Contribution of multi and hyperspectral imaging to skin pigmentation evaluation

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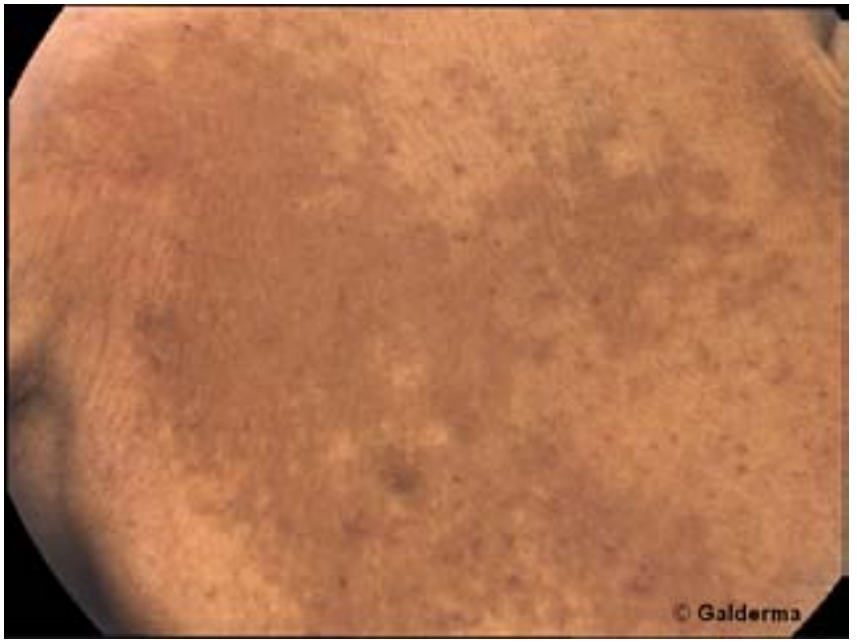
- Problematic introduced by Galderma R&D for early clinic evaluation
- **General context:**
  - Use measuring techniques such as spectrocolorimetry or imaging, to evaluate skin diseases severity during clinical studies to avoid the **variability of a human diagnosis** based evaluation and to **shorten the trial duration**.
- **Specific context:**
  - **Use multi-spectral imaging** to get both spectral and spatial description of the disease.
  - Focus on hyperpigmentation and especially on **melasma**

Melasma: hyper-pigmentation

Disease showing darker and irregular spots on the face. This disease is caused by an abnormal melanocytes activity in response to a hormonal reaction.

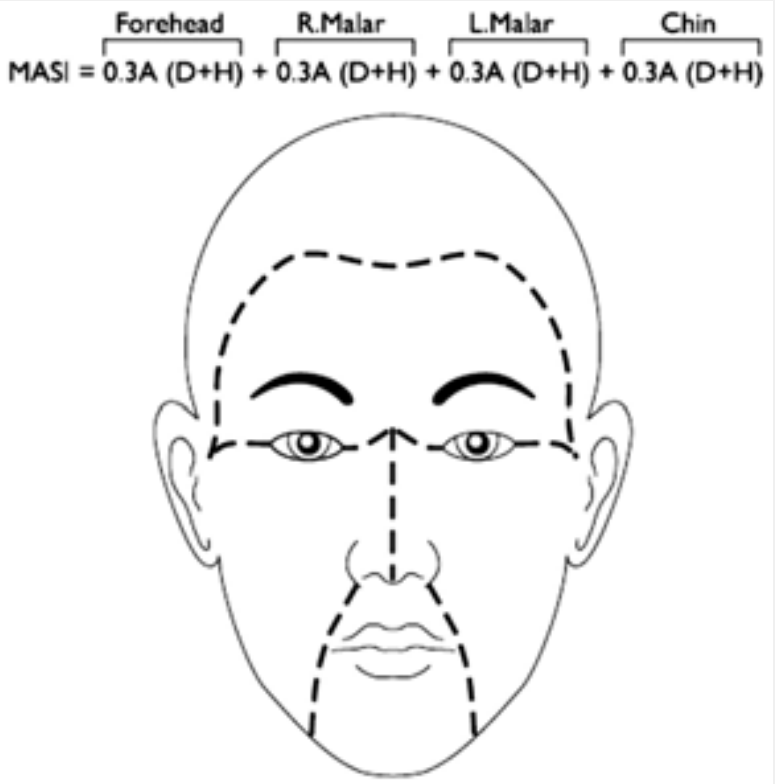


MASI: Melasma **A**rea and **S**everity **I**ndex is a clinical index to measure melasma severity. It is based on three measurements:

3 criteria

- Area (A): **0** - **6**
  - 0%
  - >90%
- Darkness (D): **0** - **4**
  - normal
  - severe
- Homogeneity (H): **0** - **4**
  - normal
  - uniform

MASI definition



Source: Journal of the American Academy of Dermatology 2011; 64:78-83.e2

Data: clinical study description

We use 2 clinical studies of melasma. One is used to tune the algorithm, and the other to validate the algorithm:

Tuning clinical study

- 384 multi-spectral images (960*1280 pixels and 18 spectral bands)
- 48 patients in 3 groups of 16 (1 treatment per group)
- 3 months study: 1 measure at baseline, then 1 measure per month
- Compare 3 treatments:
  - S_t Standard product for melasma
  - A_{d2} Studied product with dose $d2$
  - A_{d3} Studied product with dose $d3$
- Comparator: A_{d1} such as $d1 < d2 < d3$

Testing clinical study

Data: clinical study description

We use 2 clinical studies of melasma. One is used to tune the algorithm, and the other to validate the algorithm:

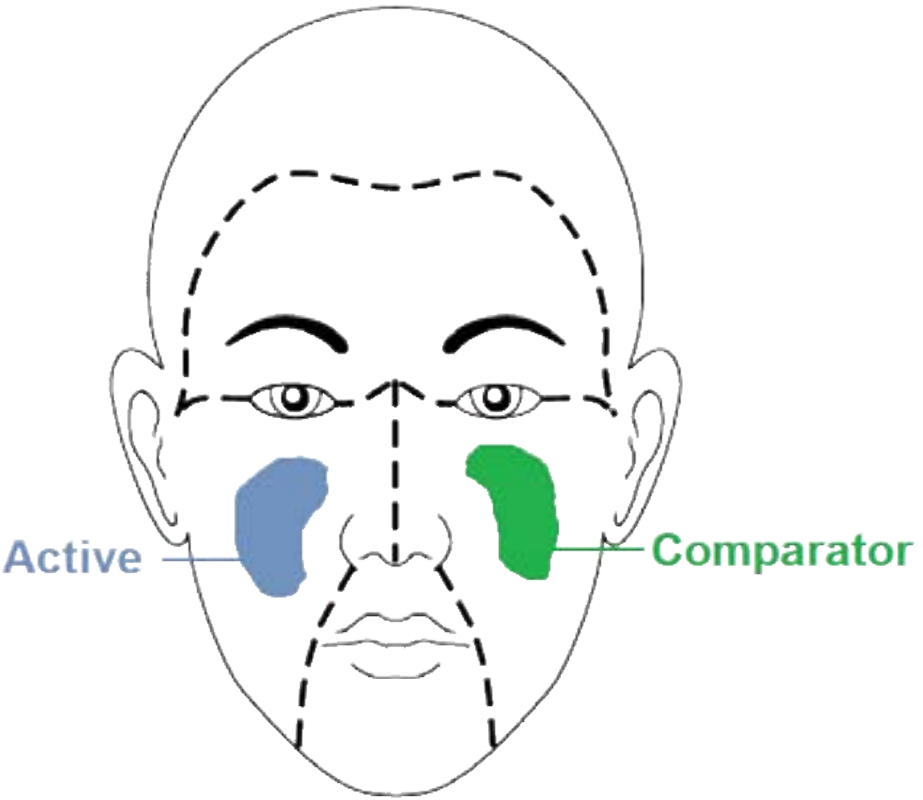
Tuning clinical study

Testing clinical study

- 352 multi-spectral images (960*1280 pixels and 18 spectral bands)
- 44 patients in 2 groups of 22 (1 treatment per group)
- 3 months study: 1 measure at baseline, then 1 measure per month
- Compare 2 treatments:
  - A Standard product
  - T Studied product
- Comparator: Vehicle without any active product.

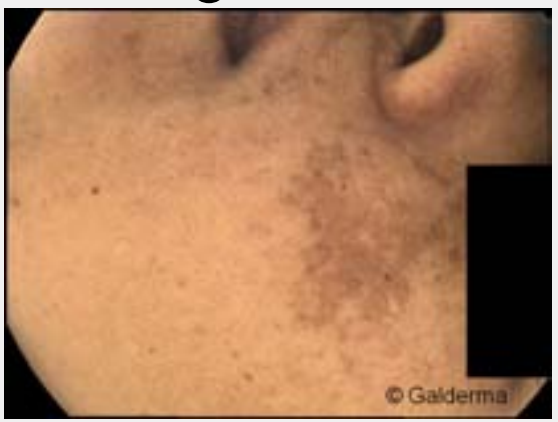
Data: clinical study description

Selected patients have a **symmetrical disease**, one cheek receive the active treatment, and one cheek the comparator.



