Electronic Supplementary Information (ESI)

A green chemistry-based classification model for the synthesis of silver nanoparticles

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Rationale for preference order of criteria values from Table 1

Choice of preference order for values of reducing agent, capping agent and solvent criteria

Renewable materials are preferred options not only for their non-exhaustible nature, but also because they are sources acknowledged as being benign, recurrently used for medicinal or even for feeding purposes. The biodegradable polymer category includes polymers that have to be synthesized but are biodegradable and not hazardous. On the other hand the synthetic category includes chemicals that are usually hazardous and require dedicated synthesis processes. Furthermore, some materials can perform both the role of reducing and capping agent [1]. In this case they allow implementing multifunctionality that is a key requirement from a green chemistry perspective.

Choice of preference order for values of equipment type criterion

Several bottom-up approaches are available starting from very simple equipment such as a stirring plate, up to a laboratory microwave oven and oil baths.
Static conditions do not imply any use of energy, which are ideal from a green chemistry perspective.
Stirring systems are placed as the next best choice as they are the processes that require the lowest amounts of energy to sustain the reaction (in the range of watts fractions depending on the rpm rate) [2]. Furthermore they are very simple pieces of equipment with higher degree of control over the process and safer reactions conditions.
Microwave (MW) was introduced as a specific class as it is a widely recognized alternative source of energy for the rapid synthesis of well-defined nanosized particles. The main advantages of MW heating compared to conventional heating techniques are [3-9]:

- Reactions kinetics increase by 1-2 orders of magnitude;
- Possibility of producing better defined (uniform) and smaller particles;
- Enhanced kinetics of crystallization;
- Reduction in waste production (as wall effects can cause crusting and degradation in conventionally-heated reactors that increases impurities and consequently byproducts).

The reduction in reactions time and faster crystallization kinetics can lead to energy savings compared to conventional techniques. This consideration coupled with the fact that MW-assisted process allows reduction in unwanted byproducts from the reactions justifies the location in a preferred position for this method compared to the conventional ones (oil baths).
The energy consumption of microwaves has been studied in the literature and it has been shown that the systems that employ MW heating in sealed vessels at small scales (up to 50 mL) use less energy than conventional techniques under comparable conditions. This consideration derives from the fact that they allow obtaining the same amount of product in a much shorter period of time and consequently with less energy consumption [8, 10-12]. However, their actual energy efficiency is under debate and so we do not assume higher energy efficiency for MW compared to conventional techniques (see for details [8, 10-14]). Nonetheless the use of MW technique with open vessels at laboratory scales does not imply a better energetic performance compared to conventional heating and so this option is placed in a lower preferred class [10], though still accounting for the reduction in byproducts, simplicity of the process and inherent safety [15] compared to conventional approaches. There can also be cases with missing information about the type of equipment used, which is considered as a worst case due to the uncertainty of the information.

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Table S1: Dataset of production protocols for silver nanoparticles

PIN = Protocol Identifi-cation Number	Criteria								Performance class by DMs	Reference
	Reducing agent class	Capping agent class	Solvent class	Local resource use class	Reaction time	Temperature (Celsius)	Equipment class	Size class	A > B > C > D > E	
1	Renewable - Primary	Biodegradable polymer	Renewable - Primary	No	45 s	80	Microwave - 1000 W - Open vessel	0-30 nm	C	[1]
2	Renewable - Primary	Renewable - Primary	Renewable - Primary	No	60 s	100*	Microwave - 1000 W - Open vessel	0-30 nm	B	[2]
3	Renewable - Primary	Renewable - Primary	Renewable - Primary	No	20 h	40	Conventional	0-30 nm	B	[3]
4	Renewable - Primary	Not needed	Renewable - Primary	No	45 s	41	Microwave - sealed vessel - < 300W	0-30 nm	A	[4]
5	Renewable - Primary	Not needed	Renewable - Primary	No	60 s	47	Microwave - sealed vessel - < 300W	0-30 nm	A	[4]
6	Renewable - Primary	Not needed	Renewable - Primary	No	30 s	39	Microwave - sealed vessel - < 300W	0-30 nm	A	[4]
7	Renewable - Primary	Not needed	Renewable - Primary	No	30 s	42	Microwave - sealed vessel - <	0-30 nm	A	[4]

