

## OS3<sup>®</sup> – The TearLab Ocular Surface Severity Scale<sup>®</sup>

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The Ocular Surface Severity Scale (OS<sup>3</sup><sup>®</sup>) was originally developed as a way to compare the diagnostic performance of different objective signs of dry eye disease. The results of this analysis were recently published in IOVS, entitled “An objective approach to dry eye disease severity.”

<http://www.ncbi.nlm.nih.gov/pubmed/20631232>

Formally, the OS<sup>3</sup> brings together common objective clinical tests for dry eye disease into a single unbiased composite score. These tests comprise tear osmolarity, Schirmer’s test without anesthetic, fluorescein tear film breakup time (TBUT), corneal staining (NEI/Industry scale), the Ocular Surface Disease Index (OSDI), a meibomian dysfunction assessment (Bron/Foulks scoring), followed by conjunctival staining (NEI/Industry scale).

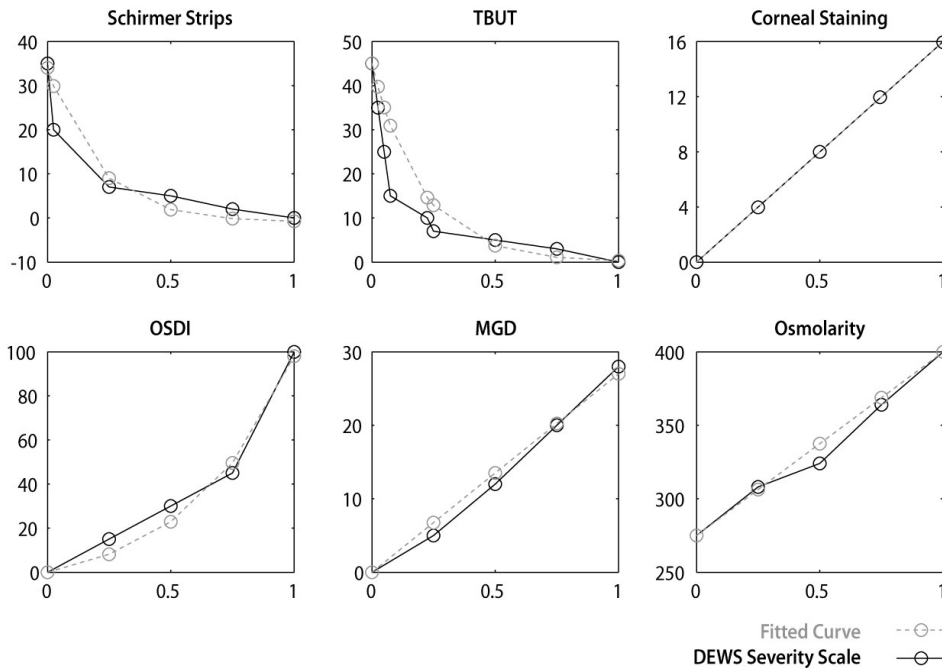
[Lemp MA. Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye. *CLAO J.* 1995;21:221-232.]

[Foulks GN, Bron AJ. Meibomian Gland Dysfunction: A Clinical Scheme for Description, Diagnosis, Classification, and Grading. *Ocul Surf.* 2003;1(3):107-126.]

If we accept as a given that at the time of a clinical visit each patient has a single severity of the disease, then we need to establish an objective method by which we define that severity, or “truth.” In lieu of a gold standard test, the next best thing is a composite severity scale that has a large number of tests in the index (to minimize the *a priori* bias for any one sign), as well as one that maintains *equal* correlation risk against the index for each sign so that you can objectively compare performance of the individual signs. In “An objective approach to dry eye disease severity,” we demonstrated that the average correlation coefficients for random data against the OS<sup>3</sup> severity index were: osmolarity ( $r^2=0.10$ ), TBUT ( $r^2=0.15$ ), Schirmers ( $r^2=0.08$ ), corneal staining ( $r^2=0.09$ ), conjunctival staining ( $r^2=0.10$ ), meibomian grading ( $r^2=0.09$ ), and OSDI ( $r^2=0.24$ ). Therefore, we know that the performance of signs is not due to inclusion in the composite, but actual relationship to overall disease severity.

### Section 1. Data Preparation

In order to implement the composite, it is first necessary to transform the raw clinical data into a normalized basis on  $\{0,1\}$ . An expert panel of clinicians provided a modified version of the Dry Eye WorkShop (DEWS) severity scale as shown in Table 1 below, and either linear or exponential curves were created to fit the expert values, resulting in the readily invertible functions shown in Table 2. In the Excel file attached to this tutorial, raw clinical data is passed through the inverted equations to produce values ranging from 0 (representing the least evidence of disease) to 1 (representing the most evidence of dry eye).



**Table 1.** Quantified DEWS Severity Scale [No Authors Listed. 2007 Report of the International Dry Eye Workshop (DEWS). *Ocul Surf.* 2007;5(2):65-204].

