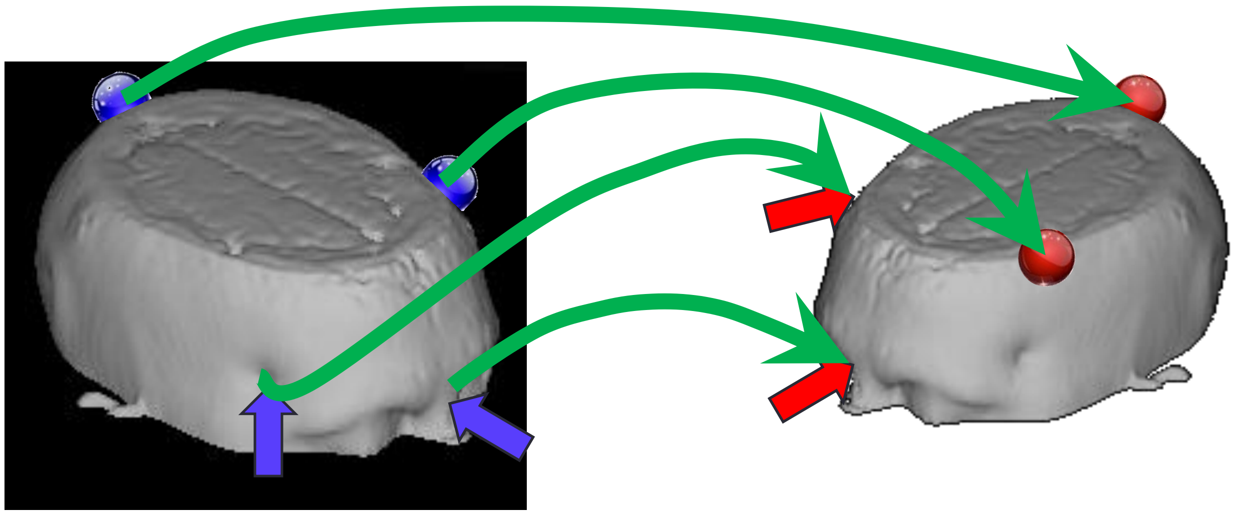
What we will learn

- Three definitions
- Five algorithms
- Three formulas
- Three Myths
- And some history

What is “fiducial registration”?

Localize a set of points in a 3D patient image.

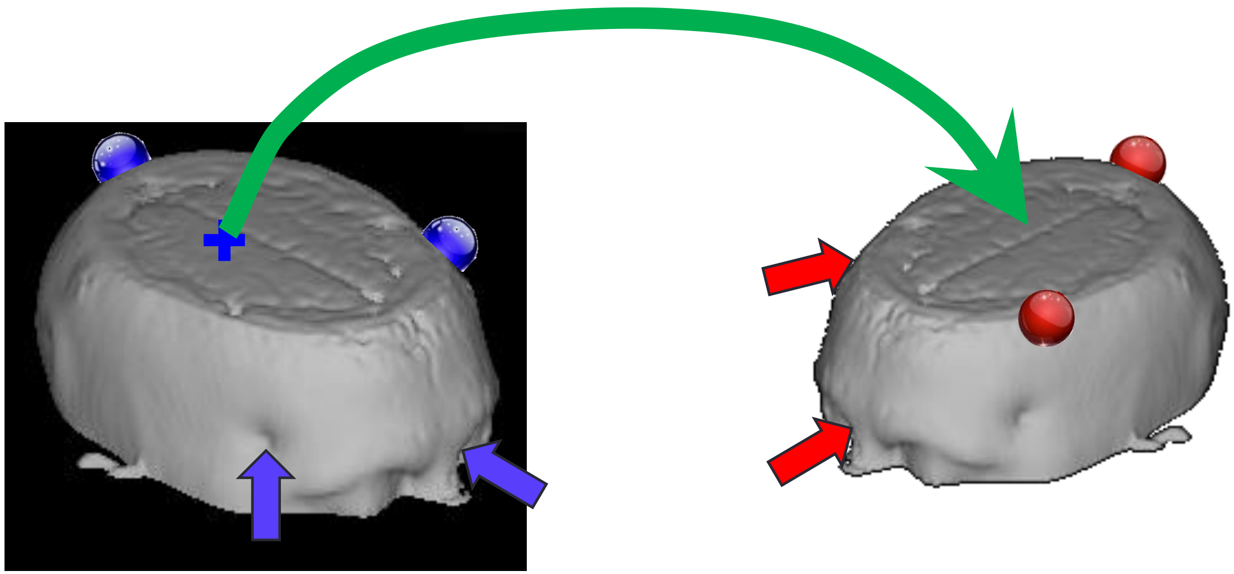
Localize the corresponding points in the OR (or another image of the same patient)



Find a <u>rigid</u> transformation that registers the first set of points to the second set.

What is “fiducial registration”?

…and use that same transformation to map other points to their corresponding points.



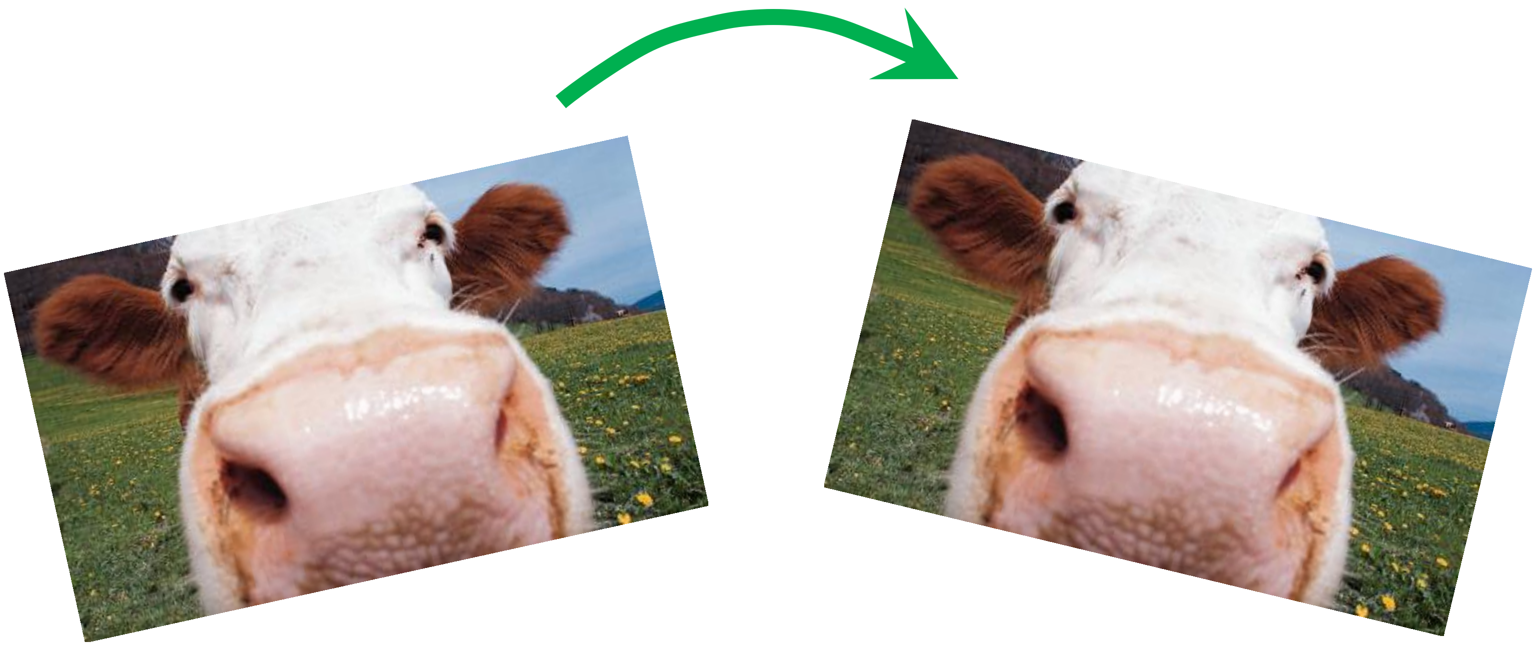
Points that are used to determine the transformation are called ***fiducials***. Non-fiducial points are called ***targets***.

What is a rigid transformation?

What is a rigid transformation?

Cow

What is a rigid transformation?

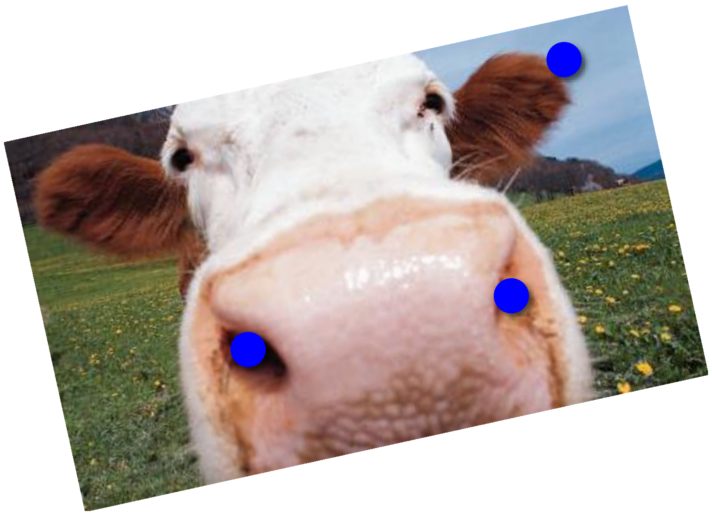


Cow

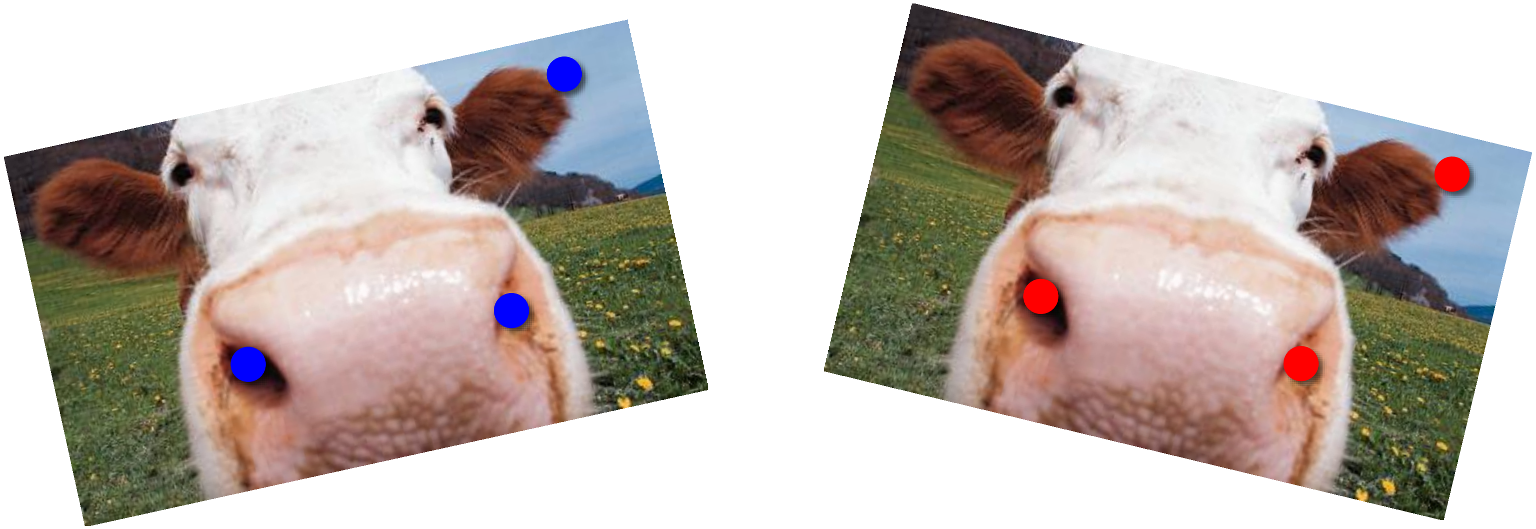
Transformed cow

Now let's see how to tell whether this is a rigid transformation…

What is a rigid transformation?



What is a rigid transformation?



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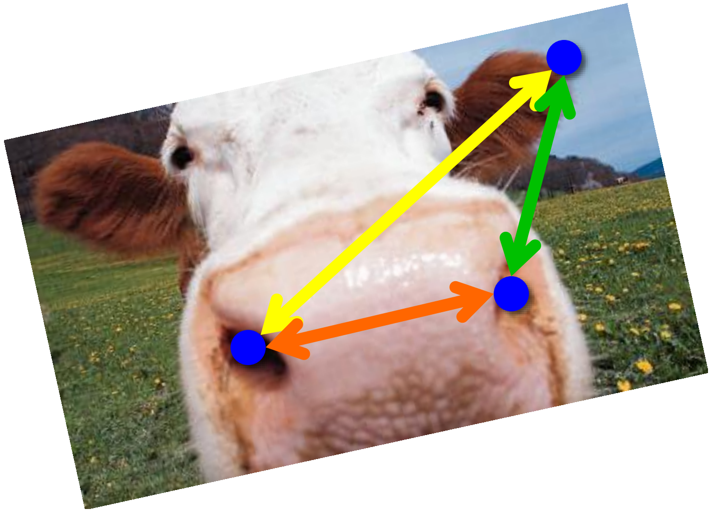

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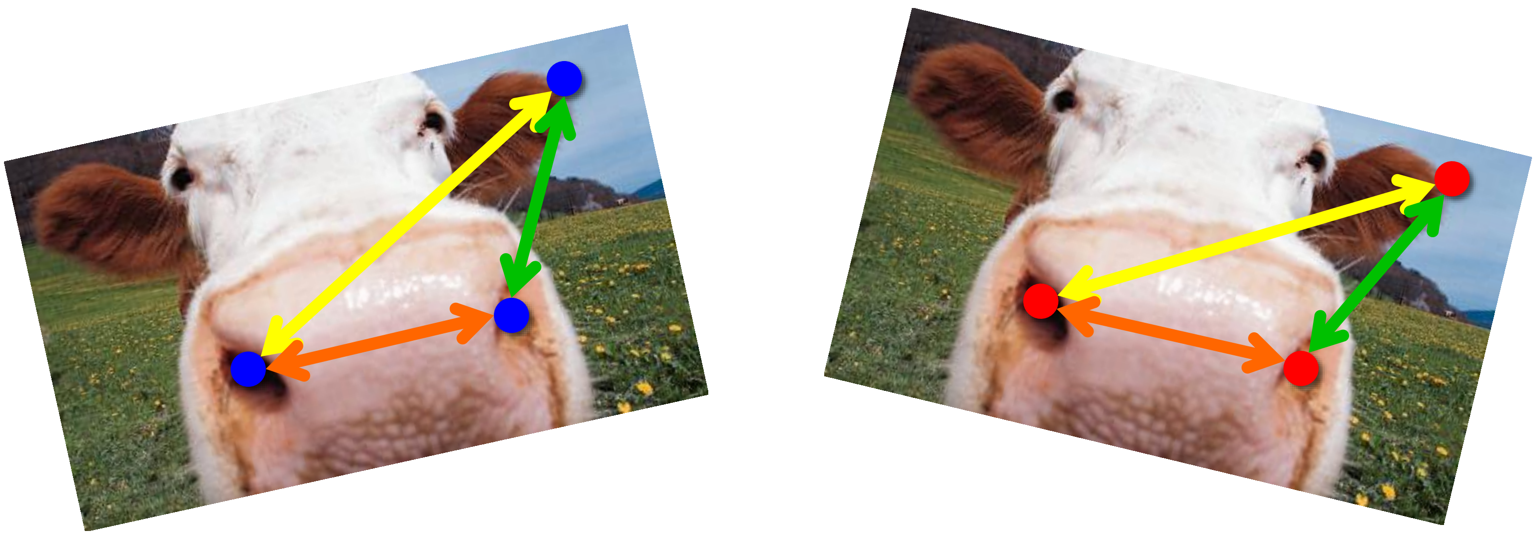
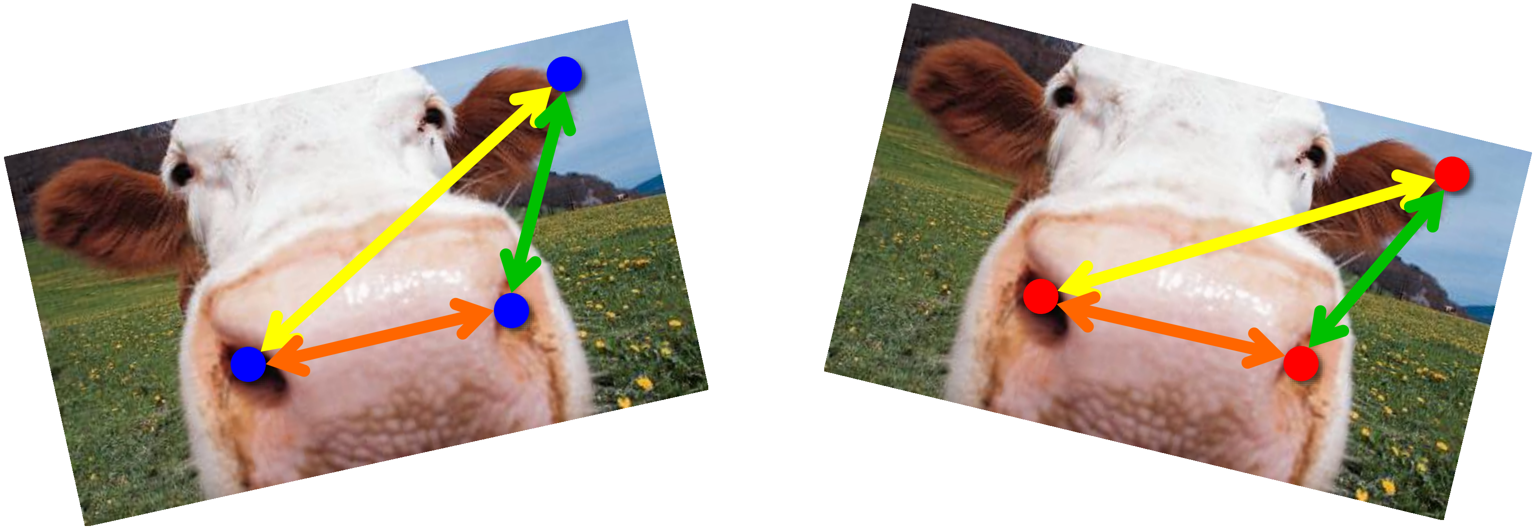


What is a rigid transformation?



If the distance between all corresponding pairs of points remains unchanged (for example, yellow = yellow, green = green, orange = orange), then transformation is rigid.

Rigid transformation = 1 rotation + 1 translation

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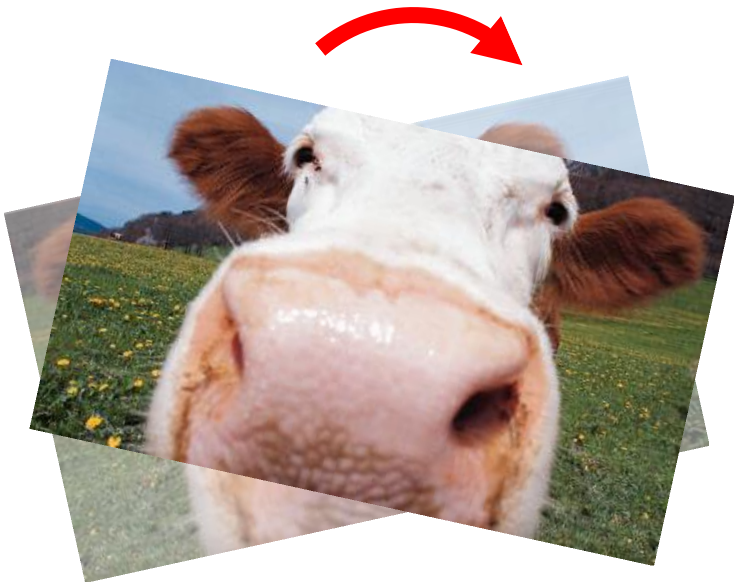
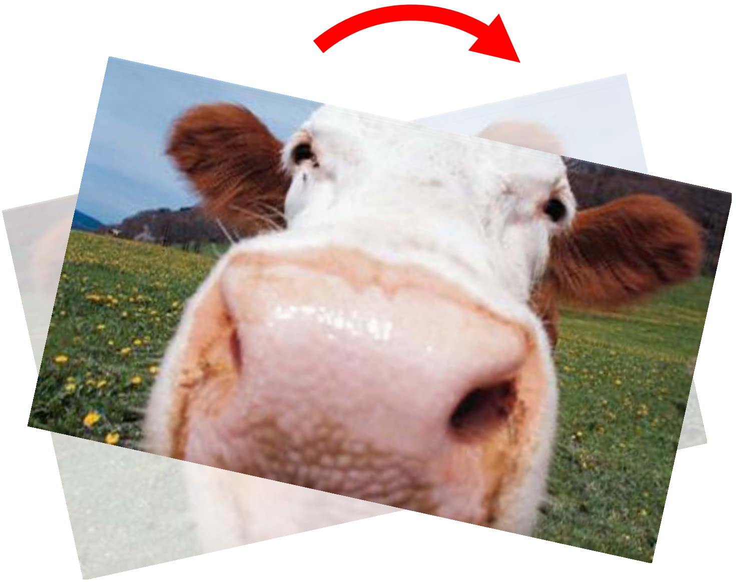


Rigid transformation = 1 rotation + 1 translation



Performing Rigid Point Registration

= fiducial in image

= target in image

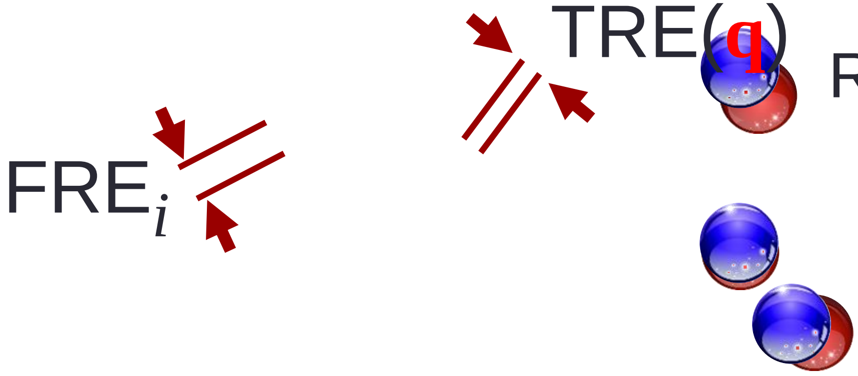
= fiducial in OR

= target in OR

The misalignments after registration are the result of ***Fiducial Localization Error*** (**FLE**).

