Supporting information for:

A new method for optimizing coating properties based on an evolutionary algorithm approach

Davide Carta[a,b,‡], Laura Villanova[c,d,‡,], Stefano Costacurta[a], Alessandro Patelli[a], Irene Poli[b,e], Simone Vezzù[a], Paolo Scopece[a], Fabio Lisi[f], Kate Smith-Miles[d], Rob J Hyndman[g], Anita J Hill[f], Paolo Falcaro[a,f,*]*

[a] Associazione CIVEN, Via delle Industrie 5, 30175 Venezia, Italy
[b] European Center for Living Technology, Ca' Minich, San Marco 2940, 30124 Venezia, Italy
[c] Dipartimento di Scienze Statistiche, Università di Padova, Via Cesare Battisti 241, 35121 Padova, Italy
[d] School of Mathematical Sciences, Faculty of Science, Monash University, Building 28, Wellington Road, Clayton, Australia
[e] Dipartimento di Statistica, Università Ca' Foscari di Venezia, San Giobbe, Cannareggio 873, 30121 Venice, Italy
[f] CSIRO, Materials Science & Engineering, Gate 5 Normanby Rd, Clayton VIC 3168, Australia
[g] Department of Econometrics and Business Statistics, Faculty of Business and Economics, Monash University, Building 11, Wellington Road, Clayton, Australia.

S1: Coating Preparation

Tetraethyl orthosilicate (TEOS), 3-aminopropyltriethoxysilane (APTES), methyltriethoxysilane (MTES), hydrochloric acid (HCl 1M), ethanol (EtOH) and fluorescein isothiocyanate (FITC) were purchased from Aldrich and used as-received. P-type/boron doped, (100) oriented, 400 μm thick silicon wafers (Si-Mat) and silica slides (76 mm 26 mm, 1.2 mm thick from knittel Glaser) were used as substrates. The silicon substrates have been rinsed with EtOH and acetone. Each silica slide has been cleaned using a solution obtained by mixing H_2O_2 (25 mL) and NH_4OH (25 mL). After 5 minutes under sonication, the slides have been rinsed with water, EtOH, acetone and then dried under nitrogen gas flux prior to use. Water was purified with a Milli-Q Synthesis A10 system.

APTES, MTES, TEOS have been used as silane precursors. Two constraints have been imposed: the total number of the three precursor moles are kept constant and in the $4.5\text{-}5\cdot10^{-3}$ mol range; the moles of TEOS are required to be more than $2.5\cdot10^{-3}$. The components are added one at a time and in the following order: EtOH, TEOS, MTES, H_2O, HCl. The solution is stirred for 15 minutes. APTES is then added dropwise and kept under vigorous stirring conditions for 20 minutes (aging time). Information on the stability of the sol is collected with a variable (stability, S_t), that assumes value 0 if gelation occurs within 20 minutes or 1 if the sol is stable (no gelation within at least 20 min). Gelation is measured visually as a change from transparent to opaque solution. Fresh

solutions (5 minutes aging) were used for dip-coating (2.5 mm s^{-1} withdrawal speed, 20% relative humidity). Films are then dried for 30 minutes at 100°C.

The recipe identified during the study based on the OFAT approach (Sample A) is 30 mL EtOH, 0.75 mL TEOS, 0.25 mL MTES, 0.5 mL H_2O, 0.25 mL HCl 1M, 0.1 mL APTES. The recipe optimized by EMMA (Sample F) is 29.8 mL EtOH, 1.8 mL TEOS, 0.98 mL MTES, 0.76 mL H_2O, 1.38 mL HCl 1M, 0.418 mL APTES.

Triton X has been added to a sodium phosphate buffer solution, commonly used in microarray protocols,[1,2] to simulate the wettability properties of a microarray spotting solution. 2X Print Buffer 300 mM sodium phosphate (pH 8.5) was prepared dissolving sodium phosphate monobasic (0.41 g) and sodium phosphate dibasic (3.785 g) in 90 ml of water. The pH was adjusted to 8.5 using NaOH (1M) and HCl (1M). The final volume was brought to 100 ml with water. The solution was diluted 2:1 with water to obtain 1X Print Buffer solution. FITC (7 μg mL^{-1}) has been added to the buffer-surfactant mixture giving the FITC-buffer solution.

Amino-functionalized glass slides were spotted using a FTA 1000 contact angle tester by depositing a 50 μL drop to simulate the microarray spotting procedure. Three drops were deposited on each coating. The needle-substrate distance and the pumping rate used to drop the FITC sample solution were kept constant at 3 mm and 5 μL s^{-1}, respectively ensuring microarray spot sizes in the mm range. The coating with the 3 drops was left in a closed vessel (70% relative humidity and 40°C) for 12 hours to perform the grafting process under the same conditions used in a typical microarray process, then the excess dye was removed with a two-step cleaning process: first, the slide was dipped in a 50 mL closed vessel with 40 mL of methanol for 10 minutes; second, the slide was immersed in a 50 mL closed vessel with 40 mL of water for 10 minutes. The coating was then dried under nitrogen flux.

Laser scanner GenePix 4000B (Axon Instruments), has been used to investigate the spot quality. Such a scanner is a standard facility in the acquisition and analysis of gene expression data from DNA microarrays.[3] Measurements were performed with the maximum resolution (5 μm), under excitation with 532 and 633 nm wavelengths (electronic gain set to 50). Contact angle measurements on 1X Print Buffer solution with and without the reporter molecule FITC showed that the solution wetting characteristics were not altered by the FITC.

S2: Algorithm description (EMMA)

EMMA has been written in-house using the R programming language; open-source R software has also been used.[4] EMMA has been applied in this case study to optimize a sol-gel coating for FTIC immobilization. The algorithm flow chart is presented in **Figure S2_F1**. The EMMA algorithm will be released as a freeware package for R.

