Developing the research prototypes to a software product, a case study of medical imaging application

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Presentation outline

- Introduction - 5 min
- MIP research a case study - 5
- Overview of research - 10
- Prototype to product phases - 10
- Novelty and business idea - 10
- Discussion - 10

Introduction

Discipline and domain

Interdisciplinary work - **Radio-diagnosis + Gastroenterology** + **Engineering** disciplines, **Medical Image Processing** stream.

Specific area of investigation

Solving the technical problems in computer aided diagnosis of colon polyp using image processing techniques.

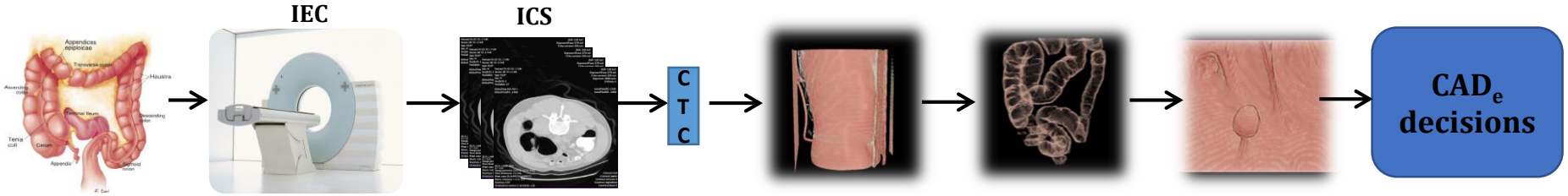


Fig. 1: CTC workflow (Image source: Sliesenger, 2010, SIEMENS, 2017, Kalender, 2006)

What is needed in polyp diagnosis

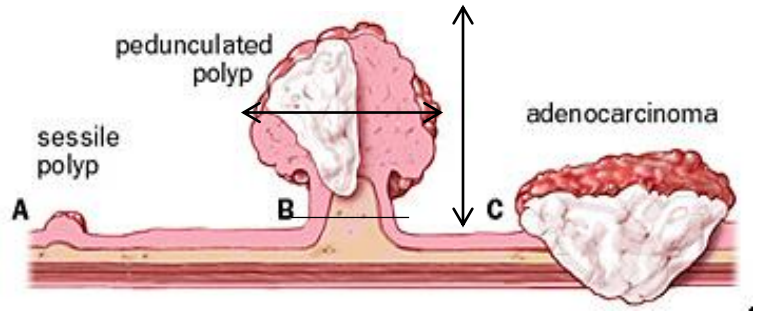


Fig. 2: Polyp growth (Sleisenger 2010)

Key determinants of colon cancer

Size, *shape*, type and grade of dysplasia of polyp

Polyp size classification

1-5mm, 6-9mm, >10mm

Polyp shapes

Sessile, flat, pedunculated and mass

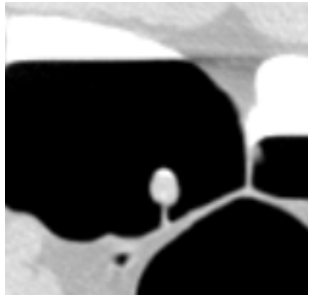


Fig. 3: Polyp growth as seen on axial MPR

MIP research – a case study

Motivation

The rationale behind this study was to find novel Image Processing techniques through **exploratory research** to identify the polyps accurately through CTC software.

Problems statement

Inaccurate measurement of polyp in computer aided systems can mislead the diagnosis (**problem**). Improved engineering solution is required for Radiologists (**clients**) and they evaluate the research results (**scope**).

Objectives

a) Colon segmentation,
b) Virtual (electronic) colon cleansing and
c) Measuring the smaller polyps of size less than 10 mm

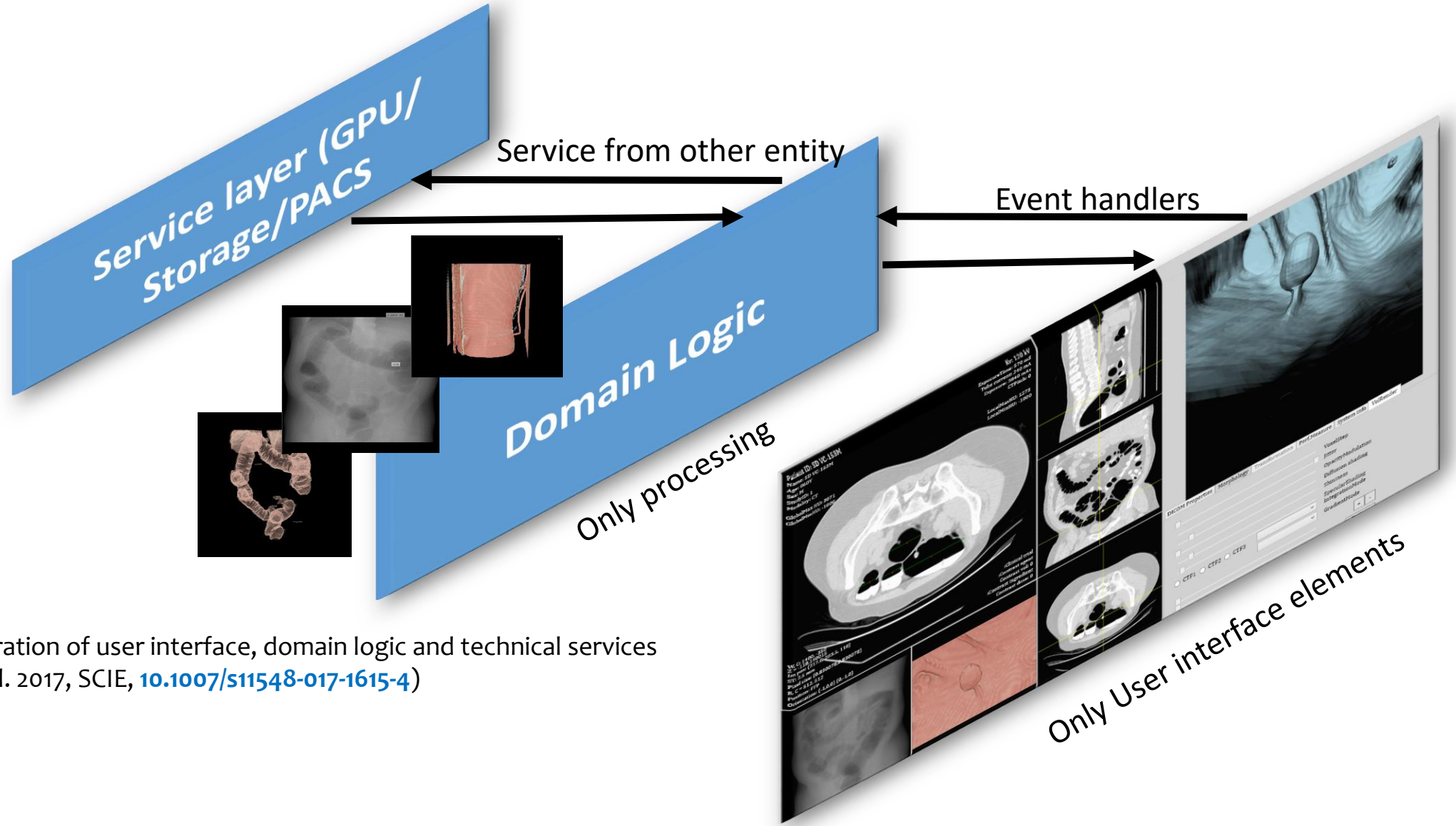
Implementation: C# (NET™ 4.5) + MS Volume rendering SDK™ (Melancoln, 2012) + MarchingCube (Paul, 2014).

Image source

National Cancer Institute (**NCI**) and National Institute of Health (**NIH**), USA (Clark, 2017)

Overview of research (1/2) – 3 layers of s/w architecture

Layers



Clear separation of user interface, domain logic and technical services (MKN et. al. 2017, SCIE, 10.1007/s11548-017-1615-4)

Fig. 4: The research and development phases

Overview of research (2/2)

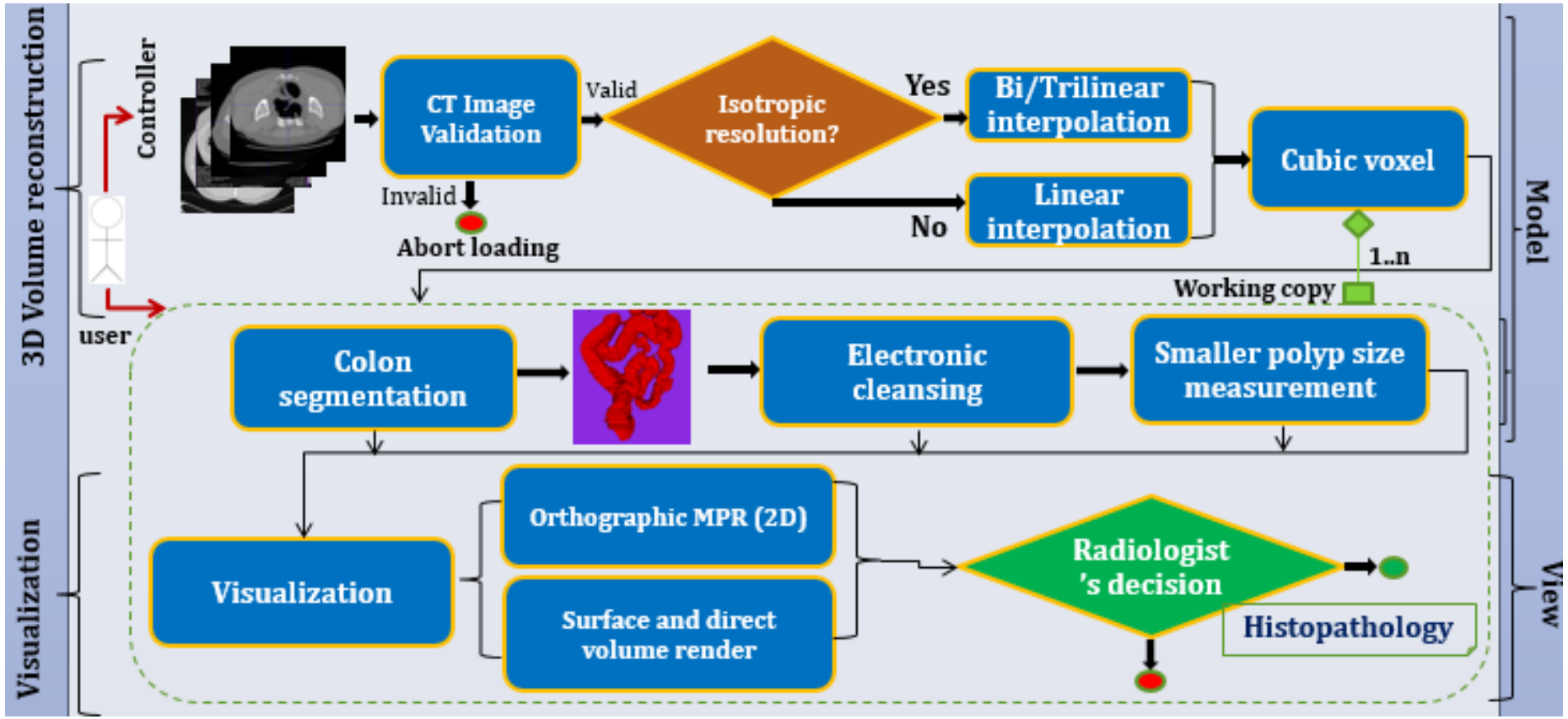


Fig. 5: The research and development phases (MKN, et. al., DOI:10.31557/APJCP.2019.20.2.629

Software pattern:

Based on Model-View-Controller architectural pattern

Computing Resources:

Software:

Microsoft - Win 2012 Server 64 bit, VS 2010 with SP1, .NET 4.5, Volume Rendering SDK, Marching cube.

