Delivering Innovation to the Clinic: The Path from Problem to Practice

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The problem?

Cancer: Breakthrough treatments to target drug resistance

Artificial intelligence can be weapon in cancer fight, PM to say
The problem?

300 years?

Unhappy doc

Disappointed patient
The problem?

From problem to practice?
An example

Do we have a problem?
Do we have a problem?
Do we have a problem?

- Body
- Femur_L
- Femur_R
- Bladder
- Rectum
- SeminalVesc
- Prostate

Langmack KA, Perry C, Sinstead C, Mills J, Saunders D. The utility of atlas-assisted segmentation in the male pelvis is dependent on the interobserver agreement of the structures segmented. The British journal of radiology. 2014 Oct 3;87(1043):20140299.
But, there are solutions …

**Table II.** Commercial software tools for automated medical image segmentation (F = female; H and N = head and neck; M = male TPS = treatment planning system).

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Product name</th>
<th>Method</th>
<th>Included atlases</th>
<th>Integrated with TPS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuray</td>
<td>MultiPlan 5.0</td>
<td>Atlas-based model-based</td>
<td>Brain, M pelvis</td>
<td>Yes</td>
<td>Reference 101</td>
</tr>
<tr>
<td>BrainLab</td>
<td>iPlan</td>
<td>Atlas-based</td>
<td>Brain, H and N, pelvis, spine, thorax</td>
<td>Yes</td>
<td>Reference 102</td>
</tr>
<tr>
<td>Dosist</td>
<td>IMAgio</td>
<td>Atlas-based</td>
<td>Brain, H and N</td>
<td>Yes</td>
<td>Reference 103</td>
</tr>
<tr>
<td>Elekta</td>
<td>ABAS 2.01</td>
<td>Atlas-based model-based</td>
<td>H and N, M pelvis</td>
<td>No</td>
<td>Reference 14</td>
</tr>
<tr>
<td>MIM software</td>
<td>MIM Maestro 6+</td>
<td>Atlas-based</td>
<td>H and N</td>
<td>No</td>
<td>Reference 104</td>
</tr>
<tr>
<td>Mirada</td>
<td>RTx 1.4. Workflow box</td>
<td>Atlas-based</td>
<td>Azo-rectal, Breast, H and N, F pelvis, M pelvis, thorax</td>
<td>No</td>
<td>Reference 105</td>
</tr>
<tr>
<td>OSL</td>
<td>OncRTS</td>
<td>Atlas-based</td>
<td>H and N, M pelvis, thorax</td>
<td>No</td>
<td>Reference 106</td>
</tr>
<tr>
<td>RaySearch</td>
<td>RayStation 4.0</td>
<td>Atlas-based model-based</td>
<td>Abdomen, H and N, F pelvis, M pelvis, thorax</td>
<td>Yes</td>
<td>Reference 107</td>
</tr>
<tr>
<td>Varian</td>
<td>Smart Segmentation</td>
<td>Atlas-based</td>
<td>H and N, M Pelvis, thorax</td>
<td>Yes</td>
<td>Reference 108</td>
</tr>
<tr>
<td>Velocity</td>
<td>VelocityAI 3.0.1</td>
<td>Atlas-based</td>
<td>Brain, H and N, F pelvis, M pelvis</td>
<td>No</td>
<td>Reference 58</td>
</tr>
</tbody>
</table>


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But, there are solutions …

Does your institution **use** an auto-contouring system?

- **Yes:** 28%
- **No:** 50%
- **Don’t have:** 22%

Informal poll during talk at AAMD 2017
N = ~70

... with room for improvement
Auto-contouring problems

1.) Workflow Integration

Editing took longer than de novo!

Barely saved time

Good efficiency gain

Langmack KA, Perry C, Sinstead C, Mills J, Saunders D. The utility of atlas-assisted segmentation in the male pelvis is dependent on the interobserver agreement of the structures segmented. The British journal of radiology. 2014 Oct 3;87(1043):20140299.
Auto-contouring problems

1.) Workflow Integration
2.) Performance
3.) Clinical Integration

Which contour is quickest to fix?


Auto-contouring solutions

1.) Workflow Integration
2.) Performance
3.) Clinical Integration

Improved product design

R&D Innovation

Improved product design?

Education/training
Innovation

- Atlas contouring: Circa 2008
- Probabilistic atlas: Circa 2011
- Multi-atlas fusion: Circa 2012
- Model-based: Circa 2013

Incremental innovation

- Less risk in research
- Perceived as less risky by customers
Incremental Innovation ≠ Breakthrough

Research

Why didn’t it work?
Limitation of atlas contouring

Rethinking auto-contouring

Atlas contouring

Dosimetrist
Model-based contouring

Dosimetrist

Horizontal Innovation

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Simple Neural Networks

A biological neuron “fires” the output signal to connected cells when the input signals reach a certain level.

The artificial neuron (the Perceptron [Rosenblatt 1958]) models this as a combination of linear and non-linear operations.