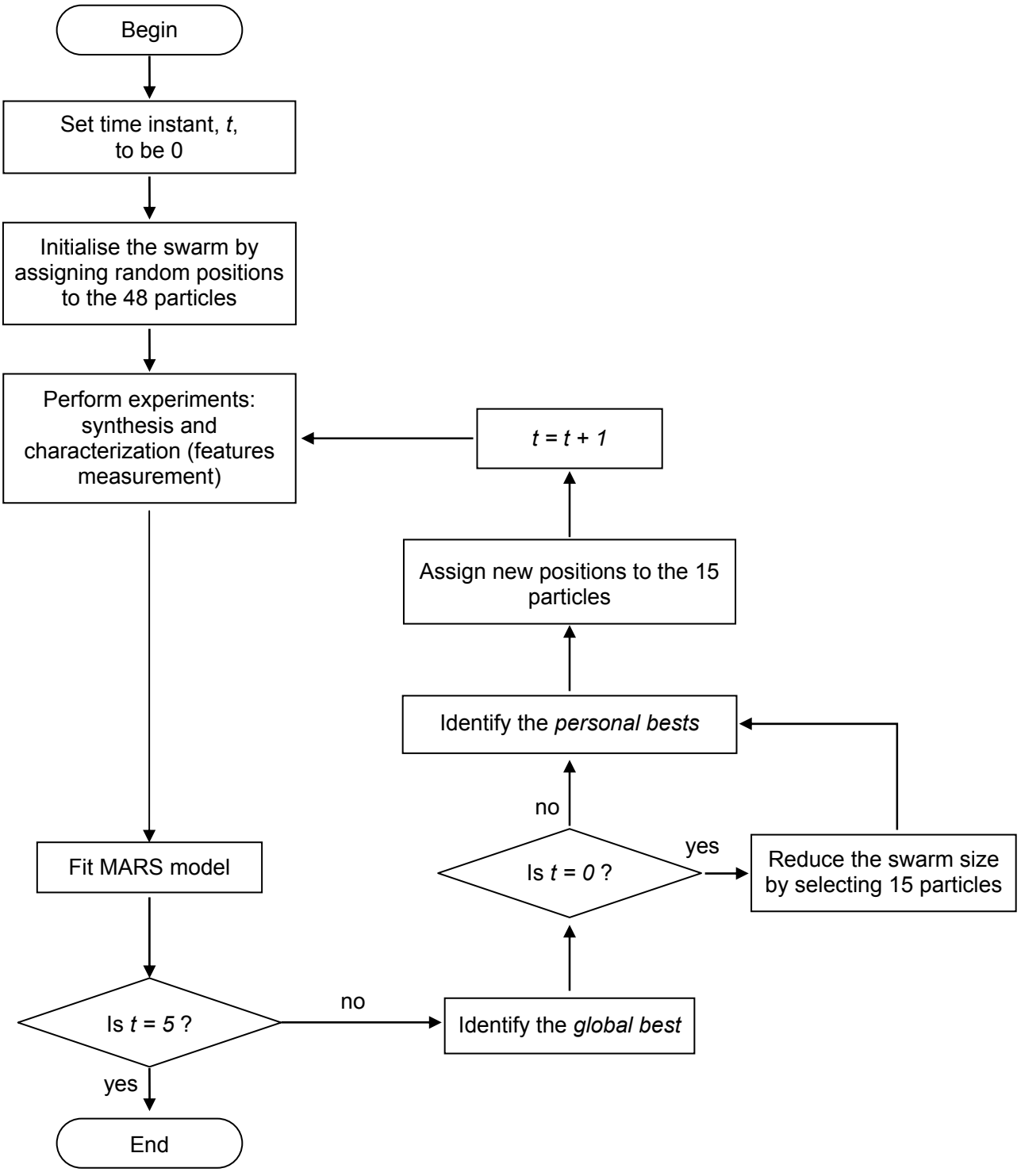

Figure S2_F1. *Block diagram of EMMA.*

The heuristic component (PSO[5] algorithm) has been selected by means of an empirical study that compared the performance of the PSO algorithm with other heuristic methodologies. The modelling component (MARS model - see section **S5: Modelling using the MARS approach**), has been chosen because of its many attractive features.[6,7] The evolution control strategy has been employed to improve the convergence to the optimal solution.

PSO is a stochastic optimization procedure inspired by the social behavior of flocking birds. With this approach, the birds are called particles and the population of birds is called a swarm. In EMMA each particle's position corresponds to an experiment, and the swarm identifies a set of experiments used to study the variable space. Each bird is associated with a set of variables (moles of TEOS, APTES, MTES, EtOH, HCl, H_2O) and with a set of responses (St, S, I_M, I_B and H). The values of the variables (number of moles) define the position of each single experiment in the experimental space. Once an experiment is performed (an amino-silane coating is obtained), a set of performance values is measured and associated with each particle position. Each particle is then allowed to move through the space in order to define a new set of values for the compositional variables (new experiment) and discover a new set of performance values. The new position of each single particle is determined according to different contributions: the MARS model, the position associated with the best set of performances previously discovered by the swarm (*global best*), and the position associated with the best set of performances found by the bird itself (*personal best*). In this way for each particle a proper trajectory is delineated and an efficient combination between exploration and exploitation of the experimental space can be achieved.

When the time instant is set to t=0, 48 experiments are randomly selected using quantities from **Table S2_T1**.

Table S2_T1. *Discrete quantities for the investigation of the sol-gel recipe compositional range. Considering the 2 constraints (the total number of the three precursor moles are kept constant and in the 4.5-5·10^{-3} mol range; the moles of TEOS are required to be more than 2.5·10^{-3}), the total number of possible experiments is 8424. The 123 experiments performed have been selected as combinations of the listed quantities.*

TEOS (mM)	MTES (mM)	APTES (mM)	EtOH (M)	H_2O (M)	HCl (M)
2.19	0.25	0.21	0.170	0.014	0.010
2.63	0.70	0.58	0.306	0.039	0.028
3.07	1.15	0.97	0.442	0.064	0.046
3.51	1.60	1.34	0.578	0.089	0.064
3.95	2.05	1.72	0.714	0.114	0.082
4.39	2.50	2.10	0.850	0.139	0.100

The 48 corresponding solutions are prepared and are coated onto glass slides. The coating features are measured as described in the **Experimental Section** (main text) using FITC spotting solution and a laser scanner. Then, the selected compositions and measured features are used to build a MARS model. The model is subsequently used to estimate the features of the uninvestigated compositions. This information is considered during the identification process of the new set of experiments. In particular, if t≠5 the algorithm identifies the *global best*. If t=0, the 15 experiments with the best features are selected and their positions are set as *personal bests*. Considering the MARS models, the *personal bests* and the *global best*, a new set of 15 experiments is identified by EMMA. Then the time instant is updated to t=1. Again, the list of compositions is used to prepare 15 new solutions. The slides are coated and the coating features are measured. The MARS model is updated by adding the new set of data. The new *global best* is assigned to the best result. Each *personal best* is assigned by comparing the coating properties found in a previous time instant with the current one. A new set of 15 experiments is generated by EMMA (selecting the quantities from **Table S2_T1**) considering the updated *global best*, *personal bests*, and MARS model. The new time instant is then updated to t=2. The algorithm and the experimentalist stopped the activities after 6 cycles (t=5).