Hardware:

Intel Xeon® CPU E52620 2.0GHz, NVidia CUDA 4GB GPU, 64 GB DDR3 RAM

Materials and methods

Image source (secondary data) and CTC protocol

- National Cancer Institute, USA (Clark, 2016), ACRIN 6664 (www.acrin.org, 2016) protocol, fecal tagged

Ethical committee clearance

KMC/KH IEC 211/2014 dated 9th April, 2014

Dataset validation

Validated for **type 1** and **type 2** attributes against DICOM 2012 standard (DICOM PS 3.2, 2012)

Table 1: CTC Image acquisition details

Parameter	Value
ST in mm	{ 1.0, 1.25, 2.5 }
kVp (peak kilo voltage)	{ 100, 120 }
mA (milli ampere)	{ 60, 100, 120, 140, 141, 200, 240, 250, 280, 300 }
Pixel size in mm	{ 0.58 – 0.93 } square size pixels
Image Resolution	512,512
Radiometric Resolution	16 bit
Patient positions	{ FFS, FFP, FFS+FFP, HFS+HFP } Prone:  Supine: 
CT images/position scan	~ 1000 (for both FFS and FFP)
Age	{ 40...90 } both male and female
Machine manufacturer	SIEMENS Sensation 16, 64^{TM,} GE Lightspeed 16^{TM,} Philips Brilliance 16^{TM,} Toshiba 64^{TM}
Multi Detector CT	8/16 slices

Research Methodology

Table 2: Research components applied (Kothari, 2004)

Hypothesis	H_o – IP doesn't influence sensitivity, H_a – IP influences the sensitivity
Type	Experimental(method of study), Exploratory (intent)
Approach	Qualitative (subjective) + Quantitative (objective)
Variables	Dependent + Independent + Extraneous variables
Experimental error	Follow right CTC protocol
Sampling design	Stratified sampling, n = 150, N was 950
Data collection	Questionnaire (secondary data)
Data analysis	Tabulated and classified. No edit (unethical , incompleteness)
Consistency check	Reliability + Suitability + Adequate (DICOM CT validation)
Design of experiments	Principle of randomization + Randomized Block design
Hypothesis testing	"Paired t" test + Volumetric overlap computation
Variance analysis	No analysis due to variation in independent variables

SDLC in research

Understanding the requirements and a proper design is more than anything and everything

First poster : A man lying in the hot desert sand totally exhausted and fainting.
Second poster : The man is drinking Coca-Cola.
Third poster : Our man is now totally refreshed.
And then these posters were pasted all over the place.

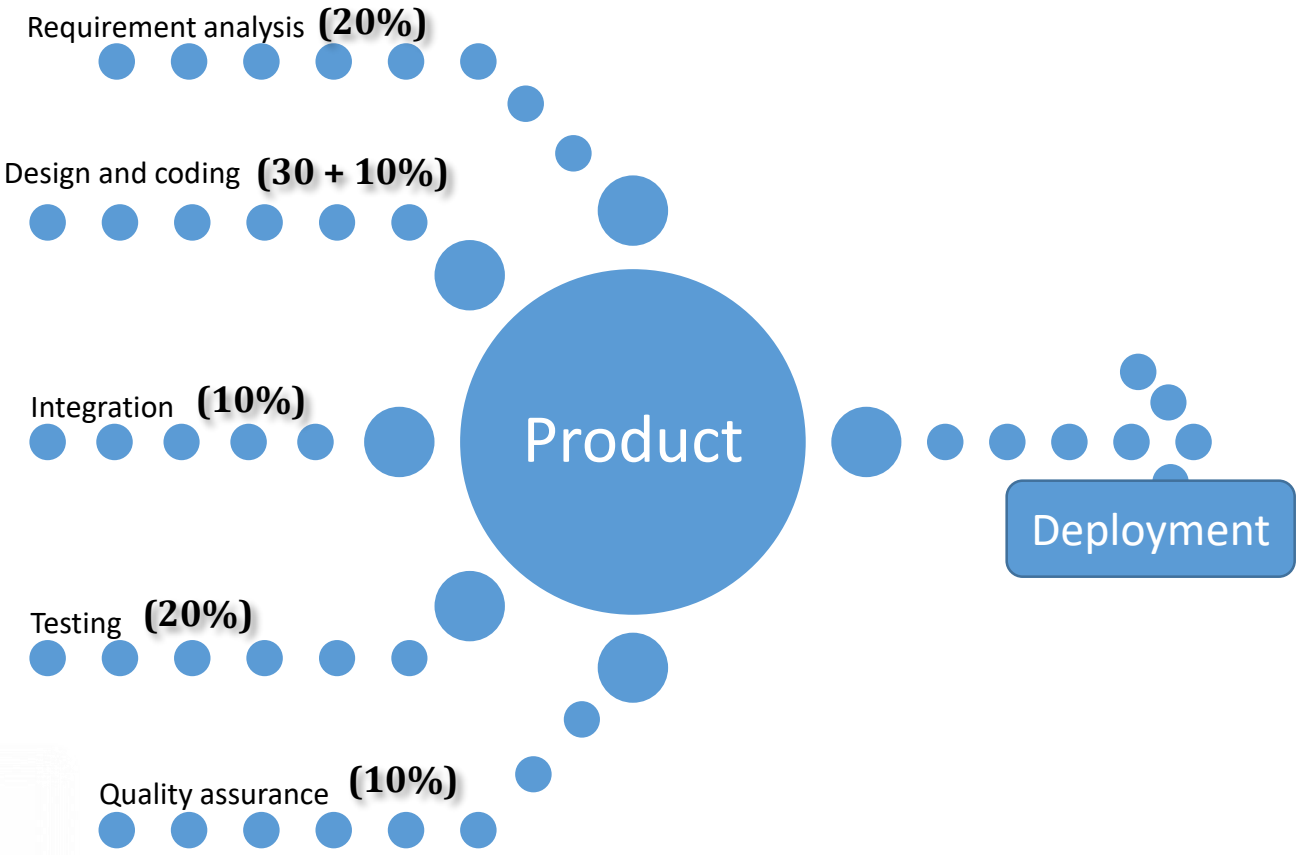


Fig. 6: The SDLC phases

- This is not seen in research environment
- It doesn't mean that it is not possible in research

How to write the proper code

Document every line of program for better understandability

```
/// <summary>
/// This method
/// 1. Computes the number of pixels in the manually segmented region
/// 2. Does pixel to pixel matching between the results and the reference
/// 3. Computes the overlap error
/// 4. Updates the UI with the values
/// </summary>
private void ValidateResult_Click(object sender, RoutedEventArgs e)
{
    // 1. The list is having duplicate entries (due to bug in mousemove and mousedown in 2D axial segment). Consider distinct elements.
    referenceContour = referenceContour.Distinct().ToList();

    // 2. From the contour points, find those voxels which has same y coordinate. This gives the pair of geometrical locations.
    var result = from l in referenceContour group l by l.Y into r select new { key = r.Key, Value = r.ToList() };

    // A new list for matching the voxels of segmented volume and reference
    List<System.Drawing.Point> pointsInResultContour = new List<System.Drawing.Point>();
    List<System.Drawing.Point> pointsInReferenceContour = new List<System.Drawing.Point>();
    List<System.Drawing.Point> pointsInIntersection = new List<System.Drawing.Point>();
    List<System.Drawing.Point> pointsInUnion = new List<System.Drawing.Point>();

    // Variables to count the number of pixels within the boundary and for finding the common pixels between result and reference.
    int numberOfpixelsInReferenceContour = 0, numberOfpixelsInResultContour = 0, intersection = 0;

    // For each pair of left and right points
    foreach (var avar in result)
    {
        double ak = avar.key; List<System.Drawing.Point> av = avar.Value;

        // Find the extreme left and extreme right points
        int xCordinate_Min = av.Min<System.Drawing.Point>(aP => aP.X); int xCordinate_Max = av.Max<System.Drawing.Point>(aP => aP.X);
        int yCordinate_Min = av.Min<System.Drawing.Point>(aP => aP.Y); int yCordinate_Max = av.Max<System.Drawing.Point>(aP => aP.Y);

        // Count the number of pixels between left and right in each scan line
        numberOfpixelsInReferenceContour += (xCordinate_Max - xCordinate_Min);

        // Collect all the points that happenes within the left and right points (these points are properly checked with the simulation
        for (int col = xCordinate_Min; col < xCordinate_Max; col++)
        {
```

Different software testing methods

ACCEPTANCE TESTING: Software testing where a system is tested for acceptability. The purpose of this test is to evaluate the system's compliance with the business requirements.

SYSTEM TESTING: Where a complete and integrated software is tested.

INTEGRATION TESTING: Interaction between the modules is checked.

UNIT TESTING: Individual units/components of a software are tested. Involves testing the class methods.

- In research we test the **results** whereas in software development we test **both the result and the application**. In both cases we use statistical analysis methods
- In research environment achieving all these testing methods is very time consuming

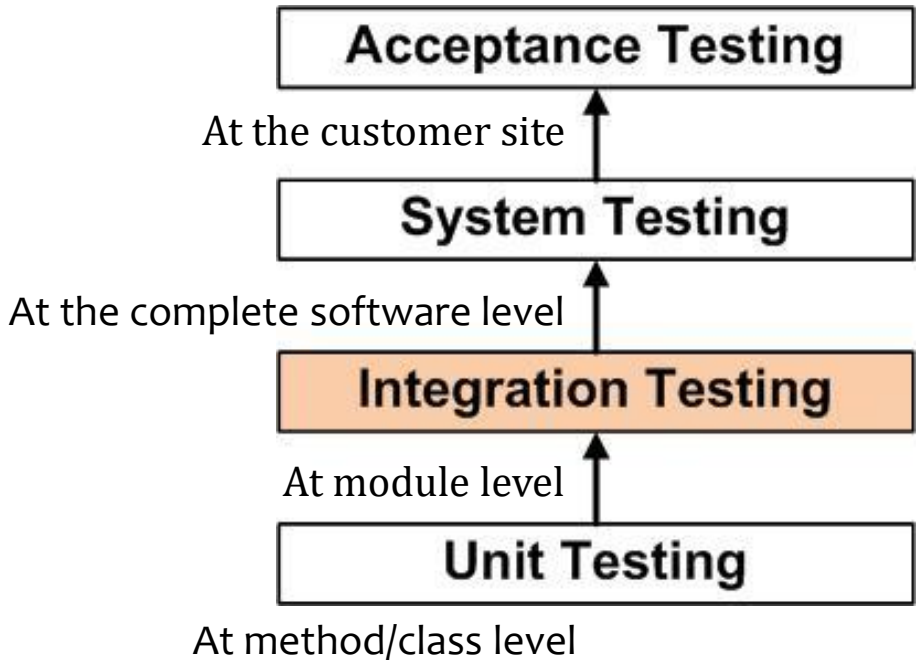


Fig 7: Different levels of software testing

Testing the class methods

```
/**@param TheToken, @return Bill, For RQ_HAS_1 */
Bill HotelAutomationSystem::CheckoutRoom(int TheToken)
{
    Bill TheBill = null; List<Bill> ListOfBills;

    // First condition check to know whether it is valid number or not
    if(TheToken<0)
        throw exception ("Invalid token number");

    // Second condition to know whether the bill already exist for this bill nu
    else if(ListOfBills.Contains(TheToken))
        thrown exception ("There exists a bill already for this token number");

    // If not, then generate the bill object and return to the caller.
    else
    {
        TheBill = new Bill();
        TheBill.Customer = "Altaf";
        TheBill.Amount = 20,000;
        TheBill.NumberOfDays = 2;
    }
    ListOfBills.Add(TheBill); //Add to the list of bills.
    return TheBill;
}
```

- Each test case represents one distinct input check.
- The test cases are mapped with the requirement key.