<b>DED Severity Grade</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
Schirmer Test (mm)	35	7	5	2	0
TBUT (seconds)	45	7	5	3	0
Staining (NEI/Industry scale)	0	3	8	12	16
OSDI	0	15	30	45	100
Meibomian Grading Score	0	5	12	20	27
Osmolarity (mOsms/L)	275	308	324	364	400

**Table 2.** Results of Continuous Mapping. To generate a severity value between {0,1}, clinical data is substituted into the inverted curves. For instance, a Schirmer value of 4 mm would be converted as  $1.4063 \cdot \ln((4+1)/35) / -5 = 0.55$ , which is equivalent to a value between the DEWS severity grades of 2 & 3. Similarly, a corneal staining value of 16 would be calculated as  $16/16 = 1.00$ , representing the highest level of severity in that dimension. Note that to avoid an infinity at  $\ln(0)$  for Schirmer tests, TBUT and OSDI, appropriate offsets were added to the argument of the inverted curves.

	<b>Fitted Curve</b>	<b>Inversion</b>
Schirmer Test (mm)	$35e^{-5x}$	$1.4063 \cdot \ln((y+1)/35) / -5$
TBUT (seconds)	$45e^{-5x}$	$1.3135 \cdot \ln((y+1)/45) / -5$
Staining (NEI/Industry scale)	$16x$	$y/16$
OSDI	$10e^{2.38x} - 10$	$\ln((y+10)/10) / 2.38$
Meibomian Grading Score	$27x$	$y/27$
Osmolarity (mOsms/L)	$125x + 275$	$(y - 275) / 125$

## Section 2. De Novo Independent Components Analysis

*Note: This section is only for people that want to develop their own composite index from signs other than those referenced above (e.g., if you want to incorporate other biomarkers, dynamic optical measurements, etc.). If you just want to use the index using the signs above, skip this section and go right to the Excel file. Novel input measurements also require that the data first be transformed onto {0,1}.*

Because several of the common signs for dry eye measure similar aspects of the disease process, (e.g. conjunctival and corneal staining), it is important to equalize the information content from each input variable before mixing them together into a composite, otherwise there is a potential for bias against the index. We implemented an independent components analysis to make sure the composite carried equal information from each part of the disease process. While beyond the scope of this document, there are many good tutorials on implementing ICA, for instance:

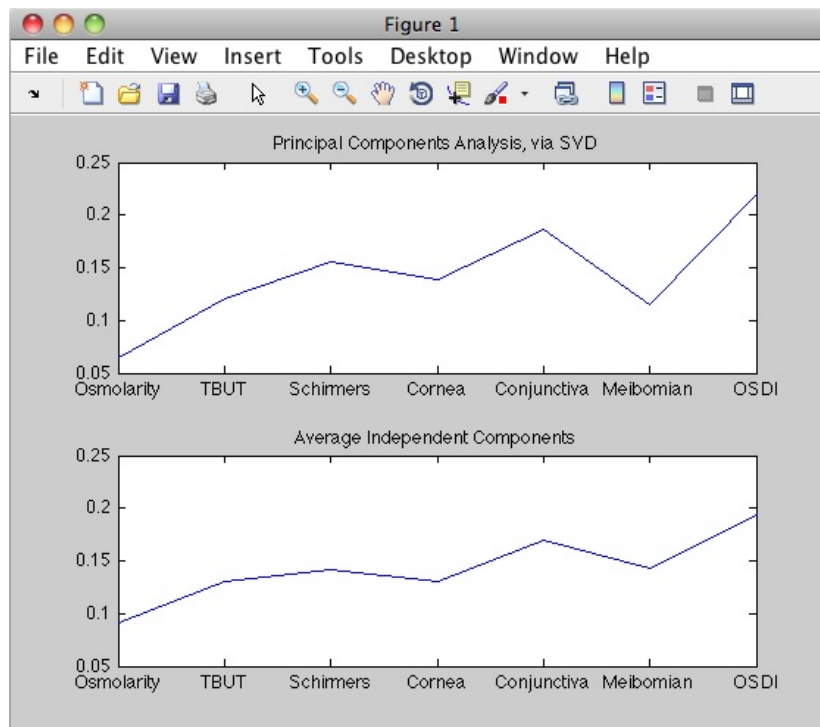
[http://www.cis.hut.fi/aapo/papers/IJCNN99\\_tutorialweb/](http://www.cis.hut.fi/aapo/papers/IJCNN99_tutorialweb/)

and

<http://www.nlpca.de/ica.html>

which contains a nice repository of code, including a link to EEGLAB.

