**Supplementary Materials**

Prediction of Drug Solubility in Complex Micro-Environments: Machine Learning Study Based on Hansen Solubility Parameters

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The supplementary materials have been provided by the authors to give readers additional information about their work.

**Table S1**. Hyperparameter search space and optimal configuration of the RF model.

|  |  |  |
| --- | --- | --- |
| **Hyperparameter** | **Search space** | **Optimal value** |
| n\_estimators (number of trees) | 100, 300, 500, 600 | 500 |
| max\_depth (maximum depth) | 5, 15, 25, None | 25 |
| min\_samples\_split (minimum samples to split a node) | 2, 5, 10 | 2 |
| min\_samples\_leaf (minimum samples at a leaf) | 1, 2, 4 | 1 |
| max\_features (features per split) | "sqrt" (fixed) | "sqrt" |
| Mean cross-validation *R²* | – | 0.982 |

**Table S2**. Descriptive statistics of the descriptors used in this study.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Descriptor** | **Minimum** | **Maximum** | **Mean** | **Median** | **Skewness** | **Kurtosis** |
| δd1 | 0 | 26.18 | 10.686 | 11.05 | -0.4 | -0.154 |
| δp1 | 0 | 26.6 | 15.555 | 15.72 | -3.43 | 19.408 |
| δh1 | 0 | 45.94 | 19.839 | 18.49 | 0.474 | -0.686 |
| w1 | 0 | 1 | 0.393 | 0.45 | 0.293 | -1.312 |
| δp2 | 0 | 29.8 | 8.744 | 7.71 | 1.295 | 1.428 |
| δd2 | 0 | 34.3 | 16.563 | 19.55 | -1.267 | 0.254 |
| δh2 | 0 | 67 | 9.669 | 8.66 | 3.266 | 21.886 |
| MW | 138.121 | 853.13 | 293.923 | 280.28 | 3.408 | 22.189 |
| MV | 0 | 1870 | 40.096 | 298.2 | 6.954 | 57.183 |
| Tem | 0 | 338 | 294.247 | 302.7 | -5.61 | 32.443 |
| P | 0 | 270 | 85.859 | 101.2 | -1.797 | 2.173 |
| pH | 0 | 7.4 | 0.179 | 6.6 | 6.286 | 38.766 |
| MFS | 0 | 3751 | 60.766 | 5.231 | 7.333 | 75.58 |