# Web-4D-QSAR: A Web-Based Application to Generate 4D-QSAR Descriptors

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A web-based application is developed to generate 4D-QSAR descriptors using the LQTA-QSAR methodology, based on molecular dynamics (MD) trajectories and topology information retrieved from the GROMACS package. The LQTAGrid module calculates the intermolecular interaction energies at each grid point, considering probes and all aligned conformations resulting from MD simulations. These interaction energies are the independent variables or descriptors employed in a QSAR analysis. A friendly front end web interface, built using the Django framework and Python programming language, integrates all steps of the LQTA-QSAR methodology in a way that is transparent to the user, and in the backend, GROMACS and LQTAGrid are executed to generate 4D-QSAR descriptors to be used later in the process of QSAR model building.

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## Introduction

The quantitative structure activity relationship (QSAR) is an important research field in theoretical medicinal chemistry, which predicts the biological activities of new compounds using mathematical relationships based on structural, physicochemical, and conformational properties of previously tested potential agents. QSARs help us to understand and explain the mechanism of drug action at a molecular level, and allow the design and development of new compounds that present desirable biological properties.[1]

After Cramer et al.[2] proposed the comparative molecular field analysis (CoMFA) in 1988, the methodology diffused quickly in medicinal chemistry and related fields, becoming a cornerstone for 3D-QSAR studies.[3,4] In CoMFA formalism, field descriptors, or three-dimensional properties (electronic, steric, hydrophobic, and hydrogen bond), are determined in a 3D virtual lattice. Its grid corresponds to a rigid hypothetical receptor, and must be large enough to contain all aligned molecules. At each grid point, energies of interaction (descriptors) between a probe and all the atoms of each molecule in the investigated set are computed. Here, a partial least squares (PLS) regression[5–8] is employed to model the relationships between the biological activity of a set of aligned compounds and their calculated 3D descriptors.

The 4D-QSAR analysis, originally proposed by Hopfinger et al.,[9] incorporates conformational and alignment freedom in the development of 3D-QSAR models by performing molecular state ensemble averaging, which is the fourth "dimension." In this approach, the descriptors values in each cell of the cubic grid are the occupancy measures for the atoms making up the molecules of the investigated set from the sampling of conformation and alignment spaces. The grid cell occupancy descriptors (GCODs) are generated for different atom types (polar positive, polar negative, aromatic, hydrogen bond acceptor, hydrogen bond donor), called interaction pharmacophore elements (IPE). In a 4D-QSAR analysis, each compound of the investigated set can be partitioned into classes (IPE), which are chosen based on possible interactions with a common receptor. The idea underlying a 4D-QSAR analysis is that variations in biological responses are related to differences in the Boltzmann average spatial distribution of molecular shape with respect to the IPE.[9]

The original Hopfinger 4D-QSAR analysis has since been modified, leading to significantly better results. An additional set of GCOD was incorporated into the 4D-QSAR analysis, called the absolute charge occupancy. This type of GCOD is generated using the mean value of partial atom charges, and is calculated using the semi-empirical AM1 Hamiltonian, present in some cells of the grid in a determined time of the molecular dynamics.[10] The classical Hopfinger's strategy uses a PLS regression and genetic algorithm (GA) for variable selection and a multiple linear regression (MLR) for model building. Polanski and Bak[10] used a different approach to the generated descriptors matrix that led to better statistical results. They use a neural formalism with a self-organizing Kohonen network to produce a fuzzy 4D-QSAR-like representation of the conformational space. The competitive SOM algorithm is applied to generate a two-dimensional topographic map representing the signals from particular atoms of the molecular trajectory. In such an approach, a sphere specified in space by a single neuron substitutes a singular unit cube.[10] Several works use this modified 4D-QSAR approach, with excellent results.[11–16]

A different 4D-QSAR approach, called LQTA-QSAR,[17] is based on the generation of a conformational ensemble profile

