**The electronic patient diary in clinical trials**

Statistical analysis of images to detect skin lesions and applied topical medicine

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**Introduction**

To evaluate the effect, safety and tolerability of a new compound in a clinical trail appropriate dosing is required to reach therapeutic concentrations.{Lee:2006tb} Compliance to the study protocol is necessary to reach and sustain those concentration. When adherence is measured with unreliable methods it is generally assumed that adherence is nearly ideal in clinical trials.{Vrijens:2014hx} This assumption can result in incorrect assessments of clinical trials.{Feldman:2009cf} Czobor et al.{Czobor:2011un} re-analysed two trials utilizing their reported compliance. Originally without considering compliance, the trials reported no differences between the compound and placebo, however the reanalysis by Czobor et al. found statistical significant therapeutic effects.

Compliance is often measured using pill counting, paper diaries or blood analysis. These methods are found to be unreliable. Previous studies have shown that participants will not always fill in these questionnaires on the desired times, with patients ‘hoarding' information until the last day, termed ‘parking lot compliance'.{Morren:2009ti, Stone:2003wi} Furthermore, pill counts also didn’t correlate to blood concentrations.{Czobor:2011un} As Czobor showed, without reliable compliance information incorrect conclusions of the novel drug could be drawn.

During the last decade we have grown normal to carrying a computer device with us all the time; the smartphone.{Dediu:2014up} Therefore, we are able to receive and record information almost everywhere, all the time. This provides opportunities to use these devices in clinical trials.

An electronic questionnaire, running on a handheld device, can store precise time stamps whenever users enter data. This provides an objective way to monitor the participant. In addition, these electronic diaries are able to send reminders to users, further improving compliance. Earlier studies with text messages (SMS) as reminders to apply medicine or score symptoms show an improved compliance.{Balato:2013hc}

There have been multiple trials reported with electronic diaries{Lane:2006in}, however only a few{Bryant:2013ig, Thriemer:2012bz, Hensel:2012ii, Knipe:2014ji, Allena:2012if, Hon:2013ia, Blake:2015kq, Ratcliff:2014ca, So:2013fb, Zhou:2014ce, Turk:2013bv, Priebe:2013em} after the introduction and general adoption of the smartphone (around 2012{Dediu:2014up}). Interestingly, electronic patient diaries are being used in rural areas to make research available where it wasn’t before.{Thriemer:2012bz, Knipe:2014ji, Zhou:2014ce}

Next to improving compliance, the electronic patient diary has advantages in data handling. A systematic review conducted in 2005 concerning the effectiveness of handheld computers versus paper methods suggests that the timeliness of data handling is improved. Furthermore, since the original data entry is digital, there are no errors when translating paper to digital.{Lane:2006in} One study done in 1997 reported an 80% reduction in time spent on data handling when using electronic devices.{Tiplady:1997vv}

Furthermore, sensors on handheld devices will allow for new information to be gathered. It will offer the potential for a deep well of data in clinical trials. In addition, the use of electronics may reduce or eliminate the Hawthorne effect, the effect of being observed during the measurement.{McCambridge:2014dq} With wearable devices and biosensors, new standards to measure disease severity and progression may emerge.{Mombers:2016es}

We developed a framework for Apple’s iOS devices which we can use to create electronic diaries for different studies. We report the results of the use of this framework in three dermatological trials. One of the mobile application was used in a phase 2, randomized, vehicle-controlled, double-blind, proof-of-concept study, to evaluate efficacy and safety of Topical Ionic Contra-viral Therapy (ICVT) comprised of digoxin and furosemide in cutaneous !![…..]. Additionally, a mobile application was developed for a randomized, double-blind, placebo controlled study to assess the pharmacodynamics, safety/tolerability and efficacy of omiganan in patients with mild to moderate atopic dermatitis. Finally, a mobile application used in a phase 2, randomized, double-blind, parallel-group study to assess the pharmacodynamics, safety/tolerability and efficacy of topical omniganan in patients with usual type vulvar intraepithelial neoplasia (uVIN). The trial results will be published elsewhere. This study evaluates the compliance in these trials, as well as the value-added of data gathered at home, using the electronic patient diary.

**2.0 Methods**

**2.1 generating manual classification set**

*2.1.1 finding ROI*

*2.1.2 classifying ROI*

**2.2 generating model**

*2.2.1 feature detectors and descriptors*

*2.2.2 generating bag of words*

2.2.2.1 binary descriptors

*2.2.3 generating histograms*

*2.2.4 testing detectors/descriptors*

*2.2.5 evaluating with tsne*

**2.3 cross validation**

*2.3.1 training cheap model (k nearest neighbor)*

*2.3.2 Bayesian optimization*

*2.3.3 error/cost function*

*2.3.4 with hyperparameters generate svm and or random forest*

*2.3.3 running on test set*

*2.3.4 Non maximum suppression on positive windows*

*2.3.5 Hard negative finding (adding false positive windows to training set)*

**2.4 human versus model test**

**Generating training set**

To recognize skin lesions with applied medicine, supervised machine learning algorithms can be used. Supervised means that these algorithms are trained on a predefined dataset. In our case this dataset should contain images of skin lesions with and without topical medicine applied. Since the differences between these two states will be slight, it is of importance to have a negative training set of skin lesions without medication.

