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# SUPPORTING INFORMATION

## DADNP: Dual Antibacterial Drug-Nanoparticle Systems Computational Design Approach

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### Nanoparticles Dataset (NP-set).

We used a previously reported dataset with the outcomes of $N_n$ = 300 pre-clinical assays of metal, metal salt, and metal oxide NPs against different bacteria species (s).[1] The metal NP have a core made of: gold (Au), silver (Ag), or copper (Cu). The metal salt NP cores are made of cadmium(II) sulfide (CdS) or copper(I) iodide. The metal oxide NP include: cadmium(II) oxide (CdO), zinc oxide (ZnO), copper(II) oxide (CuO), lanthanum(III) oxide ($La_2O_3$), aluminium oxide ($Al_2O_3$), iron(III) oxide ($Fe_2O_3$), tin(IV) oxide ($SnO_2$), titanium(IV) oxide ($TiO_2$), iron(II, III) oxide ($Fe_3O_4$), and silicon dioxide ($SiO_2$). These assays of these 15 nanomaterials involved multiple experimental conditions $c_{nj}$. We listed all the specific conditions of one assay as a vector $\mathbf{c}_{nj} = [c_{nj}, c_{nj}, c_{nj} \ldots\ldots c_{nmax}]$. These conditions of assay include the measurement of 1 out of 4 possible Antimicrobial activity parameters, against 1 out of 34 possible bacteria species (different strains included). Other labels or experimental conditions considered are selecting at least 1 out of 3 NPs shape and running the experiment in 1 out of 4 possible intervals time during. The original data was downloaded from OCHEM database (https://ochem.eu/home/show.do)[2] and other sources.[3-14] The dataset also included information about physicochemical parameters of the NP and the coating agents used (see next sections). [1]

### Shannon-entropy scaling of NP structural information.

The original NP-set contains different experimental/theoretical physicochemical parameter to characterize the NP structure/composition details. These parameters were the Average Molar Volume (AMV), the Average Atomic Electronegativity (AAE), and the Average Atomic Polarizability (AAP). These physicochemical properties were retrieved from the website Chemicool Periodic Table (http://www.chemicool.com/elements).[15] The fourth parameter was the Average Particle Size (APS) expressed in nanometers (nm). However, in order to carry out the IF process making a fusion of the NP and AD on the same working dataset we decided to express all the information in the same scale. Consequently, the information of 2 datasets was transformed into a Shannon's entropy scale previously to fusion. The information about NP core and coating agents has been scaled using the following formulae to calculate the Shannon's entropy values.

$$p(D_k) = \frac{1}{(1+\mathrm{Exp}(-D_k/1000))} \quad (1)$$

$$Sh(D_k) = -p(D_k) \cdot \log(p(D_k)) \quad (2)$$

The value of 1000 in the ratio $D_k/1000$ was used as a scaling value. The same kind of operators $Sh_k(D_k)$ were used to scale all up the descriptors quantifying the information about structure of different subsystems. It means that we applied the same operator $Sh_k(D_k)$ to the structural descriptors of the NP core ($D_{kn}$). After that, we obtained the values of entropy $Sh_k(D_{kn})$, see **Table S1**. With the $Sh_k(D_{kn})$ values we can calculate the PTOs of the NP assays used as input for the PTMLIF model. The PTOs calculated here has the form of multi-condition MAs by analogy to previous reports. The formula of these PTOs is the following $\Delta Sh(D_{kn}) = Sh_{kn} - \langle Sh_{kn} \rangle_{cn}$. In **Table S1** we show selected examples of the average values $\langle Sh_{kn} \rangle_{cn}$ for different subsets of NP assay conditions $\mathbf{c}_n$ (Supporting Information file SI00.doc). The information about all the NPs, shape, type, and values of $Sh_{kn}$ and $\langle Sh_{kn} \rangle_{cn}$ appear in the Supporting Information file SI01.xlsx, see NP sheet.