S3: Preliminary study.

We performed a preliminary study to investigate the convergence properties of EMMA and its suitability for the sol-gel chemical system. EMMA has been used to determine the absolute maximum of different mathematical test functions. One example is shown in **Figure S3_F1**. In this figure, the following test function with 3 maxima in three dimensions is shown:

$$z = 10 \cdot (1-x)^2 \cdot e^{-x^2-(y+1)^2} - 20 \cdot \left(\frac{x}{5} - x^3 - y^5 \right) \cdot e^{-x^2-y^2} - \frac{1}{3} \cdot e^{-x^2-y^2}$$, where x,y $\in$ [-3,3].

For t=0 the 48 particles are randomly chosen (green dots). The subsequent time instants show the 15 particles investigating the maxima and identifying the absolute maximum within 4 time instants.

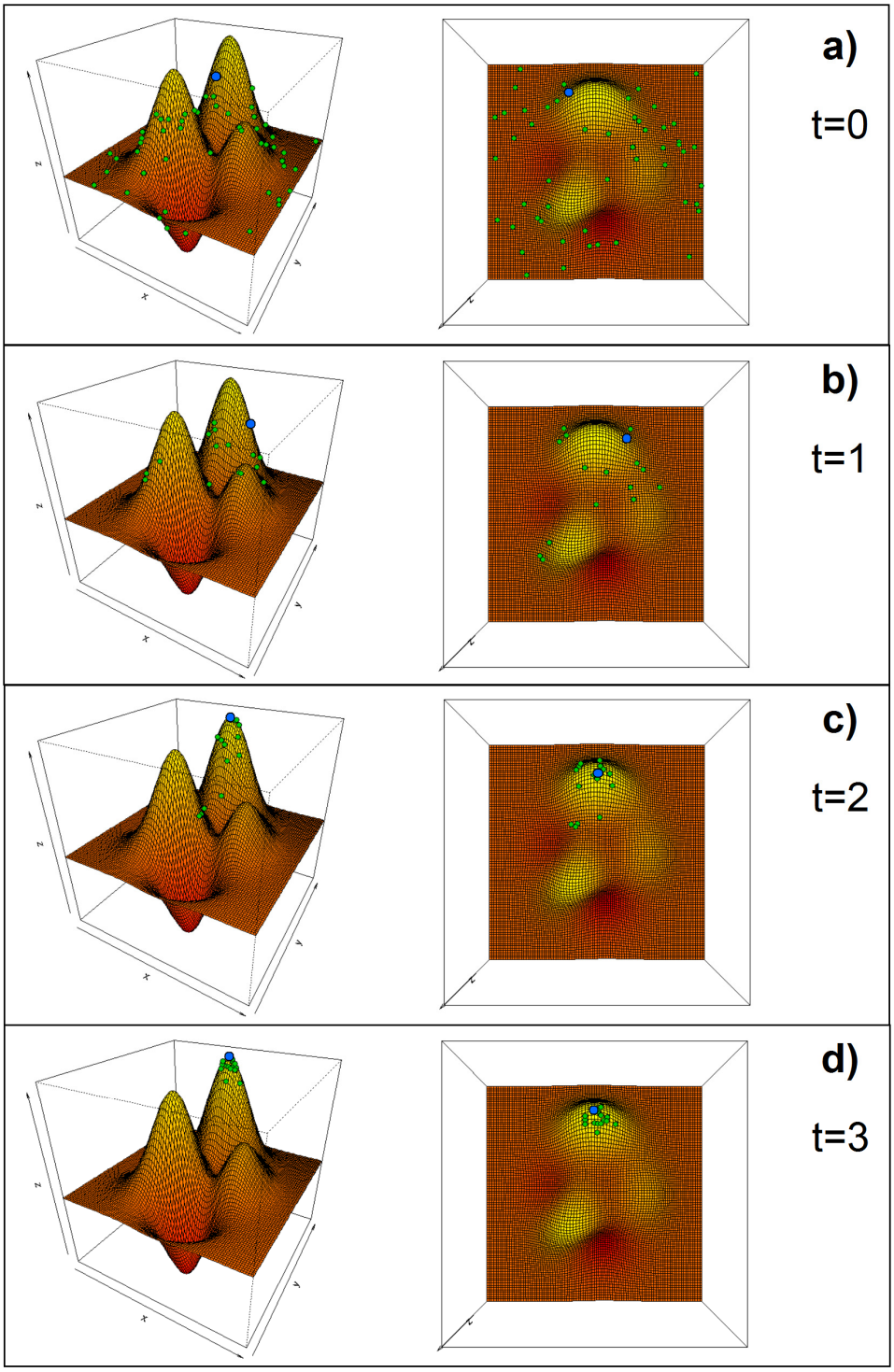

Figure S3_F1. *Test of the EMMA algorithm on the test function. Just 4 time instants ((a) t=0, (b) t=1, (c) t=2, (d) t=3)) are enough to identify the absolute maxima of the 3D test function (green dots: particles; blue dot: global best).*

Because of the success of EMMA with a variety of test functions, we proceeded to apply EMMA to the material optimization case study. The first random set of 48 chemical compositions was generated by EMMA (t = 0). The 48 solutions were prepared, and the corresponding coatings were

deposited and then tested. The chemical compositions and the measured features have been used by EMMA to calculate a preliminary model. The functions are:

$$I_M = -0.13 + 2.21(\text{EtOH} - 0.578)_+ + 2289.63(\text{MTES} - 0.00025)_+ + 5.40\,(0.089 - \text{H20})_+ + 285.39(\text{HCl} - 0.0004)_+ - 3640.97(\text{EtOH} - 0.34)_+ \cdot (\text{MTES} - 0.00025)_+ - 1060162.03(\text{TEOS} - 0.00263)_+ \cdot (\text{MTES} - 0.00025)_+ + 9517.89(\text{TEOS} - 0.00329)_+ \cdot (\text{H20} - 0.089)_+ - 9236.04(\text{MTES} - 0.00078)_+ \cdot (0.089 - \text{H20})_+ - 1166947.08\,(\text{MTES} - 0.00025)_+ \cdot (\text{HCl} - 0.00046)_+$$