Unit testing frameworks

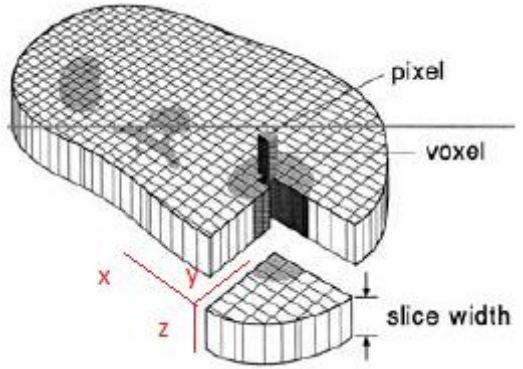
Nunit – C#, Junit – Java, CPPTest – C++

```
// This class defines the unit test cases to check the generation
// of the customer bill requirement (RQ_HAS_1)
public void UnitTest
{
    // Need an instance variable
    HotelAutomationSystem HAS = new HotelAutomationSystem();

    // Test case for CheckutRoom method. Test case id: RQ_HAS_1_UT
    public bool CheckoutRoomTestCase_1(int Parameter)
    {
        // First condition check with invalid token number
        HAS.CheckoutRoom(-1);
    }

    // Test case for CheckutRoom method. Test case id: RQ_HAS_1_UT
    public bool CheckoutRoomTestCase_2(int Parameter)
    {
        // Second condition check with already existing bill details
        HAS.CheckoutRoom(100);
    }

    // Test case for CheckutRoom method. Test case id: RQ_HAS_1_UT
    public bool CheckoutRoomTestCase_3(int Parameter)
    {
        // Third condition check is the return object should not be null
        Bill TheReturnValue = HAS.CheckoutRoom(145);
        if(TheReturnValue==null)
            throw the exception;
    }
}
```

Results (1/10) - 3D volume reconstruction

Isotropic voxel creation

- ST or $Size_z$ = {0.75, 1.25, 2.5} mm
- $Size_x$={0.546875 – 0.9765625} mm,
- Applied linear interpolation.
- **R²** to **R³** conversion through matrix.



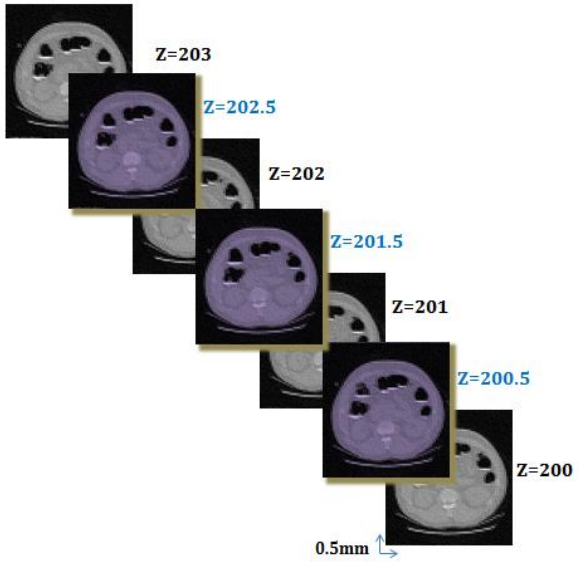


Fig. 8: Linear interpolation in z axis

$$if\left(x \le c - 0.5 - \frac{w-1}{2}\right), then\ y = y_{min}$$

$$else\ if\left(x > c - 0.5 + \frac{w-1}{2}\right), then\ y = y_{max}$$

$$else\ y = \left(\frac{x-(c-0.5)}{w-1} + 0.5\right) * (y_{max} - y_{min}) + y_{min}$$

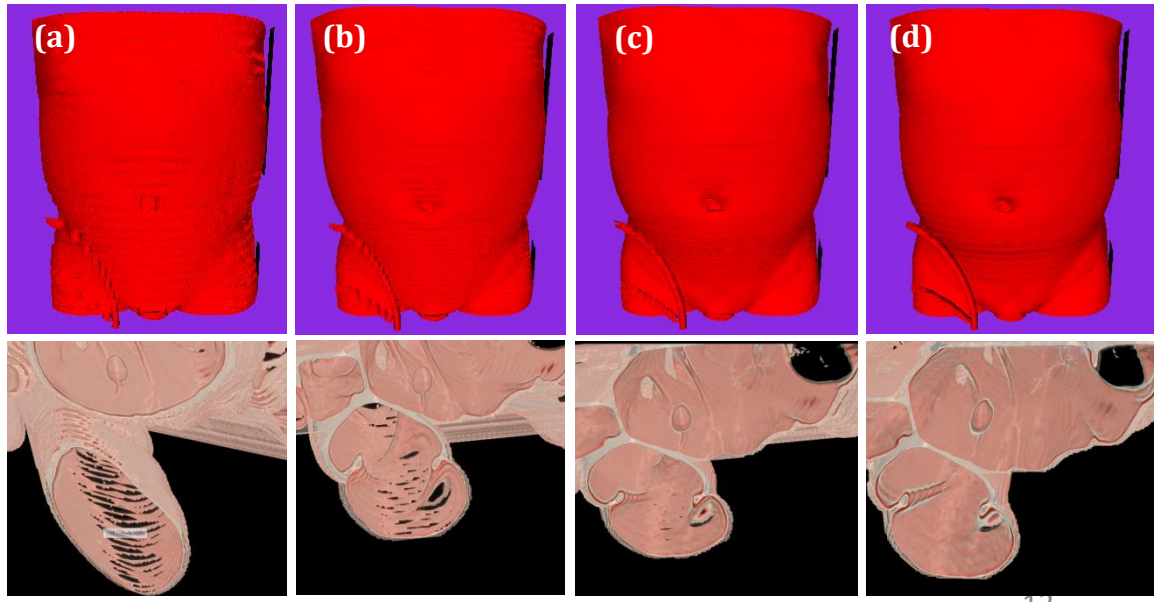


Fig. 9: Surface rendering and direct volume rendering in 3D with variable slice thickness (5mm, 2.5, 1.25 and 0.75 respectively).

Contd..

Results (2/10) - Colon segmentation

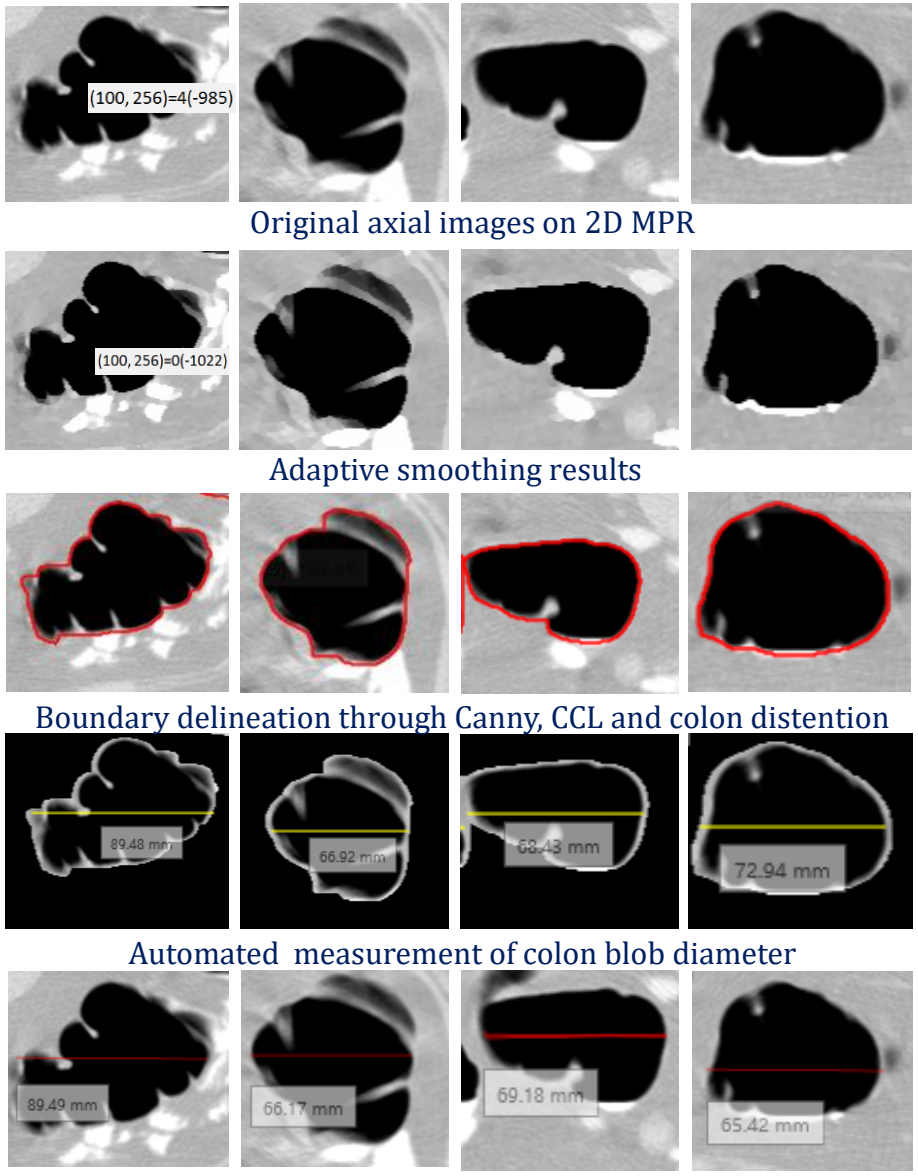


Fig. 10: Results of each step shown in different rows on 2D MPR

- **Problem:** Delineation of colon wall at the base of the colonic structures was not addressed so far
- **Objective:** To segment the colon without losing colonic structures.
- **Methodology:** Based on prior knowledge of colon distension grading ($d>2cm$). (MKN et. al., 2016, JMIHI, SCI, 10.1166/jmihi.2016.1786)

Contrast correction

$$z = T(r) = 255 * \left(\frac{f(m,n) - \min(f(m,n))}{\max(f(m,n)) - \min(f(m,n))} \right)$$

Gamma correction

$$V_{out(i=0..255)} = A * \left(\frac{V_{in}}{255} \right)^{\gamma}$$

Adaptive smoothing

$$1.\, G_m(m,n) = \frac{f(m+1,n) - f(m-1,n)}{2}$$

$$weight(m,n) = e^{-\frac{{G_m}^2 + {G_n}^2}{2 * factor^2}}$$

$$total = \frac{\sum_{i=-1}^{1} \sum_{j=-1}^{1} f(m+i,n+j) * weight(m+i,n+j)}{\sum_{i=-1}^{1} \sum_{j=-1}^{1} weight(m+i,n+j)}$$

$$weighttotal = \sum_{i=-1}^{1} \sum_{j=-1}^{1} weight(m+i,n+j)$$

Segmented colon

$S=(c, f) \Rightarrow S_0=(c, f_0)$

Results (3/10) - Colon segmentation

Final result

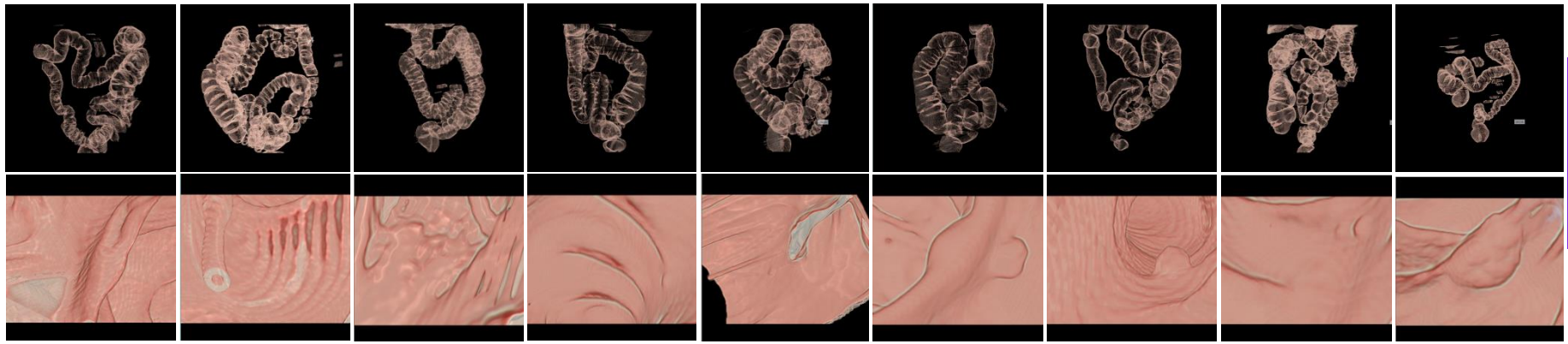


Fig. 11: volume rendering of segmented colon and colon interior

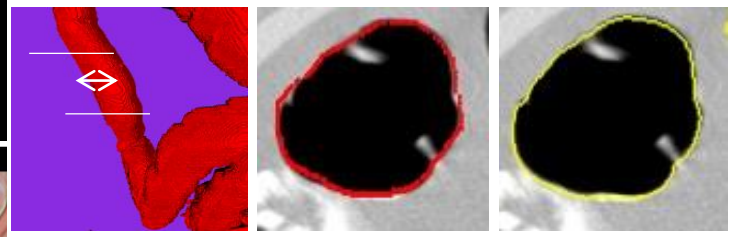


Fig. 12: a) set of slices, b) Reference, c) result

$$Accuracy = \frac{A \cap B}{A \cup B} * 100$$

Validation

- Supervised evaluation method (Observer's rating).
- Verified with Philips DICOM Viewer ™ & SIEMENS Syngo Fast View ™
- Volumetric overlap calculation: Achieved 95.2% accuracy.