**Table S1.** NP Shannon entropy information measures and averages (selected examples)

| NP Type | NP | Shape | $Sh(MW_n)$ | $Sh(AMV_n)$ | $Sh(AAE_n)$ | $Sh(AAP_n)$ | $Sh(APS_n)$ |
|---|---|---|---|---|---|---|---|
| Oxide | ZnO | Acicular | 0.1476 | 0.1501 | 0.1504 | 0.1504 | 0.1497 |
| | ZnO | N/A | 0.1476 | 0.1501 | 0.1504 | 0.1504 | 0.1493 |
| | CuO | N/A | 0.1477 | 0.1502 | 0.1504 | 0.1504 | 0.1493 |
| | La2O3 | N/A | 0.1371 | 0.1499 | 0.1504 | 0.1501 | 0.1493 |
| | Al2O3 | N/A | 0.1468 | 0.1501 | 0.1504 | 0.1504 | 0.1493 |
| | Fe2O3 | N/A | 0.1445 | 0.1501 | 0.1504 | 0.1504 | 0.1493 |
| | SnO2 | N/A | 0.1449 | 0.15 | 0.1504 | 0.1504 | 0.1493 |
| | TiO2 | N/A | 0.1477 | 0.1501 | 0.1504 | 0.1503 | 0.1493 |
| | SiO2 | N/A | 0.1484 | 0.1501 | 0.1504 | 0.1504 | 0.1493 |
| | CdO | Spherical | 0.1458 | 0.1501 | 0.1504 | 0.1504 | 0.1498 |
| | Fe3O4 | Spherical | 0.1414 | 0.1501 | 0.1504 | 0.1504 | 0.1501 |
| Metal | CuI | N/A | 0.1432 | 0.15 | 0.1504 | 0.1503 | 0.1502 |
| | CdS | Spherical | 0.1452 | 0.15 | 0.1504 | 0.1503 | 0.1504 |
| | Au | Spherical | 0.143 | 0.1502 | 0.1504 | 0.1503 | 0.1505 |
| | Ag | Spherical | 0.1466 | 0.1502 | 0.1505 | 0.1503 | 0.1504 |
| | Cu | Spherical | 0.1483 | 0.1503 | 0.1504 | 0.1503 | 0.1502 |

| NP | Org. | Strain | Shape | Average Values | | | |
|---|---|---|---|---|---|---|---|
| Type | $cn_1$ | $cn_2$ | $cn_3$ | $\langle Sh(AMV_n)_{cnj} \rangle$ | $\langle Sh(AAE_n)_{cnj} \rangle$ | $\langle Sh(AAP_n)_{cnj} \rangle$ | $\langle Sh(APS_n)_{cnj} \rangle$ |
| All | EC | K-12 | Spherical | 0.14647 | 0.15013 | 0.15044 | 0.15032 |
| | EC | MDR | | 0.14296 | 0.15017 | 0.15043 | 0.15031 |
| | EC | ATCC 10536 | | 0.1471 | 0.1502 | 0.1505 | 0.1503 |
| | EF | VCM-R | | 0.1466 | 0.1502 | 0.1505 | 0.1503 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SA | ATCC 9144 | Acicular | 0.14763 | 0.15012 | 0.15043 | 0.15039 |
| EC | ATCC 10536 | | 0.14763 | 0.15012 | 0.15043 | 0.15039 |
| PA | ATCC 9027 | | 0.14763 | 0.15012 | 0.15043 | 0.15039 |

In **Table S2** we show the individual values of $Sh(D_{cak})$ and the average values $<Sh(D_{ack})_{cnj}>$ for each descriptor $D_{ack}$ of the coating agents. These MAs quantify the variability on the first coating agent, the second coating agent (if any), and the time of assay, respectively. However, the values of variance of these MAs were too low to be included in ML analysis. Consequently, we decided to encode all this information into a modified type of PTOs based on multiple Shannon's entropy information measures $\Delta Sh(D_{ca1}, D_{ca2}, D_{dk})$. The use of many different types of PTOs in PTMLIF analysis applied to Nanotechnology was discussed in the literature before.[16-18]