$$I_B = -0.32 + 4.49(\text{EtOH} - 0.578)_+ + 2374.50(\text{MTES} - 0.00025)_+ + 12.46\ \ (0.089 - \text{H20})_+ + 1954.18(\text{HCl} - 0.0004)_+ - 2656.62(\text{EtOH} - 0.34)_+ \cdot (\text{MTES} - 0.00025)_+ - 853387.04(\text{TEOS} - 0.00263)_+ \cdot (\text{MTES} - 0.00025)_+ + 13157.73(\text{TEOS} - 0.00329)_+ \cdot (\text{H20} - 0.089)_+ - 32284.76(\text{MTES} - 0.00078)_+ \cdot (0.089 - \text{H20})_+ - 2632579.11\,(\text{MTES} - 0.00025)_+ \cdot (\text{HCl} - 0.00046)_+$$

$$S = -0.20 + 1.53(\text{EtOH} - 0.578)_+ + 731.36(\text{MTES} - 0.00025)_+ + 7.22(0.089 - \text{H20})_+ + 930.24(\text{HCl} - 0.0004)_+ - 230.51(\text{EtOH} - 0.34)_+ \cdot (\text{MTES} - 0.00025)_+ + 155643.11(\text{TEOS} - 0.00263)_+ \cdot (\text{MTES} - 0.00025)_+ + 14635.44(\text{TEOS} - 0.00329)_+ \cdot (\text{H20} - 0.089)_+ - 6853.28(\text{MTES} - 0.00078)_+ \cdot (0.089 - \text{H20})_+ - 1037448.63\,(\text{MTES} - 0.00025)_+ \cdot (\text{HCl} - 0.00046)_+$$

$$H = -0.33 + 3.46(\text{EtOH} - 0.578)_+ + 1512.41(\text{MTES} - 0.00025)_+ + 6.97(0.089 - \text{H20})_+ + 2062.49(\text{HCl} - 0.0004)_+ - 1679.41(\text{EtOH} - 0.34)_+ \cdot (\text{MTES} - 0.00025)_+ + 148540.26(\text{TEOS} - 0.00263)_+ \cdot (\text{MTES} - 0.00025)_+ + 19207.24(\text{TEOS} - 0.00329)_+ \cdot (\text{H20} - 0.089)_+ - 15230.43(\text{MTES} - 0.00078)_+ \cdot (0.089 - \text{H20})_+ - 2178386.09\,(\text{MTES} - 0.00025)_+ \cdot (\text{HCl} - 0.00046)_+$$

Based on these functions, a semi-empirical simulation has been performed in order to verify the feasibility of the proposed statistical approach to optimize the response features of the sol-gel coating in this case study. **Figure S3_F2** shows the result of a simulation to estimate EMMA's efficiency in the optimization of this six variable, five response chemical system. The figure shows the percentage optimization versus the time instant for this problem. A fast convergence to the maximum is detected. As shown **Figure S3_F2**, 5 time instants (108 coatings) are enough to reach almost 85% response optimization (dashed-red line), while the optimum (100% response optimization; dashed-blue line) can be roughly reached in 10 time instants (183 coatings). A similar procedure can be used for any multi-variable multi-response system in order to estimate the theoretical efficiency of EMMA to solve the problem. Based on this result, t=5 has been selected for our case study as the number of time instants needed to reach a theoretical coating optimization of 85%.

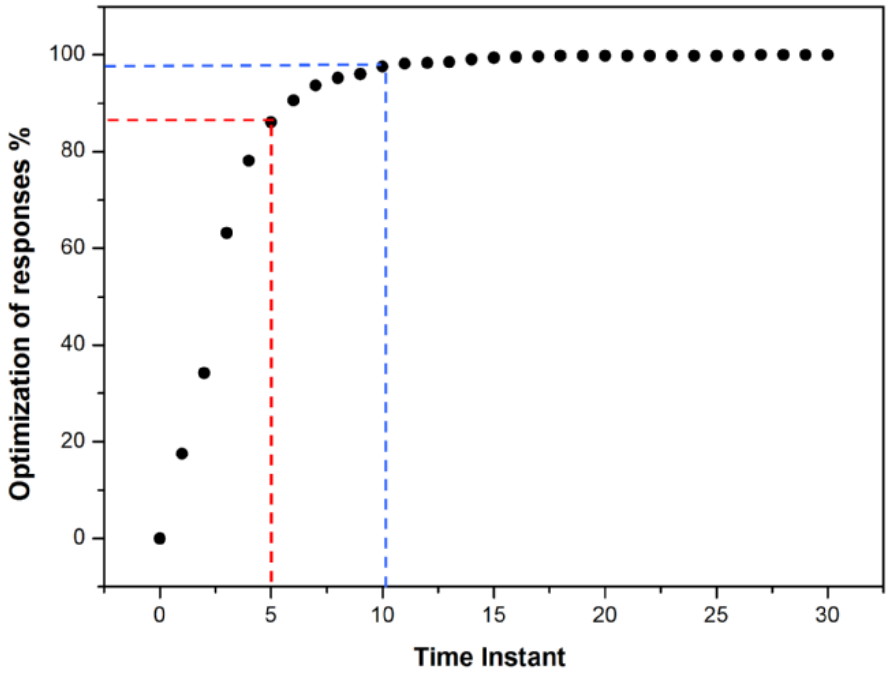

Figure S3_F2. *Plot of the optimization response versus time instants (number of cycles performed by the algorithm). The test function has been obtained modeling the first 48 experiments. Each response (I_M, S, I_B, H) is described as a mathematical function of the compositional variables. In 5 time instants an optimization of 85% is achieved (red dashed line). In 10 time instants the optimization is close to 100%.*

S4: Classification tree model

A classification tree model (see **Figure S4_F1**) defines the stability of the sol-gel solution. A stable composition (92% probability) is obtained if MTES≥$0.7\cdot10^{-3}$M; or if MTES<$7\cdot10^{-3}$M and APTES<$0.8\cdot10^{-3}$M; or if MTES<$7\cdot10^{-3}$M, APTES≥$0.8\cdot10^{-3}$M and H_2O<$51.5\cdot10^{-3}$M. The experimental evidence summarized in the classification tree model highlights the importance of the alkyl-silane contribution and is in accordance with results in the literature. According to the literature, both aminosilane and water increase the probability of a rapid sol to gel transition.[8] APTES acts as a catalyst[9] and water as a reactant.[10] MTES hinders the sol to gel transition, affecting the structure of the silica network by reducing its connectivity due to the non-hydrolyzable Si-CH_3 groups.[11,12]