Key findings

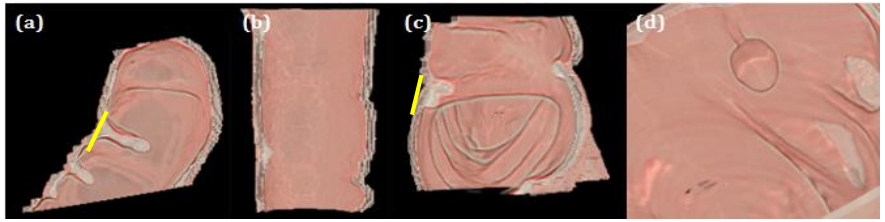


Fig. 13: Delineation of base of the colonic structures

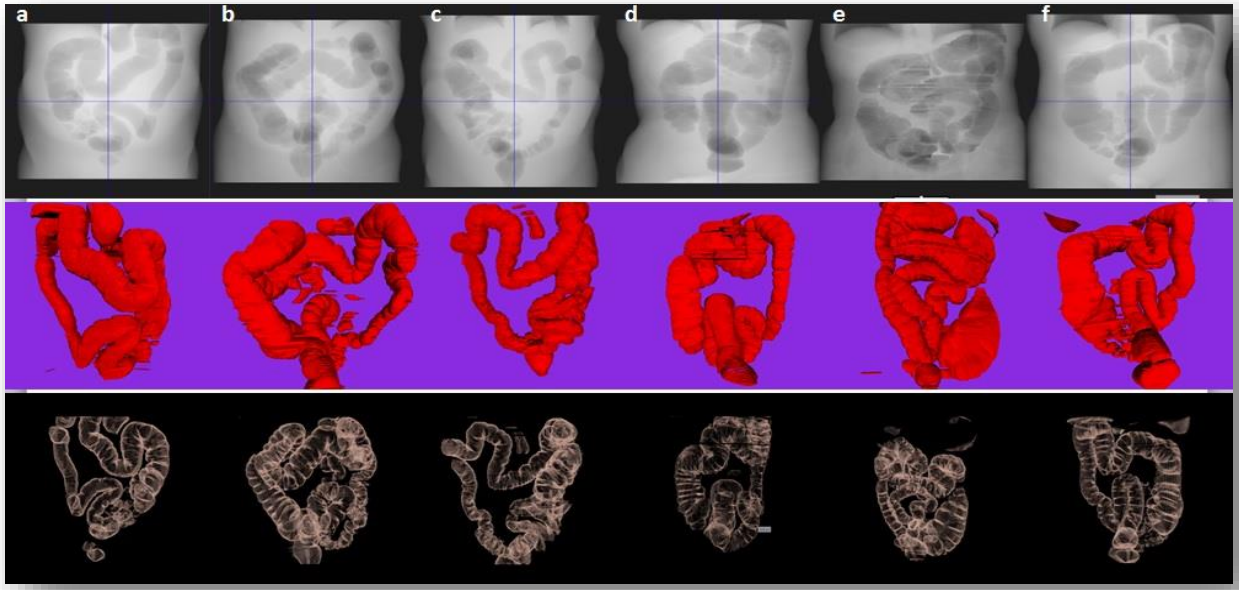


Fig. 14: DRR of unsegmented volume and surface and direct volume rendered images

Inference

1. Colon wall is delineated, 2. Boundary thickness – 1pixel, 3. No segmentation leaks. 4.

Results (4/10) - Electronic cleansing

- **Problem:** Incomplete cleansing, soft tissue erosion, pseudo enhanced soft tissues.

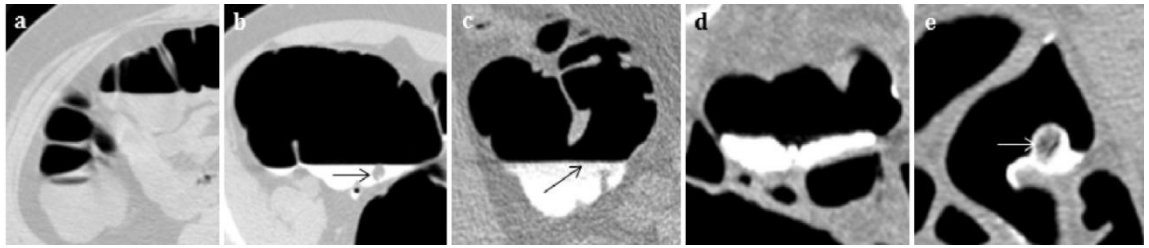


Fig. 15: Different clinical cases of fecal tagging.

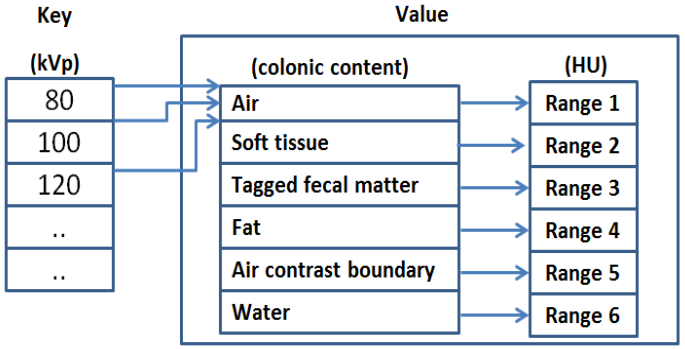
- **Objective:** To virtually clean the tagged colonic content to solve above problems.
- **Methodology:** Based on prior knowledge of material composition of colonic contents (MKN et. al., 2015, APJCP, SCI, 10.7314/APJCP.2015.16.18.8351)

Step 1: Theoretically calculate the HU of colonic contents using formula (NIST, 2016).

$$keV \rightarrow \mu_t(x,y,z) \xrightarrow{1000*\frac{\mu_t-\mu_w}{\mu_w-\mu_{air}}} CTNumber(x,y,z)$$

$$\xrightarrow{CT*m+y\ intercept} HU(x,y,z) \xrightarrow{\frac{HU-P1}{W}*2^{i-1}} f(x,y)$$

Step 2: Create lookup table of colonic contents and its HU range.



$List < kVp, List < colonic\ contents, HU\ range \gg$

Table 3: Practically observed HU from clinical studies

	From clinical studies (HU range) [3]		
kVp	**80**	**100**	**120**
Air	-1000±10	-1000±10	-1000±10
Contrast	+144	+138	+130
Soft tissue	+62	+58	+54
Water	0±5	0±5	0±5
Fat	-152	-111	-89
CO_2	-1000±25	-1000±25	-900±25

Step 3: Adaptive EC steps

$$V_{output}(x,y,z) = \begin{cases} Min_{HU}, if\ -1024HU < [\forall v_0(x,y,z) \in S_0] \leq -850HU \\ Min_{HU}, if [\forall v_0(x,y,z) \in S_0] \geq 600HU \\ V_0(x,y,z) + HU_x, if\ +200HU < [\forall v_0(x,y,z) \in S_0] \leq +600HU \\ Min_{HU}, if\ -700HU < [\forall v_0(x,y,z) \in S_0] \leq +600HU \end{cases}$$

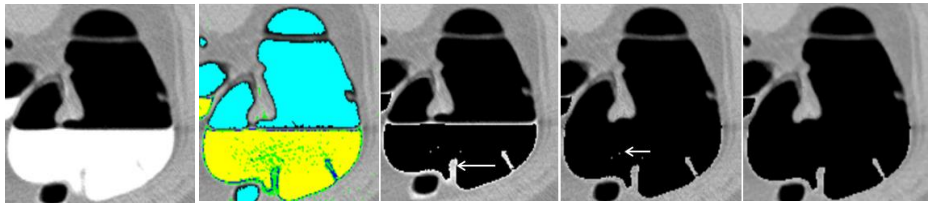


Fig. 16: Step by step cleansing

Results (5/10) - Electronic cleansing

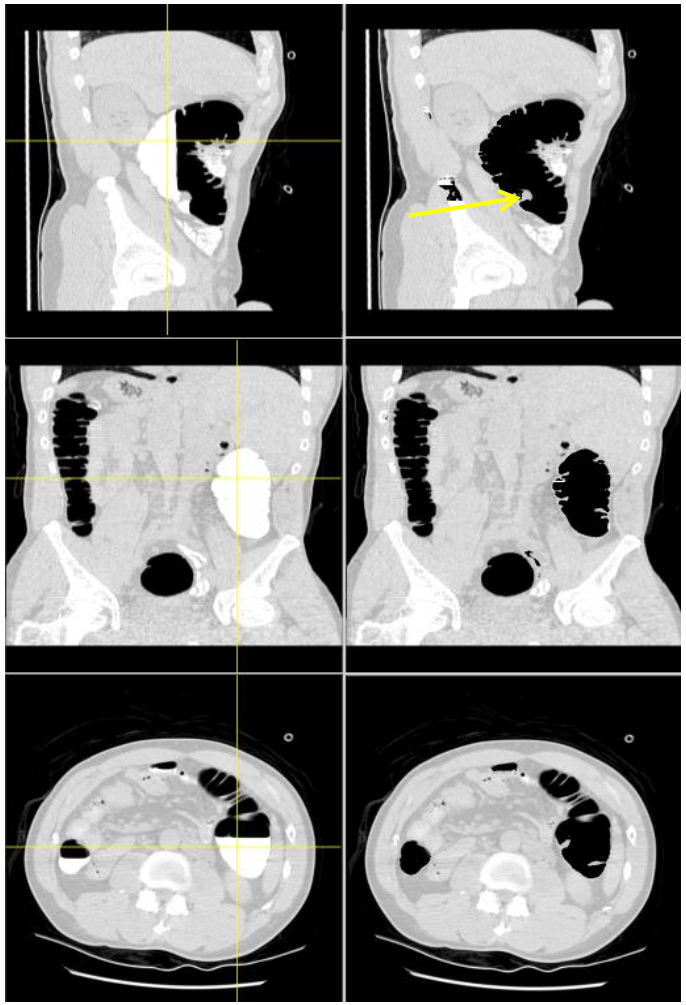
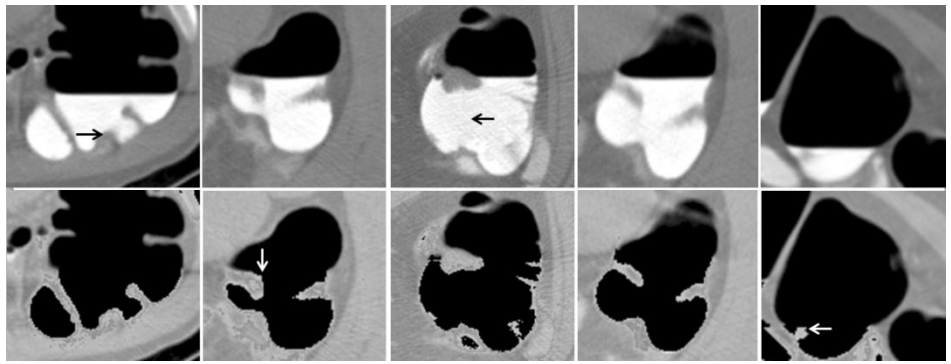