							300W			
8	Renewable - Primary	Renewable - Primary	Renewable - Primary	No	10 s	150	Microwave - sealed vesel - > 300W	0-30 nm	A	[5]
9	Synthetic	Synthetic	Renewable - Primary	No	30 min	Not known	Stirring	0-30 nm	D	[6]
10	Renewable - Primary	Synthetic	Renewable - Primary	No	15 min	25	Not known	30 -60 nm	D	[7]
11	Renewable - Primary	Synthetic	Renewable - Primary	No	15 min	25	Not known	0-30 nm	D	[7]
12	Synthetic	Synthetic	Synthetic	No	4 h 15 m	25	Stirring	0-30 nm	E	[8]
13	Renewable - Primary	Not needed	Renewable - Primary	No	8 h	25	Stirring – under 5 min	0-30 & 30 -60 nm	A	[9]
14	Renewable - Primary	Not needed	Renewable - Primary	No	8 h	25	Stirring – under 5 min	0-30 nm	A	[9]
15	Renewable - Primary	Not needed	Renewable - Primary	No	2 h	25	Stirring – under 5 min	0-30 nm	A	[10]

16	Renewable - Primary	Not needed	Renewable - Primary	No	2 h	25	Stirring – under 5 min	0-30 nm	A	[10]
17	Renewable - Primary	Not needed	Renewable - Primary	Yes	8 h	37	Static	0-30 nm	A	[11]
18	Renewable - Primary	Not needed	Renewable - Primary	Yes	2 h	26.85	Static	0-30 nm	A	[12]
19	Renewable - Primary	Not needed	Renewable - Primary	Yes	8 min	30	Not known	0-30 nm	A	[13]
20	Renewable - Primary	Not needed	Renewable - Primary	Yes	6 h	30	Static	0-30 & 30 -60 nm	A	[14]
21	Renewable - Primary	Not needed	Synthetic	No	24 h	25	Static	0-30 nm	D	[15]
22	Synthetic	Synthetic	Synthetic	No	3 h	170	Microwave - sealed vessel - > 300W	0-30 nm	E	[16]
23	Synthetic	Biodegradable polymer	Renewable - Primary	No	3 min	198	Microwave - sealed vessel - > 300W	0-30 & 30 -60 nm	D	[17]
24	Synthetic	Biodegradable polymer	Renewable - Primary	No	5 s	100*	Microwave - sealed vessel - > 300W	0-30 nm	D	[18]
25	Synthetic	Biodegradable polymer	Renewable - Primary	No	2 h	90	Conventional	0-30 nm	D	[19]
26	Synthetic	Biodegradable polymer	Synthetic	No	4 h	160	Conventional	30-60 nm	D	[20]

27	Synthetic	Biodegradable polymer	Synthetic	No	4 h	160	Conventional	0-30 nm	D	[20]
28	Renewable - Primary	Not needed	Renewable - Primary	No	30 min	80	Conventional	0-30 & 30 -60 nm	B	[21]
29	Synthetic	Not needed	Renewable - Primary	No	8 min	100	Microwave - sealed vessel - > 300W	0-30 nm	D	[22]
30	Renewable - Primary	Renewable - Primary	Renewable - Primary	No	2 h	70	Conventional	0-30 nm	C	[23]
31	Renewable - Primary	Not needed	Renewable - Primary	No	8 h	70	Conventional	0-30 nm	C	[24]
32	Synthetic	Synthetic	Synthetic	No	60 s	100*	Microwave - 1000 W - Open vessell	0-30 nm	D	[25]
33	Renewable - waste	Not needed	Renewable - Primary	No	75 min	25	Static	30-60 nm	C	[26]
34	Renewable - waste	Not needed	Renewable - Primary	No	45 min	60	Conventional	0-30 nm	C	[26]
35	Renewable - Primary	Not needed	Renewable - Primary	No	3 h	160	Conventional	0-30 nm	C	[27]
36	Renewable - waste	Not needed	Renewable - Primary	No	10 min	40	Conventional	0-30 nm	B	[28]
37	Renewable - Primary	Not needed	Renewable - Primary	No	10 min	40	Conventional	0-30 nm	B	[28]
38	Renewable - Primary	Not needed	Renewable - Primary	Yes	15 min	80	Conventional	0-30 nm	B	[29]

39	Renewable - Primary	Not needed	Renewable - Primary	No	10 min	100	Microwave - sealed vessel - > 300W	0-30 & 30 -60 nm	B	[30]
40	Renewable - Primary	Not needed	Renewable - Primary	Yes	20 min	100	Stirring and heating	0-30 nm	B	[31]
41	Renewable - Primary	Not needed	Renewable - Primary	No	8 h	25	Stirring	0-30 & 30 -60 nm	C	[32]
42	Renewable - waste	Not needed	Renewable - Primary	No	60 s	55	Microwave - sealed vessel - < 300W	0-30 nm	B	[33]
43	Renewable - Primary	Not needed	Renewable - Primary	Yes	10 min	40	Conventional	0-30 nm	B	[34]
44	Renewable - Primary	Not needed	Renewable - Primary	Yes	20 min	80	Conventional	30_60	B	[35]
45	Renewable - Primary	Not needed	Renewable - Primary	Yes	15 min	95	Conventional	0_30	B	[36]
46	Renewable - Primary	Not needed	Renewable - Primary	Yes	20 min	25	Stirring_5 min	0_30	A	[37]
47	Synthetic	Synthetic	Renewable - Primary	No	60 s	100*	Micro_sealed_o300W	0_30	D	[38]
48	Renewable - Primary	Synthetic	Renewable - Primary	No	24 h	25	Static	0_30	A	[39]