RGB

Mixed hemoglobin and melanin



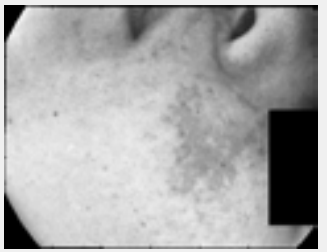
Pigmentation analysis

L^* or "Individual Topology Angle: ITA":

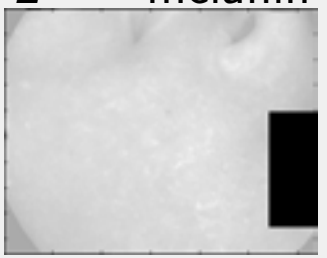
$ITA = arctg(\frac{L^*-50}{b^*})\frac{180}{\pi} \rightsquigarrow$ melanin

[Stamatas et al., Pigment cell res, 2004]

CIE L^*a^*b



$L^* \rightsquigarrow$ melanin



$a^* \rightsquigarrow$ hemoglobin

$b^* \rightsquigarrow$ melanin et hemoglobin

Skin spectrum

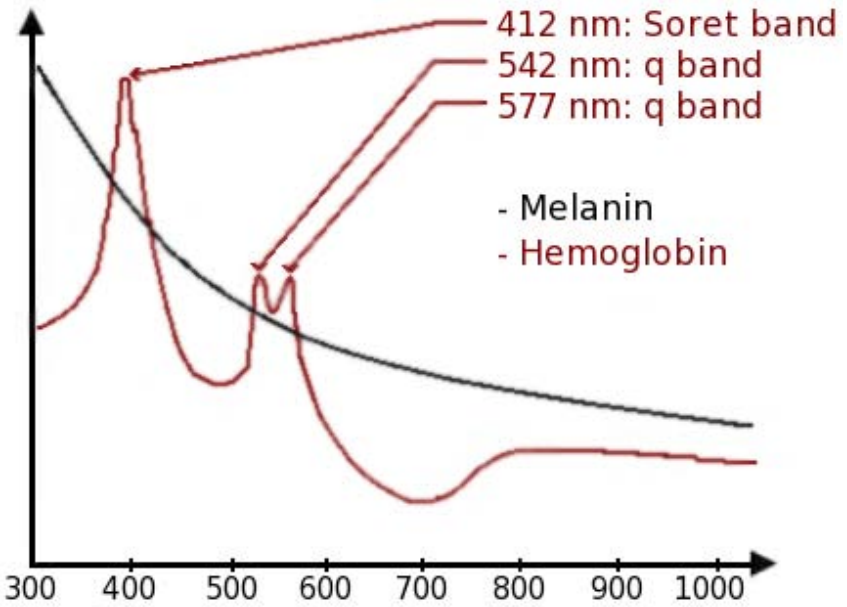


Figure: X-axis: wavelength in *nm*. Y-axis: relative absorption (%)

Stamatas et al. algorithm

$A_{melanine}(\lambda) = a\lambda + b, \quad \forall \lambda \in [600nm, 700nm],$
$A_c(\lambda) = A(\lambda) - A_{melanine}(\lambda).$
$A_c \rightsquigarrow$ corrected absorption.

Clinical study analysis

- Being able to evaluate a treatment efficacy with multi-spectral imaging:
  - **With** a statistical test on a population of patients
  - **By** creating a **"differential MASI"** related to the **clinical MASI**

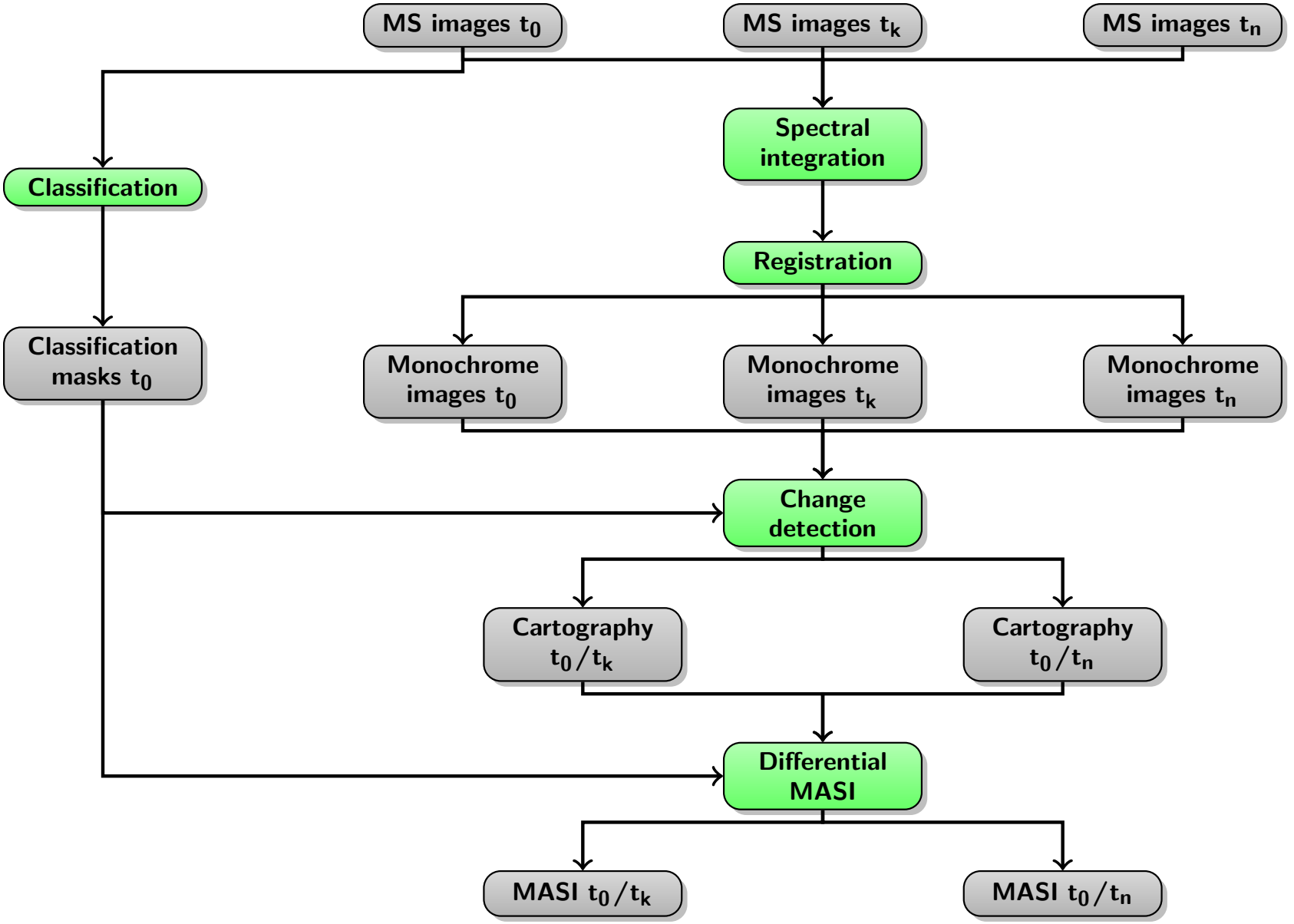
Technologies comparison

- Compare spectral imaging with other technologies:
  - Spectrocolorimeter
  - Color imaging
  - Hyper-spectral imaging

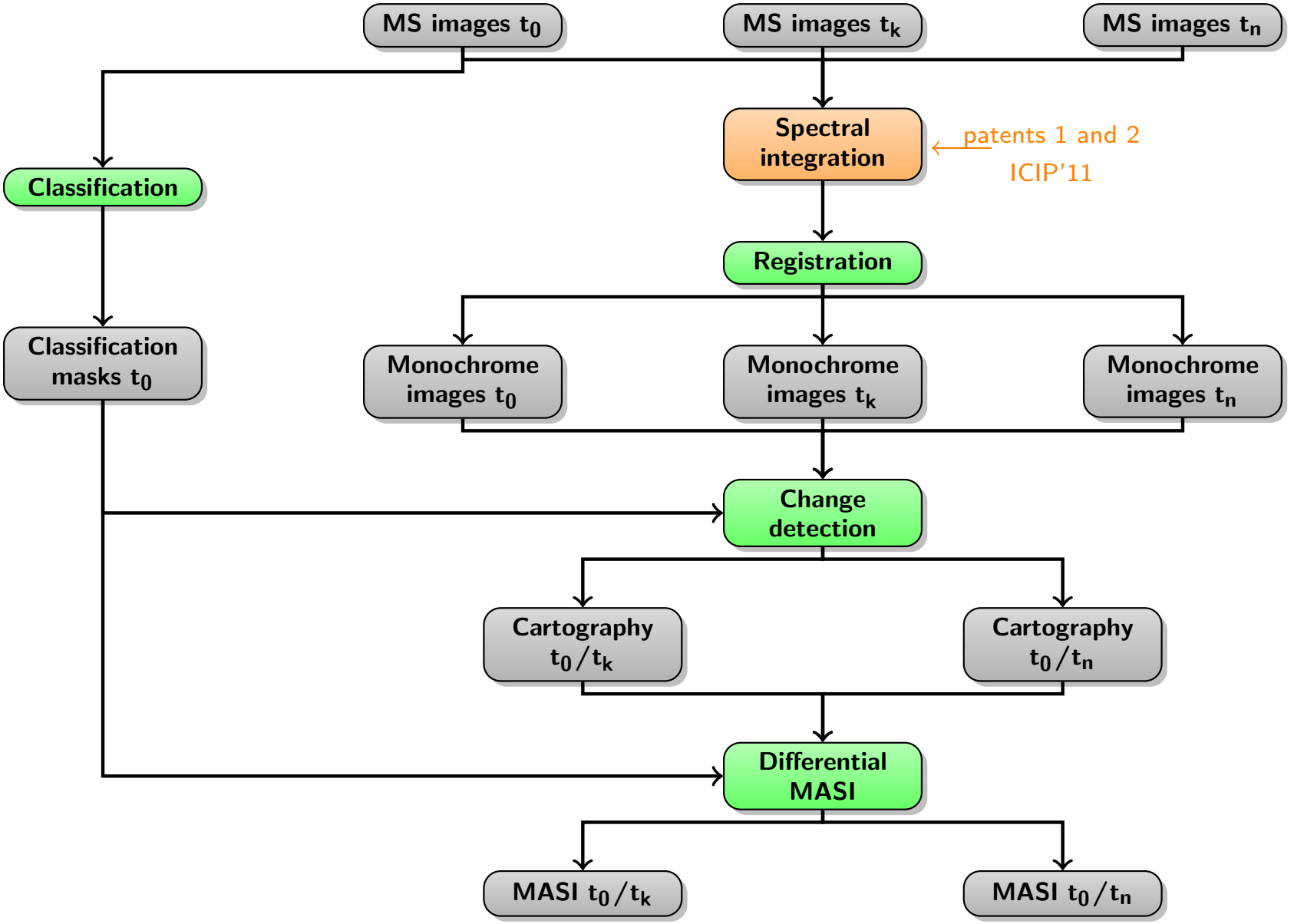
Outlines

- We choose to consider **sequentially** the extraction of the **spectral**, the **spatial**, and the **temporal** information
  - For an easier understanding of the results
  - For computation complexity
- We prefer to use a **differential** disease measurement
  - It allows to fully use the image information
  - It gives intermediate results (changes maps) in addition to MASI values

Proposed method



Proposed method



Spectral criterion: definition

- Find the spectral criterion M that allows to highlight the evolution of the pathology in a group of patients receiving a treatment.
- We define the criterion M as the vector of the weights assigned to each spectral bands: $M = [\alpha_1, ..., \alpha_{N_b}]$
- Then the spectral integration is:

$$I_M = \sum_{b=1}^{N_b} \alpha_i I(b),$$

where I is the original spectral image, N_b the number of bands in the initial image, and I_M the integrated image.