Performing Rigid Point Registration

Fiducial Registration Error of Fiducial ***i***



Target Registration Error at point **q**

= fiducial in image

= target in image

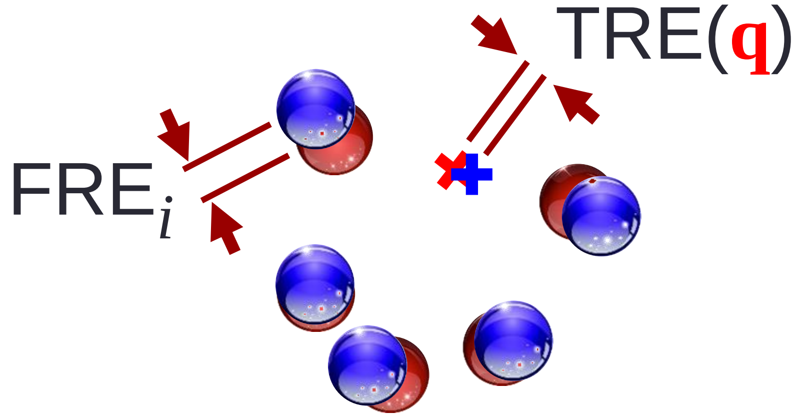
= fiducial in OR

= target in OR

The misalignments after registration are the result of ***Fiducial Localization Error*** (**FLE**).

Performing Rigid Point Registration

Fiducial Registration Error of Fiducial ***i***



Target Registration Error at point **q**

$$\text{FRE}_i = \left| R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i \right|$$

$$\text{TRE}(\mathbf{q}) = \left| R\mathbf{p} + \mathbf{t} - \mathbf{q} \right|$$

Registration: Find R and $\mathbf{t}$ that minimize FRE in the <u>least squares</u> sense:

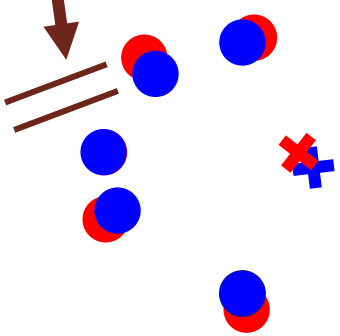
$$\text{FRE}^2 = \frac{1}{N} \sum_{i=1}^{N} \text{FRE}_i^2$$

Why least squares?

Why do we minimize the sum of squared errors (not the median, not the sum of absolute errors, etc.)?

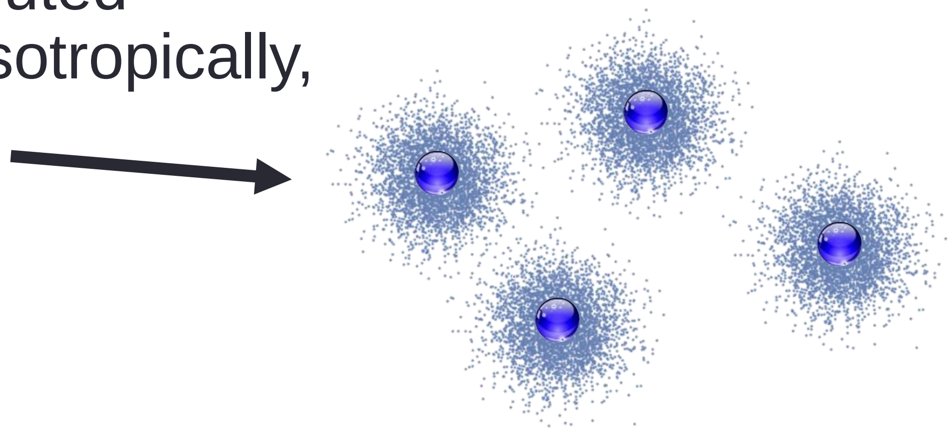
In other words, why do we look for R and $\mathbf{t}$ to minimize this? → $\sum_{i=1}^{N} \mathrm{FRE}_i^2$

$$\mathrm{FRE}_i = R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i =$$



Maximum likelihood

ANSWER: If FLE is distributed normally, independently, isotropically, and identically, like this…



…then minimizing the mean squared FRE gives the transformation that has the maximum likelihood of being the true one.

And how exactly does one minimize the mean squared FRE?

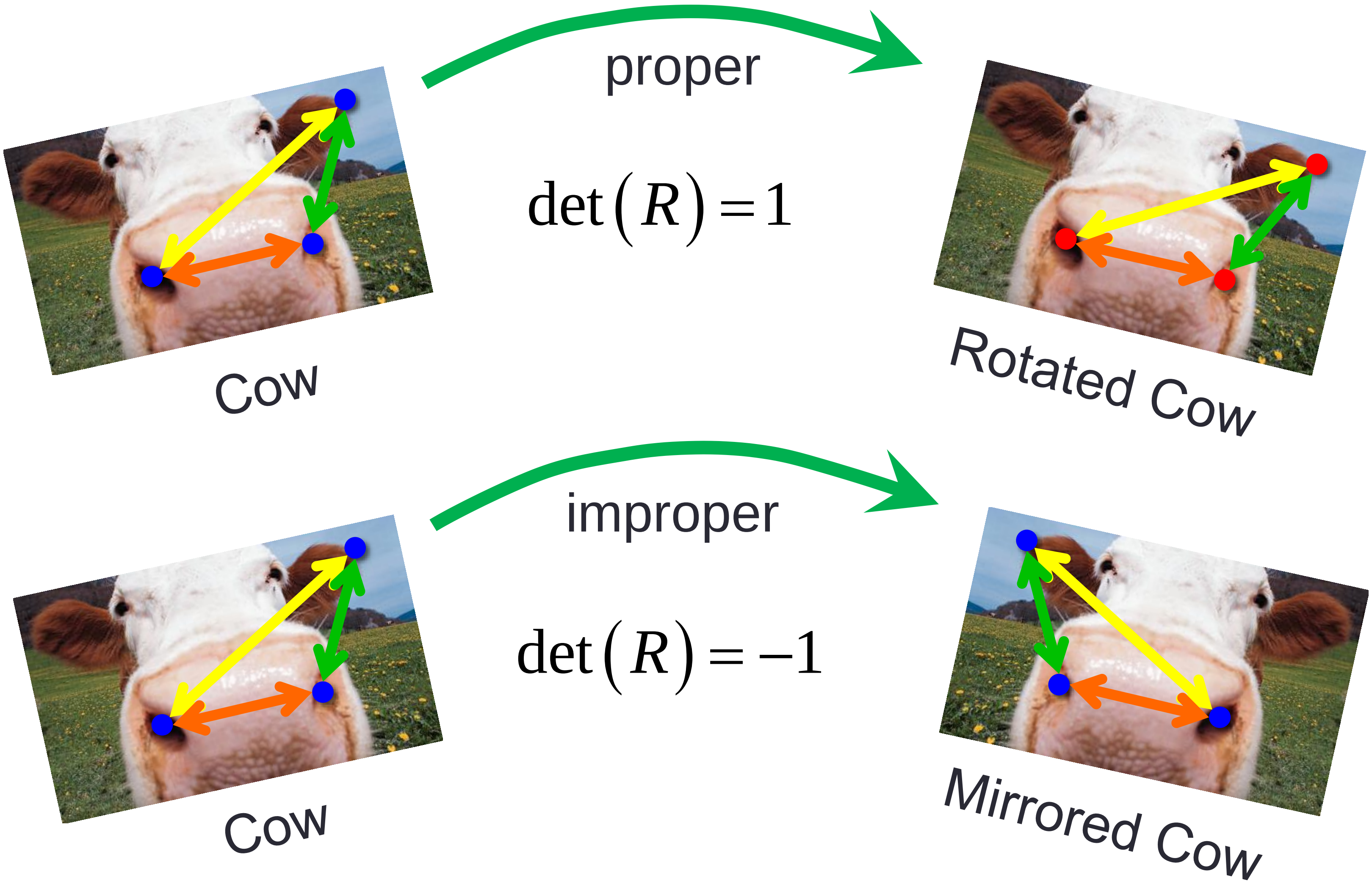
Here's how—Times TWELVE!

1. Green, *Psychometrika*, 1952
2. Mackenzie, *Acta Chrystallographica*, 1957
3. Schönemann, *Psychometrika*, 1966
4. Farrell & Stuelpnagel, *SIAM Review*, 1966
5. Wessner, SIAM Review, 1966
6. Golub & van Loan, *Matrix Computations*, 1983
7. Faugeras & Hebert, *Int J Robotics Res*, 1986
8. Froimowitz & Matthysse, *J Med Chem*, 1986
9. Arun, Huang, & Blostein, *IEEE PAMI*, 1987
10. Horn, J Opt Soc Amer, 1987
11. Horn, Hilden, & Negahdaripour, *J Opt Soc Amer*, 1988
12. Umeyama, *IEEE PAMI*, 1991

Same color means same method.

Only the circled ones give *proper* rotations,

What makes a rigid transformation proper ?

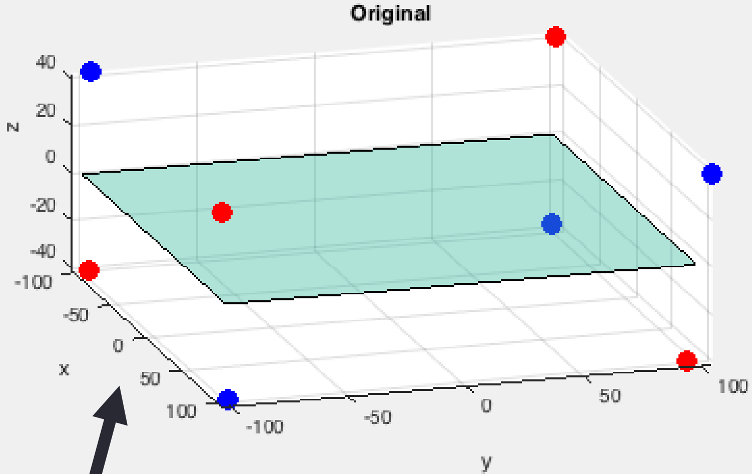


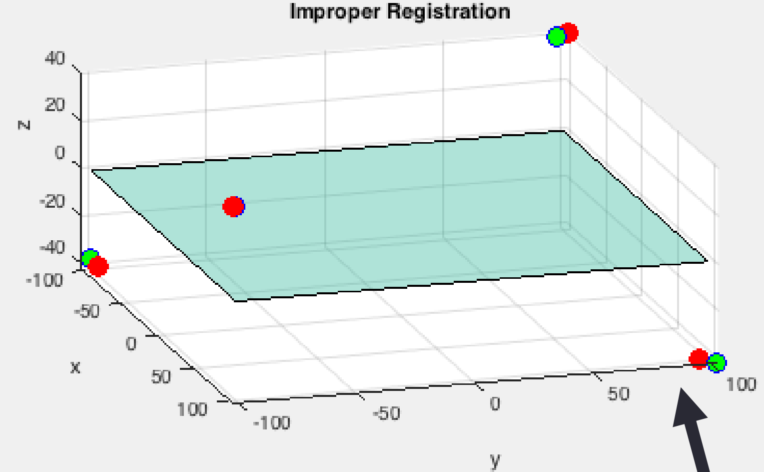
Proper registration algorithms

Proper registration algorithms produce a transformation with $\det(R) = +1$ even if a transformation with $\det(R) = -1$ exists that will produce a smaller mean-square FRE.

A simple example involving four fiducials shows the idea…

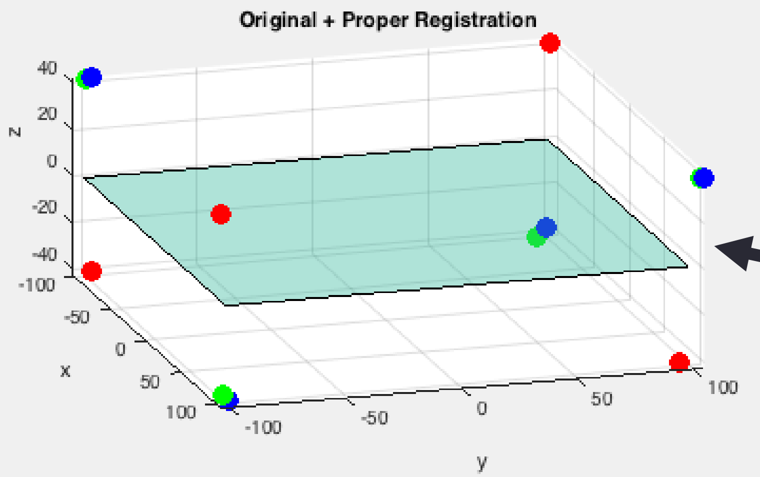
blue = Space 1, red = Space 2





Before registration. FLE_z is exaggerated to illustrate the idea.

green = registered points. Improper registration changes sign of all z components for <u>all</u> points registered from Space 1. TREs will be huge!



green = registered points.
Proper registration does almost nothing, but this is most likely to be the right transformation because the movement in the z direction was due mostly FLE. TREs will be small.

39 years of work = six lines of MATLAB

```
function [R,t] = point_register(X,Y)
Xc = X - repmat(mean(X,2),1,size(X,2));
Yc = Y - repmat(mean(Y,2),1,size(X,2));
[U,~,V] = svd(Xc*Yc');
R = V*diag([1, 1, det(V*U)])*U';
t = mean(Y,2) - R*mean(X,2);
```

`R` and `t` = rotation and translation that minimize FRE

All cases of all the problems that all these people treated all these years are solved by this little MATLAB function:

Philosophical question:
Does a short algorithm imply that the problem is easy?

http://eecs.vanderbilt.edu/people/mikefitzpatrick/

What the code does:

```
function [R,t] = point_register(X,Y)
Xc = X - repmat(mean(X,2),1,size(X,2));
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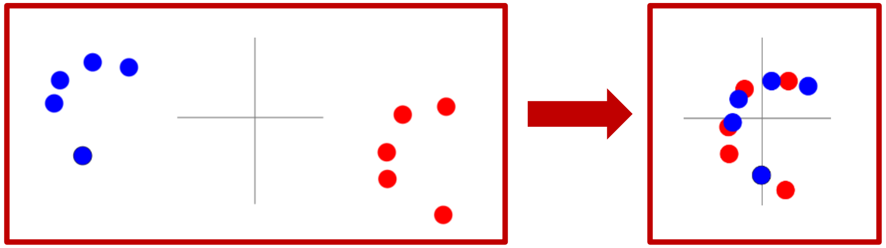
R = V*diag([1, 1, det(V*U)])*U';
t = mean(Y,2) - R*mean(X,2);
```

1. "Demean" each point set, i.e., translate each set so its mean = the origin



2. Form a matrix of points for each set:

$$X = \begin{bmatrix} \tilde{x}_{11} & \tilde{x}_{21} & \cdots & \tilde{x}_{N1} \\ \tilde{x}_{12} & \tilde{x}_{22} & \cdots & \tilde{x}_{N2} \\ \tilde{x}_{13} & \tilde{x}_{23} & \cdots & \tilde{x}_{N3} \end{bmatrix}, \quad Y = \begin{bmatrix} \tilde{y}_{11} & \tilde{y}_{21} & \cdots & \tilde{y}_{N1} \\ \tilde{y}_{12} & \tilde{y}_{22} & \cdots & \tilde{y}_{N2} \\ \tilde{y}_{13} & \tilde{y}_{23} & \cdots & \tilde{y}_{N3} \end{bmatrix}$$

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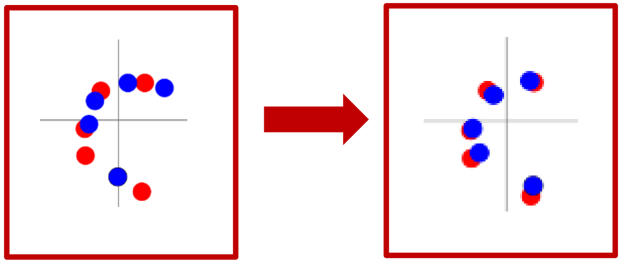
R = V*diag([1, 1, det(V*U)])*U';
t = mean(Y,2) - R*mean(X,2);
```

3. Find the singular-value decomposition of XY^t: $U\Lambda V^t = XY^t$

4. $R = VDU^t$

$$\text{where } D = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & \det(VU) \end{bmatrix}$$



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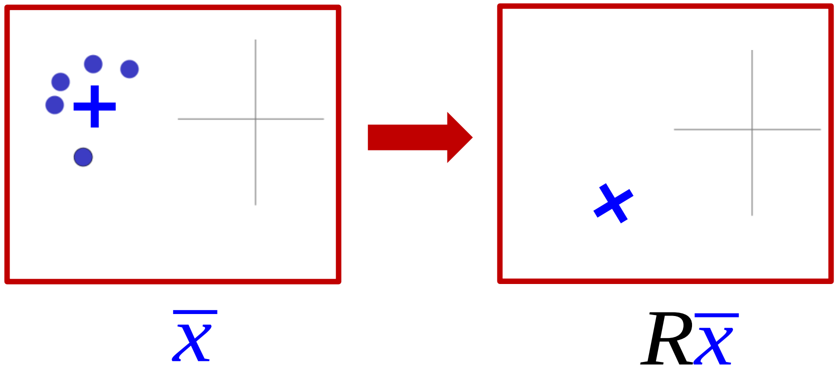
R = V*diag([1, 1, det(V*U)])*U';
t = mean(Y,2) - R*mean(X,2);
```

5. Rotate the mean of the first point set by *R*:



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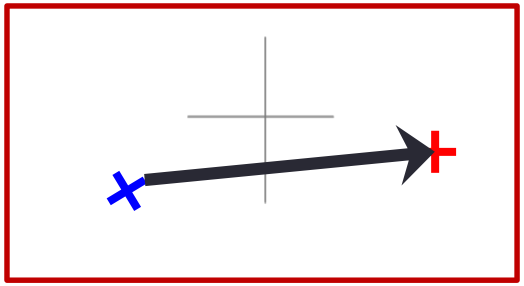
[U,~,V] = svd(Xc*Yc');
R = V*diag([1, 1, det(V*U)])*U';
t = mean(Y,2) - R*mean(X,2);
```

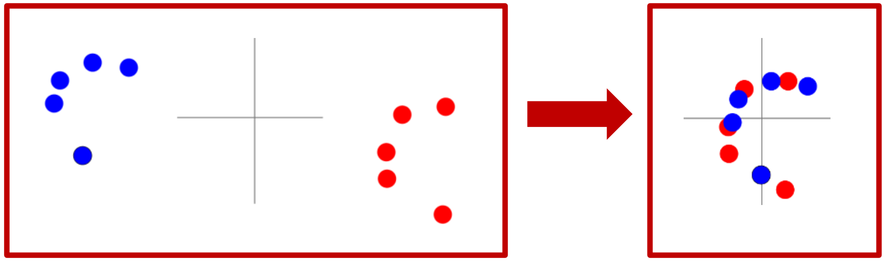
6. `t` is the vector from the rotated mean of the first point set to the mean of the second point set :



$$\mathbf{t} = \bar{y} - R\bar{x}$$

Fiducial-registration algorithm: review

1. "Demean" each point set, i.e., translate each set so its mean = the origin:



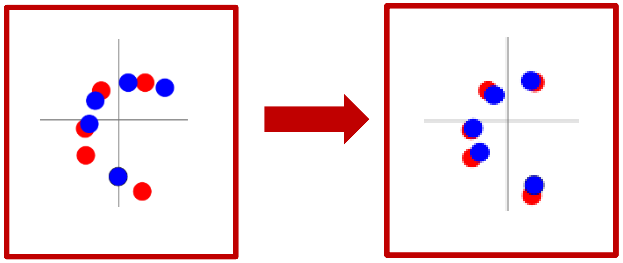
2. Form a matrix of points for each set:

$$X = \begin{bmatrix} \tilde{x}_{11} & \tilde{x}_{21} & \cdots & \tilde{x}_{N1} \\ \tilde{x}_{12} & \tilde{x}_{22} & \cdots & \tilde{x}_{N2} \\ \tilde{x}_{13} & \tilde{x}_{23} & \cdots & \tilde{x}_{N3} \end{bmatrix}, \quad Y = \begin{bmatrix} \tilde{y}_{11} & \tilde{y}_{21} & \cdots & \tilde{y}_{N1} \\ \tilde{y}_{12} & \tilde{y}_{22} & \cdots & \tilde{y}_{N2} \\ \tilde{y}_{13} & \tilde{y}_{23} & \cdots & \tilde{y}_{N3} \end{bmatrix}$$

3. Find the singular-value decomposition of XY^t: $U\Lambda V^t = XY^t$

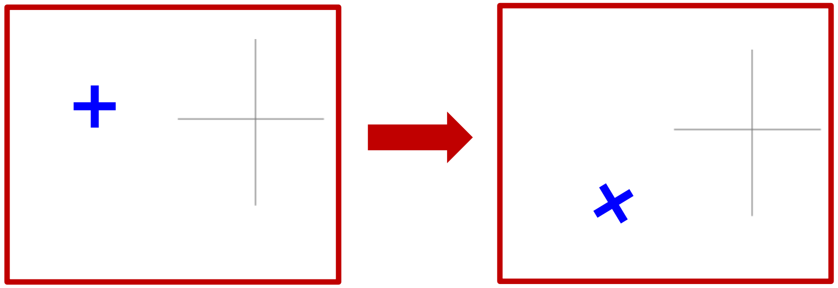
4. Rotate the first set by $R = VDU^t$:

   where $D = \mathrm{diag}\left(1, 1, \det\left(VU\right)\right)$



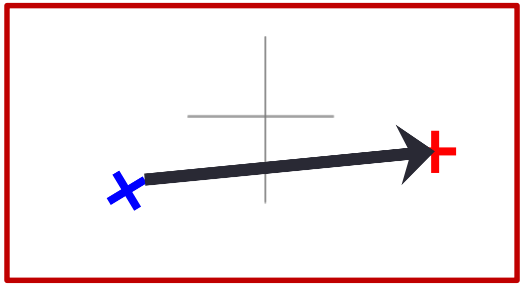
Fiducial-registration algorithm: review

5. Rotate the mean of the first point set by *R*:



$\bar{x}$ $R\bar{x}$

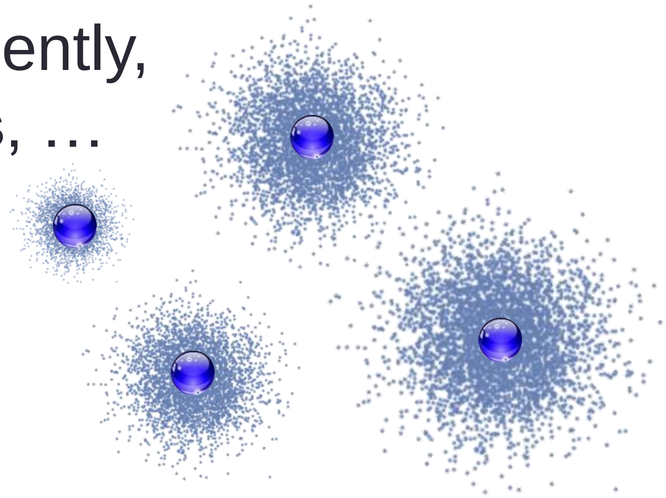
6. Translation $\mathbf{t}$ is the vector from the rotated mean of the first point set to the mean of the second point set :



$$\mathbf{t} = \bar{y} - R\bar{x}$$

And what if the distributions are not identical?

If FLE is distributed normally, independently, isotropically, but not identically, like this, … then we say that FLE is "inhomogeneous".



In that case we minimize a weighted mean-squared FRE to get the transformation that has the maximum likelihood of being the true one.

Weighted minimization

We define a weight for each point, $w_i = 1/\mathrm{FLE}_i$, which means that a point with a smaller FLE_i will have a larger influence on the registration because it is more trustworthy.

Then in the sum of squares, we multiply each FRE_i by its weight:

$$\mathrm{FRE}^2 = \frac{1}{N}\sum_{i=1}^{N}\left(w_i \times \mathrm{FRE}_i\right)^2$$

Finding R and **t** for weighted case

- Demean each set of points using the weights:
  - Calculate their weighted centroids:

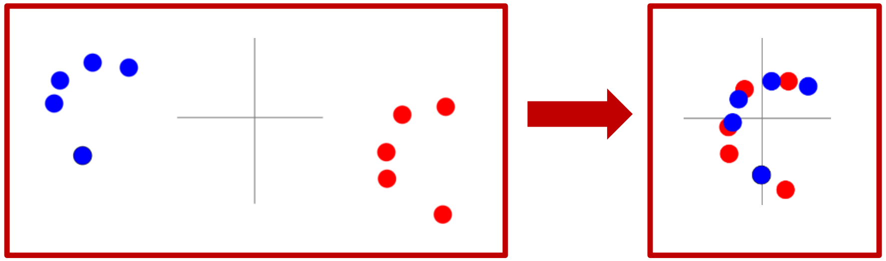
$$\bar{x} = \sum_{i=1}^{N} w_i x_i \Big/ \sum_{i=1}^{N} w_i \,,$$

$$\bar{y} = \sum_{i=1}^{N} w_i y_i \Big/ \sum_{i=1}^{N} w_i \,.$$

  - Subtract the centroid from each point:

$$\tilde{x}_i = x_i - \bar{x}$$

$$\tilde{y}_i = y_i - \bar{y}$$



Finding R and $\mathbf{t}$ for weighted case

Define weighted demeaned point matrices:

$$X = \begin{bmatrix} w_1 \tilde{x}_{11} & w_2 \tilde{x}_{21} & \cdots & w_N \tilde{x}_{N1} \\ w_1 \tilde{x}_{12} & w_2 \tilde{x}_{22} & \cdots & w_N \tilde{x}_{N2} \\ w_1 \tilde{x}_{13} & w_2 \tilde{x}_{23} & \cdots & w_N \tilde{x}_{N3} \end{bmatrix}, \quad Y = \begin{bmatrix} w_1 \tilde{y}_{11} & w_2 \tilde{y}_{21} & \cdots & w_N \tilde{y}_{N1} \\ w_1 \tilde{y}_{12} & w_2 \tilde{y}_{22} & \cdots & w_N \tilde{y}_{N2} \\ w_1 \tilde{y}_{13} & w_2 \tilde{y}_{23} & \cdots & w_N \tilde{y}_{N3} \end{bmatrix}$$

and the rest is exactly the same as before…

- SVD: $U \Lambda V^t = X Y^t$
- $R = V D U^t$
- $\mathbf{t} = \mathbf{y}_i - R\bar{\mathbf{x}}$

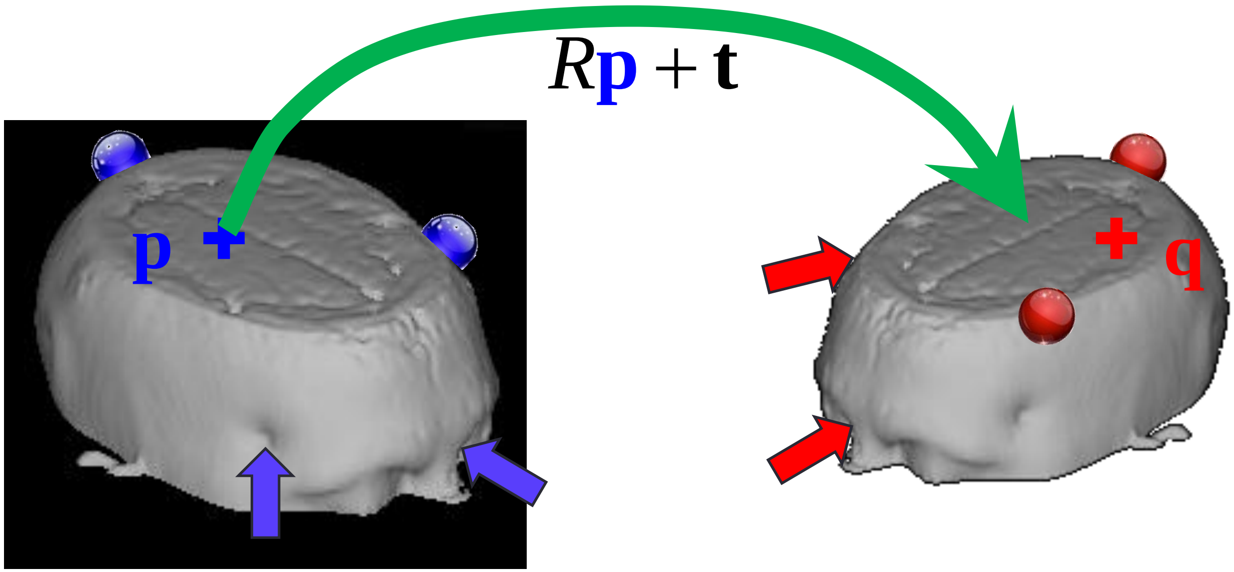
…and the MATLAB code can handle the weighted case with only minor changes.