**Table S2.** Shannon's entropy information measures for NP coating agents

| Coating systems | | | Coating systems numerical information | | | |
|---|---|---|---|---|---|---|
| $N_{coat}$ | Poly. | Coating | Coating Agent 01 | | Coating Agent 02 | |
| | | System | $Sh(LOGP_{ac1})$ | $Sh(PSA_{ac1})$ | $Sh(LOGP_{ac2})$ | $Sh(PSA_{ac2})$ |
| Double | Mono. | PDT/Mel | 0.14776 | 0.15050 | 0.14627 | 0.15054 |
| | | PDT/ACh | 0.14776 | 0.15050 | 0.14962 | 0.15055 |
| | | PDT/CQ | 0.14776 | 0.15050 | 0.14956 | 0.15037 |
| | | PDT/DMB | 0.14776 | 0.15050 | 0.14734 | 0.15049 |
| | | PDT/CPB | 0.14776 | 0.15050 | 0.14700 | 0.15045 |
| | | PDT/G | 0.14776 | 0.15050 | 0.14783 | 0.15051 |
| Single | | PDT | 0.14776 | 0.15050 | 0.15051 | 0.15051 |
| | | Maltose | 0.14328 | 0.15065 | 0.15051 | 0.15051 |
| | | Lactose | 0.14328 | 0.15065 | 0.15051 | 0.15051 |
| | | Glutathione | 0.14457 | 0.15058 | 0.15051 | 0.15051 |
| | | Glucose | 0.14652 | 0.15059 | 0.15051 | 0.15051 |
| | | DMA | 0.15051 | 0.15022 | 0.15051 | 0.15051 |
| | | Galactose | 0.14652 | 0.15059 | 0.15051 | 0.15051 |
| | Poly. | PVP | 0.14983 | 0.15052 | 0.15051 | 0.15051 |
| | | PGA | 0.14690 | 0.15055 | 0.15051 | 0.15051 |
| None | None | None | 0.15051 | 0.15051 | 0.15051 | 0.15051 |
| Nc | Poly. | Coating | Coating Agent 01 | | Coating Agent 02 | |
| $cc_1$ | $cc_2$ | Type | $<Sh(LOGP_{ac1})_{cnj}>$ | $<Sh(PSA_{ac1})_{cnj}>$ | $<Sh(LOGP_{ac2})_{cnj}>$ | $<Sh(PSA_{ac2})_{cnj}>$ |
| Double | Mono | I | 0.148 | 0.150 | 0.148 | 0.150 |
| Single | Mono. | II | 0.146 | 0.151 | 0.151 | 0.151 |
| Single | Poly. | III | 0.148 | 0.151 | 0.151 | 0.151 |
| None | None | IV | 0.151 | 0.151 | 0.151 | 0.151 |

**IFPTML DADNP simulation experiment.** Last we used the IFPTML model to carry out a simulation of the values of probability of several DADNP. The study included $N_{AD}$ = 27 compounds with AD activity; which are approved by FDA and/or demonstrated to be active in various assays. They belong to 10 classes of AD including cephalosporins (CEF), quinolones (QUIN), tetracyclines (TETR), macrolides (MACRO), *etc*. We also included in the study 72 assays of NP *vs*. different bacteria species including multiple MDR strains. We calculated the value of probability $p(DADNP_{in})$ with which the $DADNP_{in}$ system formed by the $i^{th}$ $AD_i$ and the $n^{th}$ $NP_n$ is expected to has the desired level of biological activity on the assay conditions $\mathbf{c}_{dj}$ and $\mathbf{c}_{nj}$. In order to make the calculation more exigent we determined the value of probability as $p(DADNP_{in})_{\mathbf{c}dj,\mathbf{c}nj} = p(AD_i/\mathbf{c}_{dj})_{obs} \cdot p(NP_n/\mathbf{c}_{nj})_{obs} \cdot p(DADNP_{in}/\mathbf{c}_{dj}, \mathbf{c}_{nj})_{pred}$. The two first terms $p(AD_i/\mathbf{c}_{dj})_{obs}$ and $p(NP_n/\mathbf{c}_{nj})_{obs}$ are the observed probabilities with which multiple AD and the NP of reference have been found (experimentally observed) to show desired levels of activity under conditions $\mathbf{c}_{dj}$ and $\mathbf{c}_{nj}$. The third term $p(DADNP_{in}/\mathbf{c}_{dj}, \mathbf{c}_{nj})_{pred}$ is the probability calculated by the IFPTML model for this putative $DADNP_{in}$ under the same conditions $\mathbf{c}_{dj}$ and $\mathbf{c}_{nj}$. The probability $p(DADNP_{in}/\mathbf{c}_{dj}, \mathbf{c}_{nj})_{pred} = 1/(1+Exp(-f(v_{ij}(c_{d0}), v_{nj}(c_{n0}))_{calc})$ is a sigmoid function of the output $f(v_{ij}(c_{d0}), v_{nj}(c_{n0}))_{calc}$ of the IFPTML model for this DADNP on the specific assay conditions $\mathbf{c}_{dj}$ and $\mathbf{c}_{nj}$. We carried out a total $N_{tot}$ = 1944 calculations of the probability of success of the putative DADNP in the assays selected. The model identified some DADNP systems as promising for further assays. In total 760 out of this 1944 DADNP assays were predicted to be successful with $p(DADNP_{in})_{\mathbf{c}dj,\mathbf{c}nj} > 0.8$ (12.0%). Only the 1% of the DADNP calculated were predicted to be successful with p $p(DADNP_{in})_{\mathbf{c}dj,\mathbf{c}nj} > 0.9$. In **Figure S1** we can see a selection of DADNP assays predicted. The DADNP systems formed by Ciprofloxacin and Au NP coated with PDT/CQ, PDT/Mel, or PDT/Ach seems to be promising for further assays *vs*. MDR *P. aeruginosa* strains. However, the DADNP systems formed by Ciprofloxacin and Au NP coated with PDT/DMB could be unable to halt the infection of the same strain. However, this is only a punctual example and all predictions made with this method should be taken with caution and corroborated experimentally. The great advantage of this IFPTML method is not the possibility of making a good prediction with a few tests. The real use of the IFPTML model is to make fast and inexpensive preliminary *in silico* screening of large numbers of DADNP systems. After that, we can short list the more promising DADNP systems for experimental assay taking into account not only $p(DADNP_{in})_{\mathbf{c}dj,\mathbf{c}nj}$ values but also expert opinion, similar cases from literature if any, *etc*. This could be a useful tool to direct the experimental search instead of doing it by costly and slow trial and error tests only.