We generated the training set using image analysis to fasten the process. First the image is segmented, in which the image is divided in regions based on similarity. Mathematically this is the same as clustering in a matrix. After the segmentation the segment containing a finger is recognized by averaging the color in the segment and looking for skin colors. Using the location of this segment the finger in the original image can be found. This finger is further analyzed on contrast and texture differences to detect a possible region of the skin lesion.

The region of interests the above-explained method will find are manually classified for containing warts and possible applied medication. This classified set of images will be used to train a supervised machine learning algorithm.

**0. Image representation**

To analyze an image, it needs to be represented in a mathematical way. This is most often done in matrices, but images can also be represented in other representations such as frequencies and wavelets. Matrices are useful since mathematical clustering algorithms can be used on them. A grayscale image of 20x20 pixels will have a matrix representation with 20 rows and 20 columns. The amount of gray on an individual pixel can be represented between 0-255. This means that at a certain value v in the matrix at row y and column x will be the grayscale value of the pixel at location x,y in the image. For color images multi-dimensional matrices are used. Each color channel (red, green or blue) will have its own dimension.

**1. Image segmentation**

We wanted to analyze the image to in a nonparametric manner, where the analysis makes no assumption about the underlying distribution. This has the advantage that in a nonparametric analysis a predefined number of clusters is not needed. Only a few algorithms could be used for image segmentation. We tested the watershed and mean shift algorithm.

* 1. **Watershed algorithm**

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* 1. **Mean-shift algorithm**

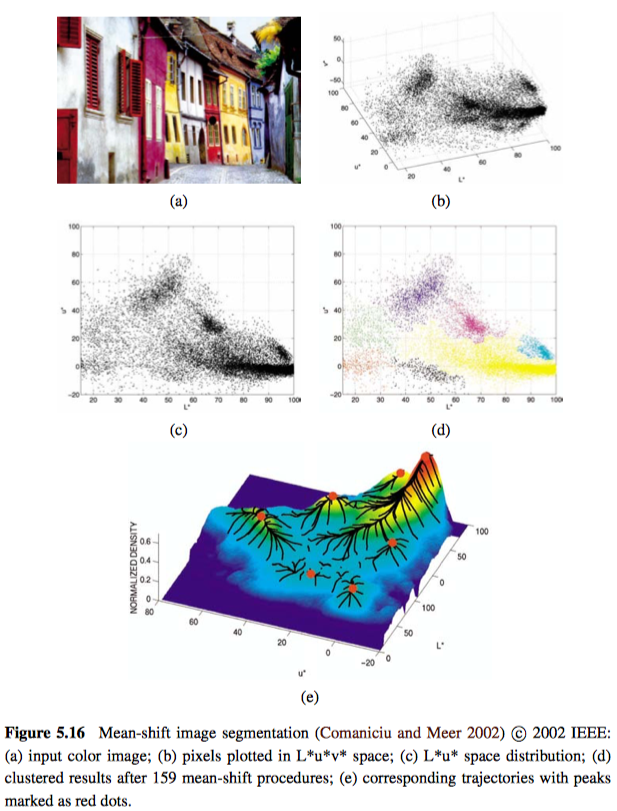
For the mean-shift algorithm the image representation is a multi-dimensional matrix by discarding spatial information and only looking at color. This resulting representation is called the *feature space*. Mean shift considers the feature space to consist of a probability density function. The probability density function is a function in which the area under the curve describes the probability of a certain value range giving the supplied data points. For example, a well-known *probability density function* (p.d.f.) is the normal distribution.

The mean shift algorithm uses a sample of points (the window) in the feature space as a sample of a pdf, calculates the pdf on these discrete values with a supplied kernel and calculates the mean shift () this pdf. This *mean shift* is calculated by the weighted mean of the change of the p.d.f.: by summing the derivative’s value at every discrete of the point in the window and dividing it by the weights provided by the kernel. Another way of looking at it is calculating the direction of the p.d.f. at a distinct point; the direction towards the mean can be derived from the derivative. This is done equal to creating a ‘gradient’ vector, a vector of the partial derivatives (the derivate considering the different variables).

The window in the feature space (containing the analyzed sample points) of the algorithm then moves by this calculated direction mean shift, thereby moving the denser area of the p.d.f. This continues until a finite number of steps or after the shift is below a certain threshold, which mean a dense region is reached (local maximum of the p.d.f.)

Applied on an image, the ultimate value of each pixel is set to the mean of the underlying probability density function. Instead of using this algorithm on every pixel (value in matrix), random location samples can be taken, the paths of these mean-shifts toward the mean are tracked. If in the end there are pixels not contained in these paths they can be classified using the nearest path.

The segmentation can then be based on the spatial information and different hues of colors in the picture with a certain threshold of difference in hue to define a segment.



Source: Szeliski R. **Computer Vision: Algorithms and Applications**, 2010

<http://imagelab.ing.unimore.it/imagelab/pubblicazioni/2013ElectronicImaging.pdf>