- **Need of a normalisation:**
  - Normalisation by the comparator treatment

$$D_t^e = d_t^{e,A} - d_t^{e,C}$$

  - Normalisation by the healthy area

$$d_t^e = \mu_{M_h} - \mu_{M_p}$$

or

$$d_t^e = \mu_{M_p}$$

Spectral criterion: normalisation

- **Need of a normalisation:**
  - Normalisation by the comparator treatment

$$D_t^e = d_t^{e,A} - d_t^{e,C}$$

  - Normalisation by the healthy area

$$d_t^e = \mu_{M_h} - \mu_{M_p}$$

or

$$d_t^e = \mu_{M_p}$$

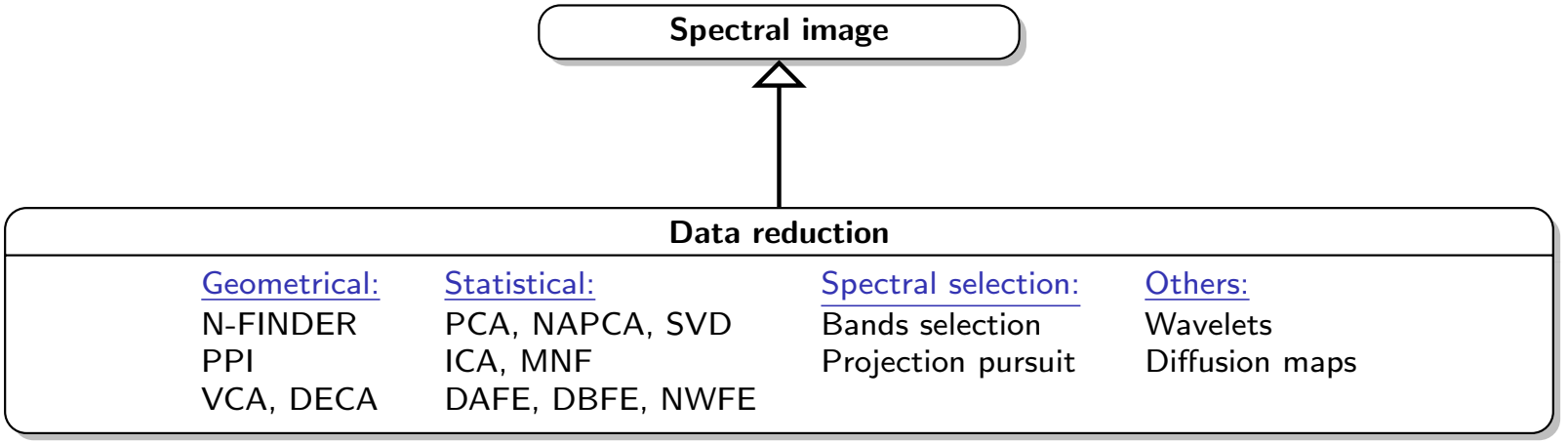
- **Finally, we get:**

$$D_t^e = (\mu_{M_h,A} - \mu_{M_p,A}) - (\mu_{M_h,C} - \mu_{M_p,C})$$

or

$$D_t^e = \mu_{M_p,A} - \mu_{M_p,C}$$

Spectral criterion: state of the art



- We focuses on methods that allow to get a linear combination of spectral bands
  - For feature interpretation.
  - For repeatability of the obtained feature.

- We look forward the spectral band that maximizes both the distance between healthy and pathological area and between the measurement at time t_0 the measurement at t:

$$f = \underset{M}{Max} f(M)$$

with

$$f(M) = [f_1(M_1), ..., f_{N_b}(M_{N_b})]$$

such as

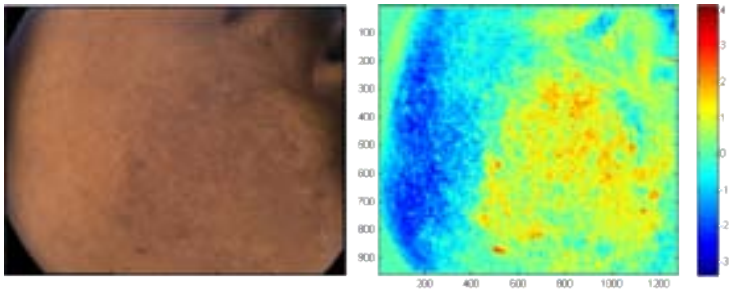
$$M_i = [0, ..., 0, 1, 0, ..., 0]$$

and

$$f_i = \sum_{t=t_1}^{t_{N_t}} \sum_{e=1}^{N_e} [D_t^e(M_i) - D_{t_0}^e(M_i)]$$

Spectral integration: by ICA

When we perform an ICA on multi-spectral image of melasma, we get a component which visually represents the disease:



To get a single spectral combination for all the images, we take the average combination for the whole images of a clinical study

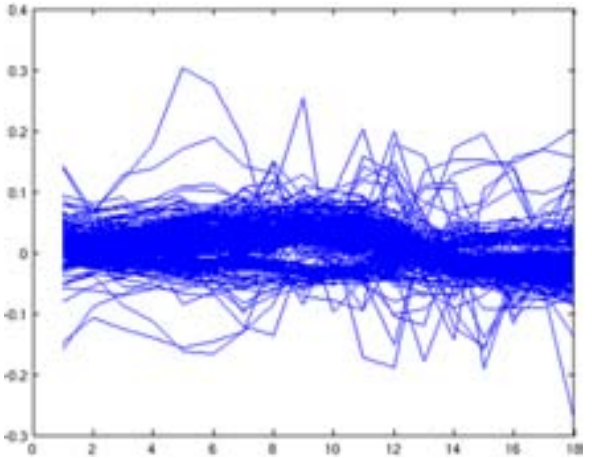
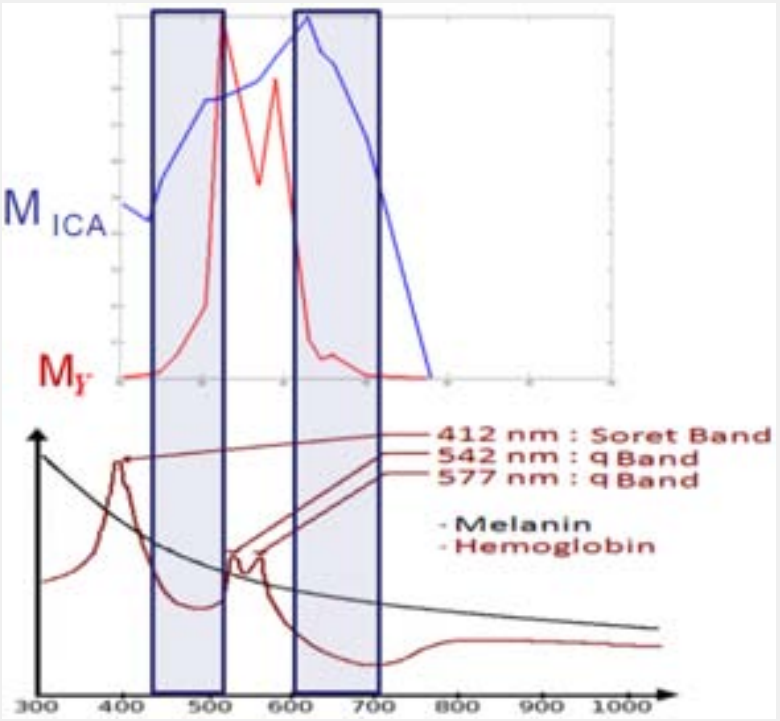


Figure: **X-axis:** spectral band index, **Y-axis:** weights

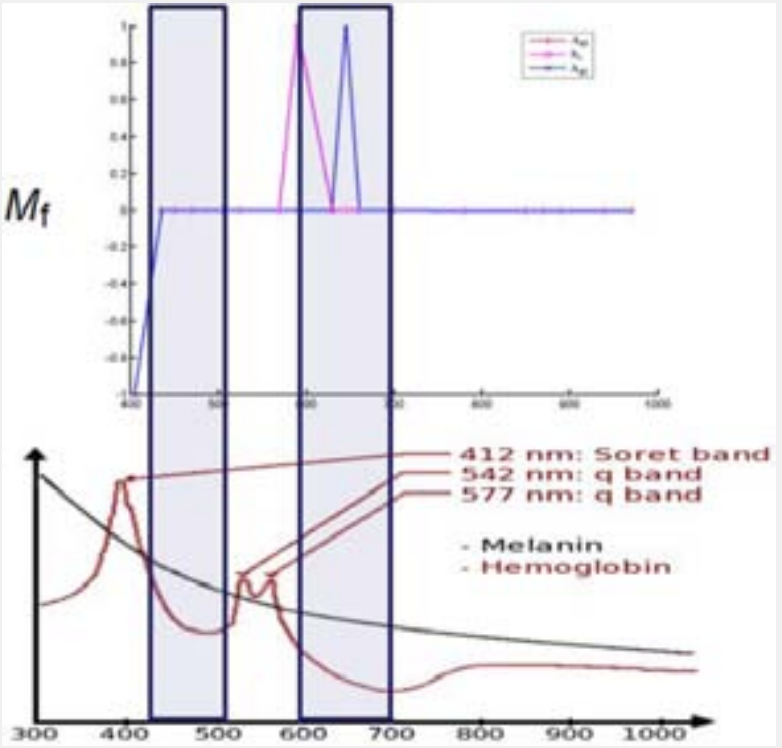
Spectral integration: Results

Criteria L^* and *ICA*



- Few correlation between M_{L*} and the interest spectral areas
- M_{ICA} and interest areas correspond only in the area 600-700 nm

Criterion *f*



- Highest weights of M (in absolute value) correspond to spectral areas where melanin curve dominates the hemoglobin one.