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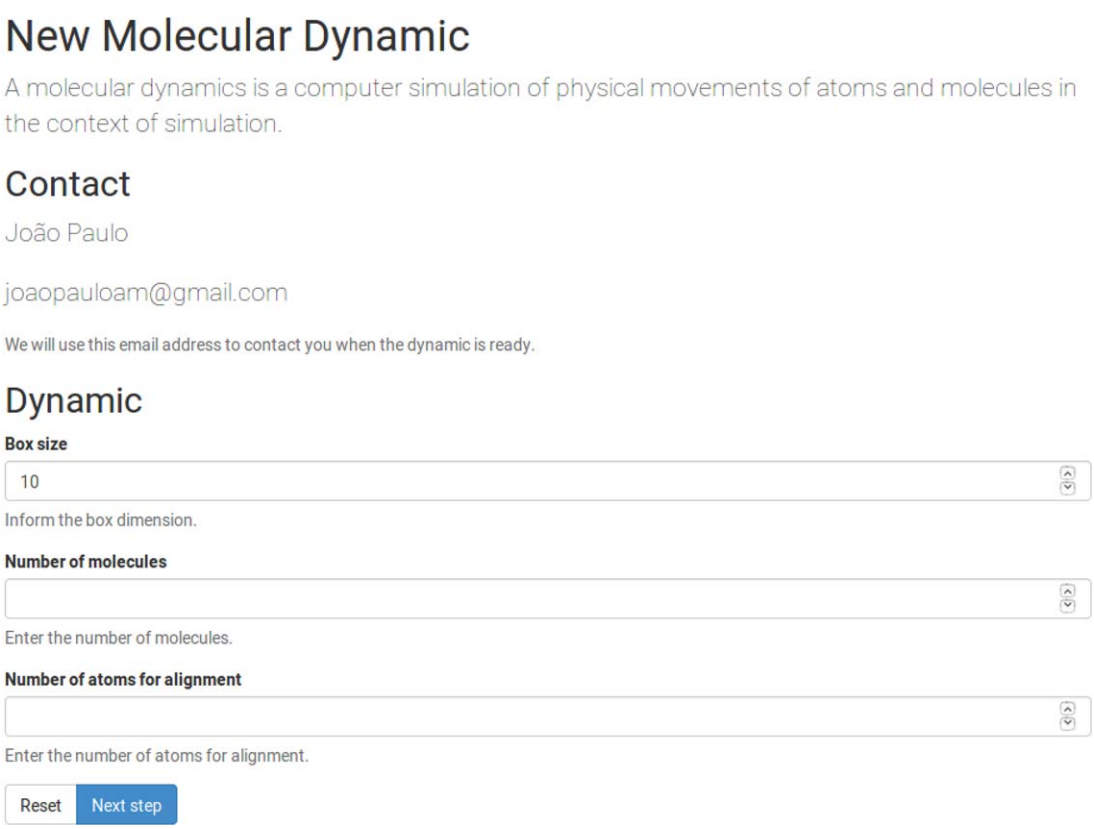


**Figure 1**. Initial screen of Web-4D-QSAR web software. [Color figure can be viewed at wileyonlinelibrary.com]

(CEP) for each compound, instead of only one conformation, followed by the calculation of 3D descriptors for a set of compounds. This methodology jointly explores the main features of CoMFA and 4D-QSAR paradigms. LQTA-QSAR uses the free GROMACS package[18] to run the molecular dynamics (MD) simulations and to estimate the CEP generated for each compound, or ligand, and then uses LQTAGrid software to generate interaction descriptors. The LQTA-QSAR has been applied successfully in a series of works using PLS regressions and the ordered predictors selection (OPS)[19] variable selection algorithm, leading to mathematical models with good, rigorous validated statistics, and with interpretable descriptors.[17,20–22]

However, the 4D-LQTA-QSAR approach is limited because it uses numerous computational packages, which may cause difficulties for users who are not experts or who are not familiar with the tools used to perform such an analysis. Thus, this work presents an application that uses a complete LQTA-QSAR analysis to generate descriptors. Through a user-friendly web interface, this new application, called Web-4D-QSAR, generates 4D-LQTA-QSAR descriptors by performing MD simulations with GROMACS, and then calculating interaction energies with LQTAGrid in an integrated way that is transparent to the user. This software, developed using the Python programming language[23] and Django framework for web development,[24] intends to make the LQTA-QSAR approach easy to use and available to researchers who need to carry out 4D-QSAR studies using free software.