```
function [R,t] =
point_register(X,Y,weights)
...
```

http://eecs.vanderbilt.edu/people/mikefitzpatrick/

And what do we do with R and $\mathbf{t}$?

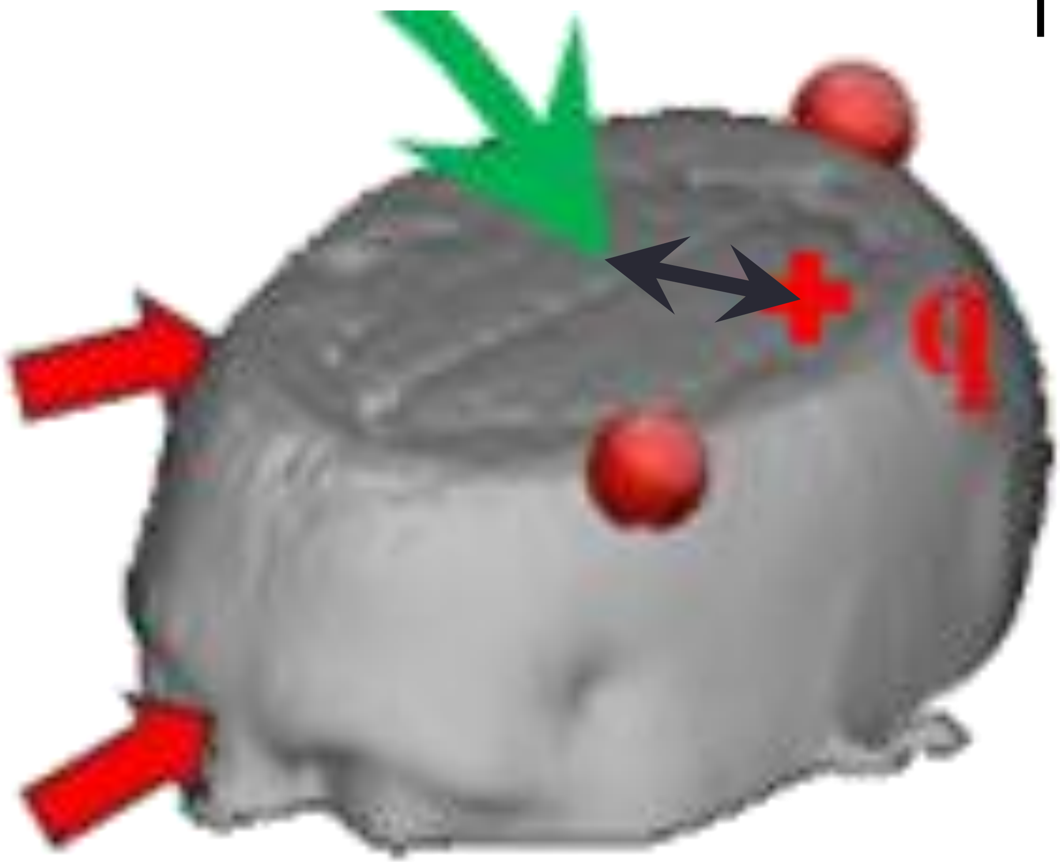
- Well, we transform a target $\mathbf{p}$ in the image like this:



And, if the fiducial localization errors were small, then, the target registration error relative to the true target **q**,

$$\text{TRE}(\mathbf{q}) = \left| R\mathbf{p} + \mathbf{t} - \mathbf{q} \right|$$

ought to be small too.



At least, that's what the surgeon (and the patient !) is hoping.

Something is missing here!

Clearly it is not enough to register with fiducials. We need to have some way of estimating target registration error too.

The fiducial registration problem was solved in 1966, and we've seen how it works.

But for the next 25 years the problem of estimating target error received very little attention.

That was about to change…

A new standard emerges: TRE-FRE-FLE

In 1991 the first comprehensive study of fiducial registration error appeared, and in 1993 TRE, FRE, & FLE, were proposed as a way to formulate the problem precisely.

Google Scholar now lists over 3,000 articles that refer to TRE, FRE, and/or FLE in scientific publications.

In fact, today this triad is the standard description of fiducial registration error.

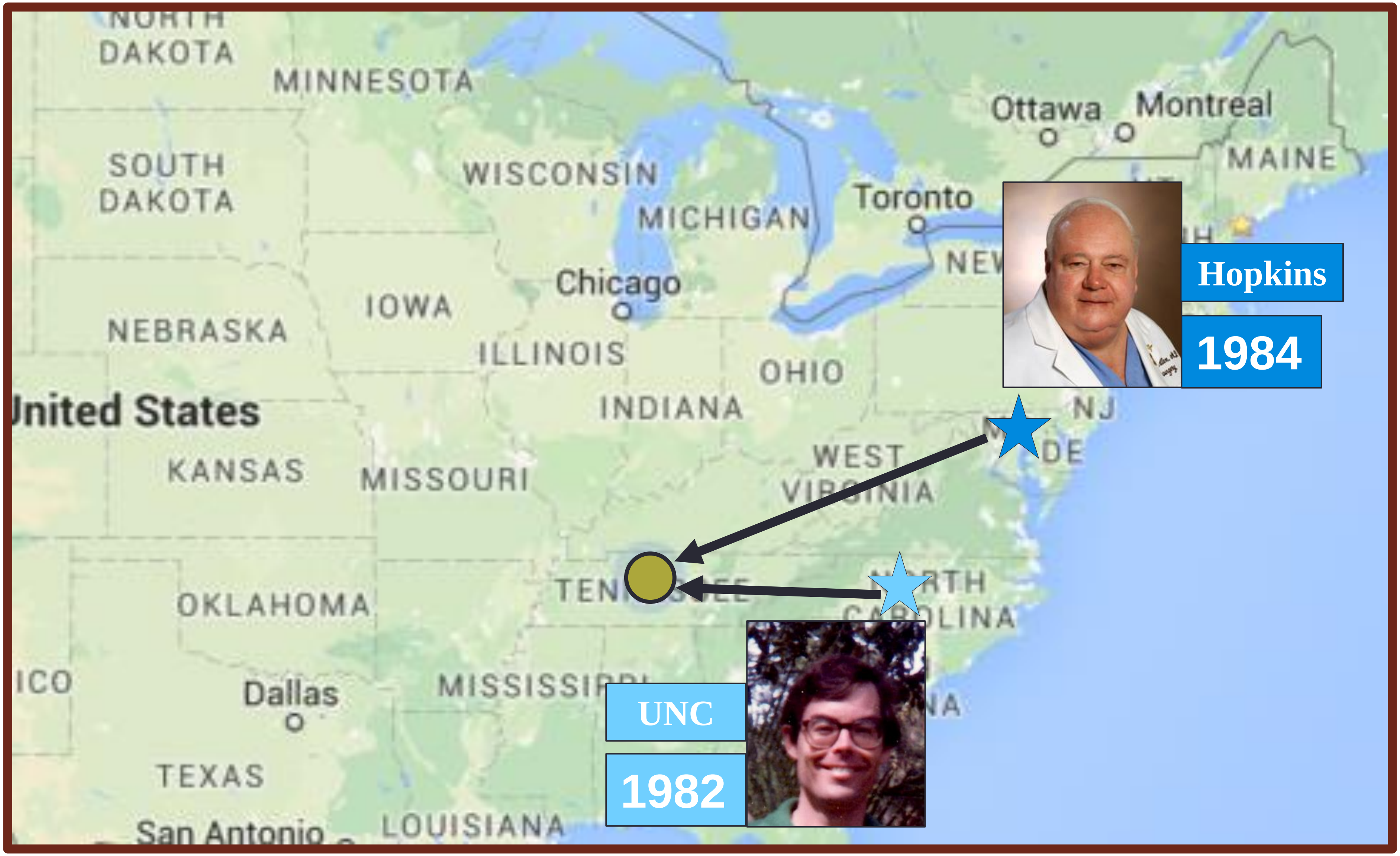
And that standard was created here—at Vanderbilt.

It’s time for a story!

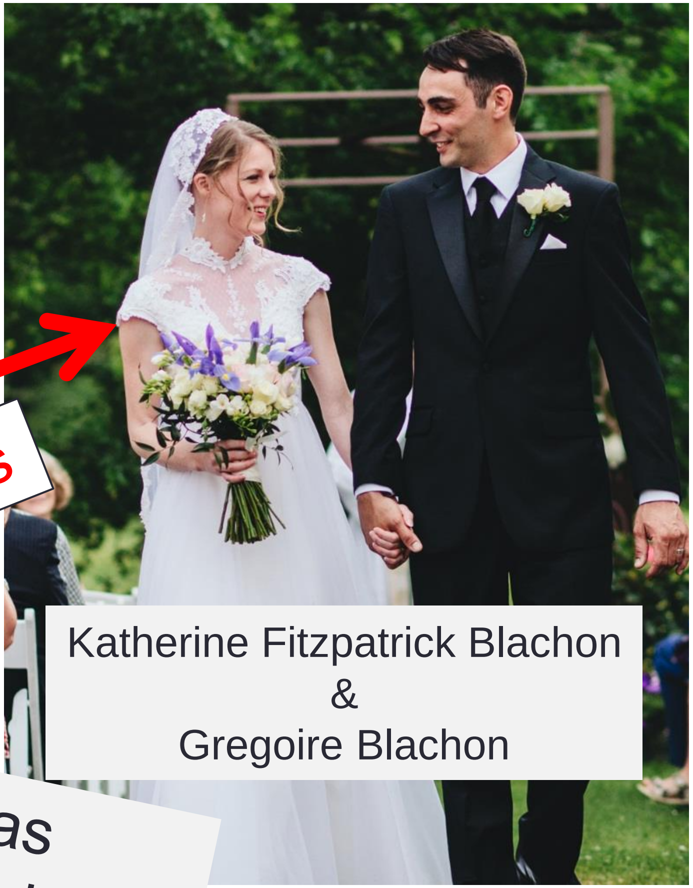
I’m going to tell you a story that I told at the SPIE Medical Imaging Symposium in February*. It’s a true story that explains why the standard for fiducial registration error came from Vanderbilt.

I know the story well because I was there when it happened.

[*video of Fitzpatrick keynote address, SPIE Medical Imaging, Feb 2015]


DAKOTA
MINNESOTA
SOUTH DAKOTA
WISCONSIN
MICHIGAN
Ottawa
Montreal
MAINE
Toronto
Hopkins
1984
IOWA
Chicago
NEBRASKA
ILLINOIS
OHIO
INDIANA
NJ
DE
KANSAS
MISSOURI
WEST VIRGINIA
OKLAHOMA
UNC
1982
Dallas
TEXAS
San Antonio
LOUISIANA

Another arrival in 1984



30 years

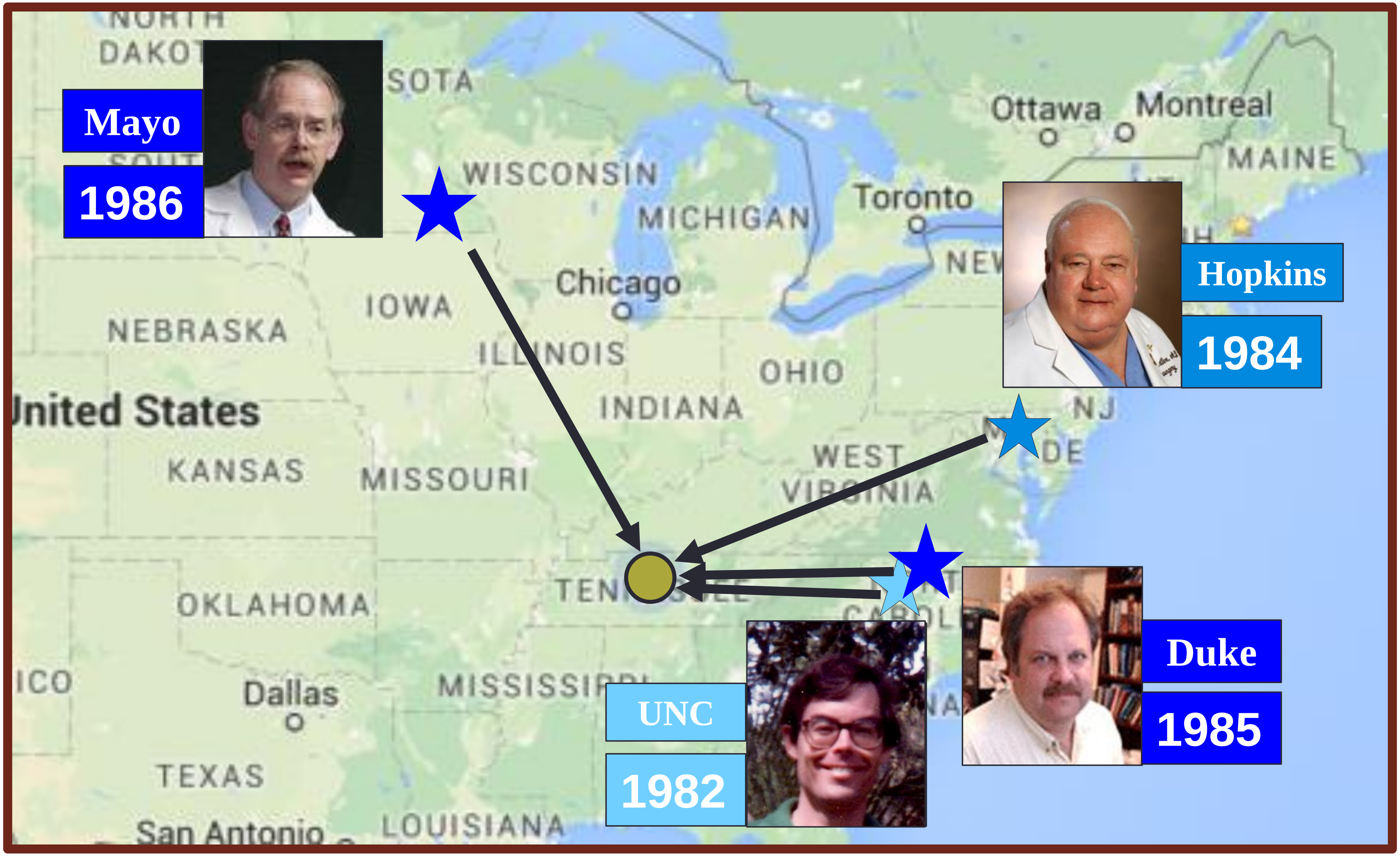
Katherine Fitzpatrick Blachon
&
Gregoire Blachon

NOTE: This has nothing to do with fiducial registration.

1984

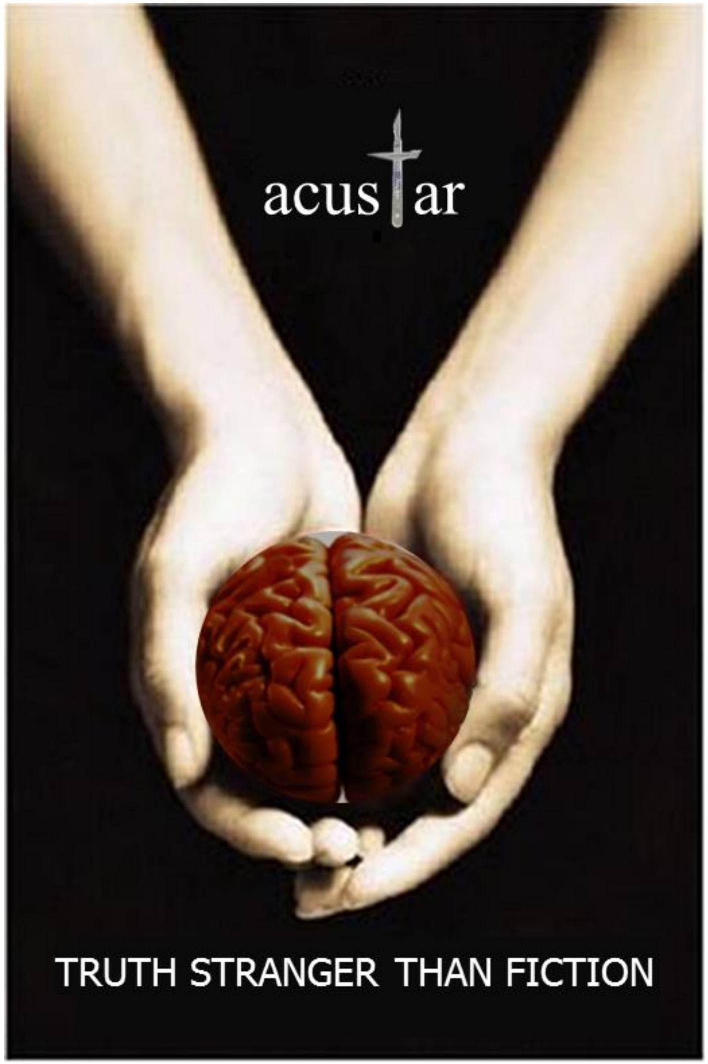
2014

Nashville Arrivals



And that gets us to the beginning of the story

The story of…


acustar
TRUTH STRANGER THAN FICTION

PROLOG

1947-1985

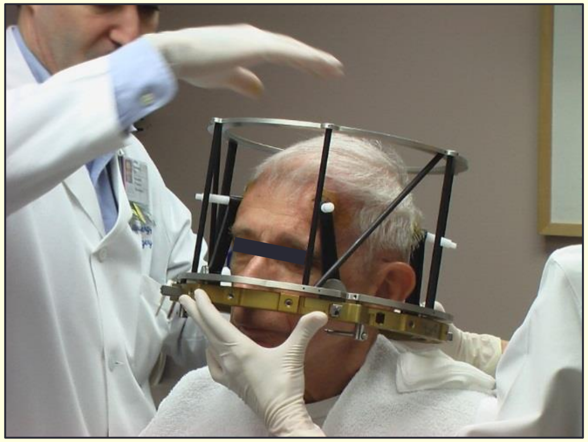
FOR THE FIRST FORTY YEARS OF SURGICAL GUIDANCE THERE WAS ONLY ONE OPTION :

THE STEREOTACTIC "FRAME"

IT LOOKED LIKE THIS…

PROLOG

1947-1985



PATIENTS DIDN'T LIKE IT.

1986

DAVE ROBERTS' GROUP
AT DARTMOUTH
INVENTED "FRAMELESS"
SURGICAL GUIDANCE.

THEY USED FIDUCIALS,
INSTRUMENT TRACKING,
AND COMPUTER DISPLAYS.

THEIR GOAL: TRE = 1 MM
THEIR RESULT: TRE = 5 MM

1988

THE NEXT STEP WAS TO BE TAKEN AT VANDERBILT.

IT WOULD TAKE SEVEN YEARS.

IT WOULD REACH ROBERT'S' GOAL.

IT WOULD BE CALLED "ACUSTAR".

1988: We started small

A one-year contract with Johnson & Johnson for a prototype…

…it would be extended each year for six more years…

…with just Maciunas and me as PIs, assisted by one of my grad students (V. Mandava).

But eventually, we would add over 50 people to the project,…

Vanderbilt would receive $1.4M,…

and J&J would spend $14M.

As of the 11th day of July 1988, VANDERBILT UNIVERSI…
…behalf of its Department of Computer Science and Department of
…institution having an address at
…er "VANDERBILT"), and CODMAN &
…principal place of

…BILT will conduct the research as
…fforts to conduct this research in
…accordance… …fessional standards.

3.02 ROBERT J. MACIUNAS, M.D. and J. MICHAEL FITZPATRICK, Ph.D., both faculty members of VANDERBILT will serve as the Principal Investigators at VANDERBILT under this Agreement and as such will have overall responsibility for the Project at VANDERBILT.

3.03 The Project will proc…
the budget…

TOTAL DIRECT AND INDIRECT $157,493.00

The Major Players

VANDERBILT UNIVERSITY

<u>*George S. Allen, MD, PhD*</u>
Hsuan Chang, PhD*
Charles A. Edwards, PhD*
<u>*J. Michael Fitzpatrick, PhD*</u>
Srikanth Gadamsetty, PhD*
<u>*Robert L. Galloway, PhD*</u>
David Goins
Allen Jackson
Robert Maciunas, MD
Venkat Mandava, PhD*
Calvin Maurer, PhD*
Matthew Wang, PhD*
Jay West, PhD*
Robert Willcott, PhD

Johnson & Johnson

Roy Black, 1st CEO
Frank Collins
Tibor Foldvari
Don Grilli, 2nd CEO
Jennifer Jandak
Peter Monteiro
Rory Randall
Charles Southworth
Charlie Worrick

NDI

David Crouch, CEO

** graduate students*

The Major Players

Surgeons at other hospitals:

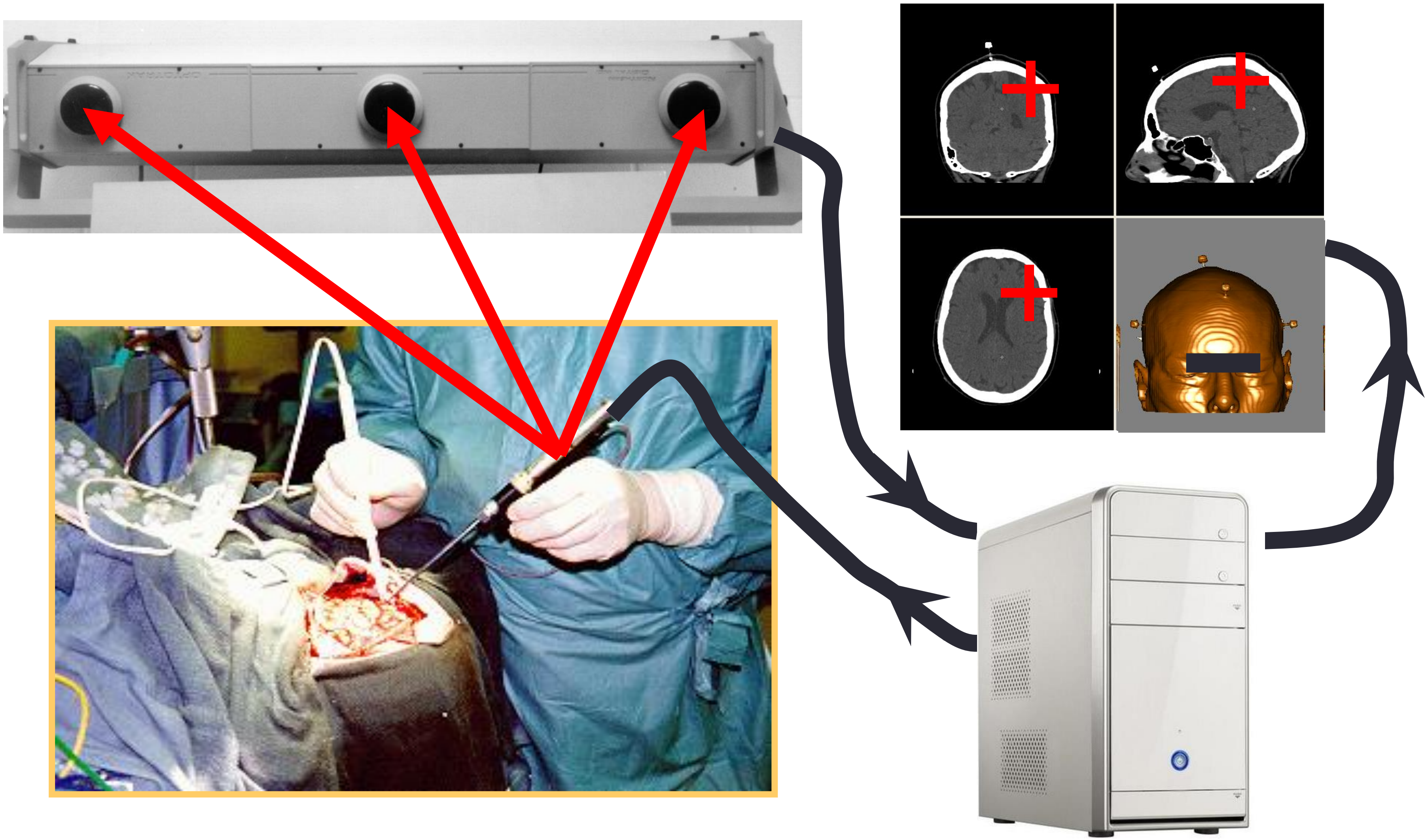
- *Mitch S. Berger, MD, U. Wash.*
- *Brian Copeland, MD, Scripps, CA*
- *Marc Mayberg, MD, U. Wash*
- *Robert G. Selker, MD, W. Penn. Hosp.*

Doug Rowitch

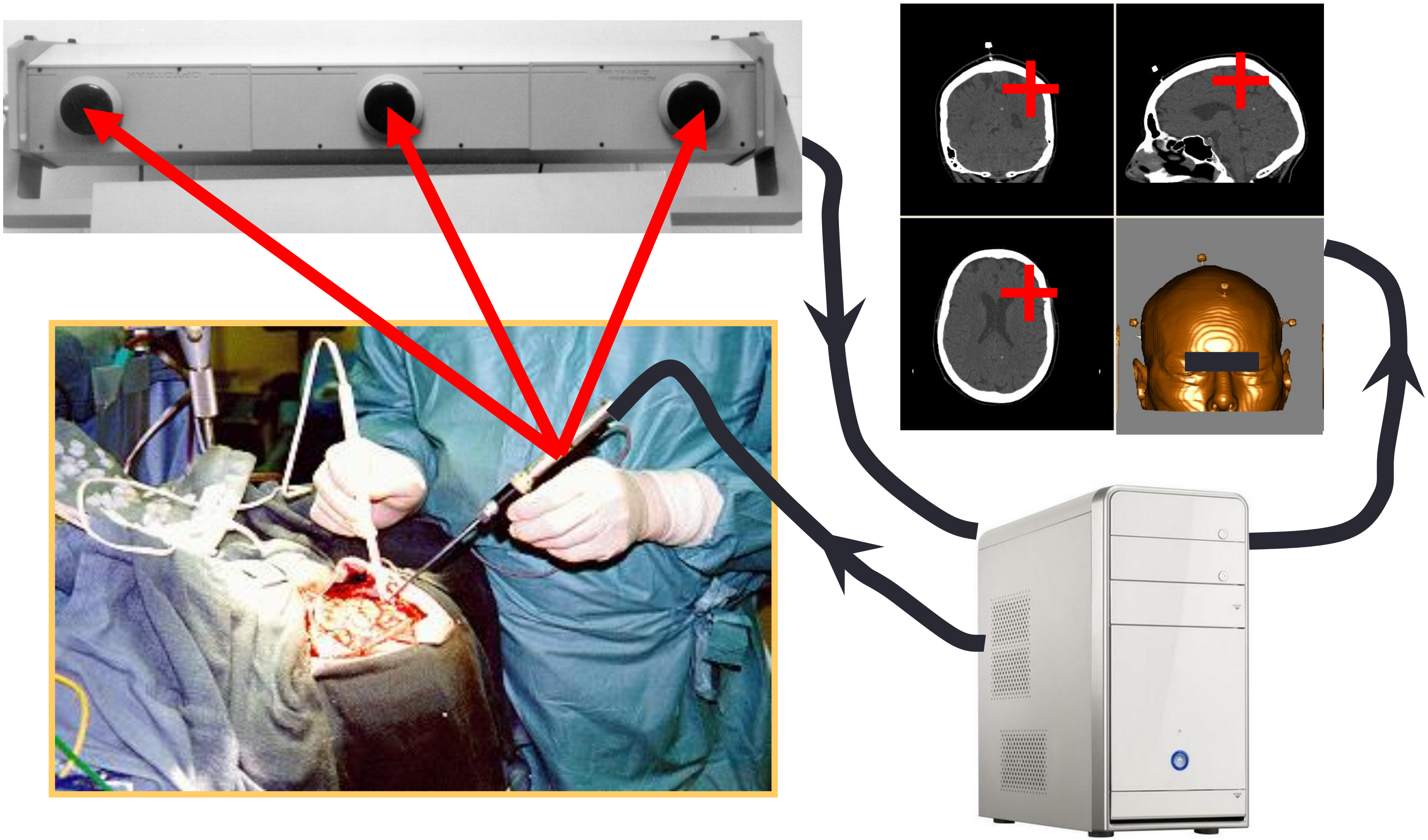
Companies directly involved (omitting suppliers):

- *Johnson & Johnson, Inc*
- *NDI (tracking technology)*
- *Scientific Applications International Corp. (software)*