*=assumed data

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Additional methodological considerations

Problem situation

The selection of the researchers involved in the case study followed the definitions of experts reported in the literature, namely those individuals who are *"highly regarded by peers,* […] *, whose performance shows consummate skill and economy of effort, and who can deal effectively with rare and "tough" cases"* [1]. Additionally, the experts who contributed to develop the model were are also *"qualified to teach those at a lower level"* and are part of *"an elite group of experts whose judgments set the regulations, standards, or ideals"*, fitting for the highest level of expertise as defined by Hoffman and colleagues [1].
Expert judgement has already been applied in the nanomanufacturing area for the identification of appropriate risk management measures. The developed model demonstrated how the use of expertise within domains that lack quantitative data and tools can advance the safety of nanomanufacturing [2].

Evaluation model

For comparison purposes, all the selected protocols lead to spherical and monodispersed nanoparticles, with size range used to account for the technical quality of the produced particles. In fact, the aim of each protocol is the synthesis of silver nanoparticles. Consequently, there is no real implementation of the green chemistry principles if the nanoparticles cannot be used in practice when they do not satisfy quality requirements [3-5]. For the sake of simplicity, the terms "implementation of green chemistry principles" will be used to include the concept of adopting the principles together with the satisfaction of the quality requirements.

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Basic notions of Dominance-based Rough Set Approach (DRSA)

An information table (Table 1) represents the starting point of any DRSA analysis. Its rows are the alternatives to be evaluated, while the columns include the condition attributes (C), the evaluation criteria that are needed to assess the alternatives, and the decision attribute (D), an overall evaluation of each object in the table.

More formally, an information table can be characterized as $S = < U,Q,V,f >$, where U = set of objects; Q = set of attributes; $V = \bigcup_{q \in Q} V_q$, V_q = domain of attribute q; and $f: U \times Q \rightarrow V$ is a total function, so that $f(x,q) \in V_q$ for every $q \in Q, x \in U$, called information function.

Alternative	Condition attributes (criteria), S_{X,C_y}*			Decision attribute (Performance class)
	C_1	C_2	C_3	
I	S_{A,C_1}	S_{A,C_2}	S_{A,C_3}	High
II	S_{B,C_1}	S_{B,C_2}	S_{B,C_3}	Low
…	…	…	…	…

Table 1: Exemplary information table for DRSA application, *: S_{X,C_y}: score of alternative X on criterion y

In this case study, U is composed of the considered nanoparticle production protocols (I, II, etc.), while Q is composed of the assessment criteria and the decision attribute representing the level of "performance" of each synthesis protocol from set U. The DM defines this decision attribute, by choosing one of five possible preference-ordered values (i.e. A > B > C > D > E) depending on the implementation of green chemistry principles and satisfaction of quality requirements that the criteria of each protocol convey.

For comparisons of objects performance in DRSA, it is necessary to use the notion of $weak\ preference\ relation \geq_q$ on U with respect to criterion q, so that $x \geq_q y$ stands for "object x is at least as good as object y with respect to criterion q".

The decision attribute is used to define a set of classes (**Cl**) for the classification of the nanoparticle production protocols, so that **Cl** = $\{Cl_t, t \in \{1,...,n\}\}$ and n is the total number of classes, and each object $x \in U$ can belong to one Cl_t. Furthermore, considering two classes r and s, with $r > s$, objects from Cl_r are better than those from Cl_s, which is in relation to the previous notation $x \geq y$, so that $[x \in Cl_r, y \in Cl_s, r > s] \Rightarrow [x \geq y \ and \ not \ y \geq x]$.

In the context of evaluation of the nanoparticle production protocols this can be seen as a decision-making process in terms of classification into different classes based on the green chemistry principles implementation: Cl_E,Cl_D, Cl_C, Cl_B and Cl_A which represent a very

low (E), low (D), medium (C), high (B) and very high (A) performance of each protocol, respectively.

The classes are ordered in increasing level of desirability, so that, e.g., $x > y$ if $x \in Cl_C \; and \; y \in Cl_D$, nanosynthesis protocol x performs at a medium level, whereas nanosynthesis protocol y is only implementing green chemistry principles at a low level.

DRSA is performing approximation of two types of unions of classes - the upward one $Cl_t^{\geq} = \bigcup_{s \geq t} Cl_s$, and the downward one $Cl_t^{\leq} = \bigcup_{s \leq t} Cl_s$, with $t = 1, \ldots, n$.