Spectral integration: Results

Results obtained in the "test study" with the **Wilcoxon test** and the normalisation: $D_t^e = (\mu_{M_h,A} - \mu_{M_p,A}) - (\mu_{M_h,C} - \mu_{M_p,C})$

Significant disease evolution: **p value** $< 0.05 = 5.10^{-2}$

Test	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
L^*	S_t	$7.959\ 10^{-1}$	$5.014\ 10^{-1}$	$7.173\ 10^{-1}$
	A_{d2}	$3.793\ 10^{-1}$	$\mathbf{1.128\ 10^{-2}}$	$8.793\ 10^{-2}$
	A_{d3}	$9.798\ 10^{-2}$	$\mathbf{3.204\ 10^{-3}}$	$\mathbf{5.312\ 10^{-4}}$
$b_{590} - b_{405}$	S_t	$1.476\ 10^{-1}$	$1.089\ 10^{-1}$	$7.563\ 10^{-1}$
	A_{d2}	$5.571\ 10^{-2}$	$\mathbf{3.400\ 10^{-2}}$	$\mathbf{4.373\ 10^{-2}}$
	A_{d3}	$\mathbf{8.360\ 10^{-3}}$	$\mathbf{3.204\ 10^{-3}}$	$\mathbf{9.350\ 10^{-4}}$
ICA no IR	S_t	$5.694\ 10^{-1}$	$8.767\ 10^{-1}$	$9.587\ 10^{-1}$
	A_{d2}	$4.080\ 10^{-1}$	$\mathbf{2.289\ 10^{-2}}$	$8.793\ 10^{-2}$
	A_{d3}	$7.873\ 10^{-2}$	$\mathbf{5.233\ 10^{-3}}$	$\mathbf{9.350\ 10^{-4}}$

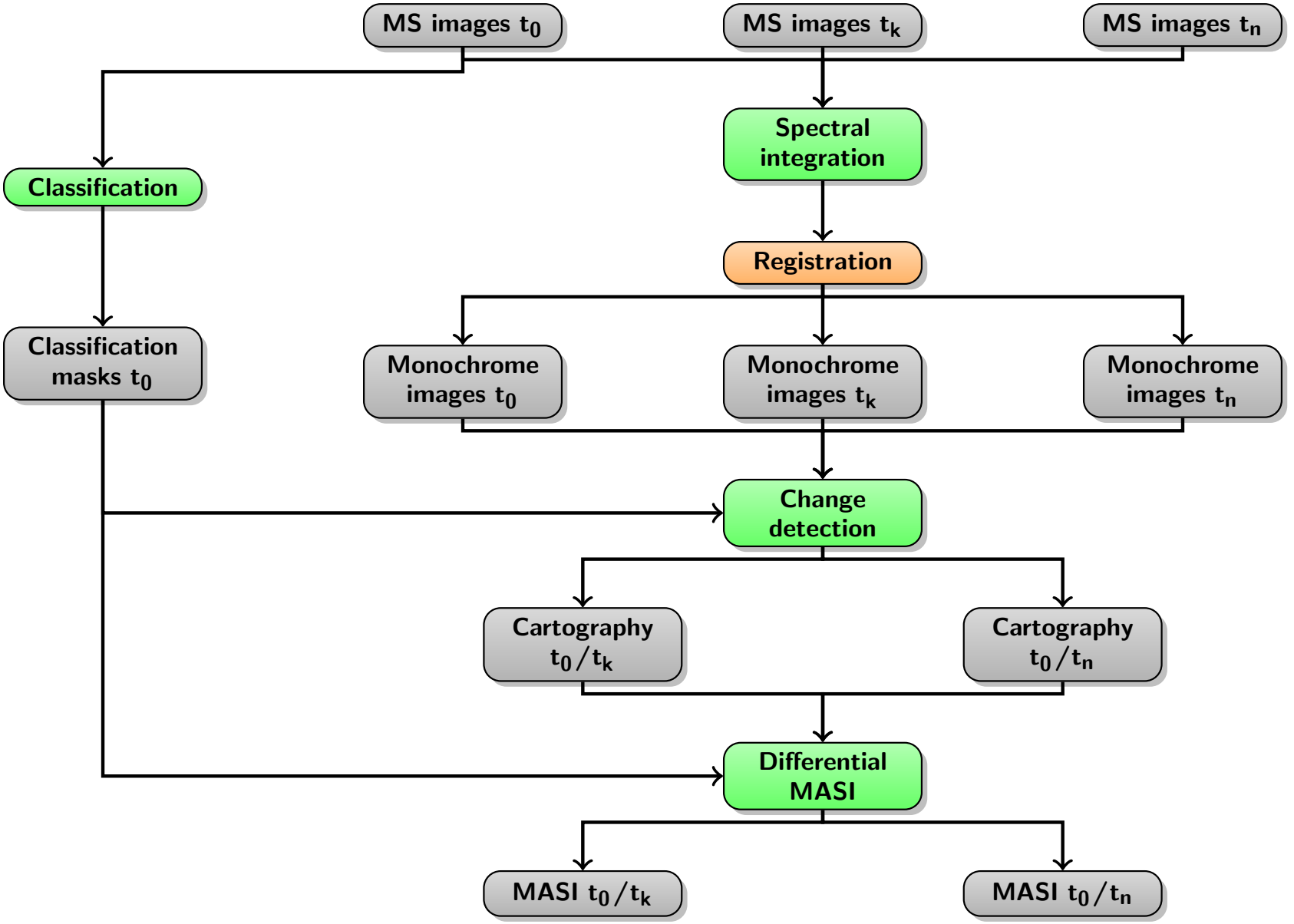
Spectral integration: Results

Results obtained in the "test study" with the **Wilcoxon test** and the normalisation: $D_t^e = (\mu_{M_p,A}) - (\mu_{M_p,C})$

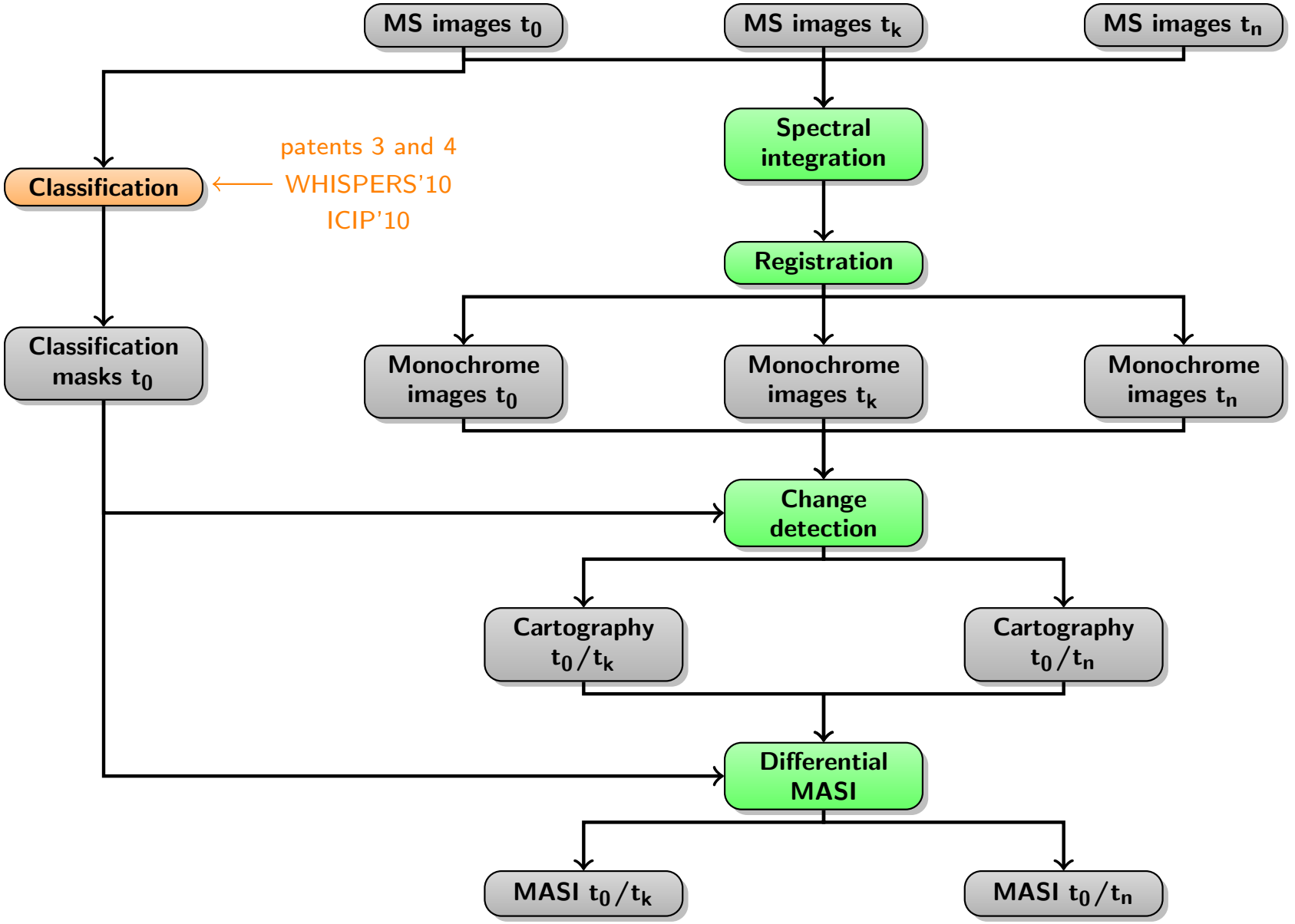
Significant disease evolution: **p value** $< 0.05 = 5.10^{-2}$

Test	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
L^*	S_t	$7.959\ 10^{-1}$	$6.791\ 10^{-1}$	$6.416\ 10^{-1}$
	A_{d2}	$\mathbf{1.306\ 10^{-2}}$	$\mathbf{2.289\ 10^{-2}}$	$9.798\ 10^{-2}$
	A_{d3}	$1.788\ 10^{-1}$	$\mathbf{7.169\ 10^{-3}}$	$\mathbf{1.918\ 10^{-3}}$
$b_{590} - b_{405}$	S_t	$7.173\ 10^{-1}$	$5.349\ 10^{-1}$	$5.014\ 10^{-1}$
	A_{d2}	$\mathbf{2.289\ 10^{-2}}$	$\mathbf{1.737\ 10^{-2}}$	$\mathbf{3.400\ 10^{-2}}$
	A_{d3}	$\mathbf{1.997\ 10^{-2}}$	$\mathbf{1.609\ 10^{-3}}$	$\mathbf{9.725\ 10^{-3}}$
ICA no IR	S_t	$6.416\ 10^{-1}$	$5.694\ 10^{-1}$	$5.014\ 10^{-1}$
	A_{d2}	$\mathbf{1.997\ 10^{-2}}$	$\mathbf{3.400\ 10^{-2}}$	$8.793\ 10^{-2}$
	A_{d3}	$1.476\ 10^{-1}$	$\mathbf{7.169\ 10^{-3}}$	$\mathbf{1.123\ 10^{-3}}$