- *Arthur D. Little, Consultancy (due diligence)*
- *Hewlett-Packard, Corp. (computers, customer service)*

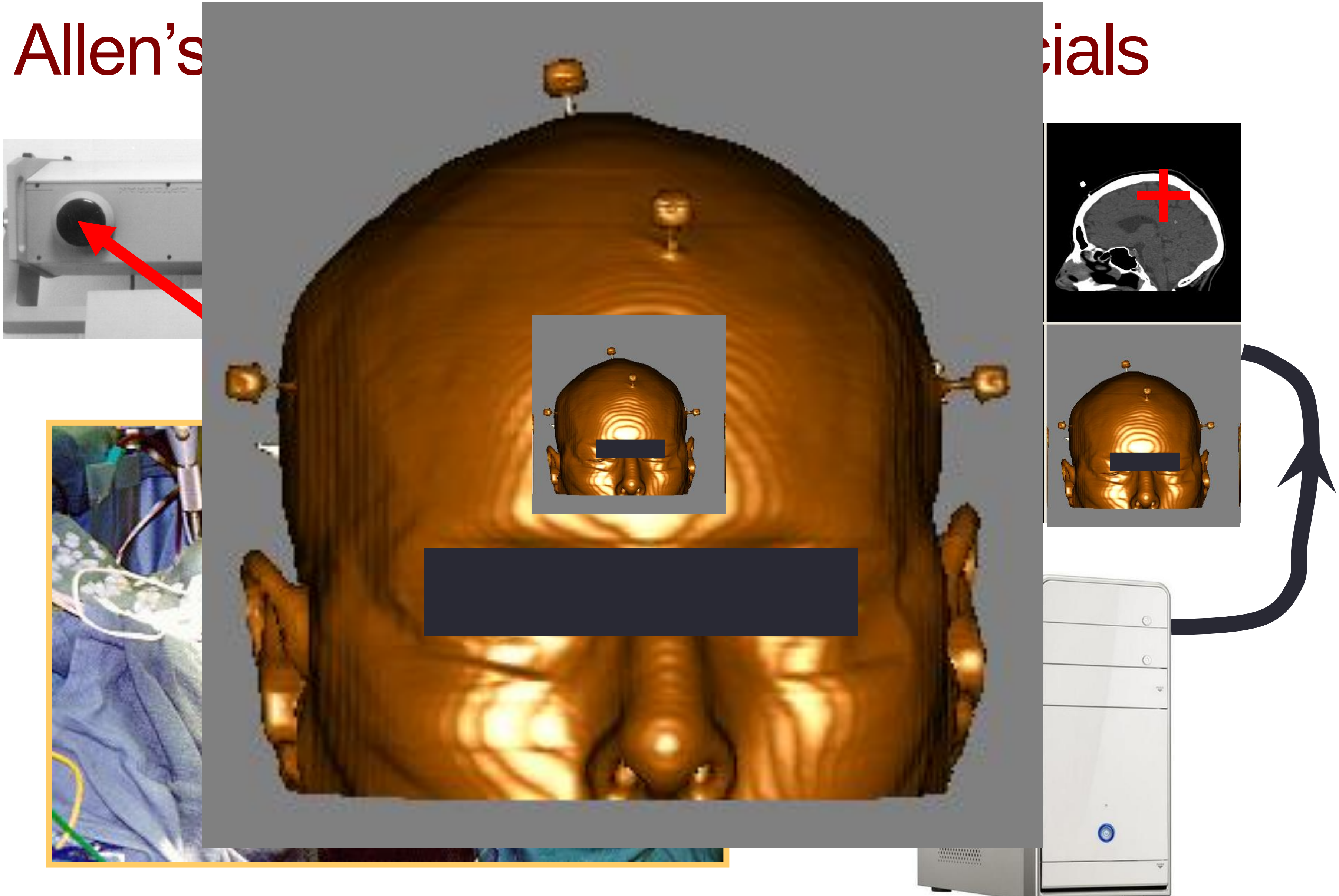
This is what we would build



Allen's Idea: Bone-Implanted Fiducials



Allen’s ials



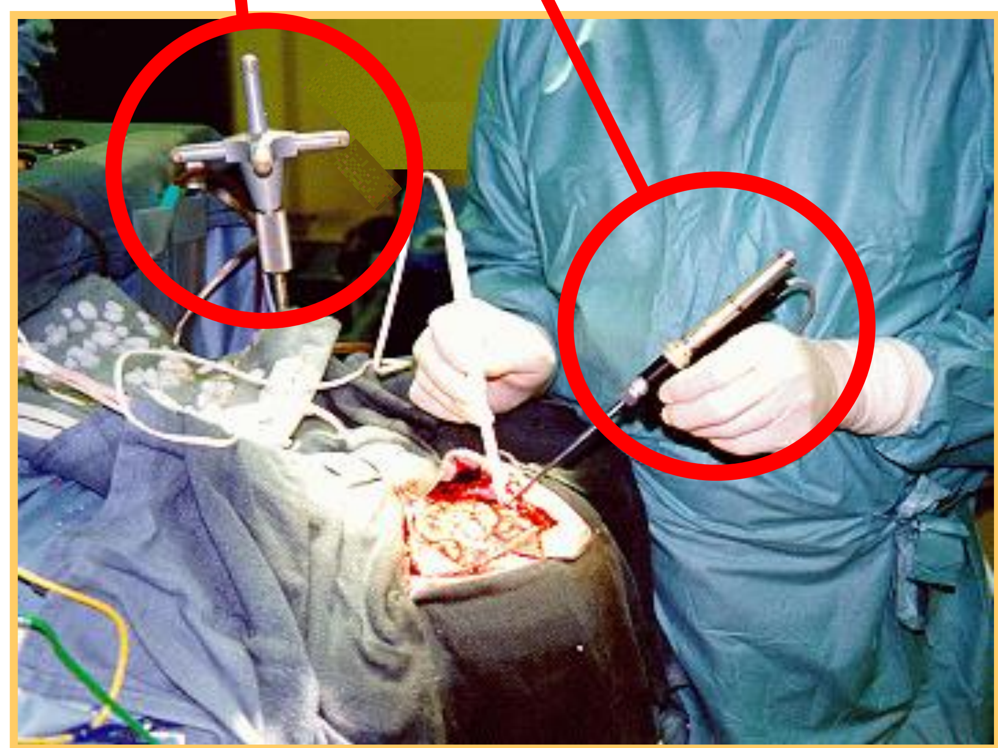
Arms

- For tracking in the OR, articulated arms were in vogue in the late eighties and early nineties.
- They were accurate, and Bob Galloway was one of the ones who proved it.
- That proof helped convince J&J to keep funding us at the beginning.
- But unfortunately arms also proved to be very awkward in the OR,
- And that approach was all we had until…

Fall 1991: Northern Digital Comes to Nashville!

J&J brought NDI in, and they presented a vision:

1. Use infrared tracking
2. Attach a reference emitter to the head



We loved it, and J&J licensed it.

And today NDI is the world standard

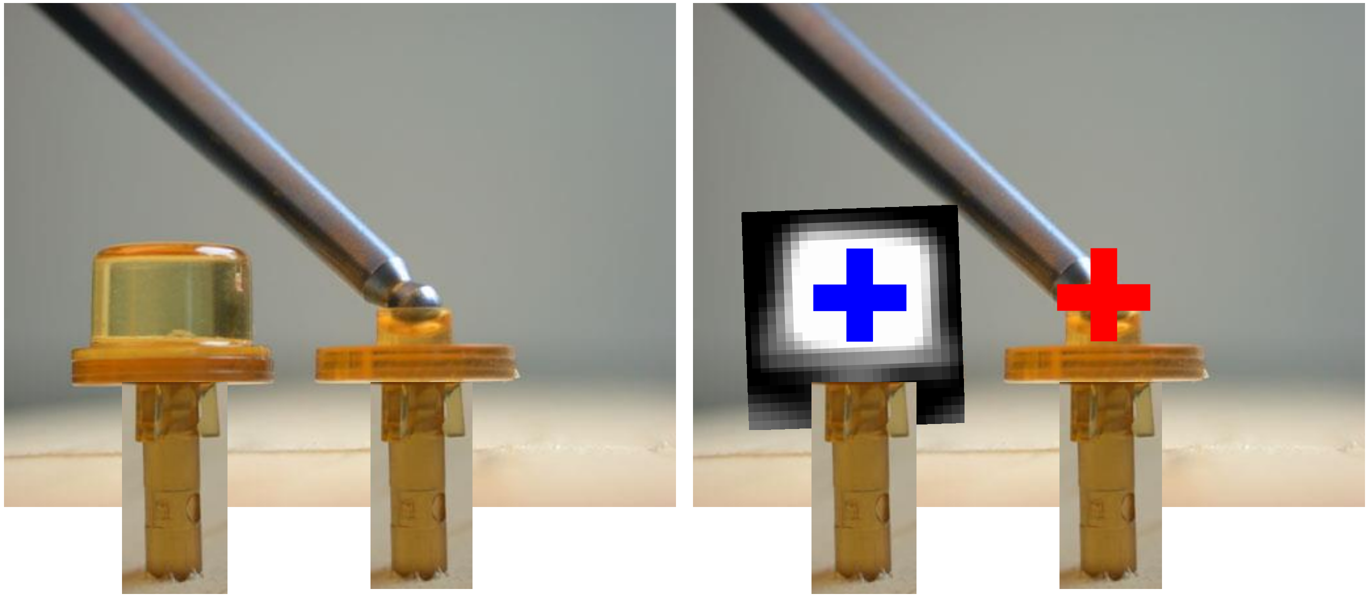
NDI
inside

StealthStation
Medtronic

VectorVision
BrainLAB

Designing Allen's Fiducial Markers

- We designed fiducial markers for image space and physical space and a localization method with submillimetric error.



- With the Markers done, the system design was frozen.

Could we please be first at something?

- In February 1994, we were ready to start clinical trials. Roberts had beaten us to frameless surgery by 7 years, but maybe we could be first to receive FDA clearance.
- In April, the FDA cleared a guidance system based on a tracking arm[1]. So we quickly lost that race too!

- Maybe we could be the first to use infrared tracking.
- In May, 1994, Lucia Zamorano at Wayne State demonstrated that—with the Optotrak![2]

- Another race lost.
- Maybe we could be first under the 1-mm hurdle?

[1. Allegro Viewing Wand, K911783, FDA, April 7, 1994]

[2. Zamorano et al., *SPIE Clin. Appl. Im. II* , May, 1994]

1994-1995: Finally, our clinical trial

- Four states, five hospitals
- Five surgeons, 102 patients.
- Analyzed at Vanderbilt by Matt Wang
- Results:
  - Mean error < 1 mm *!*
  - We'd done it. Suddenly we had the world's most accurate frameless IGS system! J&J named it "Acustar".

- On December 11, 1995, Acustar was FDA cleared, 11 systems were ready for shipping, 5 had been ordered, the help line went live, and we celebrated!!

Six days later, it was dead.

Acustar was killed on December 17, 1995, six days after it was cleared and only a few hours before the first system was to be shipped to the first customer.

Who murdered Acustar, and why?

It was killed by Johnson & Johnson

- In the year before our FDA clearance, Neurosurgery merged with Orthopedics.
- Orthopedics is a much bigger business than neurosurgery, so J&J may have felt that it would be more profitable to shift the resources required for Acustar into orthopedics products.
- Of course one would need a mole inside J&J to know what really happened, but in any case we at Vanderbilt received the news that Acustar had been killed eight days before Christmas of 1995.

Collateral damage

- George Allen:
  - Lost his dream of the “Allen Marker”.
- Johnson & Johnson:
  - Lost $14,000,000.00

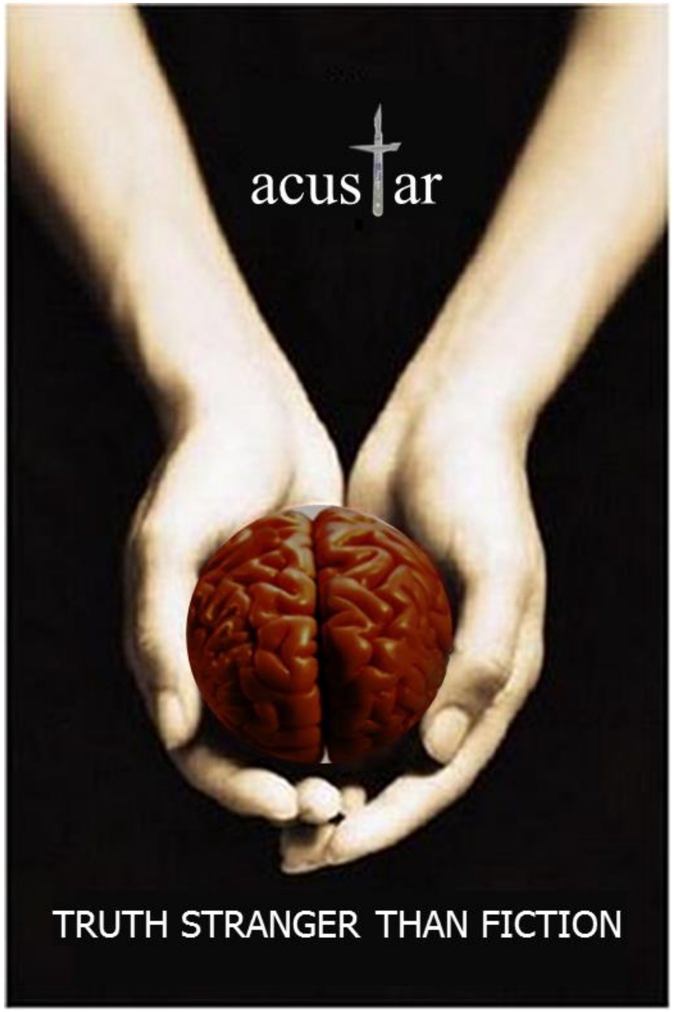
But there were big winners too…

- Medtronic and Brainlab: 100s of millions of dollars
- Bob Maciunas: Chair of Neurosurgery, U Rochester
- Mitch Berger: Chair of Neurosurgery, UCSF
- Bob Galloway: Full professorship
- Mike Fitzpatrick: Full professorship
- Graduate Students: Seven dissertations and PhDs.

But there were big winners too…

- And tens of thousands of patients have been winners as well despite the death of Acustar.
- Acustar may have died an untimely death, but it lived long enough to push surgery in a new direction.
- If it hadn’t happened at Vanderbilt, it would have happened somewhere else.

- But it didn’t happen somewhere else. It happened at Vanderbilt.



And with that, we close the book on Acustar.

Back to error

Acustar made us acutely aware of an insidious problem:

- We knew how to register by minimizing FRE.
- But FRE was never zero, and that proved that FLE was never zero, which suggested that TRE was not zero.
- And that is about all we knew.
- But we didn't have the names FRE or FLE or TRE yet. We had only vague notions about error. We struggled with it in dissertations, papers, and communications with Johnson & Johnson.
- We were floundering around, and we weren't the only ones.
- In fact,…

Registration error: a Tower of Babel

- Outside Vanderbilt there was no agreement on terminology whatever. People used all these terms:
  - "shift" error
  - "angular" error
  - "fiducial" error
  - "distance" error
  - "alignment" error

and their definitions were neither clear nor consistent.

My obsession with error begins

1989. I persuaded Venky Mandava to ignore three years of work on another topic and write his dissertation on fiducial registration. He did, and he completed it in 1991.

1992. A year later we published the first paper* explaining the TRE concept. The phrase, "target registration error", appeared in it six times.