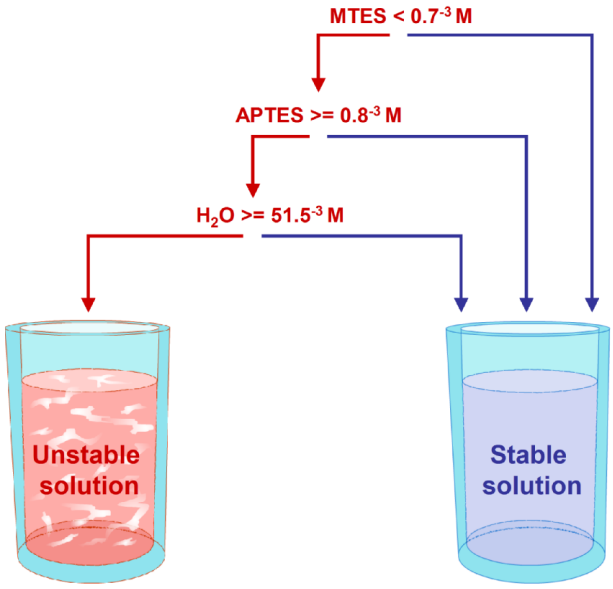

Figure S4_F1. *Classification tree model for the identification of the stability variable (S_t). With 92% probability, a stable composition (pot life > 20 min) is obtained under one of the following conditions: MTES≥0.7·10^{-3}M; MTES<7·10^{-3}M and APTES<0.8·10^{-3}M; MTES<7·10^{-3}M, APTES≥0.8·10^{-3}M and H_2O<51.5·10^{-3}M..*

S5: Correlation between coating thickness, contact angle, refractive index of the coating, and the coating responses (I_M, I_B, H, S)

Table S5_T1. *Performance of six different coatings in the case study. The table refers to* ***Figure 3*** *(main text). Sample A is the best result of the OFAT approach. Samples B to E are examples of different coatings obtained using EMMA. Sample F is the best result reached by EMMA.*

Sample	Thickness (nm)	Contact angle (°)	N (633 nm)	I_M (counts)	I_B (counts)	H	S
A	30	80	1.4385	250	55	0.45	1
B	105	70.5	1.4512	497	70	0.74	1
C	140	71	1.4474	630	140	0.97	0.34
D	40	76.3	1.5029	65	42	0.91	0.89
E	65	61.3	1.4201	258	150	0.76	0.66
F	100	73	1.4487	950	76.5	0.85	1

Coating responses (I_M, I_B, H, S) are plotted as functions of coating thickness, contact angle or refractive index. The graphs plot the values reported in **Table S5_T1**. As shown in **Figure S5_F1**, only I_M presents a weak linear correlation with coating thickness. Another weak trend can be defined by plotting I_B versus contact angle **Figure S5_F2**. Other trends are not easily defined by

evaluating the coating responses versus measured coating properties such as thickness (**Figure S5_F1**), contact angle (**Figure S5_F2**) or the refractive index (**Figure S5_F3**).