In this decision problem, we have that the upward union of classes are:

- $Cl_E^{\geq}$, nanoparticle production protocols with green chemistry principles implementation at least very low, i.e. very low or low or medium or high or very high;
- $Cl_D^{\geq}$, nanoparticle production protocols with green chemistry principles implementation at least low, i.e. low or medium or high or very high;
- $Cl_C^{\geq}$, nanoparticle production protocols with green chemistry principles implementation at least medium, i.e. medium or high or very high;
- $Cl_B^{\geq}$, nanoparticle production protocols with green chemistry principles implementation at least high, i.e. high or very high;
- $Cl_A^{\geq}$, nanoparticle production protocols with green chemistry principles implementation at least very high, i.e. very high;

On the contrary, the downward union of classes are:

- $Cl_E^{\leq}$, nanoparticle production protocols with green chemistry principles implementation at most very low, i.e. very low;
- $Cl_D^{\leq}$, nanoparticle production protocols with green chemistry principles implementation at most low, i.e. low or very low;
- $Cl_C^{\leq}$, nanoparticle production protocols with green chemistry principles implementation at most medium, i.e. medium or low or very low;
- $Cl_B^{\leq}$, nanoparticle production protocols with green chemistry principles implementation at most high, i.e. high or medium or low or very low;
- $Cl_A^{\leq}$, nanoparticle production protocols with green chemistry principles implementation at most very high, i.e. very high or high or medium or low or very low;

The notion $x \in Cl_C^{\geq}$ signifies that "protocol x belongs at least to class Cl_C", while $x \in Cl_C^{\leq}$ means that "protocol x belongs at most to class Cl_C".

One property that has to be noted here is that

$$Cl_{t-1}^{\leq} = U - Cl_t^{\geq} \quad \text{and} \quad Cl_t^{\geq} = U - Cl_{t-1}^{\leq}$$

In our case study, the nanoparticle production protocols that do not have at least C environmental sustainability, i.e. $- Cl_C^{\geq}$, are those with environmental sustainability at most D, i.e. $Cl_D^{\leq}$.

The decision rule approach approximates the information reported with the decision attributes by considering the knowledge reported in the condition attributes (criteria). In order to extract information from these attributes, the DRSA defines:

- Nanoparticle production protocols dominating *x,* i.e. nanoparticle production protocols that perform at least as good as *x* in terms of the set of condition attributes;
- Nanoparticle production protocols dominated by *x*, i.e. nanoparticle production protocols which perform worse than *x* in relation to the set of condition attributes.

x dominates *y* is denoted as $^{x\,D_P y}$ (with $P \subseteq C$), if $^{x \geq_q y}$ for every $q \in P$ (set of q). Pieces of information can be then obtained and are defined as granules of knowledge:

- Objects dominating *x*, named *P*-dominating set: $D_P^+(x) = \{y \in U : y D_P x\}$
- Objects dominated by *x*, named P-dominated set: $D_P^-(x) = \{y \in U : x D_P y\}$.

For example, if the criterion is the use of reducing agent, assessed with preference-ordered values (renewable > synthetic), and reducing agent for nanosynthesis protocol *x* is assessed as renewable, then:

- $D_P^+(x)$ includes all the nanoparticle production protocols with renewable score for type of reducing agent; whereas
- $D_P^-(x)$ includes all the nanoparticle production protocols with synthetic score for type of reducing agent.

DRSA can also handle ambiguous information, which for an object *x* and criteria from *P* arises when there is at least one object which is not worse than *x* with respect to the condition attributes but it was assigned to a lower class. For instance, in the previous example protocol *x* was assessed as renewable for the type of reducing agent. In the case that synthesis protocol *x* is assigned to Cl_C and another protocol *y* is assessed as renewable for the type of reducing agent but assigned to Cl_D, then an ambiguity is in place between *x* and *y* in relation to the criterion "type of reducing agent". Information management including ambiguity handling is performed with DRSA by means of approximation sets. With respect to $P \subseteq C$, the objects belonging to $Cl_t^{\geq}$ with no ambiguity represent the *P*-lower approximation of $Cl_t^{\geq}$ ($^{i.e.}\ \underline{P}(Cl_t^{\geq})$), while the group of objects that could belong to $Cl_t^{\geq}$ are the *P*-upper approximation of $Cl_t^{\geq}$ (i.e. $\overline{P}(Cl_t^{\geq})$):

$$\underline{P}(Cl_t^{\geq}) = \left\{x \in \bigcup : D_P^+(x) \subseteq Cl_t^{\geq}\right\},$$

$$\overline{P}(Cl_t^{\geq}) = \bigcup_{x \in Cl_t^{\geq}} D_P^+(x) \quad , \text{ for } t = 1, \ldots, n.$$