Both "fiducial localization error" and "fiducial registration error" appeared in draft of this paper, and at our lab all three phrases had become our internal standard by 1992.

[*Mandava, Fitzpatrick, Maurer, Maciunas, Allen, SPIE Medical Imaging Symposium 1992]

Going public with all three

In 1993 these terms became our external standard as well:

- "fiducial localization error"
- "fiducial registration error"
- "target registration error"

All of them appeared in a paper*.

But we still had not published the acronyms, TRE, FRE, FLE.

[*CR Maurer, JM Fitzpatrick, MY Wang, RJ Maciunas, SPIE Medical Imaging Symposium, 1993]

and the acronyms appear

As Acustar was being buried, all three acronyms emerged:

1995, CR Maurer, JM Fitzpatrick, RL Galloway, M Wang, RJ Maciunas, *CARS*, Berlin

TRE and FLE

1996, MY Wang, CR Maurer, JM Fitzpatrick, *IEEE TBME*

FLE and FRE

So, we had rational names. We had cool acronyms.

But we still had only vague notions of how they were related.

Relating TRE to FLE

- 1991: During a sabbatical leave I struggled to find a way to relate TRE to FLE. I got nowhere but kept thinking about it.
- 1995: I remembered solving intractable problems in quantum physics to 1st order using perturbation theory. I told my students Jay West and Calvin Maurer that I wanted to try that on this problem.
- 1997: That idea worked, but it took another two years of derivations, and were racing against a lab in London that was working on the same thing.
- 1998: We won the race and published at Medical Imaging*

[*Fitzpatrick, West, Maurer, SPIE Medical Imaging 1998]

Eight years of work = 15 lines of MATLAB

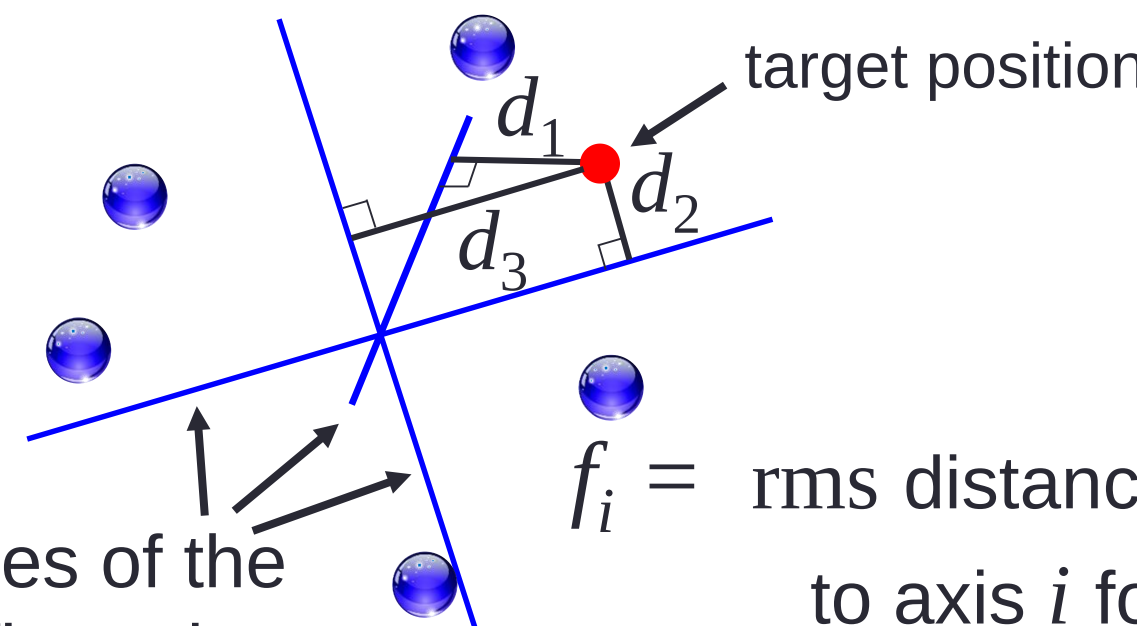
```
function TRE_RMS = treapprox(X,T,RMS_FLE)
[K,N] = size(X);
meanX = mean(X')';
Xc = X-meanX*ones(1,N);
[V, Lambda, U] = svd(Xc);
[K,M_T] = size(T);
Tc = T-meanX;  % T relative to centroid of X
Tv = V'*Tc;    % T referred to principal axes of X
D1 = Tv(2,:).^2 + Tv(3,:).^2;
D2 = Tv(3,:).^2 + Tv(1,:).^2;
D3 = Tv(1,:).^2 + Tv(2,:).^2;
F1 = (Lambda(2,2)^2 + Lambda(3,3)^2)/N;
F2 = (Lambda(3,3)^2 + Lambda(1,1)^2)/N;
F3 = (Lambda(1,1)^2 + Lambda(2,2)^2)/N;
TRE_RMS = sqrt((RMS_FLE^2/N)*(1 + (1/3)*(D1/F1 + D2/F2 + D3/F3)));
```

Do you see a recurring theme here?

End of first day

Here's what the MATLAB code calculates

$$< \mathrm{TRE}^2 > = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right] < \mathrm{FLE}^2 >$$

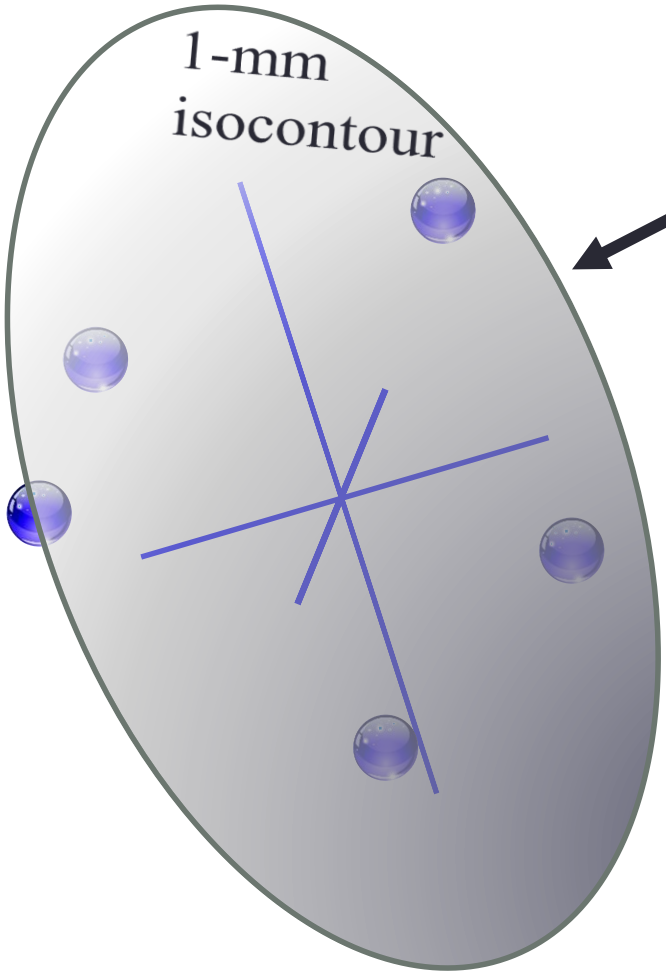


Principal axes of the fiducial configuration

f_i = rms distance to axis i for fiducials

TRE isocontours

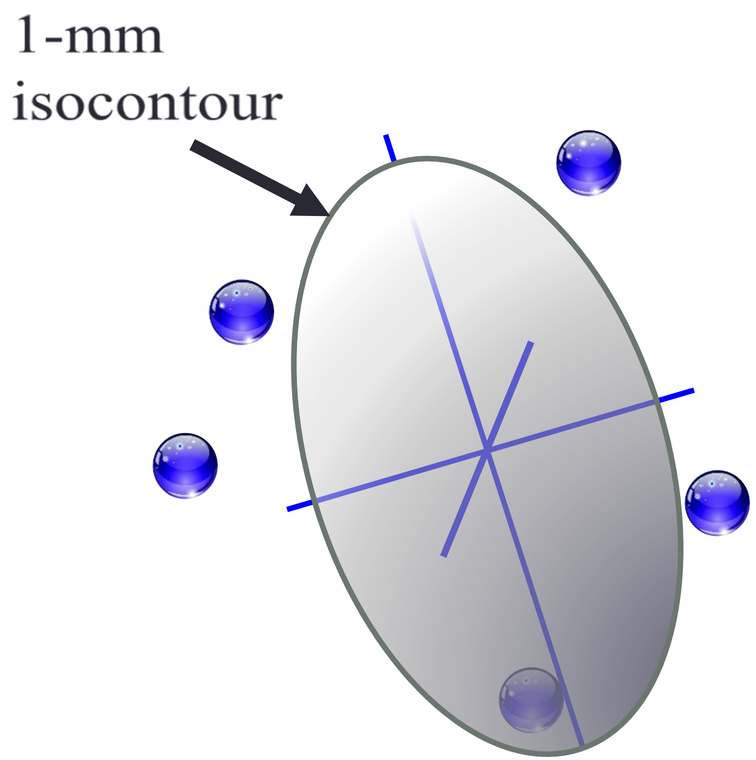
$$<\mathrm{TRE}^2> = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right]<\mathrm{FLE}^2>$$



Surface of constant TRE is an ellipsoid centered on the origin of the principal axes and the has same orientation.

TRE isocontours

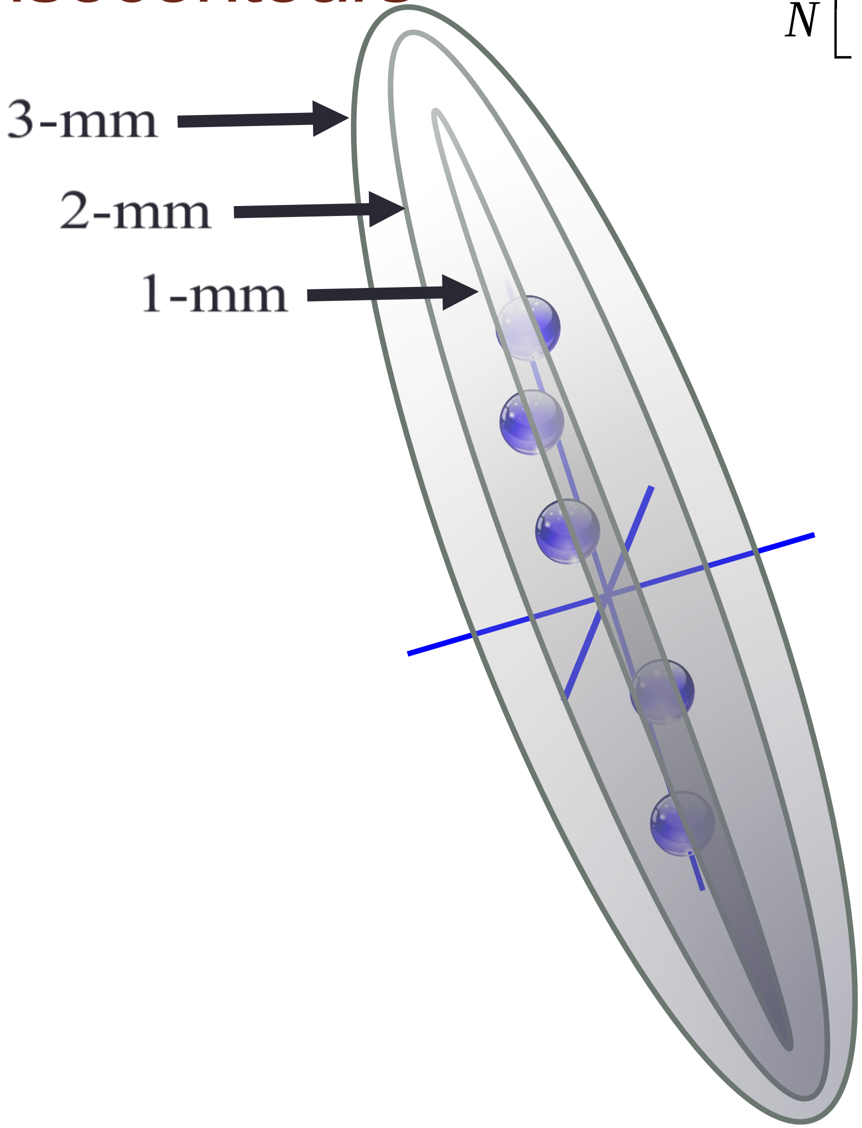
$$\langle TRE^2 \rangle = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right]\langle FLE^2 \rangle$$



A larger mean FLE-squared produces a smaller contour and a larger error at any given point.

TRE isocontours

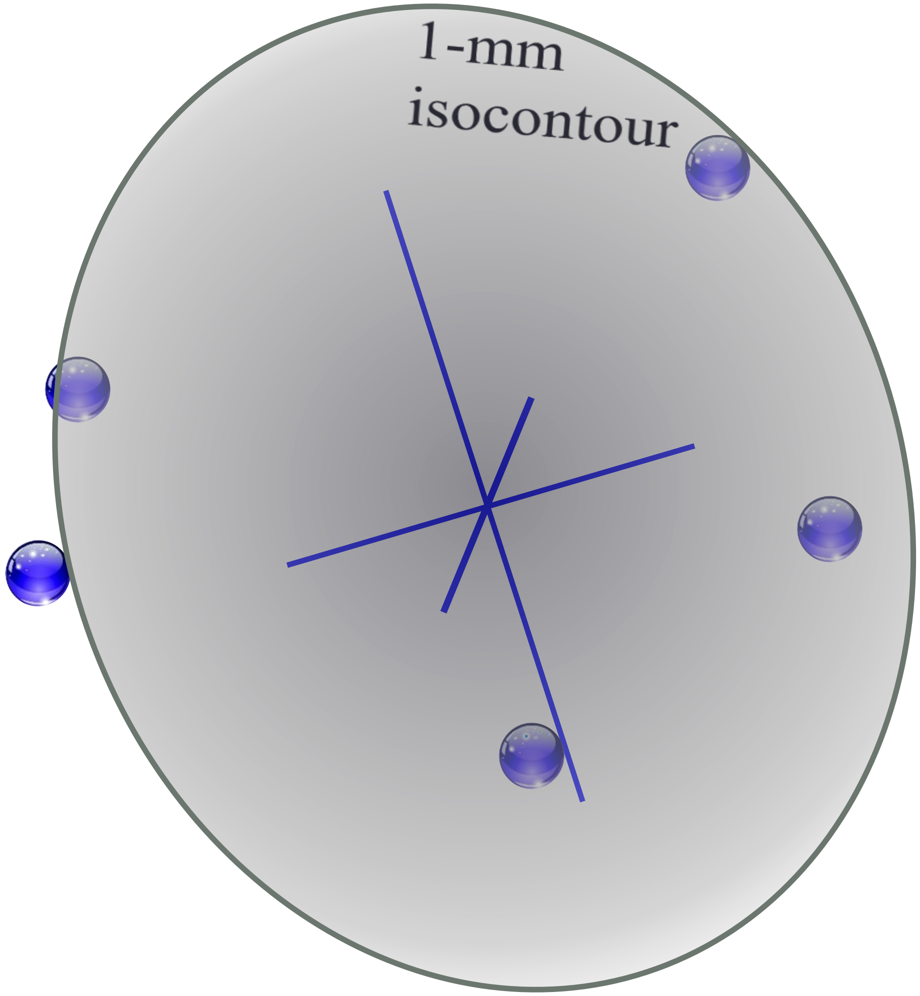
$$< \mathrm{TRE}^2 > = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right] < \mathrm{FLE}^2 >$$



A narrower fiducial spread in a given direction, like that of this nearly linear configuration, produces a narrow contour in that direction and a larger error at any given point.

TRE contours

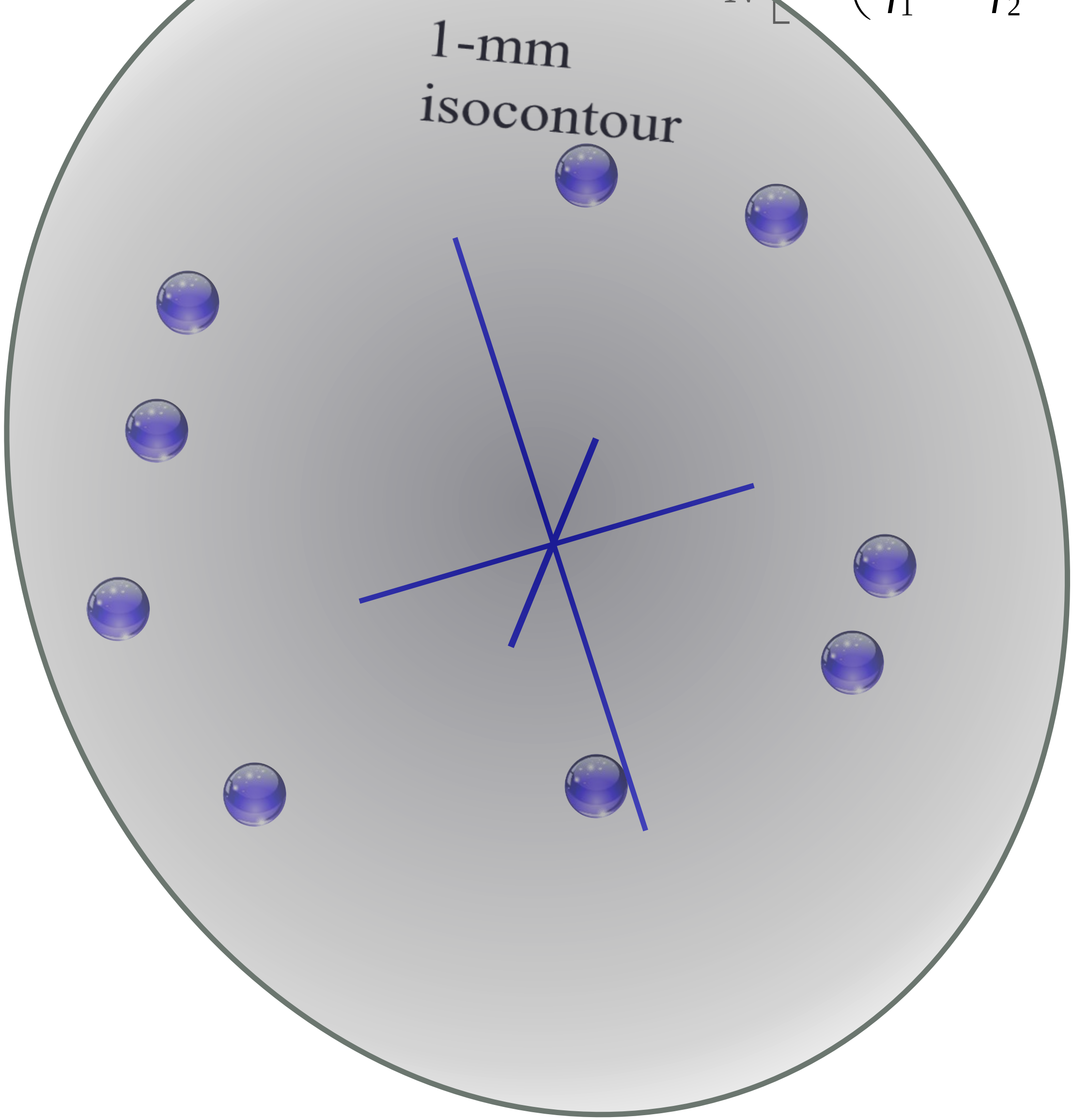
$$< \mathrm{TRE}^2 > = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right] < \mathrm{FLE}^2 >$$



A wider fiducial spread in a given direction produces a wider contour in that direction and a smaller error at any given point.

TRE contours

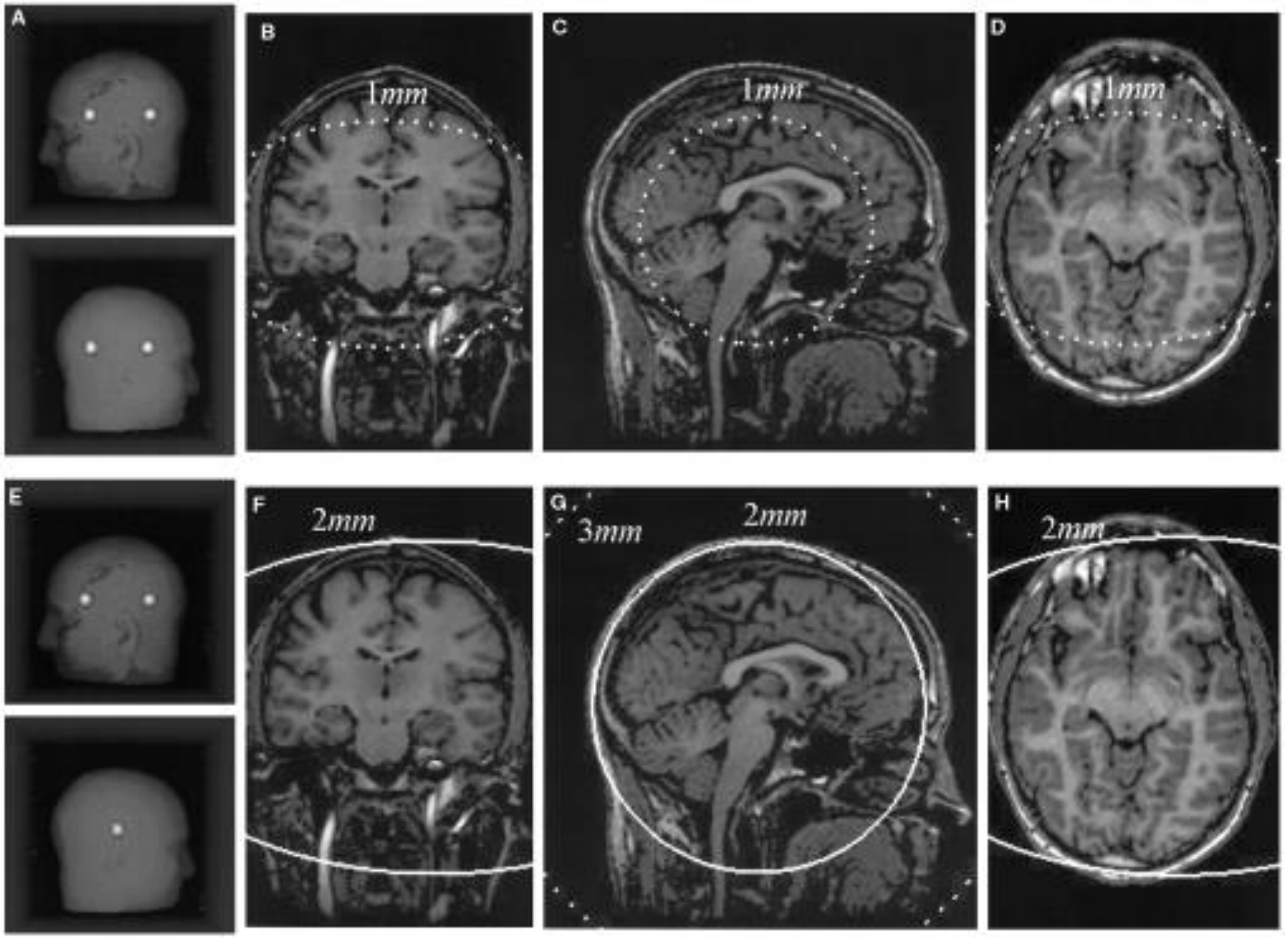
$$\langle \mathrm{TRE}^2 \rangle = \frac{1}{N}\left[1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right]\langle \mathrm{FLE}^2 \rangle$$



More fiducials widens the contour in all directions (because of the N in the denominator) and also reduces the error at any given point.

Getting the message to surgeons

We published the formula in the journal ***Neurosurgery*** with explanations and pictures of good fiducial placements…

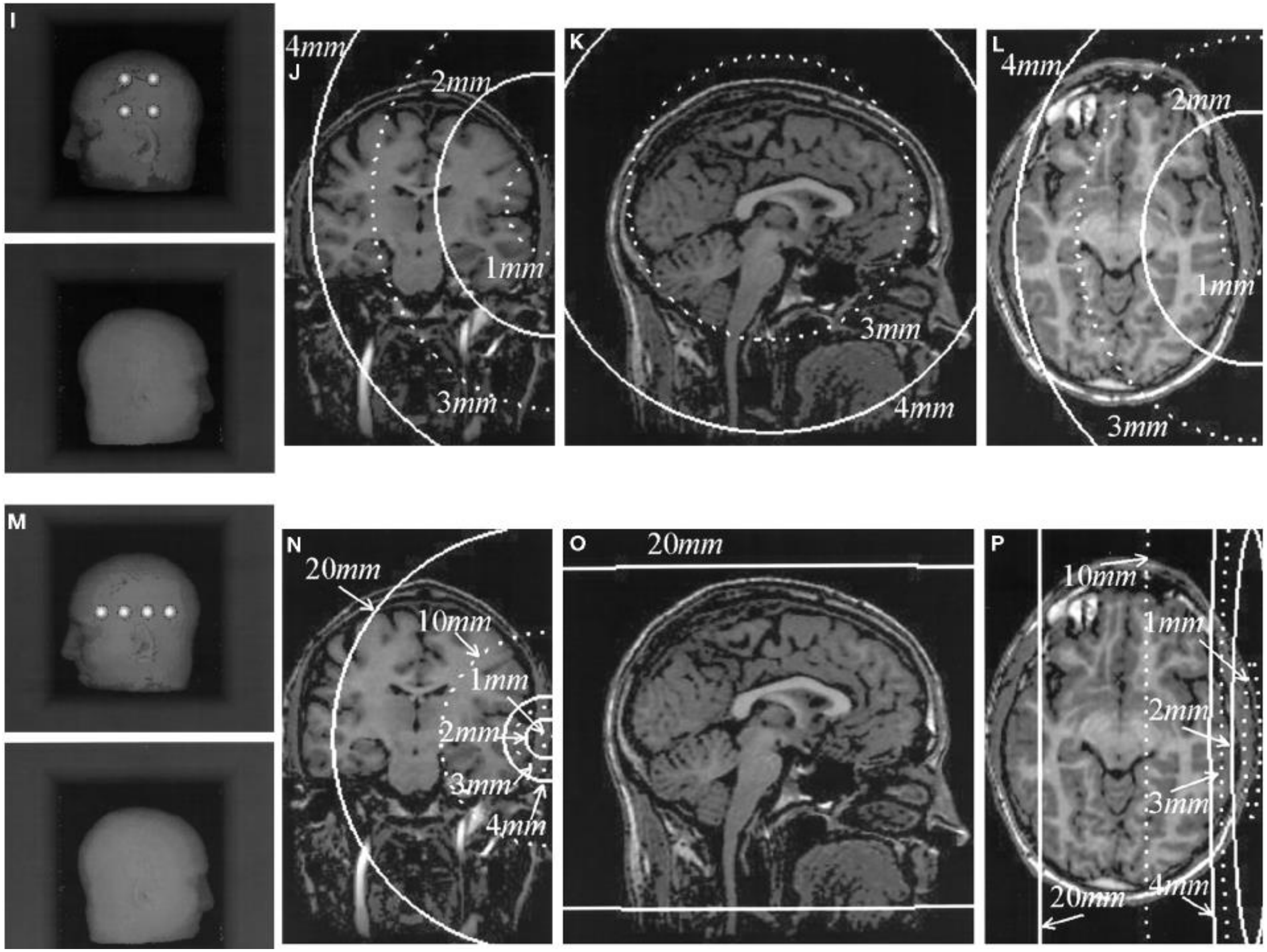


[West, Fitzpatrick, *et al*., *Neurosurg*, 2001]

Getting the message to surgeons

...and bad fiducial placements.

And we gave four simple rules that are implied by the formula for avoiding bad placements.



[West, Fitzpatrick, *et al.*, *Neurosurg*, 2001]

An eloquent (open) review

"There is something particularly seductive about the information (both graphic and numerical) presented on surgical navigational systems. The images and crosshairs are crisp. The registration error is displayed in millimeters and fractions (tenths, hundredths) thereof. It is little wonder that surgeons want to believe that what they see is what they get.