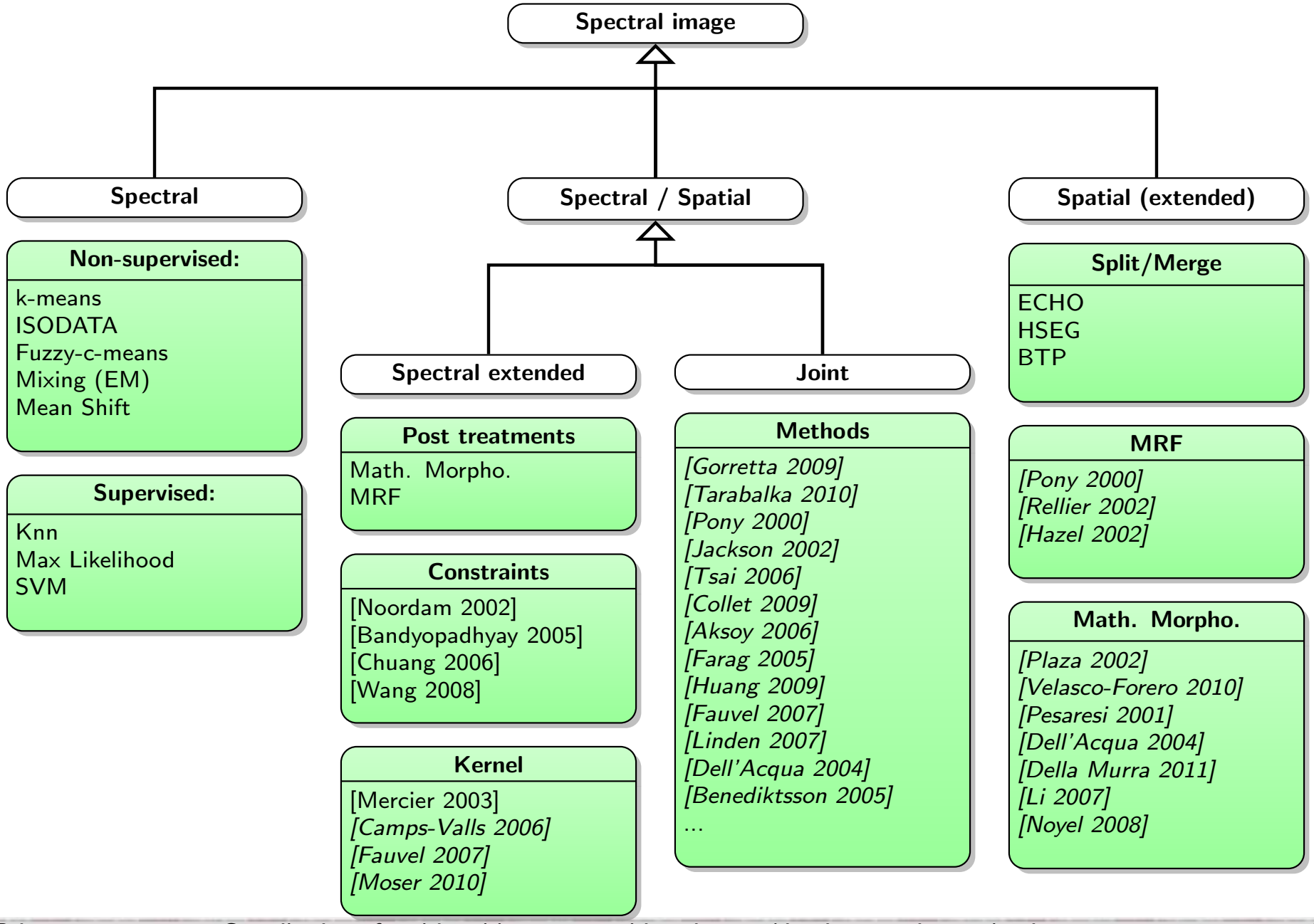
Proposed method



Proposed method



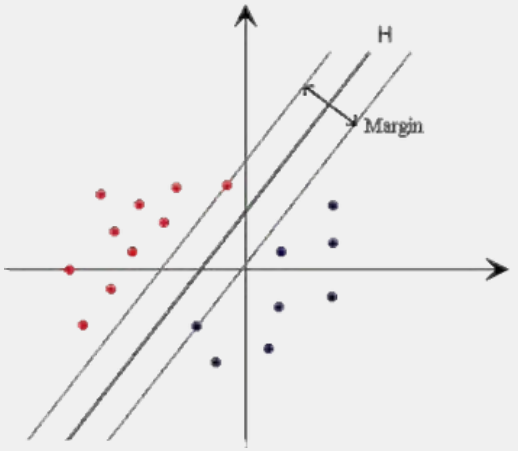
Classification: state of the art



Classification into two classes with a linear separator

1- Training

Determine the separator on a training set by maximizing the margin



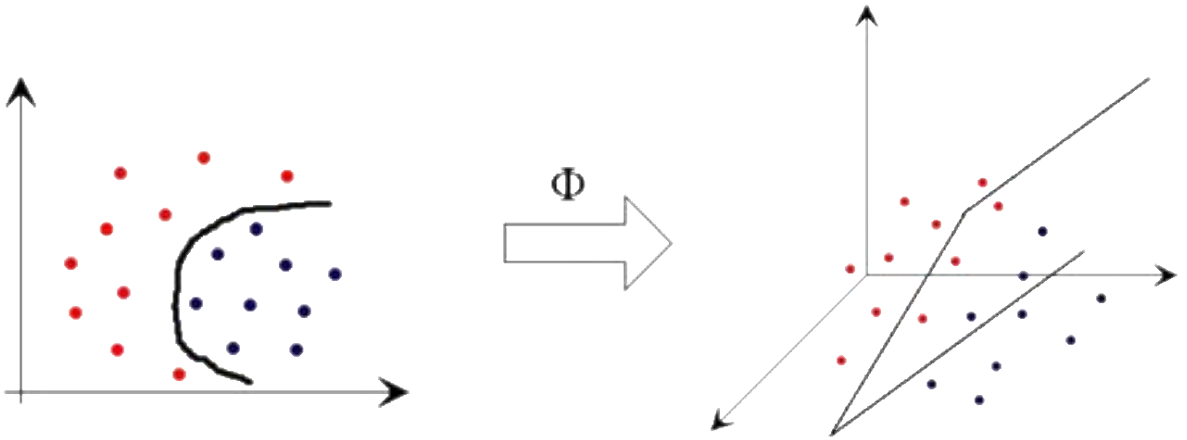
2- Classification

Assign a class to each pixel according to its relative position to the separator.

[V. Vapnik, John Wiley and sons, inc.,1998]

Classification: SVM

Non linear case

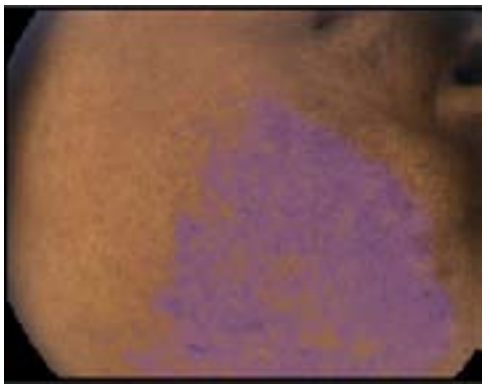


Kernel:

$$K(\vec{x_i}, \vec{x_j}) = \Phi(\vec{x_i}).\Phi(\vec{x_j}) = exp\left(-\frac{||x_i - x_j||^2}{2\sigma^2}\right)$$

Classification: SVM

(a) image couleur



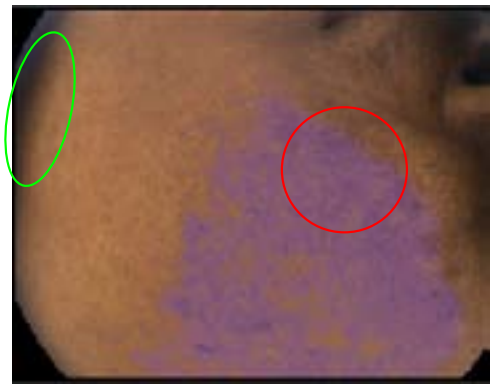
(b) PP-SVM

Accurate classification in the flat area.
No detection in area affected by the face volume.
Need a training for each image.