| | B | C | D | E | F | G | H | I | J | K | L | M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | | | | | CEF | IMIDAZOL | MACRO | PEN | QUIN | TETRA | TETRA | TRIAZ |
| 6 | cn1 = Organism | cn2 = Strain | NP | Coat | Ciprofloxacin | Metronidazole | Erythromycin | Pencillin V | Nalidic acid | Tetracycline | Minocycline | Voriconazole |
| 7 | Escherichia coli | ATCC25922 | Ag | PVP | 0.010 | 0.004 | 0.006 | 0.007 | 0.005 | 0.008 | 0.010 | 0.006 |
| 8 | Escherichia coli | ATCC25922 | Ag | Lactose | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 9 | Klebsiella pneumoniae | MDR | Au | PDT/CQ | 0.809 | 0.338 | 0.594 | 0.616 | 0.472 | 0.676 | 0.796 | 0.515 |
| 10 | Klebsiella pneumoniae | MDR | Au | PDT/CPB | 0.853 | 0.356 | 0.636 | 0.651 | 0.499 | 0.712 | 0.837 | 0.543 |
| 11 | Klebsiella pneumoniae | MDR | Au | PDT | 0.651 | 0.272 | 0.489 | 0.497 | 0.381 | 0.543 | 0.638 | 0.414 |
| 12 | Pseudomonas aeruginosa | ATCC27853 | Au | PDT/CQ | 0.853 | 0.356 | 0.636 | 0.651 | 0.499 | 0.712 | 0.837 | 0.543 |
| 13 | Pseudomonas aeruginosa | ATCC27853 | Au | PDT | 0.809 | 0.338 | 0.594 | 0.615 | 0.472 | 0.676 | 0.796 | 0.515 |
| 14 | Pseudomonas aeruginosa | ATCC27853 | Au | PDT/ACh | 0.835 | 0.348 | 0.619 | 0.636 | 0.488 | 0.697 | 0.820 | 0.531 |
| 15 | Pseudomonas aeruginosa | MDR | Au | PDT/CQ | 0.809 | 0.338 | 0.594 | 0.616 | 0.472 | 0.676 | 0.796 | 0.515 |
| 16 | Pseudomonas aeruginosa | MDR | Au | PDT/G | 0.316 | 0.132 | 0.199 | 0.234 | 0.177 | 0.267 | 0.321 | 0.201 |
| 17 | Pseudomonas aeruginosa | MDR | Au | PDT/Mel | 0.819 | 0.342 | 0.604 | 0.623 | 0.478 | 0.684 | 0.805 | 0.521 |
| 18 | Pseudomonas aeruginosa | MDR | Au | PDT/DMB | 0.260 | 0.108 | 0.161 | 0.192 | 0.145 | 0.220 | 0.265 | 0.165 |
| 19 | Pseudomonas aeruginosa | MDR | Au | PDT | 0.786 | 0.328 | 0.573 | 0.597 | 0.457 | 0.657 | 0.775 | 0.500 |
| 20 | Pseudomonas aeruginosa | MDR | Au | PDT/ACh | 0.838 | 0.350 | 0.622 | 0.638 | 0.490 | 0.700 | 0.823 | 0.533 |
| 21 | Staphylococcus aureus | ATCC6538P | Au | PDT/Mel | 0.647 | 0.270 | 0.483 | 0.494 | 0.379 | 0.540 | 0.635 | 0.412 |
| 22 | Staphylococcus aureus | ATCC6538P | Au | PDT/CQ | 0.437 | 0.183 | 0.329 | 0.334 | 0.256 | 0.365 | 0.428 | 0.278 |
| 23 | Escherichia coli | ATCC8739 | Fe3O4 | PGA | 0.586 | 0.244 | 0.400 | 0.441 | 0.336 | 0.493 | 0.586 | 0.373 |
| 24 | Staphylococcus aureus | ATCC10832 | Fe3O4 | PGA | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 25 | Staphylococcus aureus | ATCC6538 | SiO2 | DMA | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

**Figure S1.** IFPTML-LDA DADNP systems simulation (selected results)

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