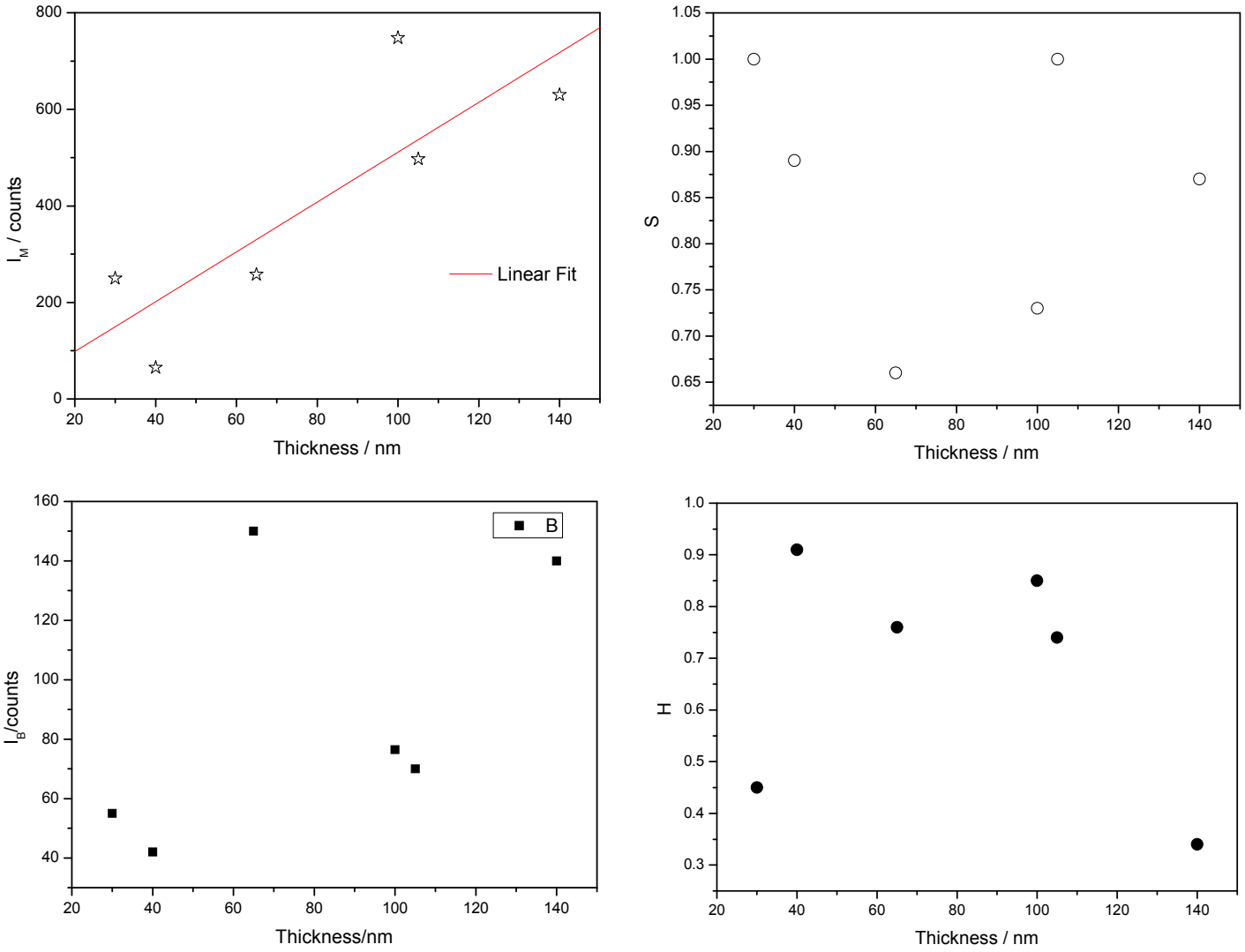

Figure S5_F1. *I_M, S, I_B, H versus coating thickness.*

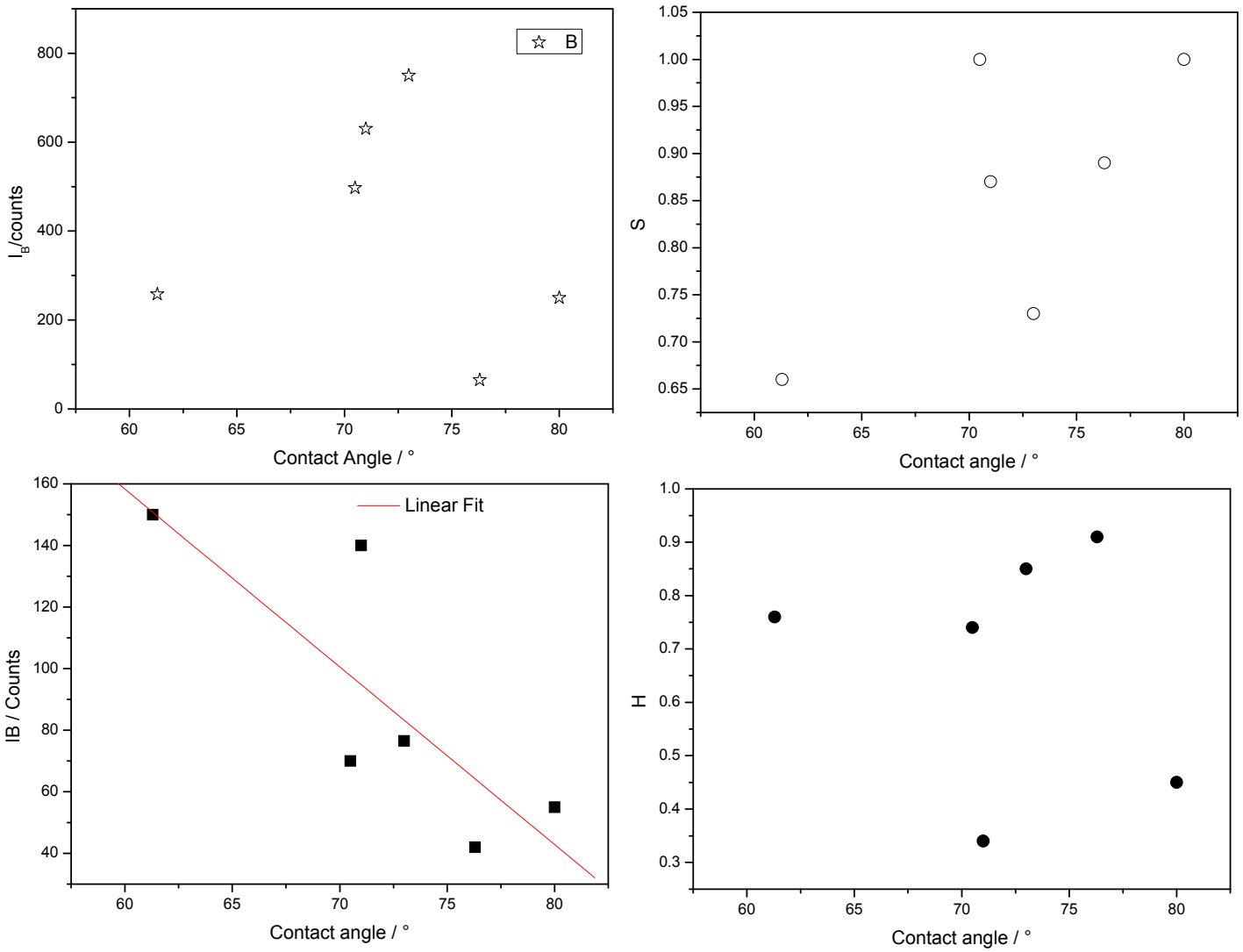

Figure S5_F2. *I_M, S, I_B, H versus contact angle.*

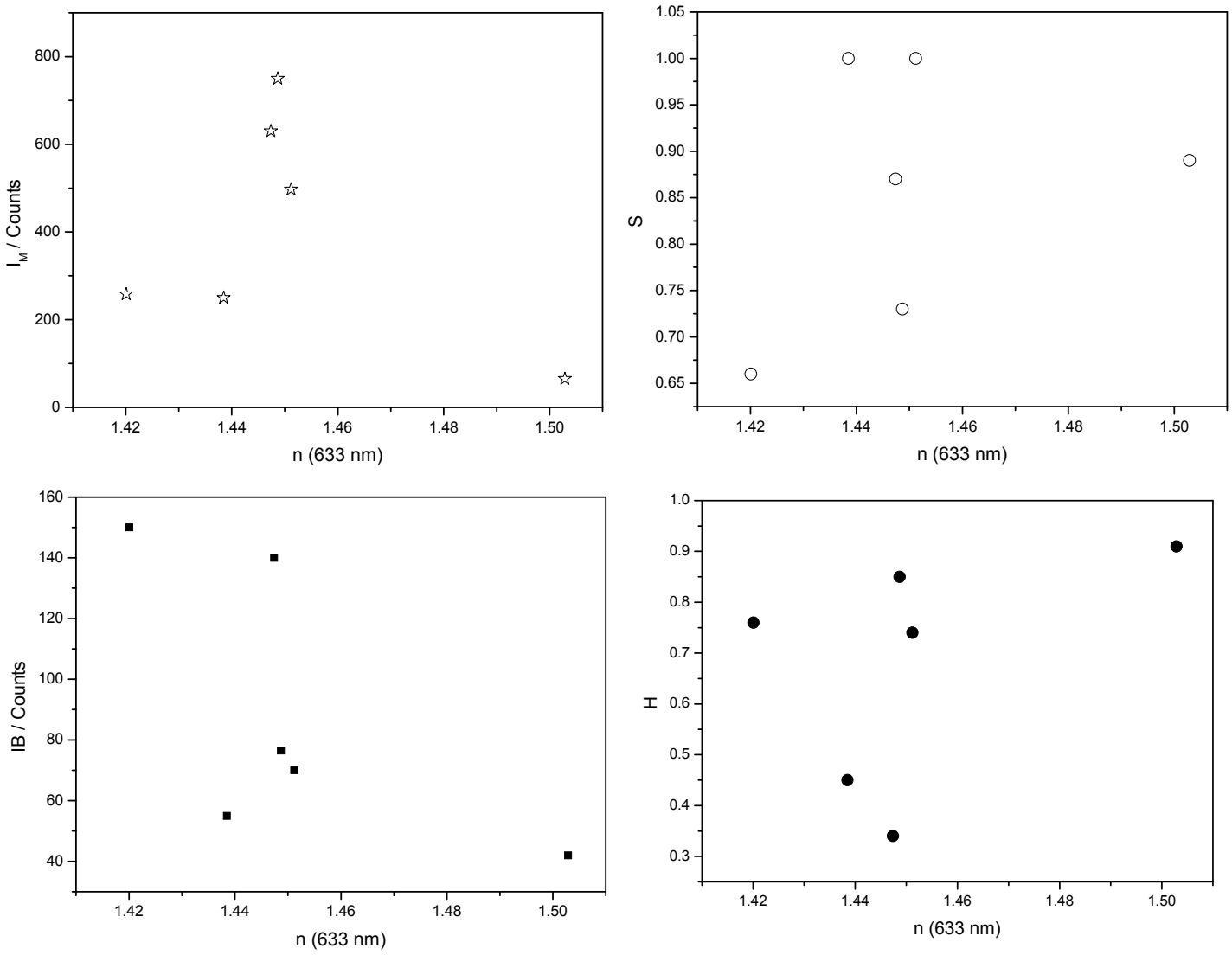

Figure S5_F3. *I_M, S, I_B, H versus refractive index.*

S6: Modeling using the MARS approach

The MARS approach[13] has been chosen as the modeling strategy due to its flexibility, limited computational cost, and ability to cope with multiple input and response variables[6,7]. The R package earth[14] has been used. MARS is an adaptive procedure for nonlinear regression.[7] It moves beyond linearity by replacing the original input variables with their transformations. The employed transformations are piecewise linear basis functions of the form $(x-t)_+$ and $(t-x)_+$ described as follows:

$$(x-t)_+ = \begin{cases} x-t, & \text{if } x > t, \\ 0, & \text{otherwise,} \end{cases} \quad \text{and} \quad (t-x)_+ = \begin{cases} t-x, & \text{if } x < t, \\ 0, & \text{otherwise.} \end{cases}$$

where **t** is an inflection point (knot).

The MARS model has the form

$$f(X) = \beta_0 + \sum_{m=1}^{M} \beta_m h_m(X)$$

where each $h_m(X)$ is a linear basis function, or a product of two or more linear basis functions. The coefficients β_m are estimated during the modeling process. The model is built in two steps: a forward strategy that ends with a very large model, and a backward deletion.[7] At each stage of the forward strategy the model selects the transformation that gives the greatest decrease in the residual sum of squares and adds it into the model.[7] When a maximum model size is reached, the backwards deletion progressively removes those basis functions that contribute least to the model fit.[7] The model resulting in the smallest residuals (difference between measured and predicted response) is selected.

S7: Influence of variables

Not all of the compositional variables are equally relevant for a response because they can differently affect the coating features. The compositional variables having a greater influence on each response are identified using a procedure that exploits the fitted MARS model and its error in prediction. The influence of the compositional variables on coating response that is theoretically estimated by EMMA can then be compared with *a priori* chemical knowledge or literature results in order to better understand the underlying chemistry in a multi-variable multi-response chemical system.