For example, if there is no ambiguity between nanoparticle production protocols *x* and *y*, then *x* and *y* are part of the lower approximations of the nanoparticle production protocols that are at least medium in performance, $\underline{P}(Cl_C^{\geq})$. If there is an ambiguity in

place, the two nanoparticle production protocols belong only to the upper approximations of the class medium, $\overline{P}(Cl_C^{\geq})$, but none to its lower approximation $\underline{P}(Cl_C^{\geq})$. The reasoning is the same for the dominated sets:

$$\underline{P}(Cl_t^{\leq}) = \left\{x \in \bigcup : D_P^-(x) \subseteq Cl_t^{\leq}\right\},$$

$$\overline{P}(Cl_t^{\leq}) = \bigcup_{x \in Cl_t^{\geq}} D_P^-(x), \quad \text{for } t = 1, \ldots, n.$$

The areas of ambiguity in relation to criteria from P are defined as P-doubtful regions and are expressed as:

$$Bn_P(Cl_t^{\geq}) = \overline{P}(Cl_t^{\geq}) - \underline{P}(Cl_t^{\geq}),$$

$$Bn_P(Cl_t^{\leq}) = \overline{P}(Cl_t^{\leq}) - \underline{P}(Cl_t^{\leq}), \quad \text{for } t = 1, \ldots, n.$$

In the illustrative example, x and y are part of the boundary regions of nanoparticle production protocols at least in the medium performance class, $Bn_P(Cl_C^{\geq})$.
For every $t = 1,\ldots,n,$ and $P \subseteq C$, the quality of the approximation is defined as:

$$\gamma_P(Cl) = \frac{card\left[U - (\bigcup_{t \in T} Bn_P(Cl_t^{\geq})\right]}{card\,(U)} = \frac{card\left[U - (\bigcup_{t \in T} Bn_P(Cl_t^{\leq})\right]}{card\,(U)}$$

This important ratio indicates the number of objects correctly classified with respect to the whole set. In general, the higher the number of criteria, the higher the quality of classification, as additional criteria can render non-ambiguous objects that were ambiguous with fewer criteria. Lastly, the minimal (with respect to inclusion) subset of criteria $P \subseteq C$ so that $\gamma_P(Cl) = \gamma_C(Cl)$ is named reduct of **Cl**, indicated as RED_{Cl}. The reduct P represents the minimal group of criteria from C so that no ambiguous object can become non-ambiguous when new criteria are added.

Decision rules from DRSA

DRSA provides useful contribution to the decision-making process, as from the upward and downward union of classes it is possible to induce structured information in the form of *"if ... , then ..."* decision rules. For unions of classes $Cl_t^{\geq}$ or $Cl_s^{\leq}$, the certain or possible decision rules are supported by objects $\in \underline{P}(Cl_t^{\geq})\ or\ \underline{P}(Cl_s^{\leq})$, or by objects $\in \overline{P}(Cl_s^{\leq})$ or $\overline{P}(Cl_t^{\geq})$, respectively; they advance the classification to "at least class Cl_t" or "at most class Cl_s", either certainly or possibly. In the other cases, the decision rules supported by objects $\in Bn_P(Cl_t^{\geq})$ or $Bn_P(Cl_t^{\leq})$ advance the approximate classification to classes between $Cl_s\ and\ Cl_t$ (s<t).
Five types of decision rules can be obtained:

- Certain $D_{\geq}$- decision rules: they present the conditions to assign object to $Cl_t^{\geq}$ without ambiguity: if $x_{q1} \geq_{q1} r_{q1}$ and $x_{q2} \geq_{q2} r_{q2}$ ...and $x_{qn} \geq_{qn} r_{qn}$, then $x \in Cl_t^{\geq}$;

- Possible $^{D}\geq$- decision rules: they present the conditions to assign object to $Cl_t^{\geq}$ with or without ambiguity: if $x_{q1} \geq_{q1} r_{q1}$ and $x_{q2} \geq_{q2} r_{q2}$... and $x_{qn} \geq_{qn} r_{qn}$, then $x\ possibly \in Cl_t^{\geq}$;
- Certain $^{D}\leq$- decision rules: they present the conditions to assign object to $Cl_t^{\leq}$ without ambiguity: if $x_{q1} \leq_{q1} r_{q1}$ and $x_{q2} \leq_{q2} r_{q2}$ ...and $x_{qn} \leq_{qn} r_{qn}$, then $x \in Cl_t^{\leq}$;
- Possible $^{D}\leq$- decision rules: they present the conditions to assign object to $Cl_t^{\leq}$ with or without ambiguity: if $x_{q1} \leq_{q1} r_{q1}$ and $x_{q2} \leq_{q2} r_{q2}$... and $x_{qn} \leq_{qn} r_{qn}$, then $x\ possibly \in Cl_t^{\leq}$;
- Approximate $^{D}\geq\leq$- decision rules: they present the conditions to assign object to $Cl_s \cup Cl_{s+1} \cup \ldots \cup Ct_t$: if $x_{q1} \geq_{q1} r_{q1}$ ... and $x_{qn} \geq_{qn} r_{qn}$ and $x_{qn+1} \leq_{qn+1} r_{qn+1}$ ... and $x_{qp} \leq_{qp} r_{qp}$, then $x \in Cl_s \cup Cl_{s+1} \cup \ldots \cup Cl_t$.