Fig. 19: 2D MPR and 3D view after cleansed colon



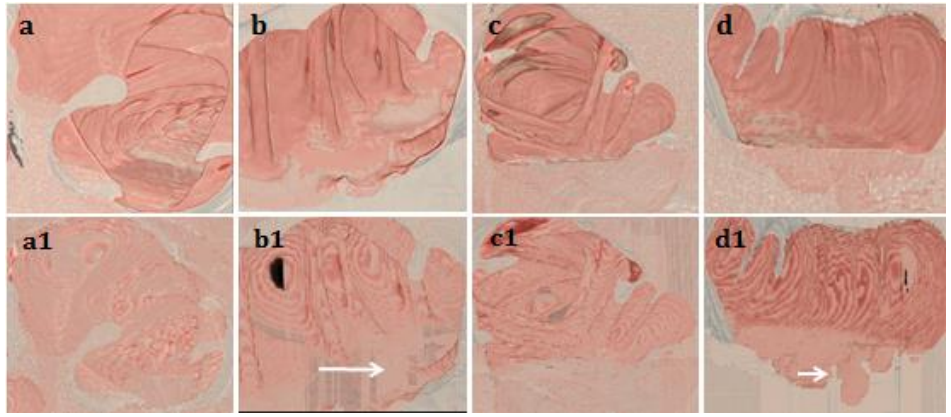
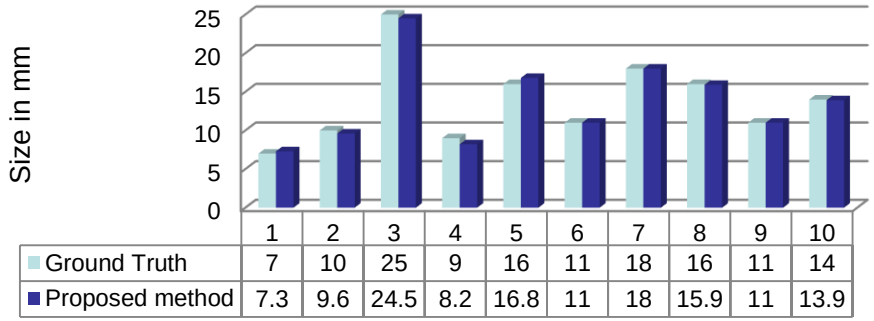


Fig. 20: Results showing different levels of contrast and cleansed colon (row1, 3: Original axial images, row 2, 4: Cleansed colon without losing colonic structures.

Polyp size measurement under two approaches



	1	2	3	4	5	6	7	8	9	10
Ground Truth	7	10	25	9	16	11	18	16	11	14
Proposed method	7.3	9.6	24.5	8.2	16.8	11	18	15.9	11	13.9

- **Validation:** Compared measurements with GT (Johnson, 2008).
- **Key findings:** Completely cleansed, no soft tissue erosion and pseudo enhance voxels are corrected.
- **Inference:** Method can be used with images acquired with various levels of kVp.

Fig. 21: Polyp size compared with GT

Results (6/10) - Smaller polyp measurement

- **Step 1:** Original axial CT slices

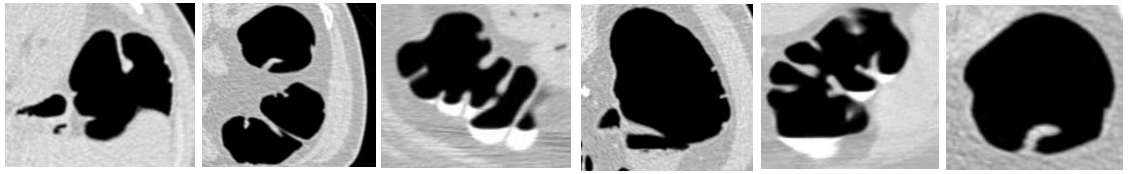


Fig. 17.1: Original axial CT images

- **Step 2:** Colon segmentation

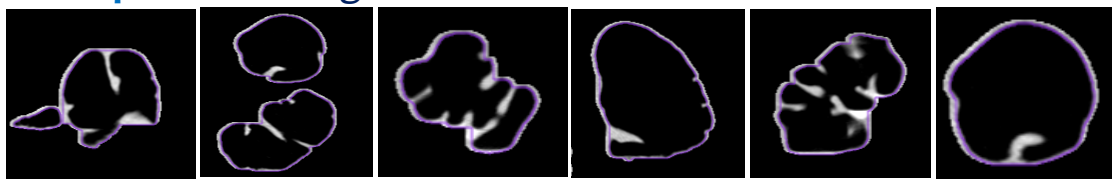


Fig. 17.2: Colon wall delineation

- **Step 3:** Skeletonization

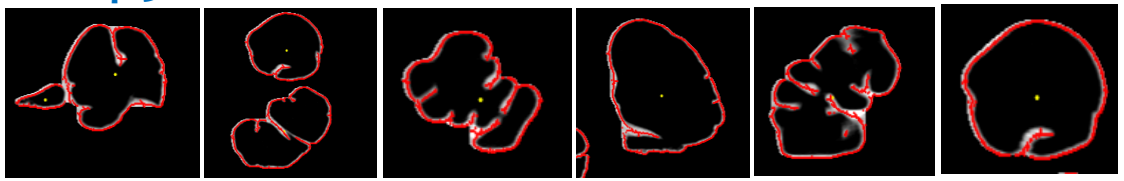


Fig. 17.3: Skeletonization after colon boundary detection

- **Step 4:** Retaining the medial axis of the desired structures

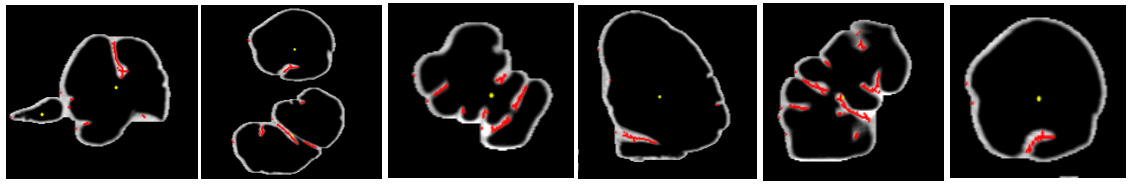


Fig. 17.4: Medial axis of colonic structures

- **Problem:** Accuracy in smaller polyp measurement is poor.
- **Objective:** To measure smaller polyp of size *<10mm*.
- **Methodology:** Based on knowledge of polyp height (*h<7mm*), height to width ratio (*h>=1.5w* or *h<=1.5w*) (Summers, 2009) and intensity distribution an automated method is developed.
  (MKN et. al., 2017, JCARS, SCIE, 10.1007/s11548-017-1615-4)

Shape descriptor

$$S(S_0) = \bigcup_{k=0}^{K} S_k(S_0) = S_k^1$$

Erosion using Structuring element

$$where, S_k(S_0) = (S_0 \theta kB) - (S_0 \theta kB) \circ B$$

$$K = \max\{k | (S_0 \theta kB) \neq \emptyset\}$$

Retaining descriptor of desired structure

$$S_k^1 = \neg\{[\forall v_k \in S_k^1] \cap [\forall v_0 \in S_0]\}$$

Gram Schmitt orthogonalization

$$\overrightarrow{v_1} . \overrightarrow{v_2} = 0$$

Results (7/10) - Smaller polyp measurement

- **Step 5:** 3D view of retained colonic structures after step 4

Fig. 18.1: the 3D view of colon in which the colonic structures are shown in green color

- **Step 6:** Measuring the structure height

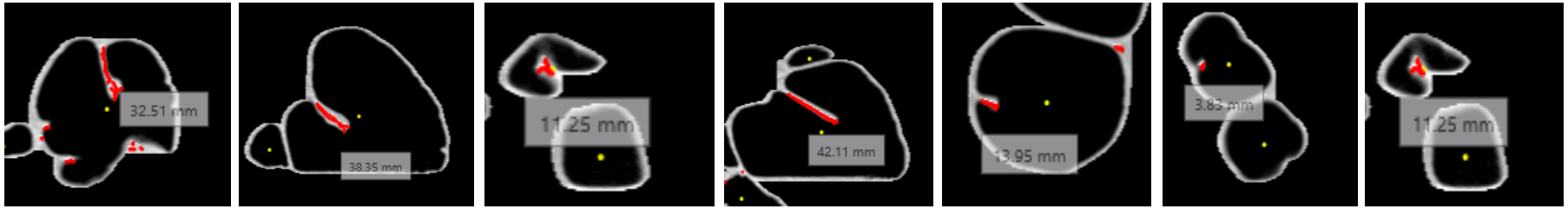
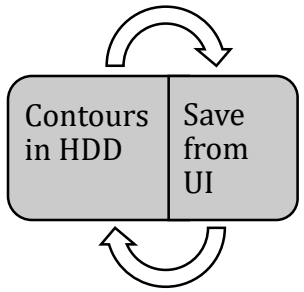


Fig. 18.2: Height calculation of colonic structures

- **Step 7:** Measuring the structure width



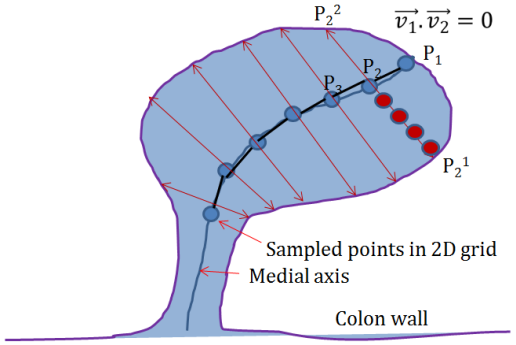


Fig. 19: Width calculation

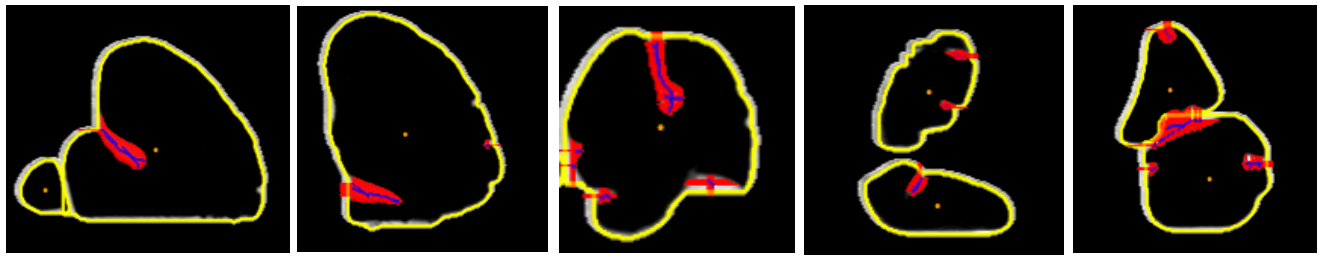


Fig. 18.3: Reconstructed shapes from the shape descriptor

Results (8/10) - Smaller polyp measurement

➢ **Step 8:** Automated delineation of smaller polyps

polyp : h<7mm
sessile: h<=1.5w
flat : h>=1.5w

Table 4: Sensitivity and specificity readings

<=10mm (n=42)	Polyp present	Polyp absent
Test says "present"	TP = 35	FP = 2
Test says "absent"	FN = 5	TN = 9

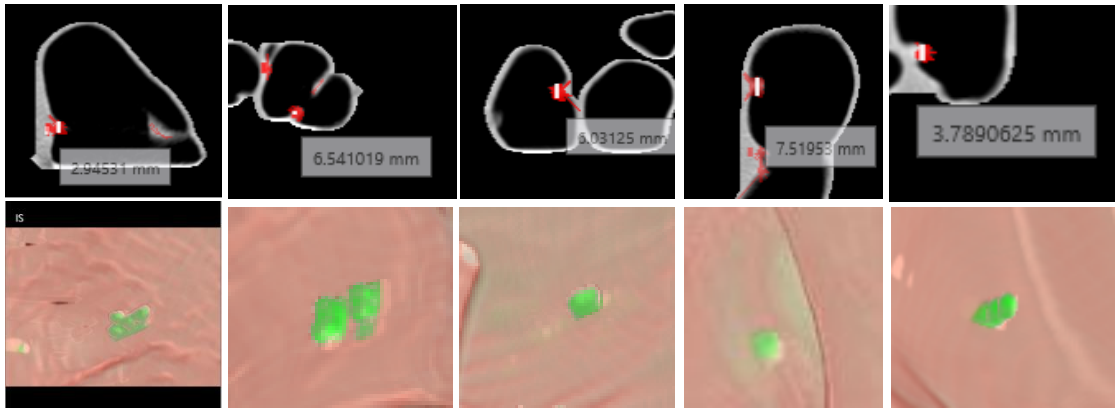


Fig. 20: Smaller polyps identified (2D MPR and 3D volume rendered)