The Generalized Cross Validation criteria (GCV)[7] has been used as a measure of the MARS model's predictive accuracy. The lower the GCV value, the higher the predictive accuracy of the model. It is important to note that, for each response, the MARS model is selected using an iterative procedure which first builds a big model (forward building) and then prunes it (backward deletion).[15,7] To identify the most relevant compositional variables, the models produced during the backward deletion are considered. Each time a model term, $h_m(X)$, is removed, the GCV of the pruned model is calculated and the difference with the GCV of the previous model is obtained. The resulting differences in the GCV values are summed and scaled so that their maximum corresponds to 100. Decreases in the GCV value are thereby associated with each compositional variable. The higher the decrease, the larger the influence of the selected variables.[7,15,16]

Figure S7_F1 presents the influence of the compositional variables for each coating feature investigated in the case study. For I_M a value of 100 is found for APTES and EtOH. HCl is around 70 and all the other variables are below 25 (**Figure S7_F1a**). These values suggest that the amounts of both amino-precursor and solvent strongly affect the maximum spot intensity, whereas the influence of HCl is limited. This information is in agreement with *a priori* and literature

knowledge[17] of surface chemistry that suggests that the FITC molecules in the test solution bind with the aminogroups of the coating (**Figure 1a** main text). EtOH has the same importance as APTES, whereas water is less influential. APTES is also the only variable with influence equal to 100 for I_B and all the other chemical components are below 25 (**Figure S7_F1b**).

The parameter S (circularity) is largely influenced by the amount of MTES. The influence of MTES on S reaches a value of 100, whereas the influence of EtOH is close to 60, and the influence values for the other variables are smaller than 25 (**Figure S7_F1c**). The concentration of methyl groups can be related to the change in the affinity between the alkyl-functionalized surface and the dye solution. This has been verified by the contact angle measurements (data not shown). A higher amount of MTES gives more circular spot shapes. This result is in agreement with a study presenting the contact angle variation for films prepared by changing the TEOS/MTES ratio where a progressive increase of the contact angle is detected if the MTES is increased up a 50%.[18]

As for the parameter H (homogeneity), the influence of HCl is 100, whereas the influence of APTES and H_2O is around 50 and the other variables are below 30 (**Figure S7_F1d**). This result suggests that H depends on the different competitive catalytic mechanisms involved in the sol-gel reaction.[10] The variables with an influence greater than 60 are presented in **Figure 4** (main text).