New classification scheme based on DRSA to classify new or existing protocols

In order to identify the recommended class for a new or existing protocol, two scores need to be calculated. The first one, $Score_R^+(Cl_t, m)$, accounts for the credibility and coverage factors of all the rules (i.e. R) that suggests the assignment of the protocol to class Cl_t. This value is the product of credibility (CR_{ρ_i}) and coverage factor (CF_{ρ_i}) of every decision rule ($^{e.g.,}\rho_i$) with respect to any individual class $^{(e.g.,}Cl_t)$:

$$CR_{\rho_i}(Cl_t) = \frac{\left|Cond_{\rho_i} \cap Cl_t\right|}{\left|Cond_{\rho_i}\right|}$$

$$CF_{\rho_i}(Cl_t) = \frac{\left|Cond_{\rho_i} \cap Cl_t\right|}{|Cl_t|}$$

where $Cond_{\rho_i}$ is the set of protocols that satisfy the conditions of rule ρ_i, and $\left|Cond_{\rho_i}\right|$, $|Cl_t|$, and $\left|Cond_{\rho_i} \cap Cl_t\right|$ are the cardinalities of the group of protocols verifying $Cond_{\rho_i}$, the protocols belonging to class Cl_t, and the protocols satisfying $Cond_{\rho_i}$ and belonging to class Cl_t, respectively. $Score_R^+(Cl_t, m)$ is calculated as follows:

$$Score_R^+(Cl_t, m) = \frac{\left|\left(Cond_{\rho_1} \cap Cl_t\right) \cup \ldots \cup \left(Cond_{\rho_k} \cap Cl_t\right)\right|^2}{\left|Cond_{\rho_1} \cup \ldots \cup Cond_{\rho_k}\right| \, |Cl_t|}$$

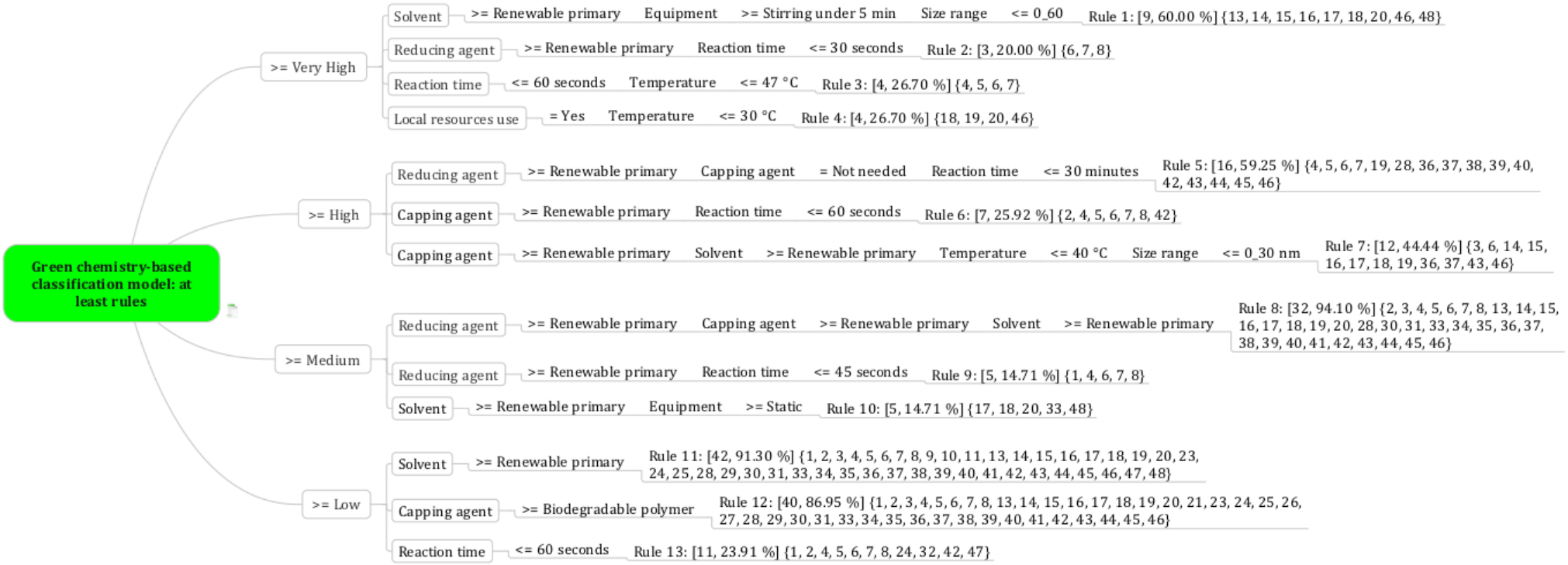
where $Cond_{\rho_1}$, …, $Cond_{\rho_k}$ are the conditions parts of the rules supporting the assignment to class of interest Cl_t.