➢ **Statistical analysis**

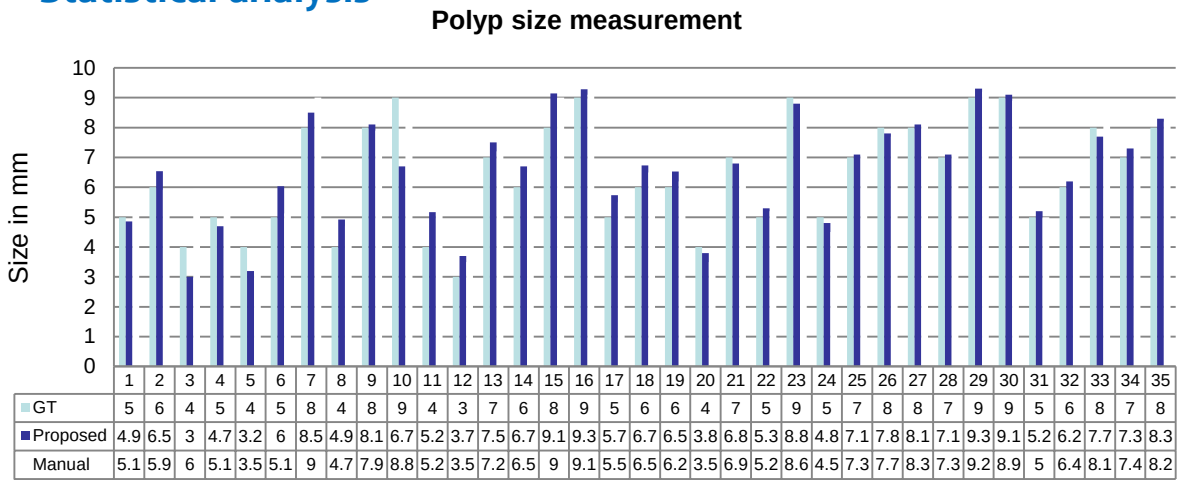


Fig. 21: Size compared with GT (Johnson, 2008)

Table 5: Results comparison

Authors	Analysis scheme	No. of patients evaluated	No. of polyps actually present	TPR in %	TNR in %
Lee et al. [9]	Per polyp	65	103	55.0	78.0
Wang et al. [15]	Per polyp	1126	106	83.0	Not reported
Johnson [20]	Per polyp	2531	547	75.0	86.0
Summers et al. [4]	Per polyp	1186	259	76.7	Not reported
Huang et al. [10]	Per polyp	29	53	90.0	Not reported
Johnson [32]	Per patient	477	65–77	Not reported	Not reported
Chu et al. [2]	Per patient	2531		90.0	86.0
Our method	Per polyp	45	40	87.5.0	82.0

➢ **Validation**

- Supervised evaluation technique.
- Sensitivity (**TPR**)=87.5%, specificity(**TNR**)=82%, **PPV**=94.45% and **accuracy**=86.26%.
- Paired t-test, @ CI=0.95, α=0.05,|t|=1.274 and p=0.218 => >0.0001. Measurements ⇔ GT.

➢ **Key findings**

Polyps <10mm are recognized successfully.

Results (9/10) - Clipping planes and endoluminal view

- **Objective:** To develop a method to visualize colon interior.
- **Methodology:** Using clipping plane selection, visualization is provided.

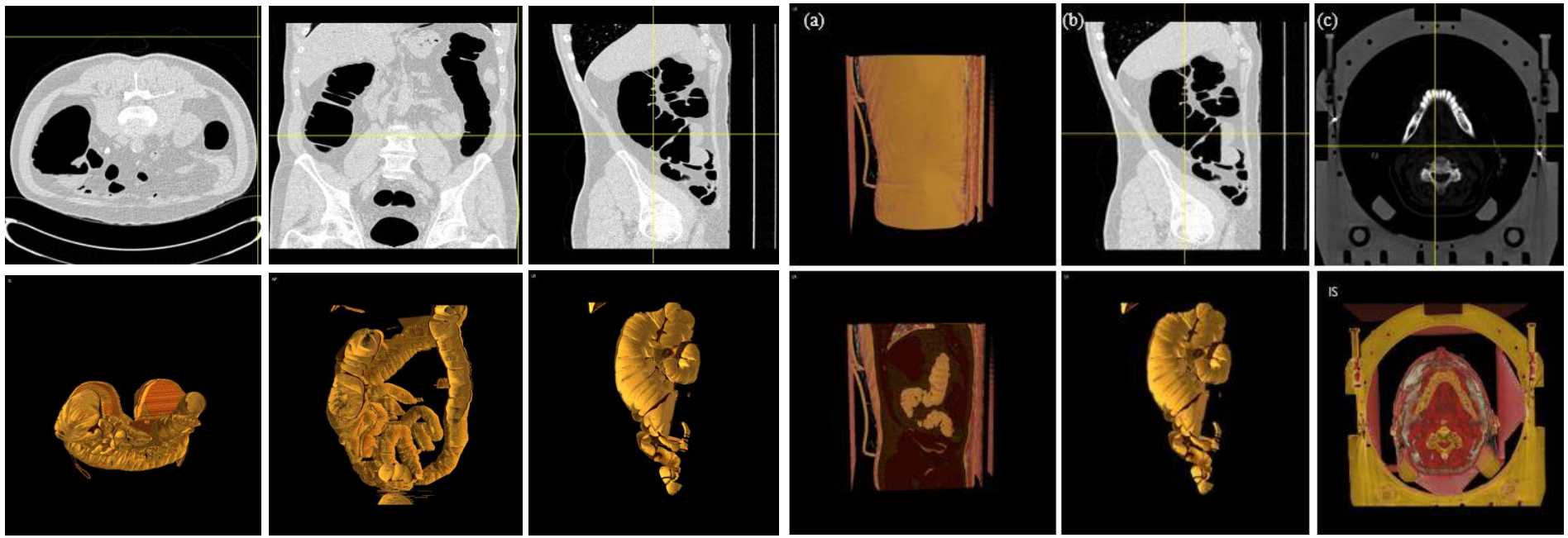


Fig. 22: Reference line selection in 2D MPR and Parallel update of both 2D and 3D view using reference line selection on MPR.
(MKN et. al., Image Science 2018, Gordon Research Conferences, Boston)

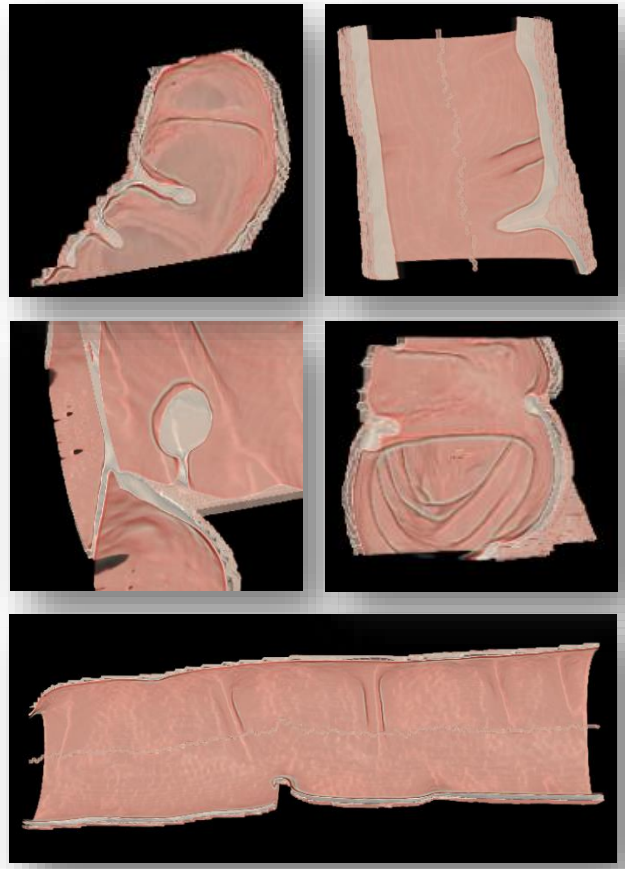


Fig. 23: Reference line selection in 2D MPR and Parallel update of both 2D and 3D view using reference line selection on MPR.

Contd..

Results (10/10) - 2D view and 3D rendering

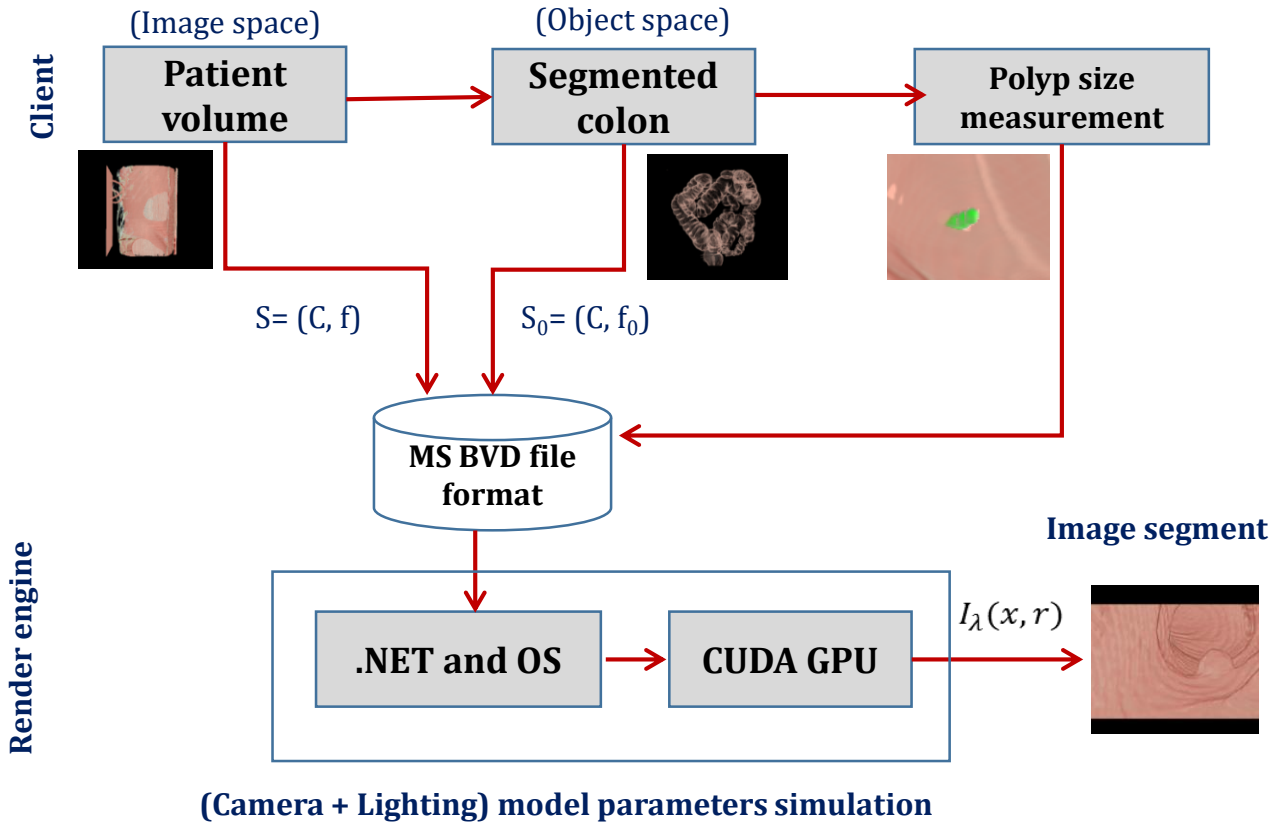
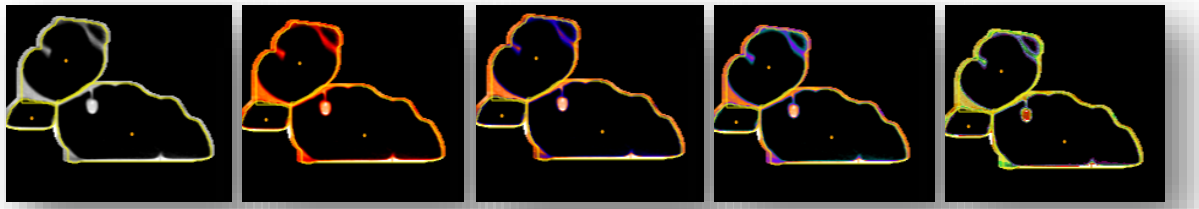
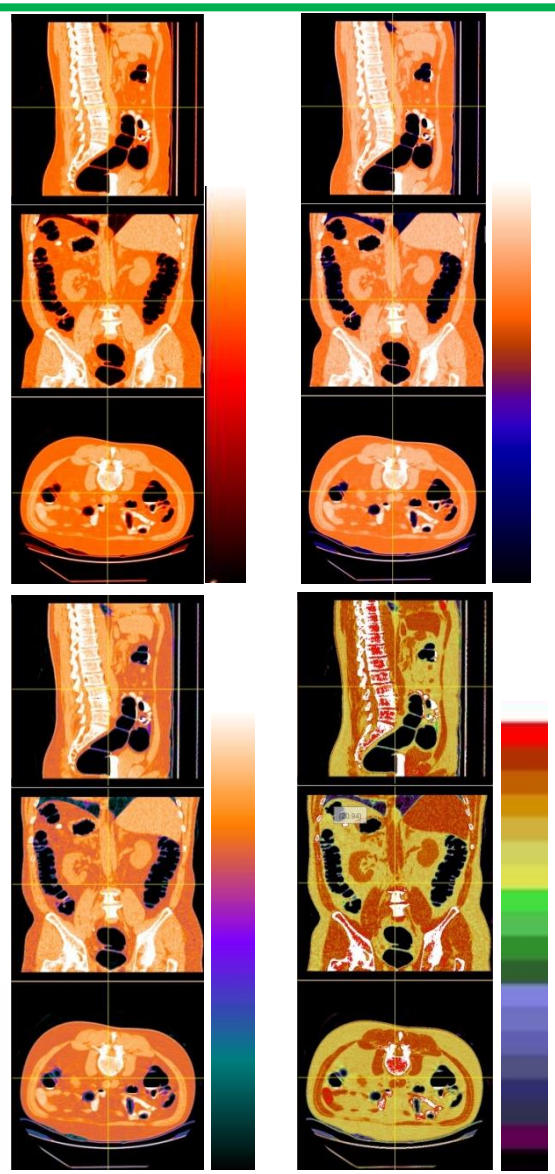