In this article, the authors show the true blur of error behind these slick facades and how the surgeon has substantial control over optimizing accuracy of registration in the area of interest. …The reader will likely get lost in the mathematical explanation, but the results are important for anyone who uses surgical navigation in operating on a patient's head or spine:

Avoid linear placement,
More is better,
Keep them far apart,
And center them on your target.

…This article should be required reading for all neurosurgeons."

Gene H. Barnett, Director
Brain Tumor Center,
Cleveland Clinic

OK, we know how TRE is related to FLE, but how is FRE related to FLE?

(and why do we care?)

The relationship is startlingly simple!

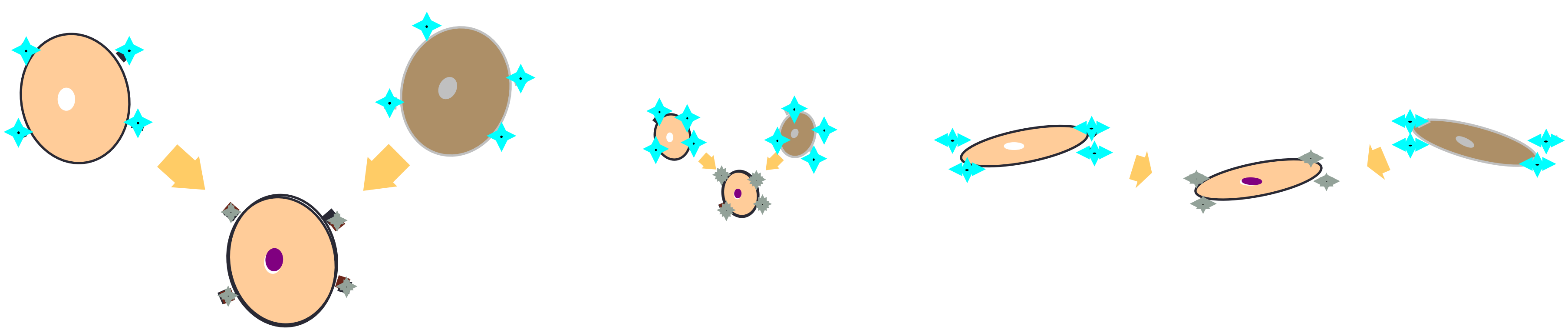
$$\langle \mathrm{FRE}^2 \rangle = \left((N-2)/N \right) \langle \mathrm{FLE}^2 \rangle^{*}$$ (see demo5)

Examples: for 4 fiducials $\langle \mathrm{FRE}^2 \rangle = 0.50 \langle \mathrm{FLE}^2 \rangle$

for 5 fiducials $\langle \mathrm{FRE}^2 \rangle = 0.60 \langle \mathrm{FLE}^2 \rangle$

for 6 fiducials $\langle \mathrm{FRE}^2 \rangle = 0.67 \langle \mathrm{FLE}^2 \rangle$

It's “startling” because the configuration doesn't matter!



[*Fitzpatrick, West, Maurer, *TMI*, 1998]

And why do we care about the FRE-FLE formula?

- Because we can use it to estimate FLE, which we can then use in the TRE formula to predict targeting accuracy.
- Algorithm for estimating FLE:
  - Set up a system as it would be used for a procedure.
  - Repeat these three things many times:
    - localize fiducials, register, measure FRE
  - Calculate $\mathrm{mean}(\mathrm{FRE}^2)$.
  - Rearrange the formula: $\langle \mathrm{FLE}^2 \rangle = (N/(N-2))\langle \mathrm{FRE}^2 \rangle$
  - $\langle \mathrm{FLE}^2 \rangle_{\mathrm{est}} = (N/(N-2)) \times \mathrm{mean}(\mathrm{FRE}^2)$
  - $\left\langle \mathrm{TRE}^2 \right\rangle = \left\langle \mathrm{FLE}^2 \right\rangle_{\mathrm{est}} / N \left(1 + \sum d_k^2 / 3 f_k^2\right)$

And how is TRE related to FRE?

$$\langle \mathrm{FRE}^2 \rangle = \left((N-2)/N\right)\langle \mathrm{FLE}^2 \rangle$$

+

$$\langle \mathrm{TRE}^2 \rangle = \frac{\langle \mathrm{FLE}^2 \rangle}{N}\left(1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right)$$

(simple algebra)

$$\langle \mathrm{TRE}^2 \rangle = \frac{\langle \mathrm{FRE}^2 \rangle}{N-2}\left(1+\left(\frac{d_1^2}{f_1^2}+\frac{d_2^2}{f_2^2}+\frac{d_3^2}{f_3^2}\right)/3\right)$$

[Fitzpatrick, West, Maurer, *TMI*, 1998]

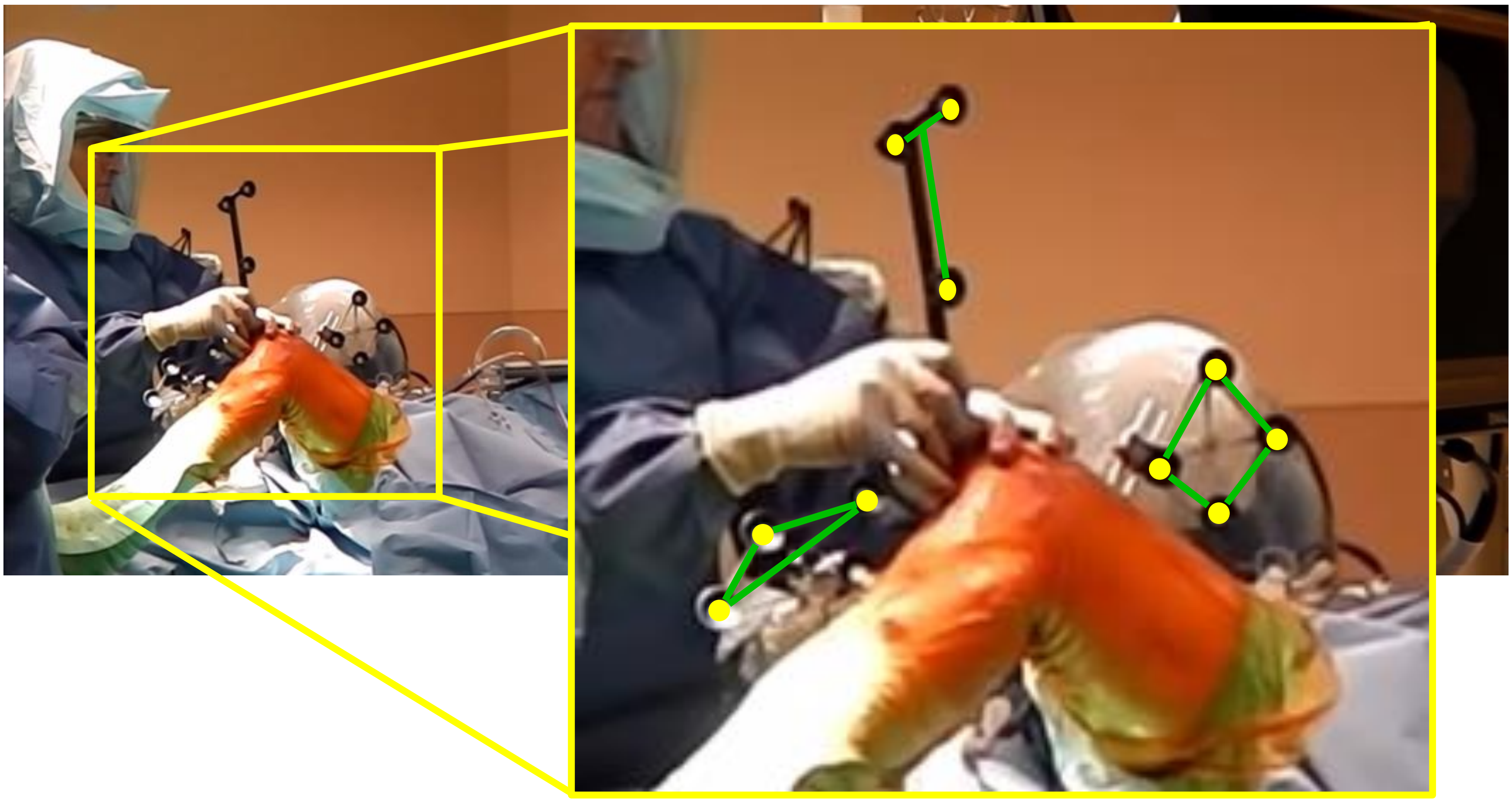
It’s time to play MYTHBUSTERS!

1. Planar configurations are bad. **FALSE!**

2. We can estimate TRE for Ms. Jones’s surgery from her FRE for that surgery. **FALSE!**

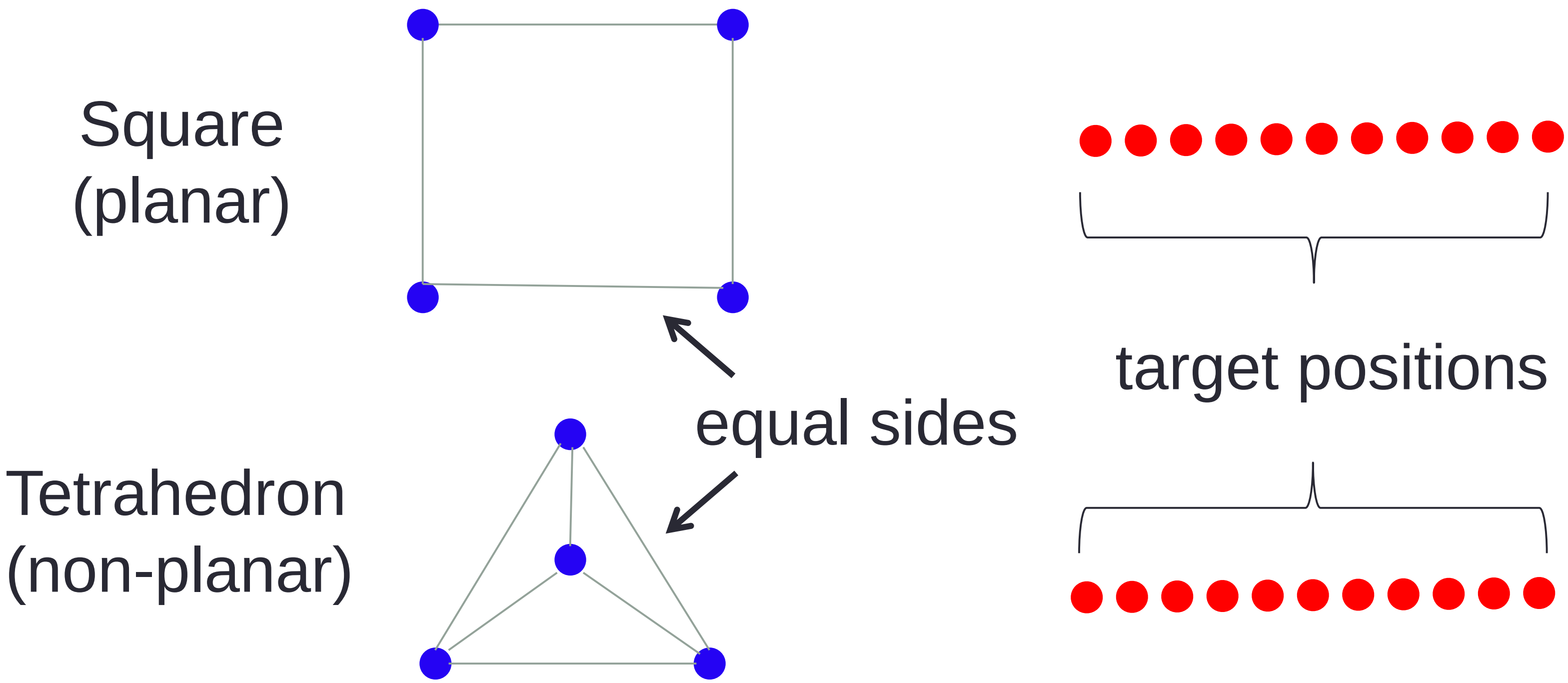
3. Dropping the fiducial with the worst FRE_i is likely to improve TRE. **FALSE!**

Example: Makoplasty Knee Surgery



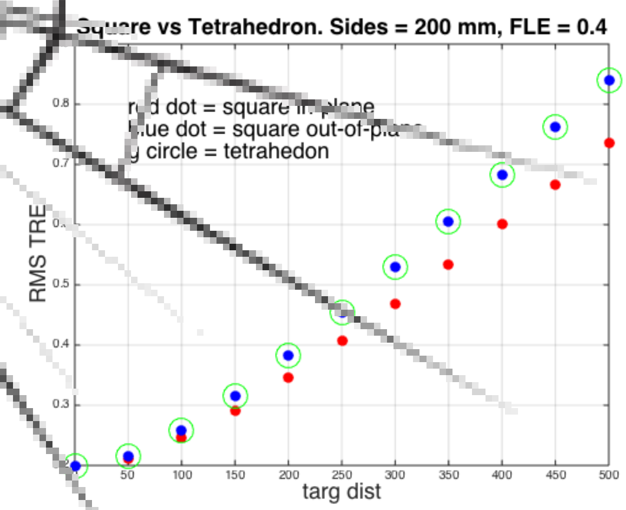
Example: Makoplasty Knee Surgery

Myth 1: Planar configurations are bad



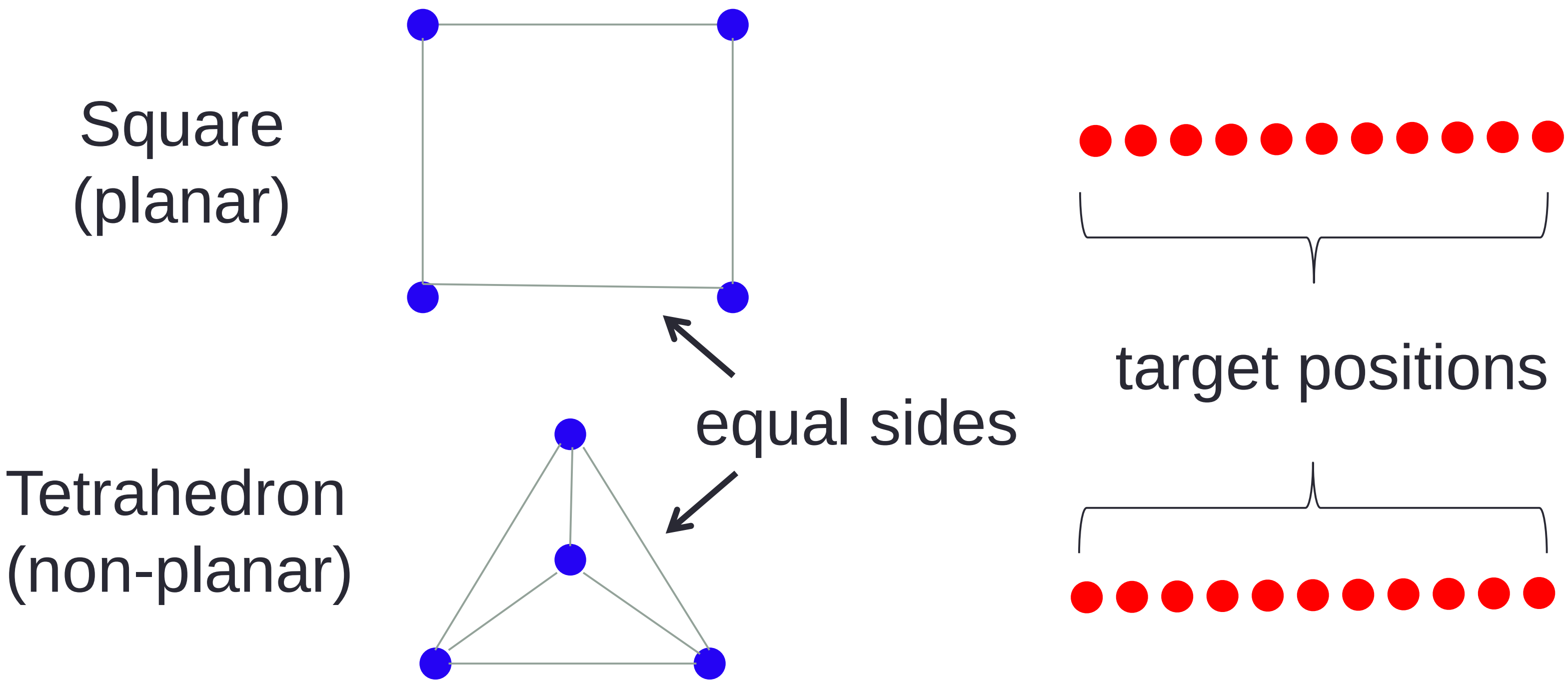
(`treta_vs_square` shows TRE relationships in MATLAB.)

Myth 1: Planar configurations are bad



A head-to-head comparison shows that a planar configuration equals or beats an equal sided non-planar version. Sorry non-planar configurations, this myth is…

Myth 1: Planar configurations are bad



(`treta_vs_square` shows TRE relationships in MATLAB.)

Myth 2: FRE is a predictor of TRE

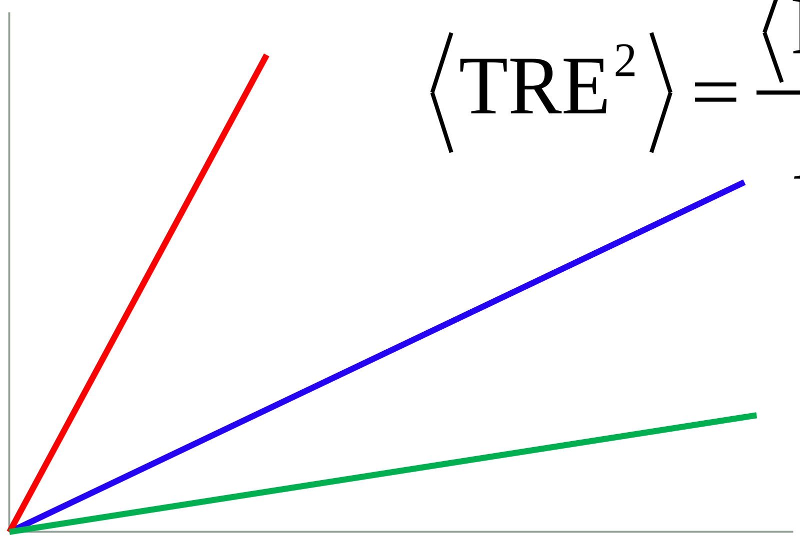
The myth is that if a FRE is lower than usual for Ms. Jones's surgery today that TRE is likely to be lower than usual in her surgery today too.

Not true! Deviations of FRE from its mean are uncorrelated to deviations of TRE from its mean.

So a surgeon should never assume that s/he can cut closer than usual to an artery because FRE was lower than usual today.

Myth 2: FRE is a predictor of TRE

$\langle \mathrm{TRE}^2 \rangle$



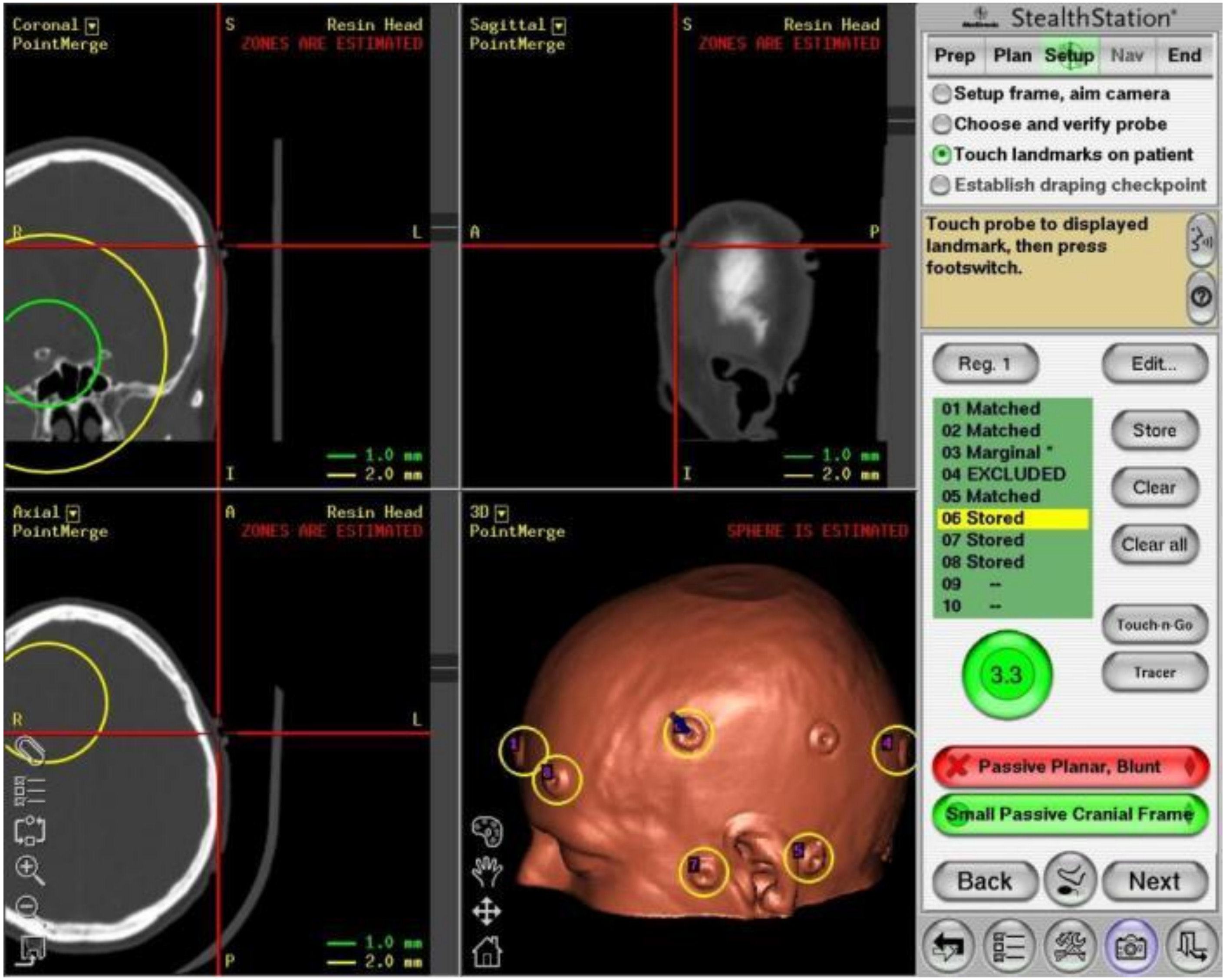
$\langle \mathrm{FRE}^2 \rangle$

$$\langle \mathrm{TRE}^2 \rangle = \frac{\langle \mathrm{FRE}^2 \rangle}{N-2}\left(1+\frac{1}{3}\sum_{k=1}^{3}\frac{d_k^2}{f_k^2}\right)$$

$$\text{Slope} = \frac{1}{N-2}\left(1+\frac{1}{3}\sum_{k=1}^{3}\frac{d_k^2}{f_k^2}\right)$$

These plots seem to support it, until you remember that < x > is the mean of x, not today's value.

Myth 2: FRE is a predictor of TRE



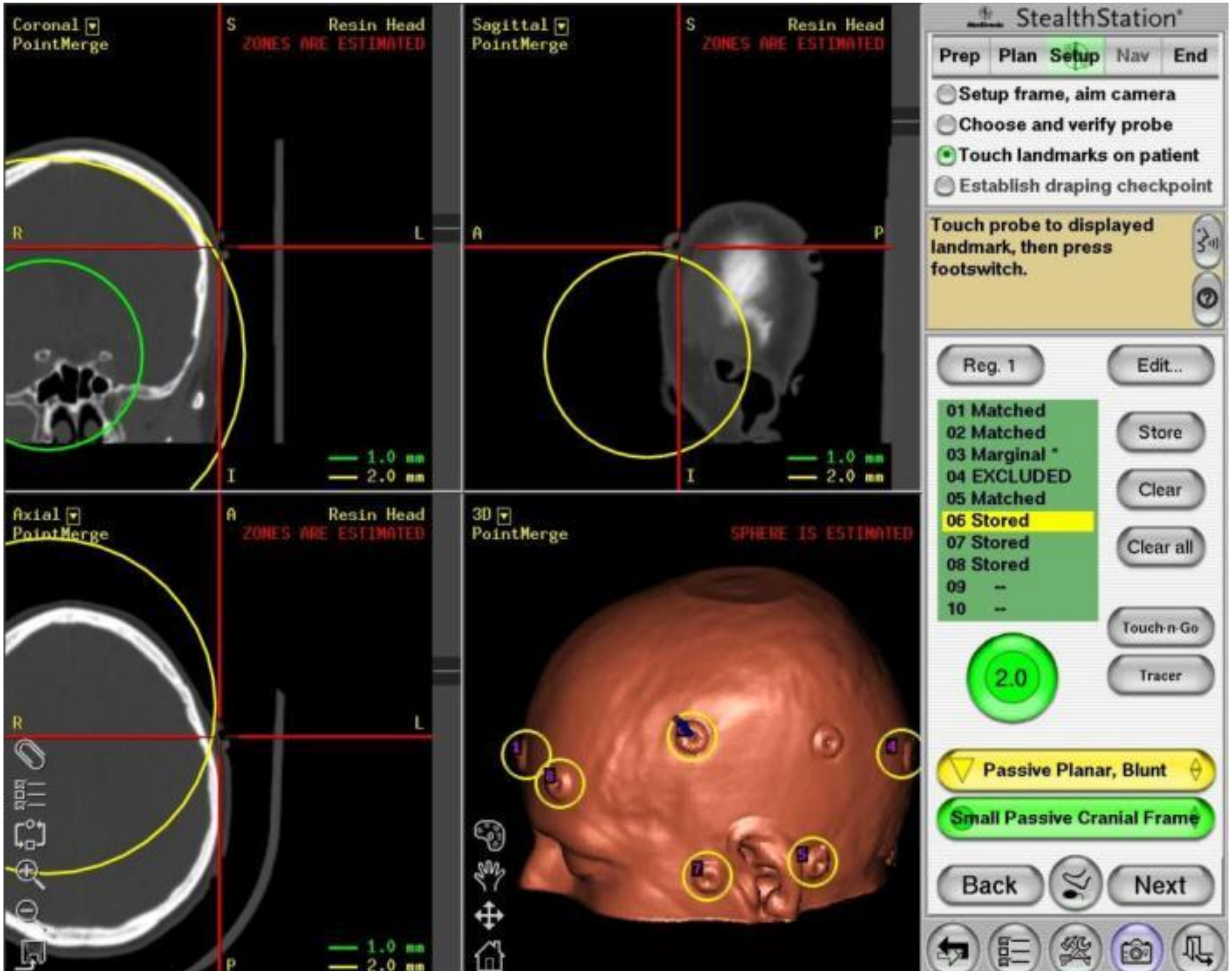
Phantom with 4 markers.

One marker mislocalized.

TRE zones are small (bad).

[by Gil Humbert, RN, Vanderbilt]

Myth 2: FRE is a predictor of TRE



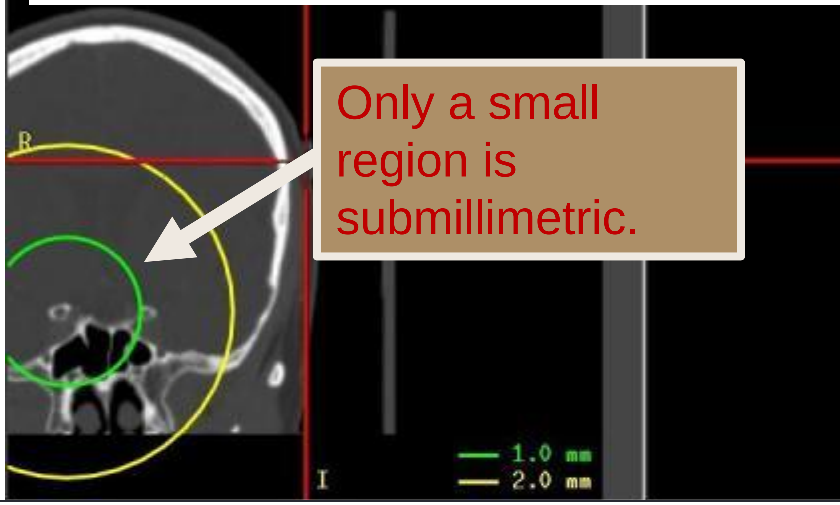
Phantom with 4 markers.

Bad one relocalized.

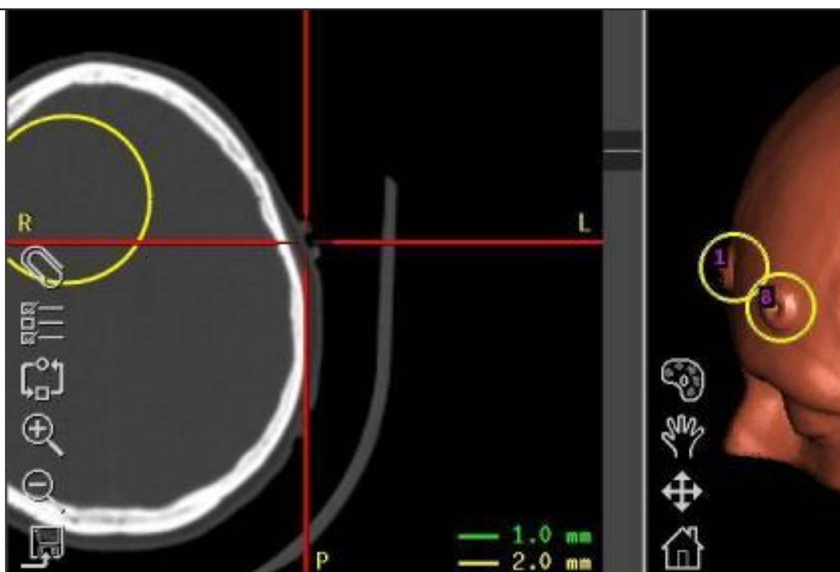
TRE zones are large (good).

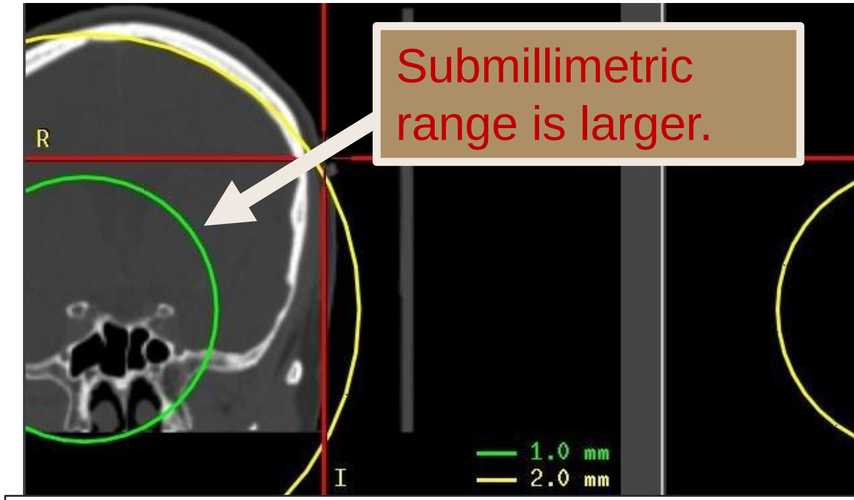
[by Gil Humbert, RN, Vanderbilt]

Myth 2: FRE is a predictor of TRE

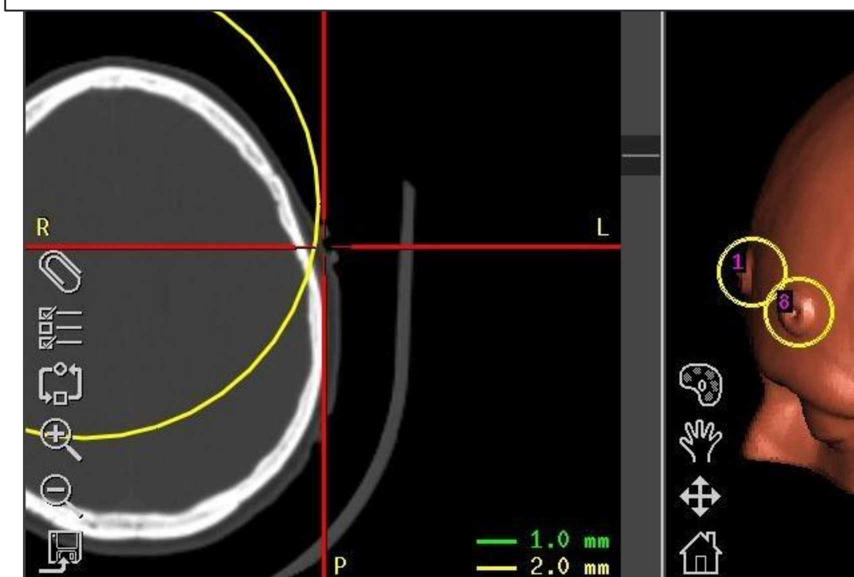


Large FRE→ Large TRE



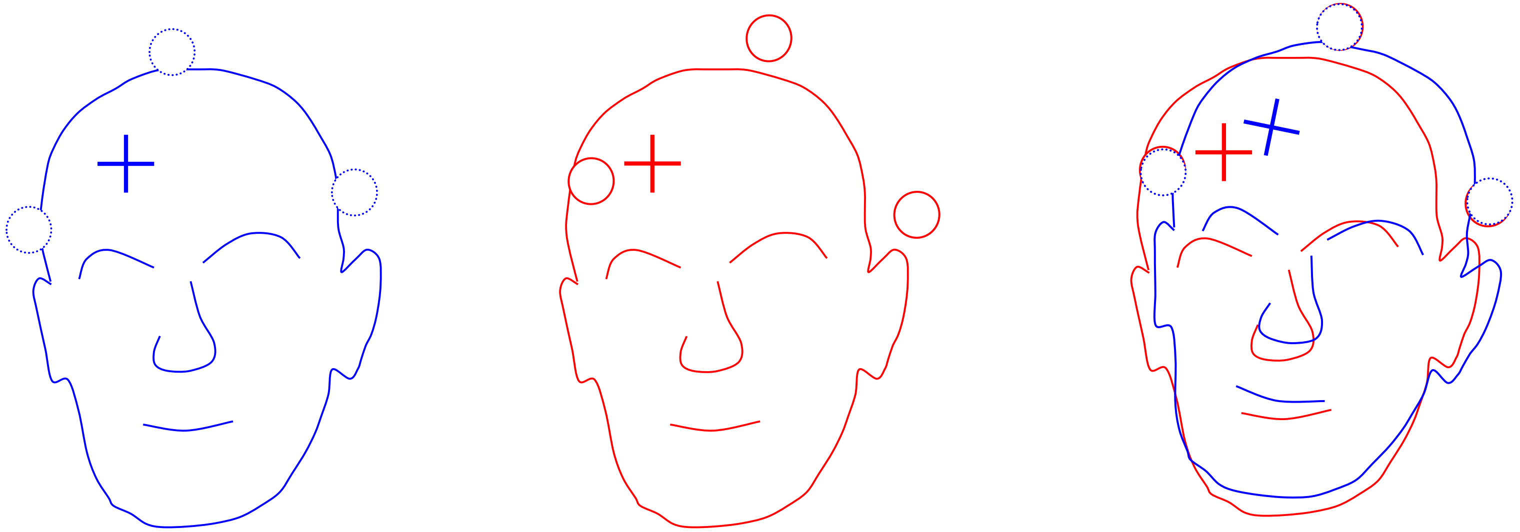


Small FRE→ Small TRE



Myth 2: FRE is a predictor of TRE

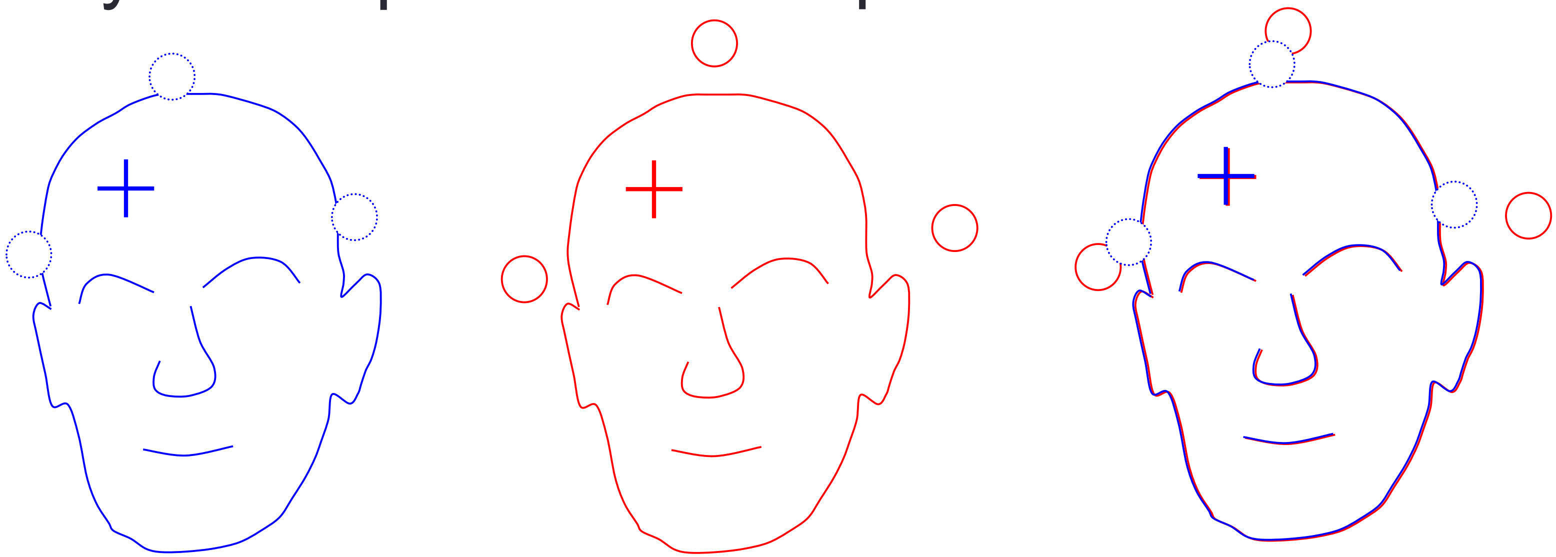
It's easy to set up counter examples…



small FRE, and
large TRE

Myth 2: FRE is a predictor of TRE

It's easy to set up counter examples…