The other score, $Score_R^-(Cl_t, m)$, embraces the credibility and coverage factors of all the rules that suggest an assignment of the protocol to a class other than Cl_t. This score has the following formula:

$$Score_R^-(Cl_t, m) = \frac{\left|\left(Cond_{\rho_{k+1}} \cap Cl_{\rho_{k+1}}^{\geq}\right) \cup \ldots \cup \left(Cond_{\rho_l} \cap Cl_{\rho_l}^{\geq}\right) \cup \left(Cond_{\rho_{l+1}} \cap Cl_{\rho}\right.\right.}{\left|Cond_{\rho_{k+1}} \cup \ldots \cup Cond_{\rho_l} \cup Cond_{\rho_{l+1}} \cup \ldots \cup Cond_{\rho_h}\right| \left|Cl_{\rho_{k+1}}^{\geq} \cup \ldots\right.}$$

where $Cl_{\rho_{k+1}}^{\geq}, \ldots, Cl_{\rho_l}^{\geq}$ and $Cl_{\rho_{l+1}}^{\leq}, \ldots, Cl_{\rho_h}^{\leq}$ are the upward and downward unions of classes other than Cl_t recommended by the decision rules. The net value, $Score_R^{net}(Cl_t, m)$, resulting from $Score_R^+(Cl_t, m) - Score_R^-(Cl_t, m)$, is an indication of the strength of the assignment to class Cl_t and the final recommendation of a class depends on the highest net score.

Figure S1: Green chemistry-based classification model - At least rules*



* = Each rule characterization is reported as follows: Rule x: [y, z%] $\{p, q, t\}$ with: x = rule number; y = number of protocols that support the rule; z = coverage factor of the rule (i.e. percentage of number of protocols that satisfy the conditions and are assigned to the class or union of classes); p, q, t = identification numbers of the protocols in the dataset

Figure S2: Green chemistry-based classification model - At most rules*

* = Each rule characterization is reported as follows: Rule x: [y, z%] $\{p, q, t\}$ with: x = rule number; y = number of protocols that support the rule; z = coverage factor of the rule (i.e. percentage of number of protocols that satisfy the conditions and are assigned to the class or union of classes); p, q, t = identification numbers of the protocols in the dataset

Extended calculations of scores for test protocol t_1 and t_3 with new classification scheme following formulas described in Section 2.2

$$Score_R^+(Cl_p, t_1) = \frac{|Protocols\ satisfying\ conditions\ of\ covering\ rules\ and\ belonging\ to}{|Protocols\ satisfying\ conditions\ of\ covering\ rules\ that\ include\ Cl_p\ as\ a\ recommendation|}$$

$$Score_R^-(Cl_p, t_1) = \frac{|Protocols\ satisfying\ conditions\ of\ covering\ rules\ and\ not\ belong}{|Protocols\ satisfying\ conditions\ of\ covering\ rules\ that\ recommend\ a\ class\ different\ from}$$

$$Score_R^{net}(Cl_p, t_1) = Score_R^+(Cl_p, t_1) - Score_R^-(Cl_p, t_1)$$

Test protocol t_1

Covering rules: 3, 5, 6, 8, 11, 12, 13.

Class A

$$Score_R^+(Cl_A, t_1) = \frac{|4,5,6,7,8,\ 13,14,15,16,17,18,19,20,46,}{|1,\ 2,\ 3,\ 4,\ 5,\ 6,\ 7,\ 8,\ 9,\ 10,\ 11,\ 13,\ 14,\ 15,\ 16,\ 17,\ 18,\ 19,\ 20,\ 21,23,\ 24,\ 25,\ 26,27,28,\ 29,\ 30,\ 31,\ 32,3}$$

$$= \frac{15^2}{(46 * 15)} = 0.33$$

$Score_R^-(Cl_A, t_1) = 0$

$Score_R^{net}(Cl_A, t_1) = 0.33 - 0 = 0.33$

Class B

$$Score_R^+(Cl_B, t_1) = \frac{|2,3,28,36,37,38,39,40,42,43,44,45|}{|1,\ 2,\ 3,4,\ 5,\ 6,\ 7,\ 8,\ 9,\ 10,\ 11,\ 13,\ 14,\ 15,\ 16,\ 17,\ 18,\ 19,\ 20,\ 21,23,\ 24,\ 25,\ 26,27,28,\ 29,\ 30,\ 31,\ 32,3}$$

$$= \frac{12^2}{(46 * 12)} = 0.27$$

$$Score_R^-(Cl_B, t_1) = \frac{|4,5,6,7|^2}{|4,5,6,7| * 36} = \frac{4^2}{(4 * 36)} = 0.05$$