Fig. 24: Integration of MSVR framework (Melancon, 2012)



Contd..

Fig. 25: 2D LUT from DICOM (DICOM, 2016) and visualization of segmented regions on 2D MPR



The prototype (1/2)

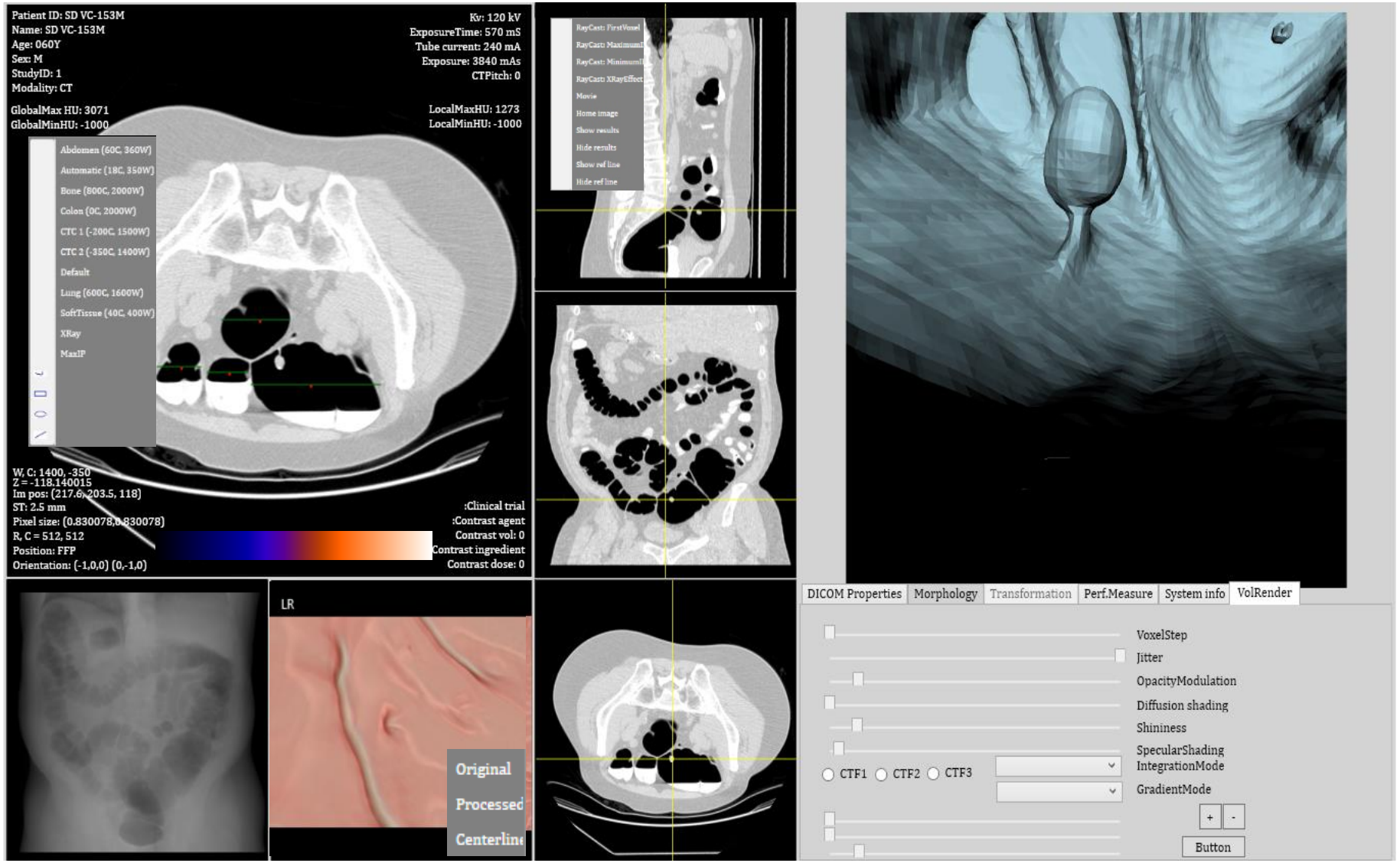


Fig. 26: The UI prototype

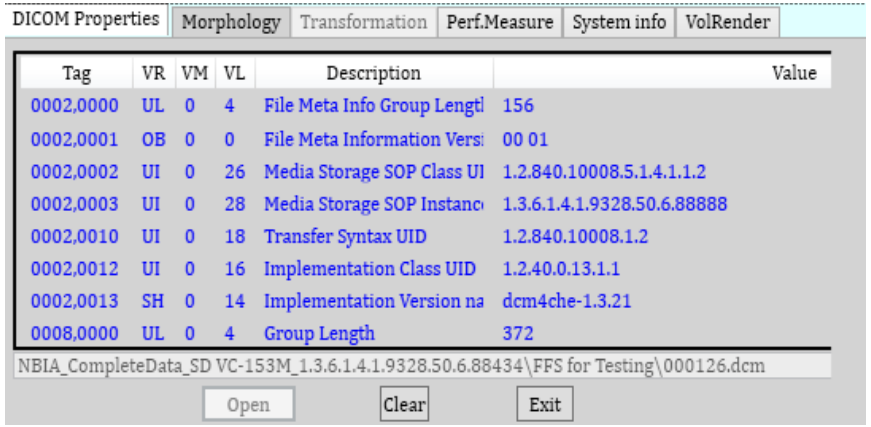
➢Key findings

- **Colon segmentation:** **95.2**% accuracy, through volumetric overlap calculation, colon wall properly delineated, **time:** 2min for 500 CT slices,

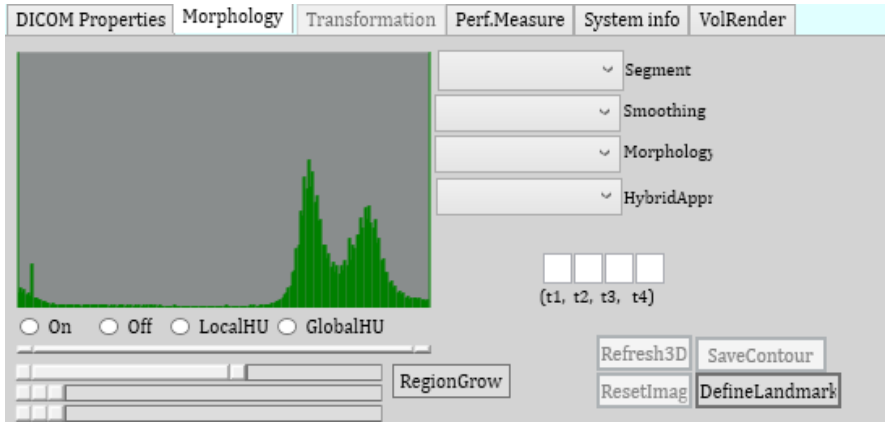
- **Electronic cleansing:** Method can be used with images acquired with various levels of kVp, **time:** 6 min for 500 slices

- **Polyp measurement:** Sensitivity (**TPR**)=87.5%, specificity(**TNR**)=82%, **PPV**=94.45%, **accuracy**=86.26%, **time:** 3min for 500 CT slices.

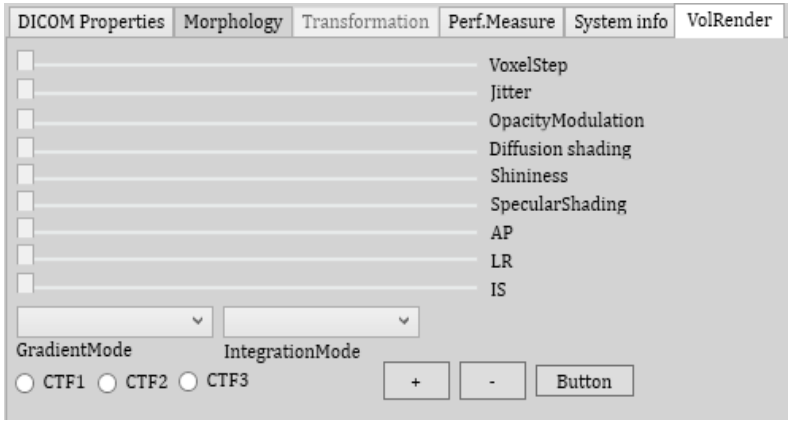
The prototype (2/2)