$\Rightarrow$ Need volume compensation
$\Rightarrow$ Need global training

Classification: SVM

(a) image couleur

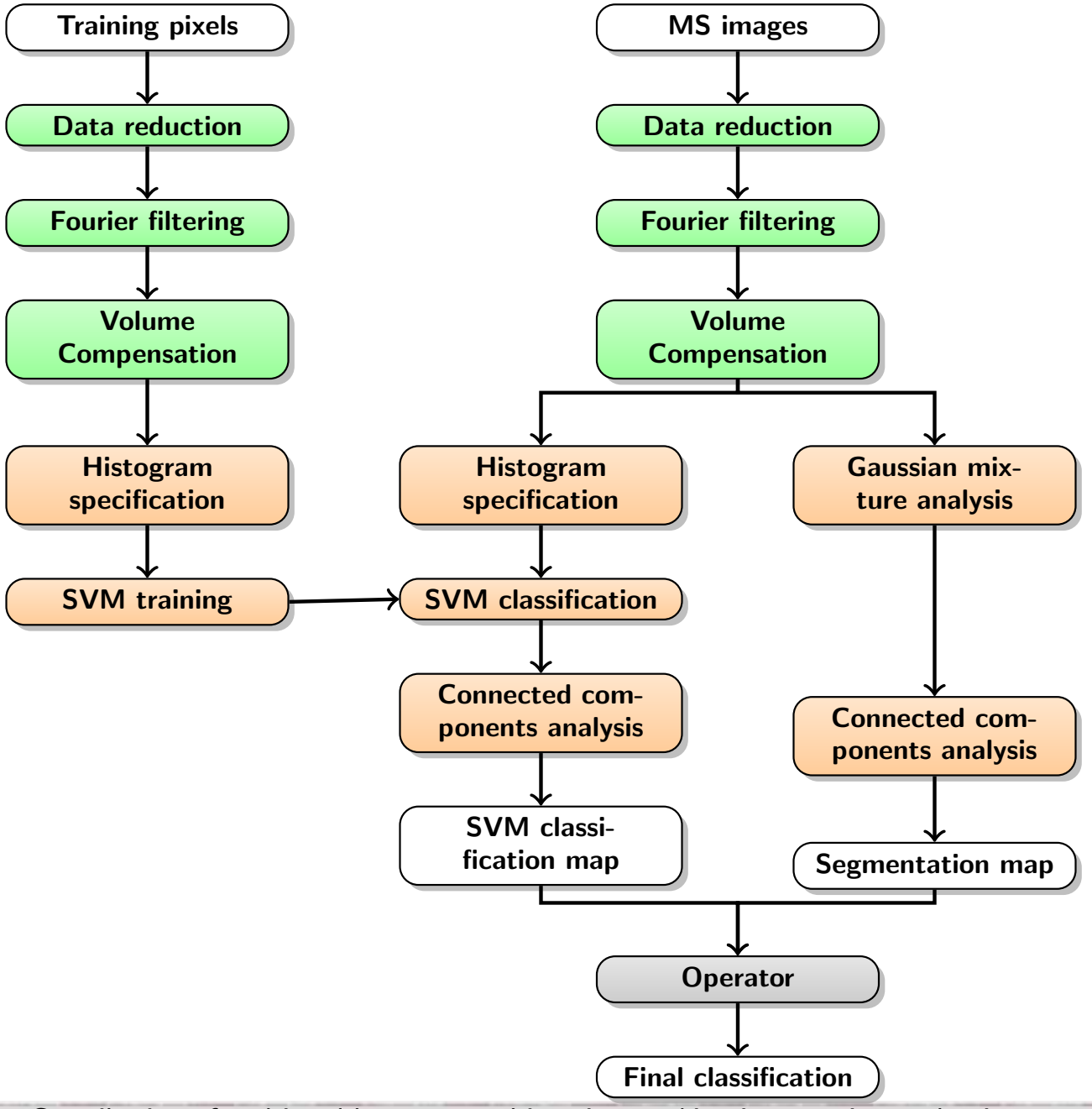


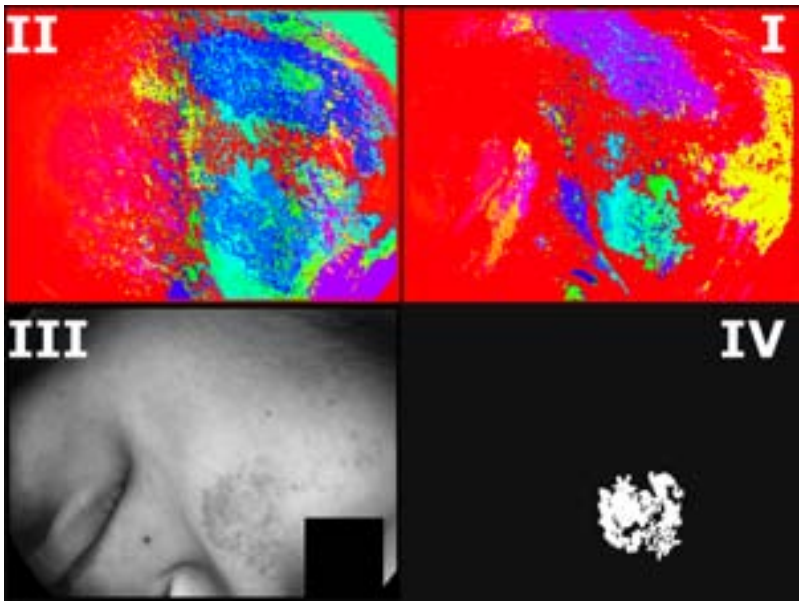
(b) PP-SVM

Accurate classification in the flat area.
No detection in area affected by the face volume.
Need a training for each image.

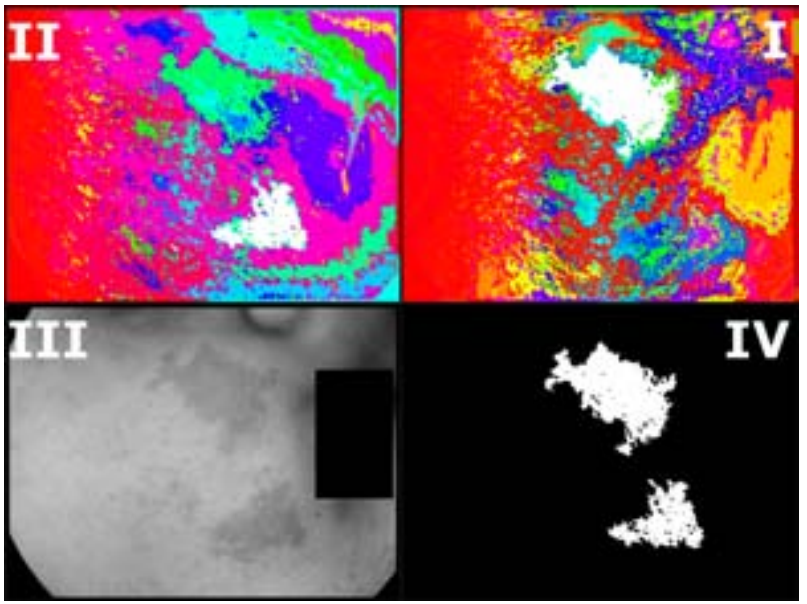
$\Rightarrow$ Need volume compensation
$\Rightarrow$ Need global training

Classification: Global scheme





(a) Selection on the SVM classification

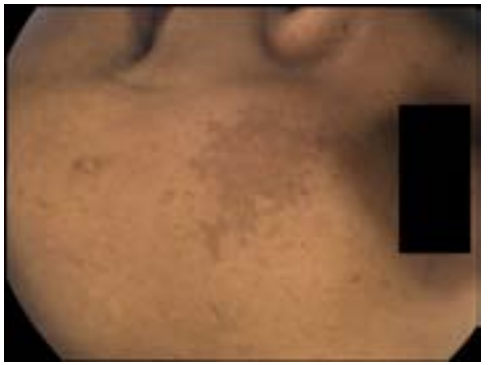


(b) Selection on the segmentation map

- I- Segmentation map with a 80% high pass Fourier filter
- II- Segmentation map with a 60% high pass Fourier filter
- III- Original interest band
- IV- Final classification

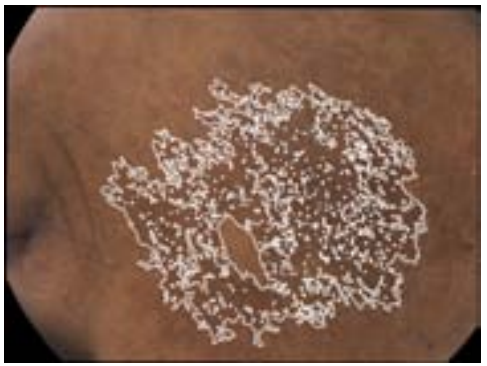
Classification: results

(a) image 1

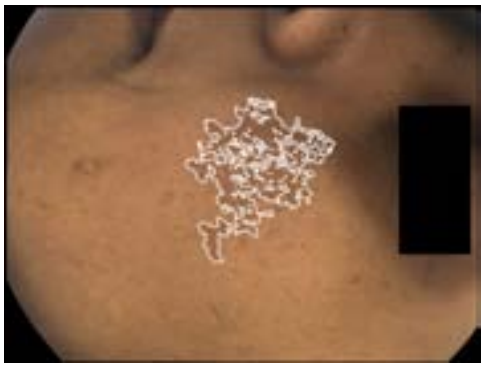


(b) image 2

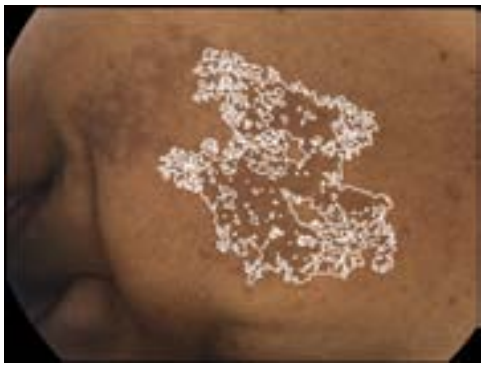
(c) image 3



(d) classification



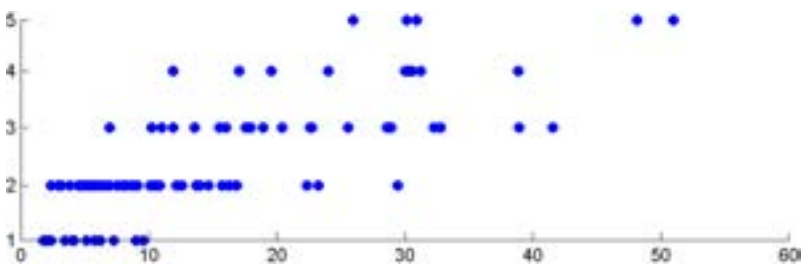
(e) classification



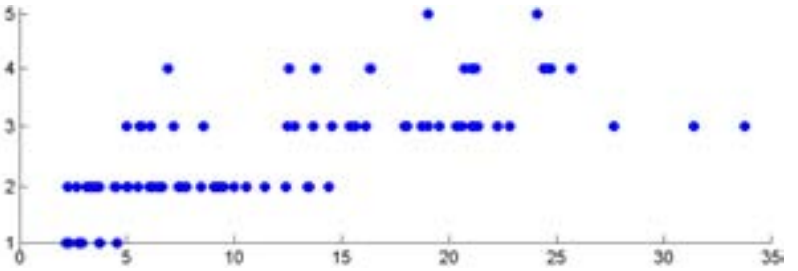
(f) classification

Correlation of the pathological area between the dermatologist and the proposed method

- Test study: **0.76** correlation (**0.58** for SVM alone)
- Validation study: **0.71** correlation (**0.45** for SVM alone)