$Score_R^{net}(Cl_B, t_1) = 0.27 - 0.05 = 0.22$

Class C

$$Score_R^{+}(Cl_C, t_1) = \frac{|1,30,31,33,34,35,41|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,3}$$

$$= \frac{7^2}{(46 * 7)} = 0.15$$

$$Score_R^{-}(Cl_C, t_1) = \frac{|2,4,5,6,7,8,19,28,36,37,38,39,40,42,43,44,45,46|^2}{|2,4,5,6,7,8,19,28,36,37,38,39,40,42,43,44,45,46| * 41} = \frac{18^2}{(18 * 41)} = 0.44$$

$Score_R^{net}(Cl_C, t_1) = 0.15 - 0.44 = -0.29$

Class D

$$Score_R^{+}(Cl_D, t_1) = \frac{|9,10,11,21,23,24,25,26,27,29,32|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,3}$$

$$= \frac{11^2}{(46 * 12)} = 0.22$$

$$Score_R^{-}(Cl_D, t_1) = \frac{|2,3,4,5,6,7,8,13,14,15,16,17,18,19,20,28,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46|^2}{|2,3,4,5,6,7,8,13,14,15,16,17,18,19,20,28,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46| * 36}$$

$$= \frac{32^2}{(32 * 36)} = 0.89$$

$Score_R^{net}(Cl_D, t_1) = 0.22 - 0.89 = -0.67$

Test protocol t_3

Covering rules: 11, 12, 19, 20, 23, 24, 25, 26.

Class E

$$Score_R^+(Cl_E, t_3) = \frac{|22|^2}{|1, 2,3,10,11,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,47,| * 2} =$$

$$\frac{1^2}{(30 * 2)} = 0.02$$

$$Score_R^-(Cl_E, t_3) = \frac{|1, 2, 3,4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,23, 24, 25, 26,27,28, 29, 30, 31,„33}{|1, 2, 3,4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,23, 24, 25, 26,27,28, 29, 30, 31,33, 3}$$

$$= \frac{45^2}{(45 * 46)} = 0.98$$

$Score_R^{net}(Cl_E, t_3) = 0.02 - 0.98 = -0.96$

Class D

$$Score_R^+(Cl_D, t_3) = \frac{|9,10,11,21,23,24,25,26,27,29,32,4}{|1,2, 3,4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,22,23, 24, 25, 26,27,28, 29, 30, 31, 3}$$

$$= \frac{12^2}{(47 * 12)} = 0.26$$

$Score_R^-(Cl_D, t_3) = 0$

$Score_R^{net}(Cl_D, t_3) = 0.26 - 0 = 0.26$

Class C

$$Score_R^+(Cl_C, t_3) = \frac{|1,30,31,33,34,35,41|^2}{|1,2, 3,4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,23, 24, 25, 26,27,28, 29, 30, 31, 32,3}$$

$$= \frac{7^2}{(47 * 7)} = 0.15$$

$Score_R^-(Cl_C, t_3) = 0$

$Score_R^{net}(Cl_C, t_3) = 0.15 - 0 = 0.15$

Class B

$$Score_R^{+}(Cl_B, t_3) = \frac{|2,3,28,36,37,38,39,40,42,43,44,45|^2}{|1, 2, 3,4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,23, 24, 25, 26,27,28, 29, 30, 31,,33,}$$

$$= \frac{12^2}{(45 * 12)} = 0.27$$

$$Score_R^{-}(Cl_B, t_3) = \frac{|1,10,22,23,24,25,26,27,32,33,47|^2}{|1,10,22,23,24,25,26,27,32,33,47| * 36} = \frac{11^2}{(11 * 36)} = 0.31$$

$$Score_R^{net}(Cl_B, t_3) = 0.27 - 0.31 = -0.04$$

Class A

$$Score_R^{+}(Cl_A, t_3) = \frac{|4,5,6,7,8, 13,14,15,16,17,18,19,20,46,48}{|1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21,23, 24, 25, 26,27,28, 29, 30, 31,33,}$$

$$= \frac{15^2}{(45 * 15)} = 0.33$$

$$Score_R^{-}(Cl_A, t_3) = \frac{|1,2,3,10,11,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,47|^2}{|1,2,3,10,11,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,47| * 33}$$

$$= \frac{30^2}{(30 * 33)} = 0.91$$

$$Score_R^{net}(Cl_A, t_3) = 0.33 - 0.91 = -0.58$$