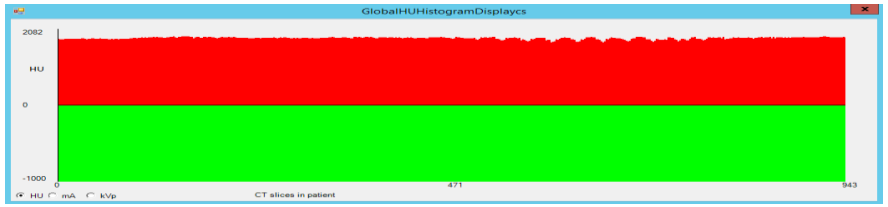
DICOM properties



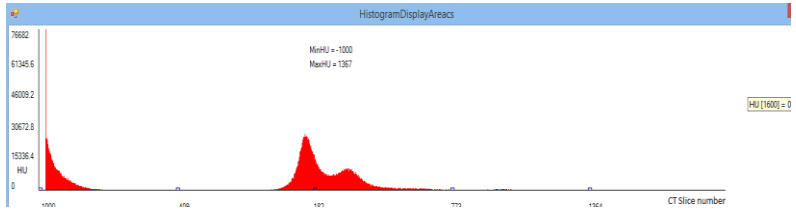
IP handling

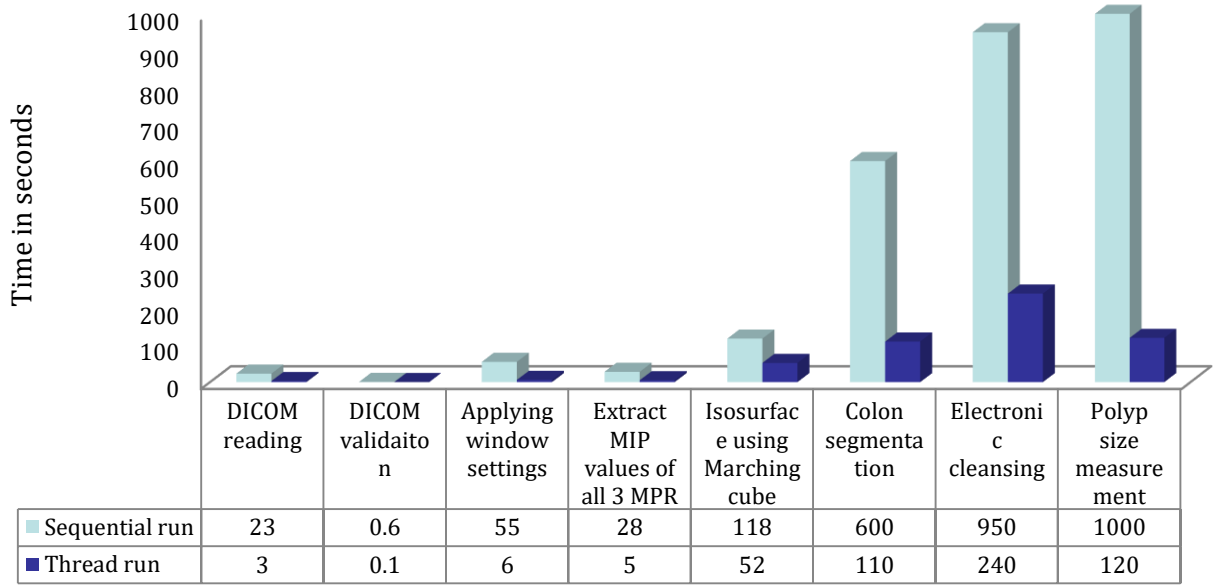


varying the volume render parameters



Histograms





	DICOM reading	DICOM validaiton	Applying window settings	Extract MIP values of all 3 MPR	Isosurface using Marching cube	Colon segmentation	Electronic cleansing	Polyp size measurement
Sequential run	23	0.6	55	28	118	600	950	1000
Thread run	3	0.1	6	5	52	110	240	120

Fig. 27: Time takes for each task in sequential run and through multithreading

Innovation steps

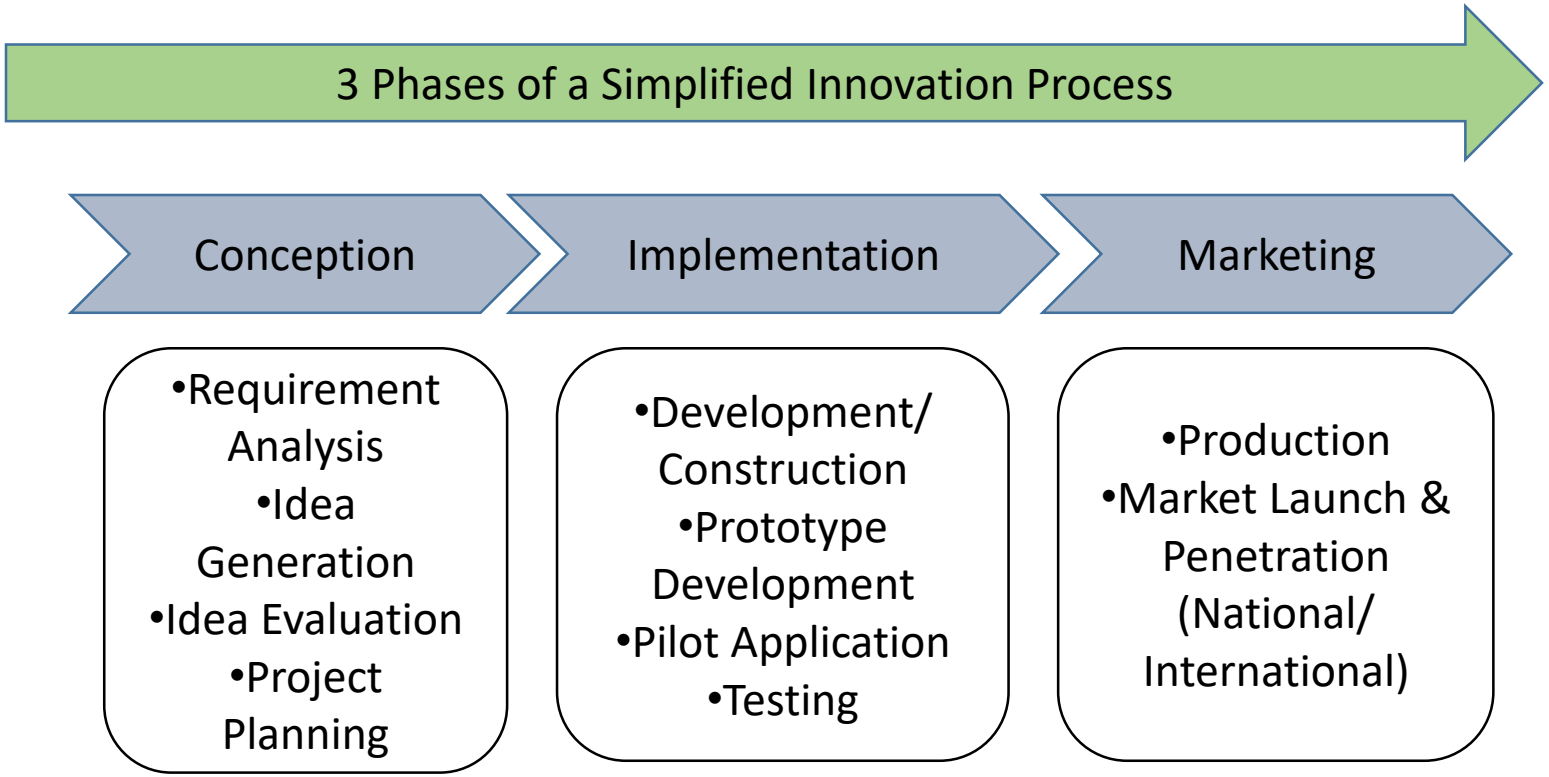


Fig. 28: The invention to innovation steps

Novelty and business idea (1/2)

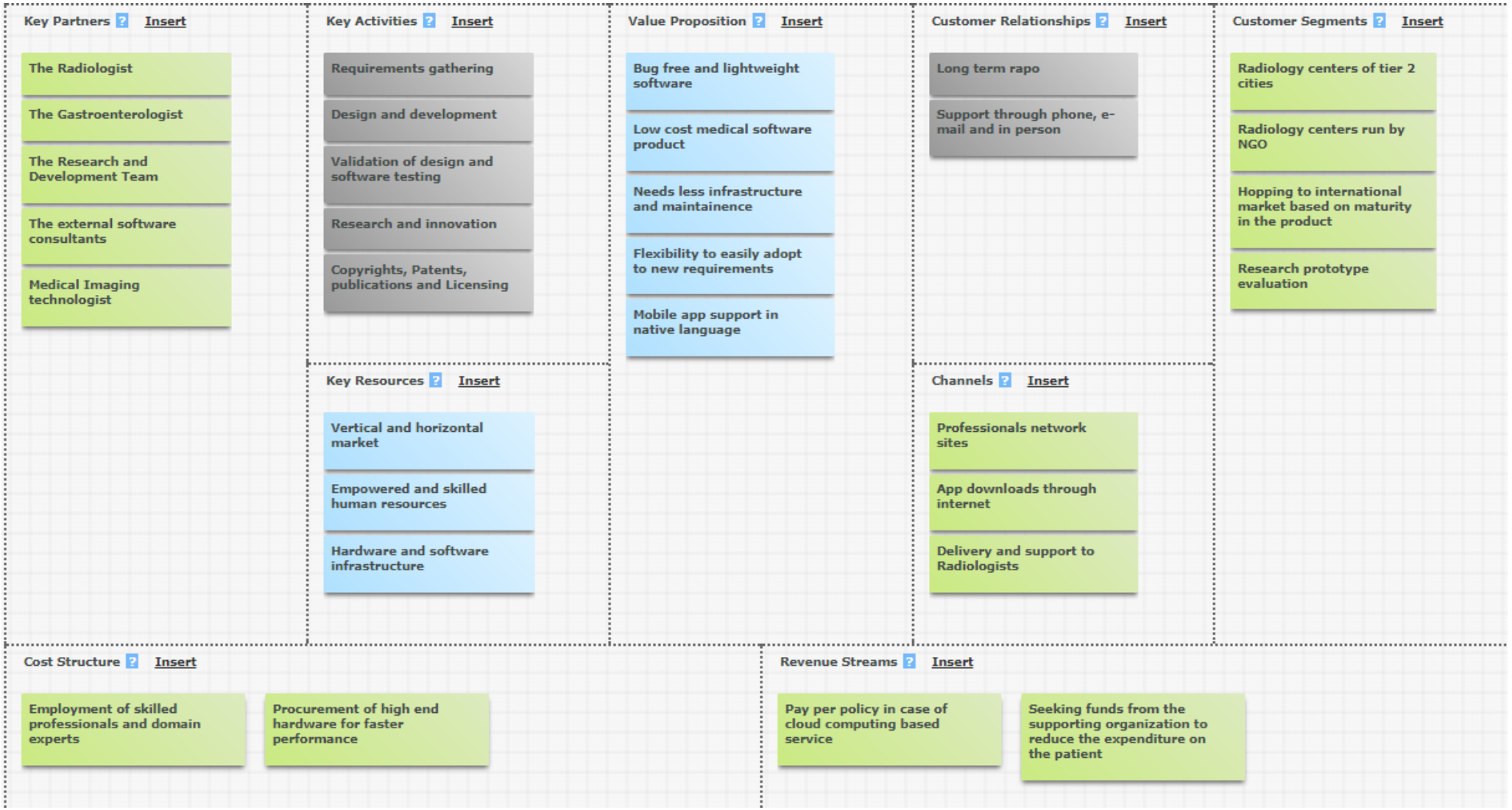


Fig. 29: The key elements of the Radio diagnosis business model canvas

The novelty and business idea (2/2)

Novelty of the business idea

- The image processing prototype can be further **developed as a software product for any other medical imaging modalities** (CT, MRI, PET, and US) and for the diagnosis of the diseases.
- The product can be developed as a **mobile application** also that helps a patient to see his scan details in his language.
- It can be extended further as **cloud computing based application** to reduce the cost.

Implementation and commercialization

- **Transforming a research prototype in to a commercial product** involves lot of steps from Software engineering perspective. Validation is a key phase before releasing a software as a product (**IEC 62304**).
- To make it a light weight and the bug free software, the agile principles are implemented as part of the software development Life Cycle (**product**). The product can be evaluated in Radiology centers through clinical validation (**place**). Once it works as expected then its cost can be reduced further if we can go as cloud based service (**price**). Two tier hospitals can be considered as the potential market for releasing this product (**promotion**).

Summary

Inference

- Domain aspects has played major role in problem solving
- Thd dlls are developed which can be customized and extended based on the need.
- Research objectives are met and also they are demonstrated with proper UI.
- CTC CAA prototype can be used as an image processing framework for other modalities also.

Future work

Clinical validation is in progress and auditing against IEC62304 standards

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