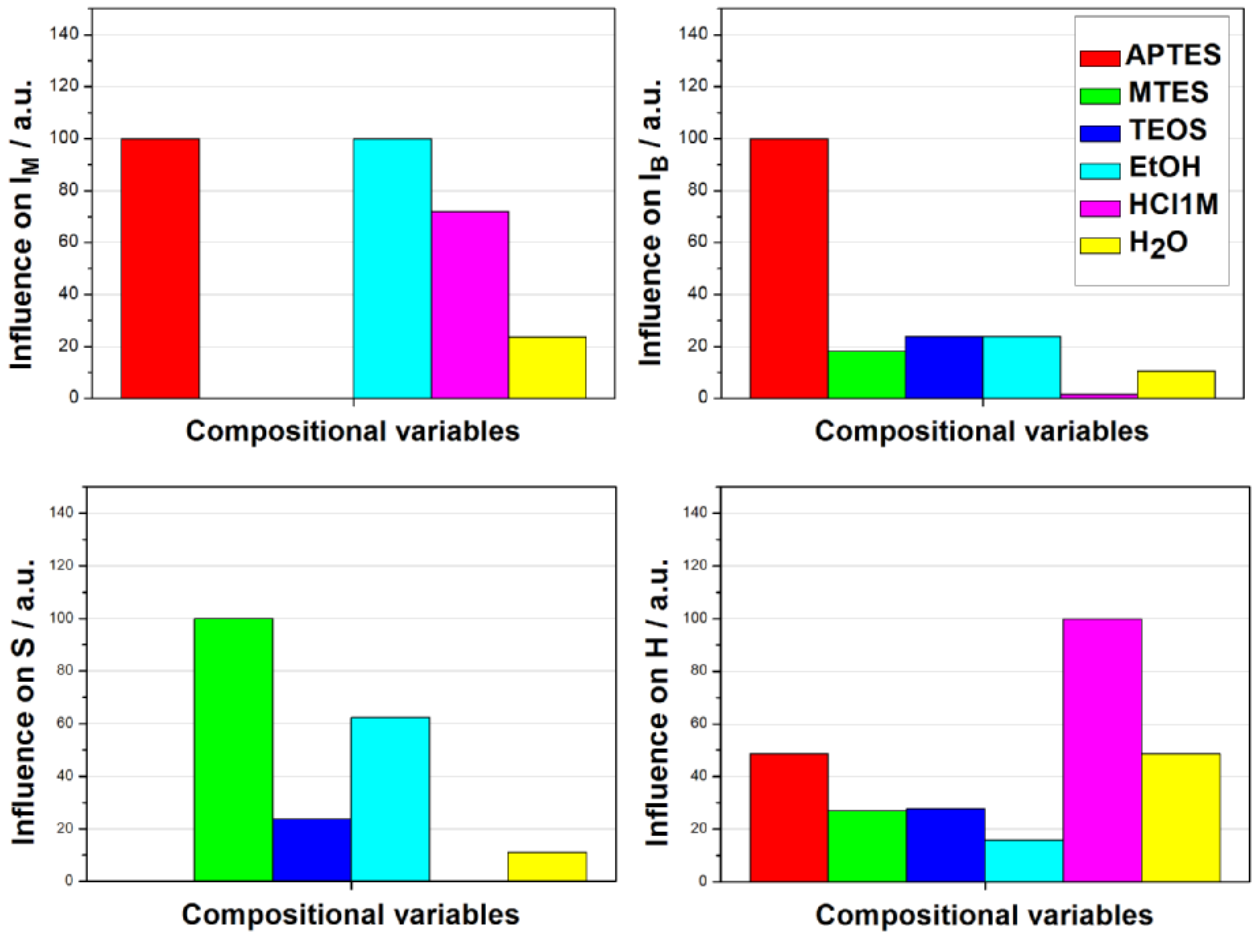

Figure S7_F1. *Influence of the compositional variables on the spot features such as maximum intensity, I_M (a); background intensity I_B (b); shape of the spot, S (c); homogeneity, H (d). The influence has been estimated by the EMMA algorithm.*

S8: Exclusion of Multicollinearity issues

In the final model, some of the variables (TEOS, APTES, MTES) can be classified as dependent due to the constraint relating them, while others can be classified as independent (H_2O, HCl, EtOH). To evaluate possible issues related to the estimation of the model parameters, the variance inflation factor (VIF) has been calculated. This factor is used to identify the presence of a multicollinearity problem (highly correlated variables). Large values of VIF (typically, VIF > 10) suggest that multicollinearity may be present.[19] In the case study, the maximum VIF calculated is 1.7 excluding any multicollinearity issue (see **Table S8_T1**).

Table S8_T1 *Calculated variance inflation factor (VIF) for the variables influencing each coating response*

Coating Response	**Variance Inflation Factor**
I_M	1.705269
S	1.319962
I_B	1.736269
H	1.163828

References

[1] Kim, J; Crooks, R.M. *Anal. Chem.* **2007**, *79*, 7267.

[2] Sun, L.; Liu, D.; Wang, Z. *Anal. Chem.* **2007**, *79*, 773.

[3] http://www.moleculardevices.com/Products/Instruments/Microarray-Scanners/GenePix-4000B.html

[4] R Development Core Team **2009** R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

[5] Kennedy, J.; Eberhart, R. *IEEE Int. Conf. on Neural Networks* **1995**, 1942.

[6] Lee, T. S.; Chen, I. F. *Expert Syst Appl* **2005**, *28*, 743.

[7] Hastie, T.; Friedman, J.H.; Tibshirani, R. *The Elements of Statistical Learning*; Springer: New York, **2009**.

[8] Zhang, X.; Wang, J.; Wu, W.; Liu, C.; Qian, S. *J. Sol-Gel Sci. Technol.* **2007**, *43*, 305.

[9] Bergna, H.E.; Roberts, W.O. *Colloidal silica: fundamentals and applications*; CRC Taylor & Francis: Boca Raton, FL, **2006**.

[10] Brinker, C.J.; Scherrer, G.W. *Sol-Gel Science*; Academic Press Inc: Boston, CA, **1990**.

[11] van Bommel, M.J.; Bernards, T.N.; Boonstra, A.H. *J. Non-Cryst. Solids* **1991**, *128*, 231.

[12] Innocenzi, P; Abdirashid, M.O.; Guglielmi, M. *J. Sol-Gel Sci. Technol.* **1994**, *4*, 47.

[13] Breiman, L.; Friedman, J. H. *J. R. Stat. Soc., Ser. B: Stat. Methodol.* **1997**, *59*, 3.

[14] Stephen Milborrow derived from mda:mars by Trevor Hastie and Rob Tibshirani. (2009). earth: Multivariate Adaptive Regression Spline Models. R package version 2.3-5. http://CRAN.R-project.org/package=earth

[15] Friedman, J.H. *Annals of Statistics* **1991**, *19*, 1.

[16] Friedman, J.H.; Roosen, C. B. *Statistical Methods in Medical Research* **1995**, *4*, 197.

[17] Falcaro, P.; Malfatti, L.; Vaccari, L.; Amenitsch, H.; Marmiroli, B.; Grenci, G.; Innocenzi, P.; *Adv. Mater.* **2009**, *21*, 4932.

[18] Iwashita, K.; Tadanaga, K.; Minami, T. *Journal of Applied Polymer Science* **1996**, *61*, 2173.

[19] Izenman, A. J. *Modern Multivariate Statistical Techniques*, Springer, New York, **2008**.