As we define the mean of the non-unique mixing matrix as our estimate of redundancy between the clinical measurements, the ICA is run multiple times to reach convergence. In this code it is only run twice to avoid long processing times. If compiled and run correctly, the output should look something like:



(Note: the Matlab code here makes use Jon Shlens' `infomax()` and `natgrad()` function [<http://www.sn1.salk.edu/~shlens/>], but we have also implemented it using `runica()` from the EEGLAB in case the Shlens code is unavailable).

```

%
% OS3 - Ocular Surface Severity Scale
% © 2010 Benjamin D. Sullivan, Ph.D. & TearLab Inc.
%
% Note - data represents the most severe of a bilateral measurement
% data is an n x 7 matrix, with n = number of patients
% Each column in data represent a different clinical sign
% Ordered as: Osmolarity, TBUT, Schirmers, Cornea, Conjunctiva, Meibomian, OSDI
%

clear all

data=[303      9.7      18      0      0      0      20.8
321      3      0      11      8      4      33.3
309      3.3      8      2      2      4      22.9
323      1.7      5      1      2      2      31.3
292      3      9      5      12      2      41.7
318      2.7      14      8      6      0      70.5
...
317      1      20      2      5      0      4.2
332      2      15      0      4      0      10.4
317      2      2      2      12      9      43.2];

dataLength=size(data,1);

% Normalize data by DEWS severity scale
dataS(:,1)=(data(:,1)-275)/125;
dataS(:,2)=1.3135*log((data(:,2)+1)/45)/-5;
dataS(:,3)=1.4063*log((data(:,3)+1)/35)/-5;
dataS(:,4)=data(:,4)/16;
dataS(:,5)=data(:,5)/12;
dataS(:,6)=data(:,6)/27;
dataS(:,7)=log((data(:,7)+10)/10)/2.38;

nn=7;
d2=dataS(:,1:nn);
d5=d2-repmat(mean(d2),dataLength,1); % mean subtracted data

[U,S,V]=svd(d5');
subplot(2,1,1)
plot(1*(abs(U(:,1))/sum(U(:,1))))
%set(gca,'YLim',[0 15])
title('Principal Components Analysis, via SVD')
set(gca,'XTickLabel',{'Osmolarity','TBUT','Schirmers','Cornea','Conjunctiva','Meibomian',
'OSDI'})

Aa=zeros(nn,nn);
mm=2;
for i=1:mm
    [signals, A, W] = infomax(d5');
    Aa=A+Aa;
end
A=Aa/mm;
subplot(2,1,2)
plot(1*(abs(mean(A'))/sum(abs(mean(A')))))
title('Average Independent Components')
set(gca,'XTickLabel',{'Osmolarity','TBUT','Schirmers','Cornea','Conjunctiva','Meibomian',
'OSDI'})
redundancy=1*(abs(mean(A'))/sum(abs(mean(A'))))

```

### Section 3. Severity calculation

Open “TearLabOS3.xls” a Microsoft Excel 2004 document.

Input values manually, or use the “Paste Special : Values” command to enter data into the OD and OS columns of the respective objective clinical tests. The severity result will be displayed in the far right Column. Note that if a value is missing, the formula will return a blank result.

Redundancy (from ICA)														
	Osm	TBUT	Sch	Cor	Conj	Meib	OSDI							
	0.09	0.13	0.16	0.13	0.14	0.14	0.21							
OD							OS							
Subject	Osm	TBUT	Sch	Cor	Conj	Meib	Osm	TBUT	Sch	Cor	Conj	Meib	OSDI	Severity
1	286	10	18	0	0	0	303	9.7	28	0	0	0	20.8	0.23
2	298	3	0	11	7	4	321	5.7	0	11	8	4	33.3	0.59
3	309	3.3	8	1	2	4	307	4.3	8	2	1	4	22.9	0.34
4	323	2.7	5	0	2	2	322	1.7	8	1	2	2	31.3	0.41
5	303	2.7	14	8	6	0	318	3	17	8	4	0	70.5	0.46

The severity formula in Excel, for the first subject with blank checking:

```
=IF(OR(ISBLANK(B10),ISBLANK(C10),ISBLANK(D10),ISBLANK(E10),ISBLANK(F10),ISBLANK(G10),ISBLANK(H10),ISBLANK(I10),ISBLANK(J10),ISBLANK(K10),ISBLANK(L10),ISBLANK(M10),ISBLANK(N10)), "",SQRT(SUM((((LN((N10+10)/10)/2.38)/$H$6)^2)+(((1.3135*LN((MIN(C10,I10)+1)/45)/(-5))/ $C$6)^2)+(((1.4063*LN((MIN(D10,J10)+1)/35)/(-5))/ $D$6)^2)+(((MAX(E10,K10)/16)/ $E$6)^2)+(((MAX(F10,L10)/12)/ $F$6)^2)+(((MAX(B10,H10)-275)/125)/ $B$6)^2)+(((MAX(G10,M10)/27)/ $G$6)^2))))/SQRT(SUM((1/ $C$6^2)+(1/ $D$6^2)+(1/ $E$6^2)+(1/ $F$6^2) +(1/ $G$6^2)+(1/ $H$6^2)+(1/ $B$6^2))))
```