## Methodology

In this section, we describe the steps in the 4D-LQTA-QSAR analysis using Web-4D-QSAR.

Prior to a 4D-LQTA-QSAR analysis, all 3D structures of the compounds under study must be constructed and optimized, and partial atomic charges must be calculated using the preferred electronic method of the user. We recommend using an *ab initio* method, such as DFT, and CHELPG partial atomic charges to calculate the LQTAGrid descriptors calculation. These are more accurate, but the user is free to choose another method, such as AM1 or PM3. Then, partial atomic charges should be calculated by the AM1-BCC method, with AMBER ff03 atom types and using UCSF Chimera, to be used in GROMACS MD simulations.

After that, the molecules should be submitted to the Web-4D-QSAR application to start the LQTA-QSAR process with the MD simulations. First, the user must specify the box size for the MD simulation, the number of molecules that will be submitted, and the number of atoms per molecule that will be used in the alignment step (Fig. 1). Then, the user is able to submit the molecules, select the reference molecule in the alignment, and determine which atoms to use in the alignment step for each molecule (Fig. 2).

When the user clicks on start dynamics, Web-4D-QSAR performs all tasks necessary to the MD simulation. First, the energy-optimized structures are submitted to the topobuild program to generate the GROMACS topology files using the generalized amber force field (GAFF).[25]