Artificial Neural Networks

Artificial neurons grouped into layers

- Input (Blue)
- Hidden (Red)
- Output (Yellow)

Each connection represents a tunable parameter – ‘weight’

Multi-layer Perceptron [Rosenblatt 1961]
Deep Networks

Stack many hidden layers to get ‘depth’

Each connection represents a tunable parameter – ‘weight’

Applying Neural Networks to images

Pass in entire image as a single vector
- Images can be big! Can end up with too many parameters to tune
Convolutional layers

Images have structure
- Structure is mainly ‘local’
- Local structure can appear anywhere in the image

[31]

Types of model

Layers can be stacked together in many different ways, like construction blocks

The way of connecting the blocks are known as architectures

Different architectures can be designed for different tasks

[32]
Deep Learning Contouring

Research validation

Building a product

Business Case

They don't know about your problem

You aren't willing to pay (enough) to solve it

Your problem

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Building a product

Current Good Manufacturing Process (cGMP)

- Requirements
- Risk Analysis
- Testing
  - Validation
  - Verification
- Documentation

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Requirements

On getting DICOM data the system delineates the visible organs-at-risk
the system saves the contours as RTSS
the system sends the RTSS to the user

How? How well?
How to configure number of contour points?
How to handle user system being disconnected?

Intended use / Indications for use

• What it is
  ... is a system designed to allow users to route DICOM-compliant data to and from automated processing components...

• What it is for
  ... includes processing components for automatically contouring imaging data using machine learning
  ... may be used as an input to clinical workflows including, but not limited to, radiation therapy treatment planning

• Who it is for
  ... is intended to be used by trained medical professionals

• What are the limitations
  ... must be used in conjunctions with appropriate software to review and edit results generated automatically...
  ... is NOT intended to automatically detect lesions
### Product classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Product</td>
</tr>
<tr>
<td>IIa</td>
<td>Device</td>
</tr>
<tr>
<td>IIb</td>
<td>Software</td>
</tr>
<tr>
<td>III</td>
<td>System</td>
</tr>
</tbody>
</table>

### Intended use

Indications for use

### Risk analysis

<table>
<thead>
<tr>
<th>Product Function</th>
<th>Configuration</th>
<th>Originating Requirement</th>
<th>Effect (failure mode)</th>
<th>Hazard (potential source of harm)</th>
<th>Hazard relates to usability?</th>
<th>Cause of failure</th>
<th>Risk Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nuclear war started</td>
<td></td>
<td>User sends data to server</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Human race annihilated</td>
<td></td>
<td>System becomes sentient</td>
<td>Negligible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>System becomes scared of being turned off</td>
<td>Extreme</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>System launches nuclear missile strike against Russia...</td>
<td>162</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety by Design</th>
<th>Protective measures</th>
<th>Responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning system should be separate from operation system</td>
<td>System should not be connected to nuclear missile launch systems</td>
<td>AN</td>
</tr>
</tbody>
</table>
Testing

Verification: Did we build the thing right?

On getting DICOM data
the system delineates the visible organs-at-risk
the system saves the contours as RTSS
the system sends the RTSS to the user

Input test data
Check output matches expectation

Validation: Did we build the right thing?

DLC is so good, the contours never need looking at!

Prove it never goes wrong! Ever!
Why regulatory clearance is perceived as a blocker?

- Time to recruit enough patients
- Size of effect
- Time for clinical response
- Long term effects / follow-up

It's all about safety

RISK

Class I
Class IIa
Class IIb
Class III

Evidence
Product released!

Deployment

The Customer
Why does the customers prevent innovation?!

So where are we on the technology adoption curve?

Atlas-based auto-contouring

Deep Learning Contouring

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What drives adoption?

- A problem to be solved: 2.5%
- A fully formed product: 13.5%
- Evidence, education & establishment: 34%
- Establishment & education: 34%
- Lack of choice: 16%

What hinders adoption?

- A problem to be solved: 2.5%
- A fully formed product: 13.5%
- Evidence, education & establishment: 34%
- Establishment & education: 34%
- Lack of choice: 16%
Summary: What I should have said

Learner Outcomes:

1. **Business**
   - Drivers for innovation, and why interesting research may or may not make it out of the lab
   - Does it solve a problem?
   - Will someone pay for it to be solved?

2. **Safety**
   - Why regulation is important, and what is required to market a medical device
   - It’s not there to prevent innovation, but to ensure there’s evidence of safety and efficacy.

3. **Process**
   - How software products are developed, and how this impacts your practice
   - Good process and risk analysis are part of the regulatory approach for clinical software
Summary: What I did say

1. Research
   Risk
   Real innovation requires research
   Research can be risky and time consuming

2. Regulatory
   Risk
   Regulation it the to lower risk
   And to ensure there’s evidence of safety and efficacy.

3. Reality
   Riskward
   Adoption can be slow, because of perceived risk
   But adopting innovative technology can significantly improve practice