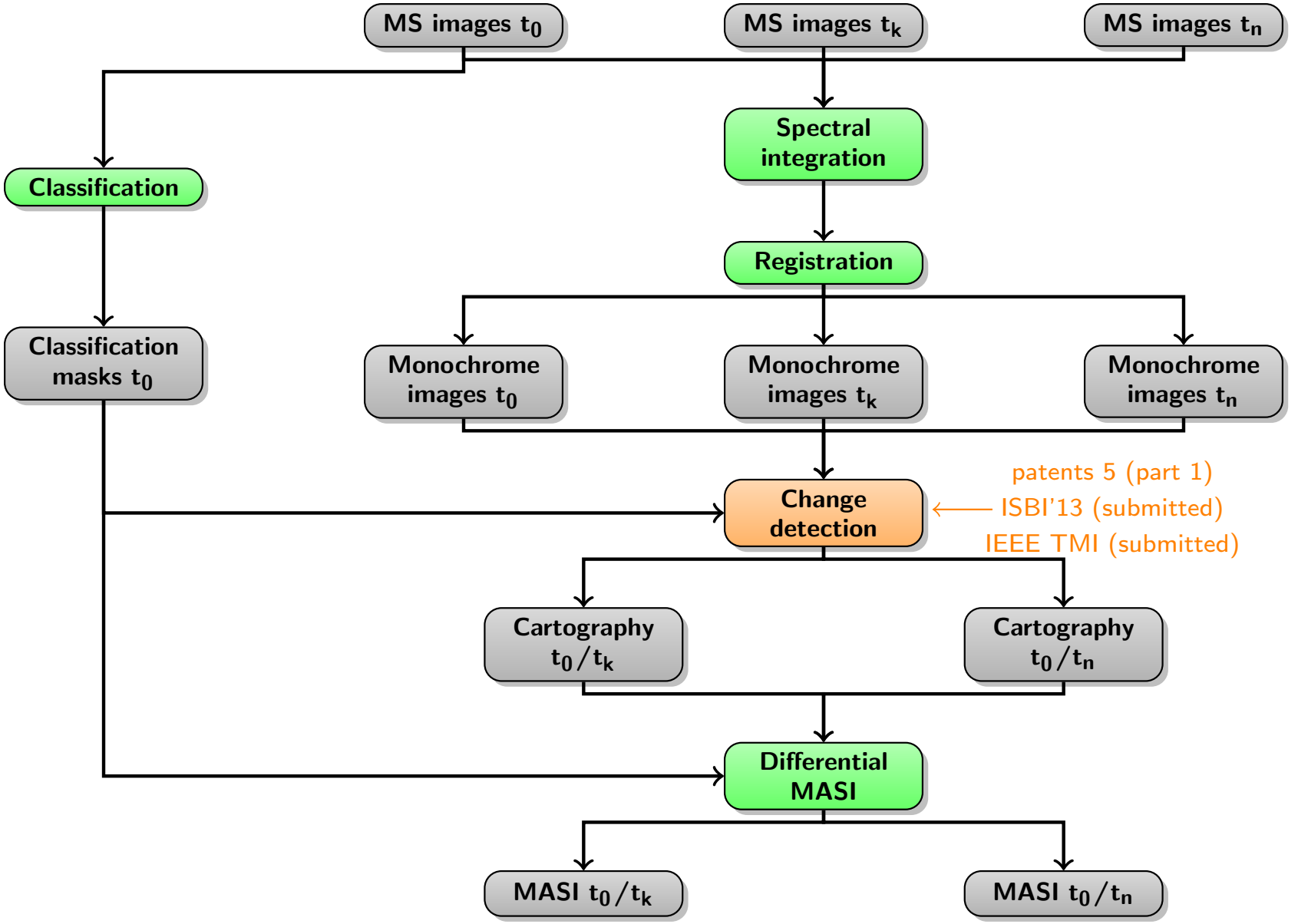
(a) Correlation on the test study



(b) Correlation on the validation study

Figure: X-axis: area measured by the algorithm, Y-axis: area measured by the dermatologist

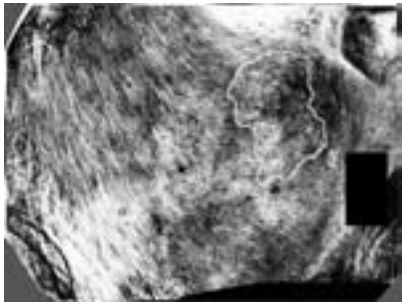
Proposed method



Change detection: state of the art

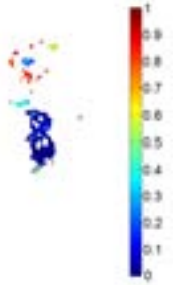
- Change detection based on image difference and thresholding
  - + Preserve the image structures
  - - Need to set a threshold (often arbitrary)
- Change detection based on a statistical test and a local analysis
  - + Good theoretical background to make the significance decision
  - - Loss of resolution
  - - Can alter the image structures
- Change detection based on transformations (PCA...)
  - Techniques for multi-variate data (video, multi-channel...)

Examples of change maps



(a) I_c^1 equalised

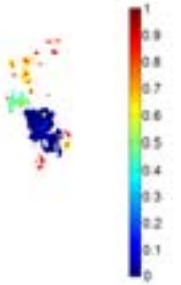
(b) Binary map t_1



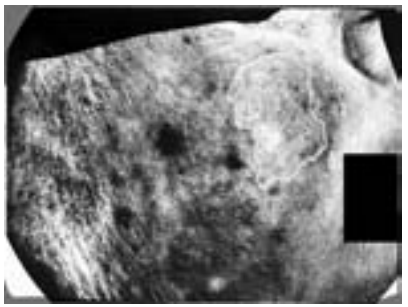
(c) Level map t_1

(d) I_c^2 equalised

(e) Binary map t_2

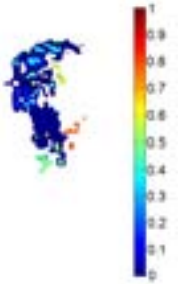


(f) Level map t_2



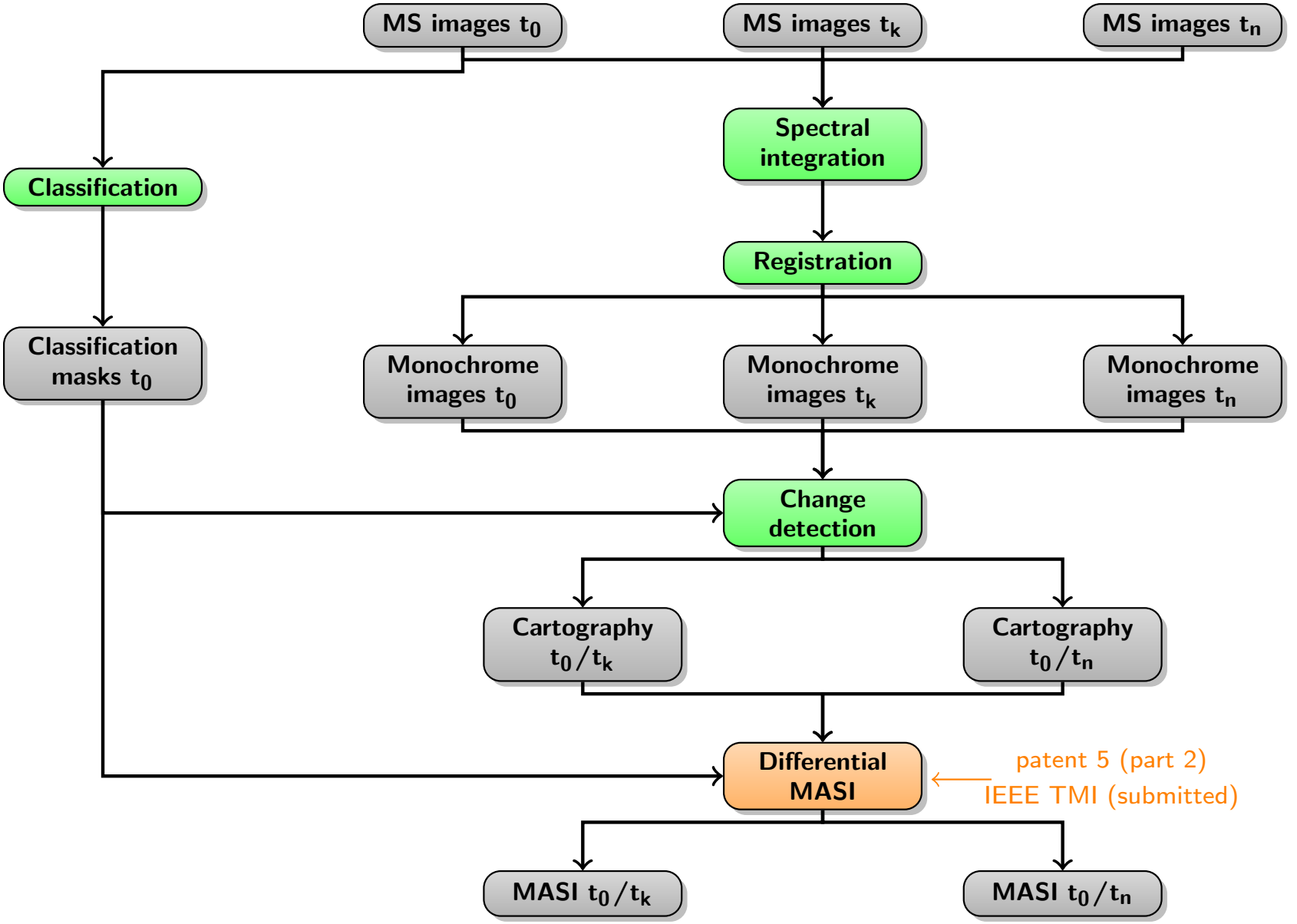
(g) I_c^3 equalised

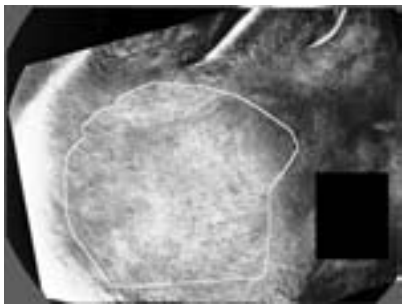
(h) Binary map t_3



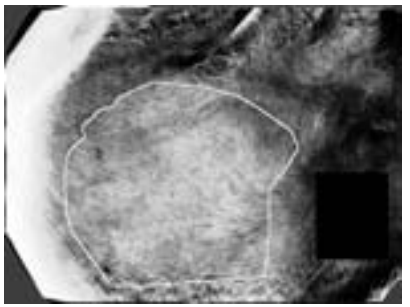
(i) Level map t_3

Proposed method

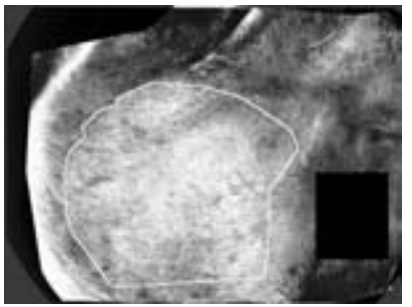




(a) I_c^1 equalised

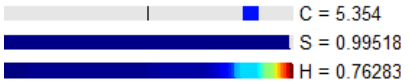


(b) I_c^2 equalised



(c) I_c^3 equalised

(d) MASI t_1



(e) MASI t_2

(f) MASI t_3

differential MASI: Examples

(a) I_c^1 equalised

(b) I_c^2 equalised

(c) I_c^3 equalised

(d) MASI t_1

(e) MASI t_2

(f) MASI t_3

differential MASI: Results

Reminder: clinical analysis of the validation study:

Test	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
L^* spectro-colorimeter	A	$9.482\ 10^{-1}$	$4.169\ 10^{-1}$	$8.582\ 10^{-1}$
	T	$1.831\ 10^{-1}$	$\mathbf{2.508\ 10^{-2}}$	$\mathbf{8.755\ 10^{-4}}$

Differential MASI results on the validation study:

- *Darkness:*

Test	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
Darkness	A	$6.494\ 10^{-1}$	$5.589\ 10^{-1}$	$1.045\ 10^{-1}$
	T	$6.729\ 10^{-1}$	$\mathbf{7.343\ 10^{-4}}$	$\mathbf{3.553\ 10^{-4}}$

- *Area:*

Test	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
Area	A	$2.840\ 10^{-1}$	$3.986\ 10^{-1}$	$1.045\ 10^{-1}$
	T	$4.552\ 10^{-1}$	$\mathbf{3.478\ 10^{-3}}$	$\mathbf{2.438\ 10^{-4}}$

differential MASI: Results

- *Homogeneity:* The homogeneity criterion makes sense only for patient whose pathological area changes. We then focus on the treatment T of the validation study:

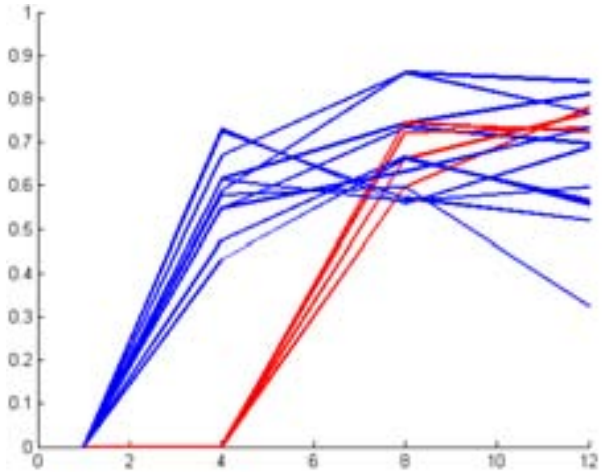


Figure: X-axis: time in weeks, Y-axis: Homogeneity for each patients receiving T

  - 11 patients evolve after 4 weeks
  - 4 patient evolve after 8 weeks
  - 7 patients did not evolve for area criterion $\hookrightarrow$ no homogeneity measurement

differential MASI: Conclusion

- **The differential MASI** allows to measure the time evolution of melasma with the three criteria defined from the clinical MASI (Area, Darkness, Homogeneity)
- The Area and Darkness criteria allow to retrieve the clinical analysis conclusions.
- The Homogeneity criterion allows to get a supplementary information for patients whose Area and Darkness evolve.

Wilcoxon test between t_0 and t:

M	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
L^* spectro-colorimeter	S_t	$2.552\ 10^{-1}$	$6.416\ 10^{-1}$	$9.176\ 10^{-1}$
	A_{d2}	$6.416\ 10^{-1}$	$1.337\ 10^{-1}$	$\mathbf{4.942\ 10^{-2}}$
	A_{d3}	$6.267\ 10^{-2}$	$\mathbf{1.609\ 10^{-3}}$	$\mathbf{9.725\ 10^{-3}}$
$b_{590} - b_{405}$ spectro-colorimeter	S_t	$1.476\ 10^{-1}$	$4.691\ 10^{-1}$	$4.379\ 10^{-1}$
	A_{d2}	$5.694\ 10^{-1}$	$1.961\ 10^{-1}$	$8.793\ 10^{-2}$
	A_{d3}	$1.089\ 10^{-1}$	$\mathbf{4.455\ 10^{-3}}$	$\mathbf{1.508\ 10^{-2}}$
ICA no IR spectro-colorimeter	S_t	$7.959\ 10^{-1}$	$9.587\ 10^{-1}$	$8.793\ 10^{-2}$
	A_{d2}	$5.014\ 10^{-1}$	$1.788\ 10^{-1}$	$\mathbf{3.400\ 10^{-2}}$
	A_{d3}	$\mathbf{2.289\ 10^{-2}}$	$\mathbf{1.609\ 10^{-3}}$	$\mathbf{4.455\ 10^{-3}}$
L^* multispectral imaging	S_t	$7.959\ 10^{-1}$	$6.791\ 10^{-1}$	$6.416\ 10^{-1}$
	A_{d2}	$\mathbf{1.306\ 10^{-2}}$	$\mathbf{2.289\ 10^{-2}}$	$9.798\ 10^{-2}$
	A_{d3}	$1.788\ 10^{-1}$	$\mathbf{7.169\ 10^{-3}}$	$\mathbf{1.918\ 10^{-3}}$
$b_{590} - b_{405}$ multispectral imaging	S_t	$7.173\ 10^{-1}$	$5.349\ 10^{-1}$	$5.014\ 10^{-1}$
	A_{d2}	$\mathbf{2.289\ 10^{-2}}$	$\mathbf{1.737\ 10^{-2}}$	$\mathbf{3.400\ 10^{-2}}$
	A_{d3}	$\mathbf{1.997\ 10^{-2}}$	$\mathbf{1.609\ 10^{-3}}$	$\mathbf{9.725\ 10^{-3}}$
ICA no IR multispectral imaging	S_t	$6.416\ 10^{-1}$	$5.694\ 10^{-1}$	$5.014\ 10^{-1}$
	A_{d2}	$\mathbf{1.997\ 10^{-2}}$	$\mathbf{3.400\ 10^{-2}}$	$8.793\ 10^{-2}$
	A_{d3}	$1.476\ 10^{-1}$	$\mathbf{7.169\ 10^{-3}}$	$\mathbf{1.123\ 10^{-3}}$

$\hookrightarrow$ The spectral imaging is equivalent to a "2D" spectrocolorimeter

Wilcoxon test between t_0 and t:

M	Treatment	$t_1 - t_0$	$t_2 - t_0$	$t_3 - t_0$
L^* color imaging	S_t	$\mathbf{4.942\ 10^{-2}}$	$9.798\ 10^{-2}$	$3.519\ 10^{-1}$
	A_{d2}	$9.587\ 10^{-1}$	$2.775\ 10^{-1}$	$6.050\ 10^{-1}$
	A_{d3}	$\mathbf{1.123\ 10^{-3}}$	$\mathbf{6.430\ 10^{-4}}$	$\mathbf{6.430\ 10^{-4}}$
ICA no IR color imaging	S_t	$6.267\ 10^{-2}$	$2.775\ 10^{-1}$	$5.349\ 10^{-1}$
	A_{d2}	$8.361\ 10^{-1}$	$4.379\ 10^{-1}$	$3.793\ 10^{-1}$
	A_{d3}	$\mathbf{2.707\ 10^{-3}}$	$\mathbf{1.123\ 10^{-3}}$	$\mathbf{9.350\ 10^{-4}}$
L^* multispectral imaging	S_t	$7.959\ 10^{-1}$	$6.791\ 10^{-1}$	$6.416\ 10^{-1}$
	A_{d2}	$\mathbf{1.306\ 10^{-2}}$	$\mathbf{2.289\ 10^{-2}}$	$9.798\ 10^{-2}$
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	A_{d3}	$1.476\ 10^{-1}$	$\mathbf{7.169\ 10^{-3}}$	$\mathbf{1.123\ 10^{-3}}$

$\hookrightarrow$ The spectral imaging is more discriminative than a RGB image.

- The spectral resolution of the hyper-spectral imaging is larger than multi-spectral imaging
  - We can think that it allows to quantify more precisely skin characteristics

- **Nevertheless:**
  - The hyper-spectral camera requires fine adjustments and a precise calibration
  - Duality between acquisition time and spatial resolution $\Rightarrow$ long aquisition time for a face

$\hookrightarrow$ Multi-spectral imaging seems to be more adapted for a practical use on in-vivo skin analysis.

Conclusion

We design a strategy to analyse a clinical study involving about 4*90 multi-spectral images:

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- Automatic analysis:
  - A registration algorithm ($\sim$ 12-24 hours on a 2.2Ghz core)
  - A feature extraction algorithm ($\sim$ 1 min on a 2.2Ghz core)
  - A classification algorithm ($\sim$ 2 hours on a 2.2Ghz core)

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  - Interactive classification (about 1 hour on about 90 images)
  - Registration control

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- Operator interactions:
  - Interactive classification (about 1 hour on about 90 images)
  - Registration control
- Automatic statistic calculation:
  - A change detection algorithm ($\sim$ 1.5 hours on a 2.2Ghz)
  - Integration of the extracted informations in a severity criterion ("differential MASI")

- We validate the methodologies on a complete clinical study
- We implement the process on a software
- We compare the multi-spectral technology with spectrocolorimetry, color imaging and hyper-spectral imaging
  - Multi-spectral imaging fits the best the problem, in terms of both provided information and practical use

- The proposed algorithms are quite general. The methodology can then be extended to other pathologies such as vitiligo, rosacea or scars.
  - The classification step should be adapted
  - The clinical criterion should match the disease clinical analysis
- Perform change detection in the spectral space and not only in the 1D feature space?
- Analyse the pathology evolution both in positive and negative senses.

Contributions summary

- **Answer to the question** "Contribution of multi-spectral imaging":
  - multi-spectral $\Leftrightarrow$ 2D spectrocolorimeter
  - multi-spectral is more addapted than RGB or hyper-spectral
- **Design** a severity score on multi-spectral images
- **Implement** the proposed methods on a software
- **Publications:**
  - 5 patents
  - 3 international conference articles (WHISPERS'10, ICIP'10, ICIP'11)
  - 1 international conference article submitted (ISBI'13)
  - 1 international journal paper submitted (IEEE TMI)
  - 2 Inria research reports (RR-8105 and RR-8136)