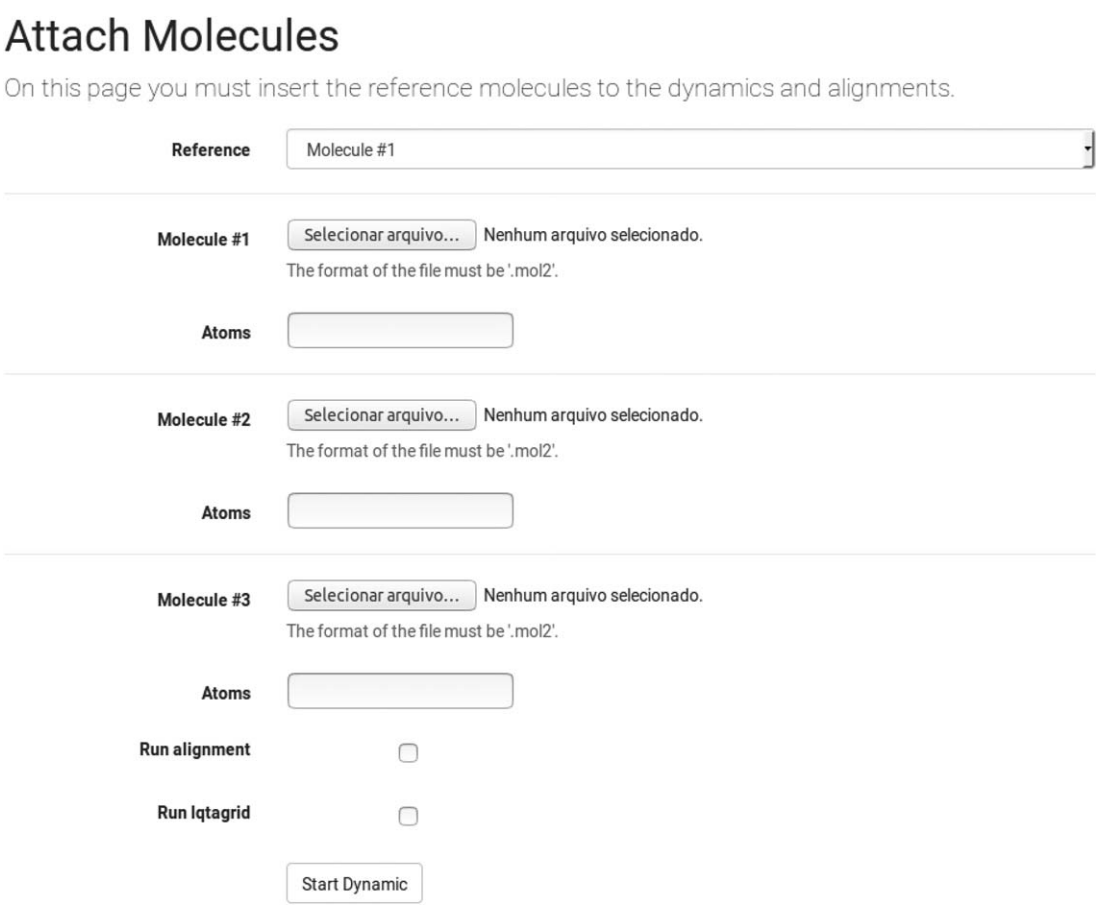


**Figure 2.** Attach molecules and determine atoms for alignment in Web-4D-QSAR.

Then, the MD simulations of all unbound ligands considering an explicit aqueous medium (extended single-point charge (SPC/E)[26] water models) are carried out. Counterions are added to satisfy the electro-neutrality condition, when necessary. Periodic boundary cubic boxes are built sufficiently large, with a distance of 10 Å between the solute (ligands models) and the water solvent molecules. The particle mesh Ewald (PME)[27] method is used to compute long-range electrostatic and van der Waals interaction energies, with a cutoff radius of 10 Å. All chemical bonds are constrained to their nominal values using the linear constraint solver (LINCS)[28] algorithm. Each component (ions, solute, and solvent) is separately coupled in the NPT (constant particle number, pressure, and temperature) ensemble. The system pressure is controlled by Parrinello–Rahman coupling[29] and the temperature is managed by a Berendsen thermostat.[30] Atomic positions are optimized using the steepest descent and conjugated gradient algorithm. The energy minimization convergence criterion is 50 N of maximum force applied to atoms in the investigated systems, where the volume is balanced using a stepwise heating of the system. The heating or warming-up scheme is as follows: 50 K, 100 K, 200 K, and 350 K for a simulation time of 20 ps performed in a 1 fs step size. Next, the system is cooled down to 300 K, and an MD simulation of 500 ps is carried out. Trajectory file is recorded every 1000 simulation steps. The CEP of all ligands are assembled in the same file, considering the ligands conformations recorded from 50 to 500 ps, and these data are used to build the QSAR models. All these parameters are configured in *mdp files in a static directory but can be changed if necessary.

After the MD simulations, the CEP of all ligands are aligned to the CEP of the reference molecule, defined by

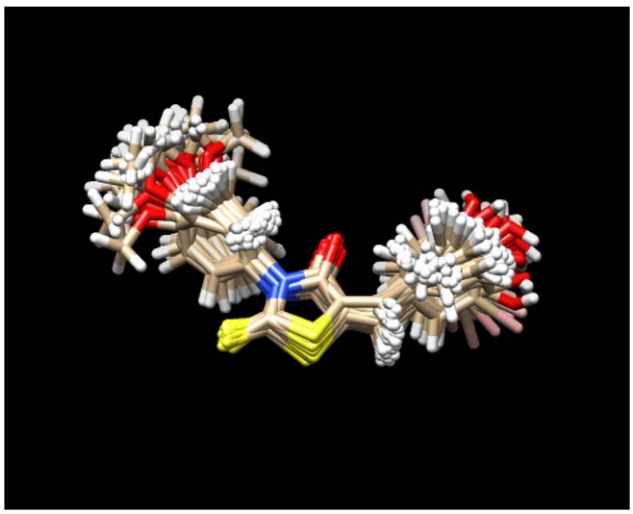

**Figure 3.** CEP of a ligand resulting from a molecular dynamics simulation followed by an alignment. [Color figure can be viewed at wileyonlinelibrary.com]