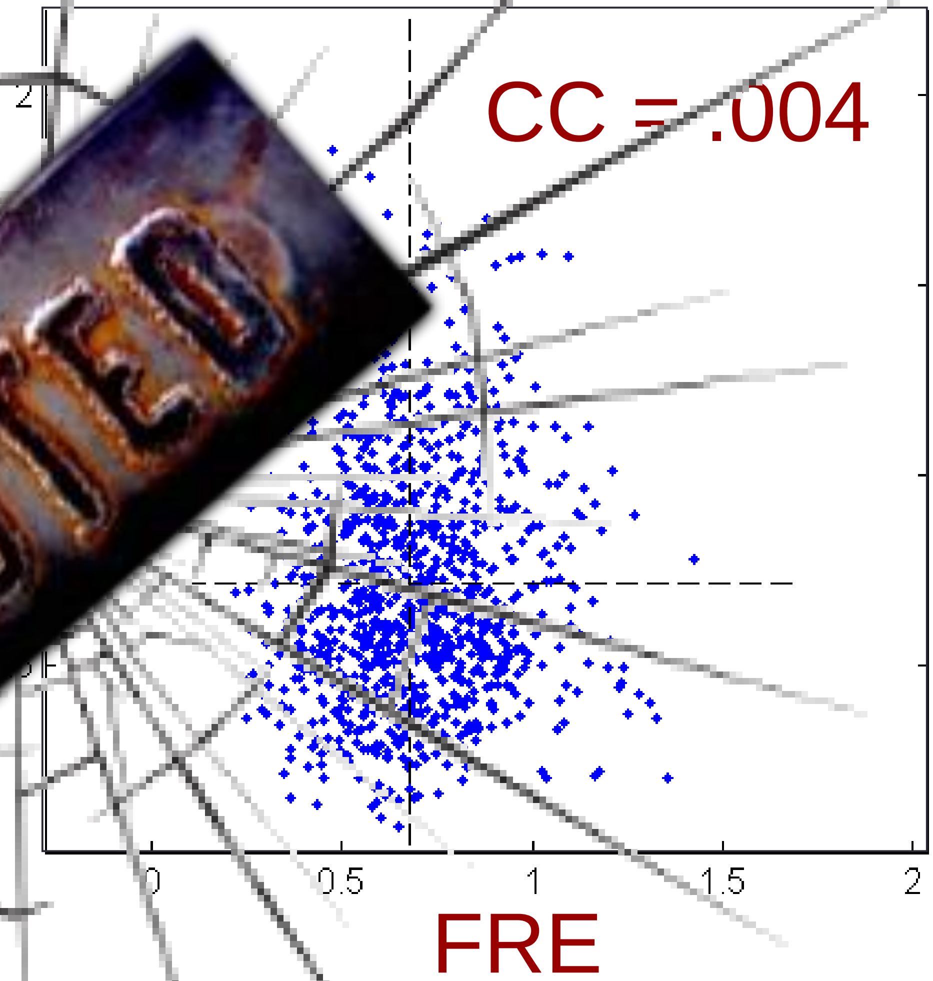


large FRE, and small TRE

Myth 2: FRE is a predictor of TRE

But it this is a statistical question and FRE-TRE has NO CORRELATION according to both theory (first-order) an simulation (ex

- 4 fiducials
- Target n
- FLE = 1 m
- 100,000 regist



[J. M. Fitzpatrick, *SPIE Medical Imaging*, Feb 2009]

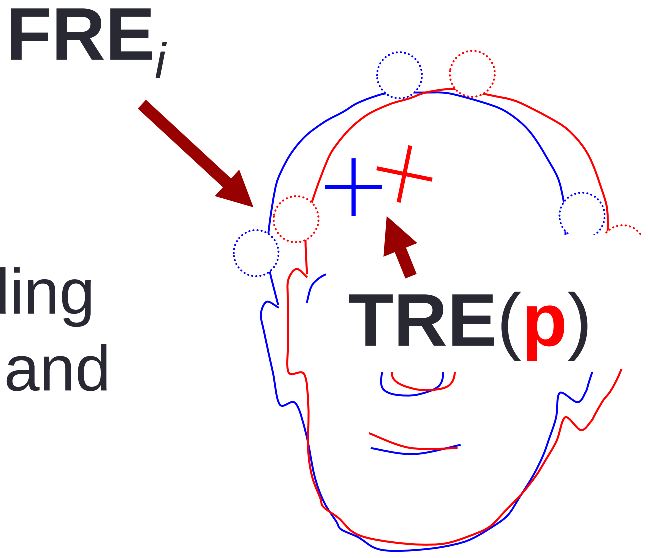
So does FRE tell the surgeon anything?

- Yes. FRE is like a sentinel watching for trouble.
- An FRE that is much smaller than usual tells the surgeon nothing more than a normal FRE. It simply says that the system appears to be working properly.
- An FRE that is much larger than usual raises a flag.
- A very large FRE indicates that the guidance system is broken or a fiducial has moved. In that case FRE serves as a warning to the surgeon that the system may be unreliable and should not be trusted.

[J. M. Fitzpatrick, *SPIE Medical Imaging*, Feb 2009]

Will some other measure of goodness-of-fit predict TRE?

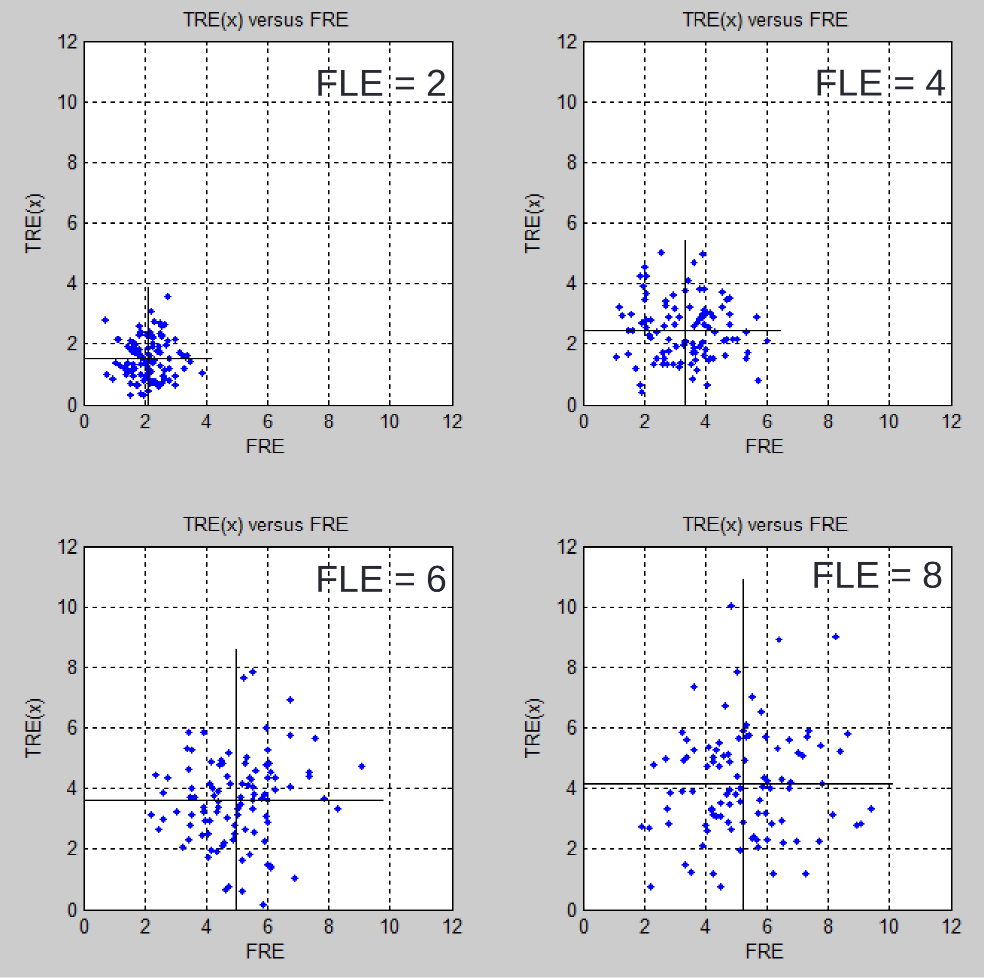
We've seen from the simulations that FRE won't work, but is there <u>any</u> combination of Ms. Jones's *N* individual **FRE**$_i$ that we can use to estimate a likely TRE for her?



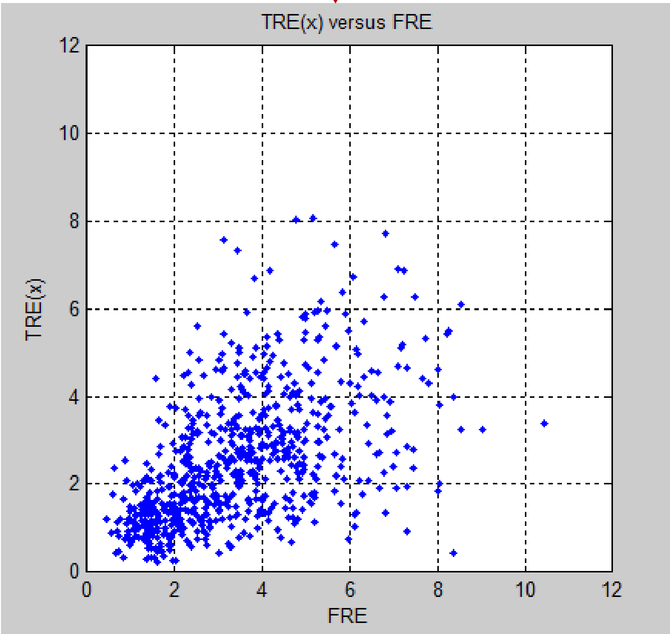
Answer: Sadly, No, according to both theory (first-order) and simulation (exact)*

[*Danilchenko and Fitzpatrick, TMI, 2011]

What makes people believe a correlation exists?



Maybe this

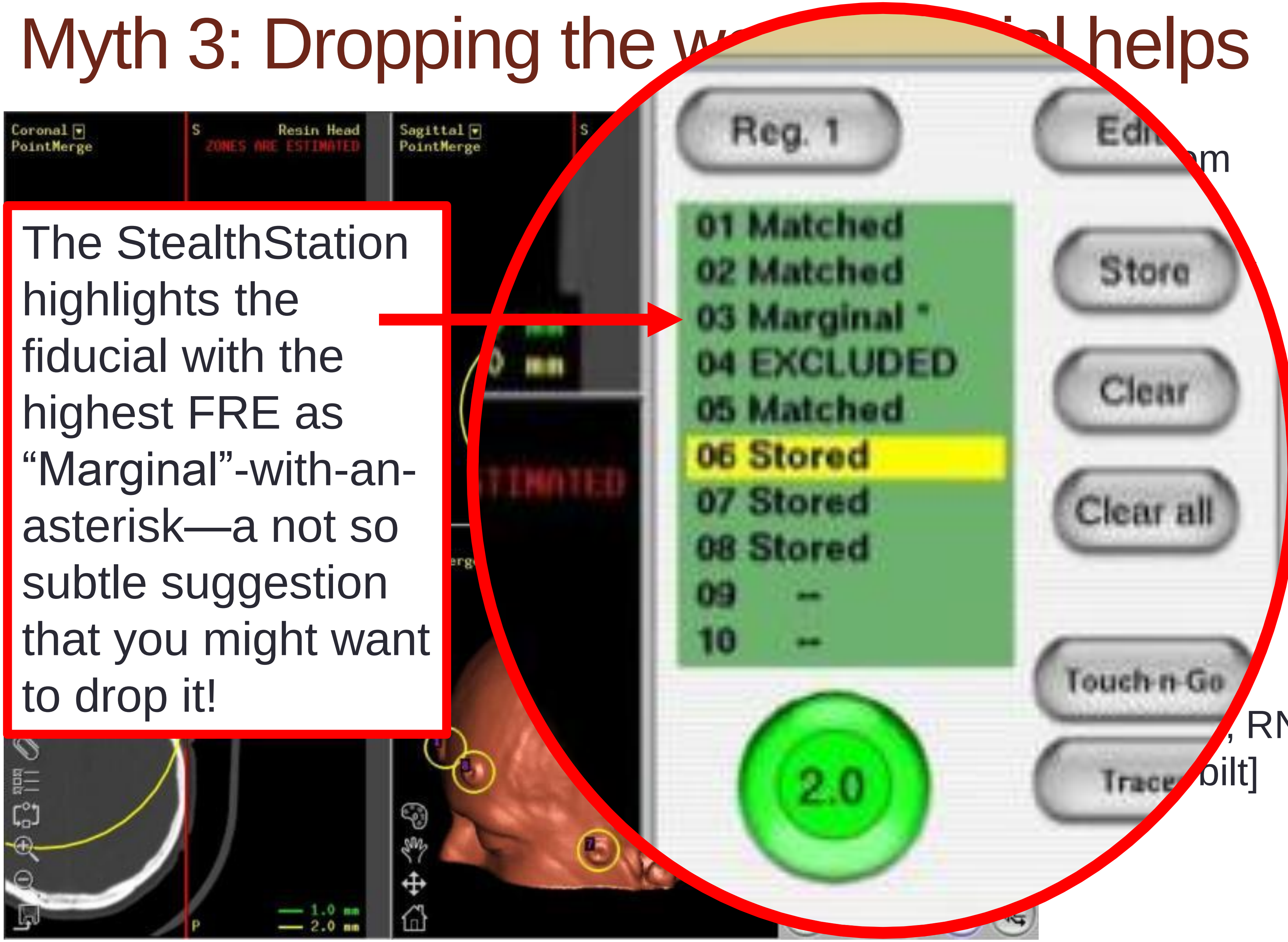


FLE = 2, 4, 6, 8 superimposed

Myth 3: Dropping the worst fiducial helps

- After registration, you can check the FREi for each fiducial and see which has the largest (“worst”) FREi. Should you drop it?
- Some systems suggest that it might make the registration more accurate if you do…

Myth 3: Dropping the w... al helps



The StealthStation highlights the fiducial with the highest FRE as "Marginal"-with-an-asterisk—a not so subtle suggestion that you might want to drop it!

Myth 3: Dropping the worst fiducial helps

- It's not yet proven false, but every simulation refutes it.

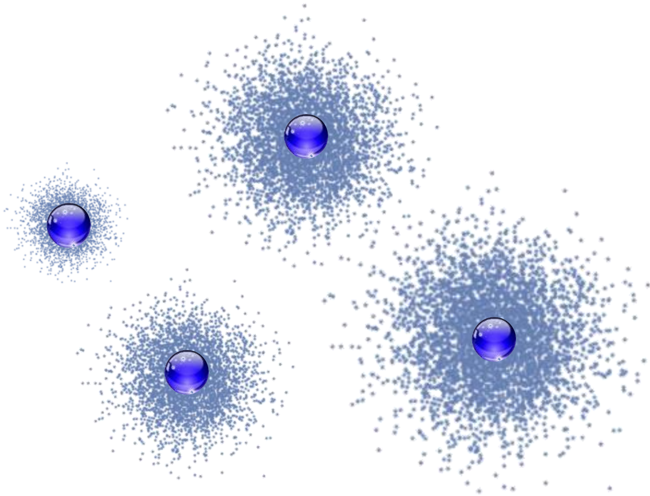
Red line is mean TRE for 1000 registrations. Green line is mean FRE.

When the "worst" fiducial is dropped, mean FRE goes down, but <u>mean TRE goes up</u>.

You are the ones!

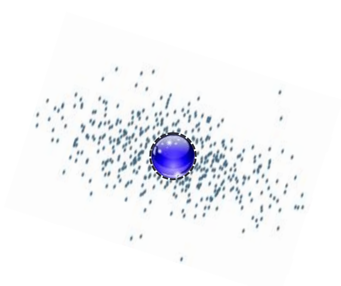
- These myths are beguiling, and they are harmful.
- Surgeons don’t have time to check them out or even the background to be able to check them out.
- Those of you on the “E” end VISE have the responsibility for keeping patients safe from these myths.

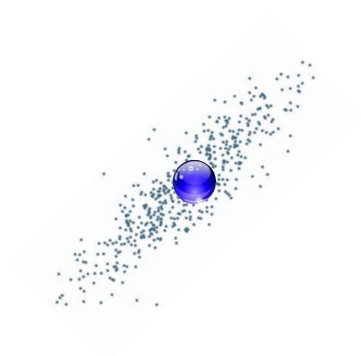
Anisotropy

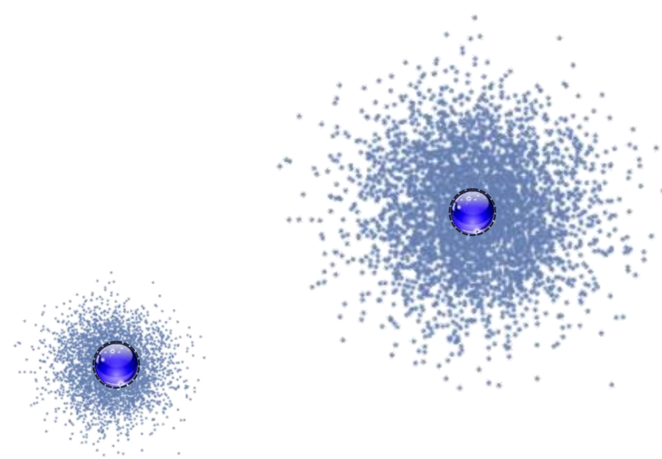


- We have both a registration algorithm and error formulas for inhomogeneous FLE but they all require FLE to be isotropic.

- So what do we do if FLE is anisotropic?







Registration algorithm for anisotropy

- Unfortunately, if FLE is anisotropic, our previous registration algorithm will not produce the rigid transformation that has the maximum likelihood of being correct.
- To get that, we must minimize an anisotropically weighted sum of squared FREs, which means that each geometric component of $R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i$ is weighted differently.

Registration algorithm for anisotropy

- To weight each component of $R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i$ differently, we can multiply it by a 3-by-3 matrix, called a "weighting matrix", like this:

$$W\left(R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i\right) \qquad W = \begin{bmatrix} W_{11} & W_{12} & W_{13} \\ W_{21} & W_{22} & W_{23} \\ W_{31} & W_{32} & W_{33} \end{bmatrix}$$

- So we need to find the minimum of this sum.

$$\mathrm{FRE}^2 = \frac{1}{N}\sum_{i=1}^{N}\left|W_i\left(R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i\right)\right|^2,$$

where each weighting matrix may be different.

Registration algorithm for anisotropy

- The weighting matrix for each fiducial is a function of the anisotropy of FLE for that fiducial in both spaces and the rotation matrix. So the sum to be minimized is this:

$$\mathrm{FRE}^2 = \frac{1}{N}\sum_{i=1}^{N}\left| W\left(\Sigma_i, \Sigma_i, R\right)\left(R\mathbf{x}_i + \mathbf{t} - \mathbf{y}_i\right)\right|^2$$

- The registration algorithm for this expression is iterative, but it converges quickly.* You can find it here: http://eecs.vanderbilt.edu/people/mikefitzpatrick/

[*R. Balachandran, J. M. Fitzpatrick, SPIE Medical Imaging 2009]

And what about predicting TRE?

- Except for a few special case, analytic formulas for TRE do not exist.
- But in 2011 an algorithm was published that handles all cases*.
- The publication of this algorithm marked the end of the search for a way to predict TRE from FLE that I had begun during my sabbatical in 1991.

[*Danilchenko and Fitzpatrick, TMI, 2011]

20 years — 12 lines

All rigid-point TRE prediction and FRE prediction problems are solved by this little MATLAB function:

```
function [Cov_TRE,Cov_FRE] = TRE(X,W,Cov_FLE,r)
T = W(:,1,:);U = W(:,2,:);V = W(:,3,:);
Xr = reshape([repmat(X(1,:),3,1);repmat(X(2,:),3,1);repmat(X(3,:),3,1)],size(W));
X1 = Xr(:,1,:);X2 = Xr(:,2,:);X3 = Xr(:,3,:);
C = reshape(permute([-U.*X3+V.*X2,T.*X3-V.*X1,-T.*X2+U.*X1,T,U,V],[1,3,2]),[],6);
W_cell = num2cell(W,[1 2]);
Cov_cell = num2cell(Cov_FLE,[1 2]);
W_Cov_Wt = blkdiag(W_cell{:})*blkdiag(Cov_cell{:})*blkdiag(W_cell{:})';
D = [[0,r(3),-r(2);-r(3),0,r(1);r(2),-r(1),0],eye(3)];
pinvC = pinv(C);
Cov_TRE  = D*pinvC*W_Cov_Wt*pinvC'*D';
Cov_FRE  = (eye(size(C,1))-C*pinvC)*W_Cov_Wt*(eye(size(C,1))-C*pinvC);
```

There is definitely a recurring theme here.

http://eecs.vanderbilt.edu/people/mikefitzpatrick/

What have we learned?

- Definitions: FLE, FRE, and TRE
- History: Why these terms originated at Vanderbilt
- Algorithm 1: Registration for homogeneous, isotropic FLE
- Algorithm 2: Registration for all isotropic FLE
- Formula 1: TRE for homogeneous, isotropic FLE
- Formula 2: FRE for homogeneous, isotropic FLE
- Algorithm 3: FLE from FRE
- Myths: Three common assumptions that are false
- Algorithm 4: Registration for all FLE
- Algorithm 5: TRE for all FLE
- Philosophy: Hard problems can be solved by short algorithms

Declaration of dependence

We hold these truths to be self-evident

that surgeons know more about human bodies than engineers
that engineers know more about machines than surgeons
that surgery on humans without machines is a dying art.

We, therefore, do solemnly publish and declare

that the surgeons and the engineers in VISE are dependent on each other and that all connections between them ought to be strengthened.

And in that vein, if I may be permitted a last word to those on the E side of VISE…

Challenge to the "E" side

Speaking to you now as one of many patients who has undergone major surgery performed with a machine and who is extremely grateful for the engineers that made that machine and made it safe and effective, I would challenge you:

If you are an engineer—or a physicist, computer scientist, or mathematician—do your very best to understand every formula and every algorithm that you encounter that might affect the safety and efficacy of machines in surgery and make it your responsibility to proactively explain these concepts to those who need to understand them.

We're all depending on you.