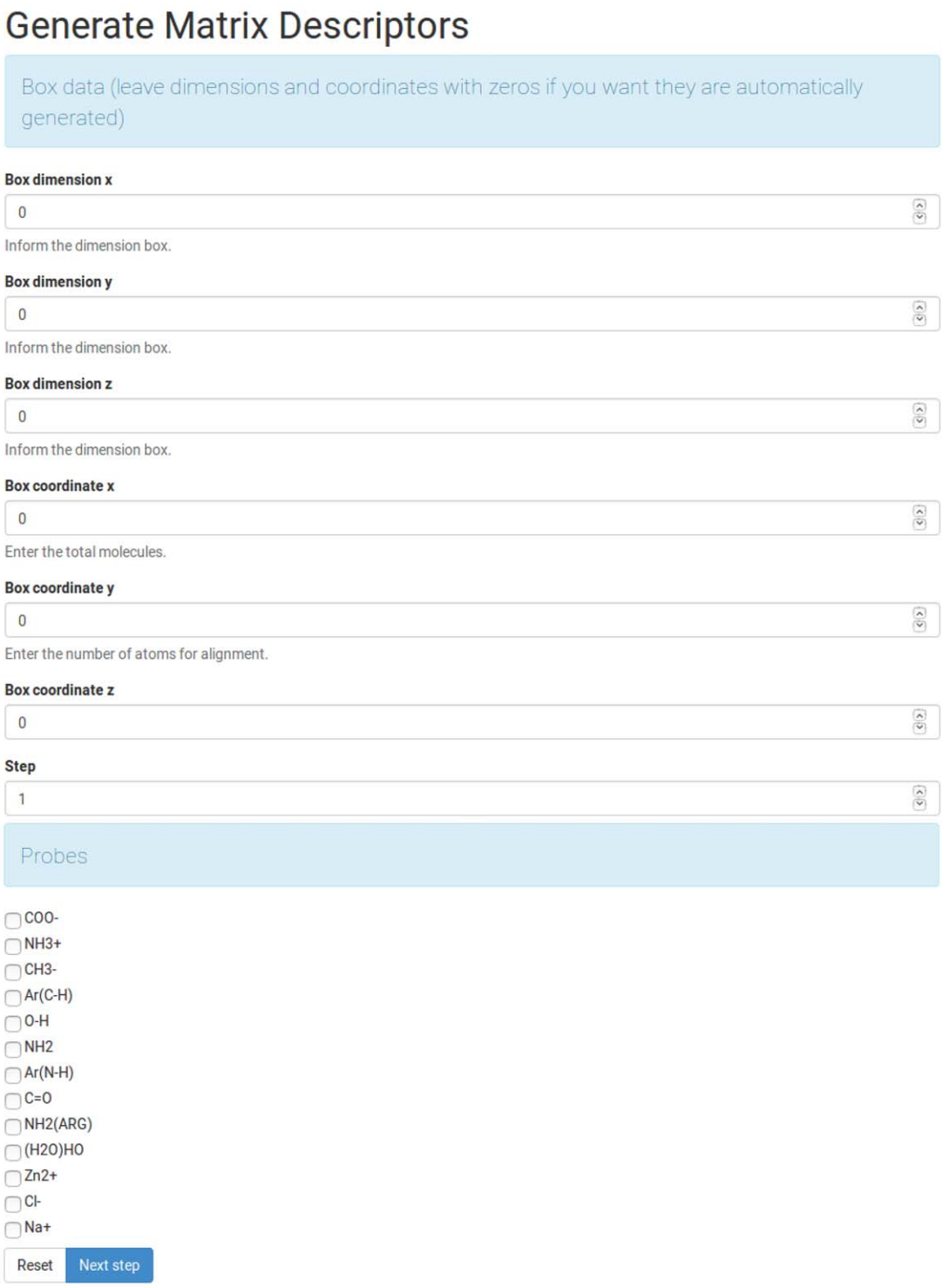


**Figure 4**. LQTAGrid descriptors generation in Web-4D-QSAR. [Color figure can be viewed at wileyonlinelibrary.com]

the user, using the Atom fit method (least-squares superposing) in terms of atom positions. This method is based on the matching of atom positions. The goodness of superposition is the root-mean-square of the distances (RMSD) between corresponding atom pairs.[22] The output of this step of the analysis are the CEP of the ligands in gro format, which are used as the input for LQTAGrid or pdb format to be visualized using, for example, USCF Chimera (Fig. 3).

The final step in the Web-4D-QSAR is to generate descriptors using LQTAGrid. In this step, the user must determine the grid coordinates and dimensions, the size of the step to be explored by the probes (grid resolution), and the probes to be used in the analysis.

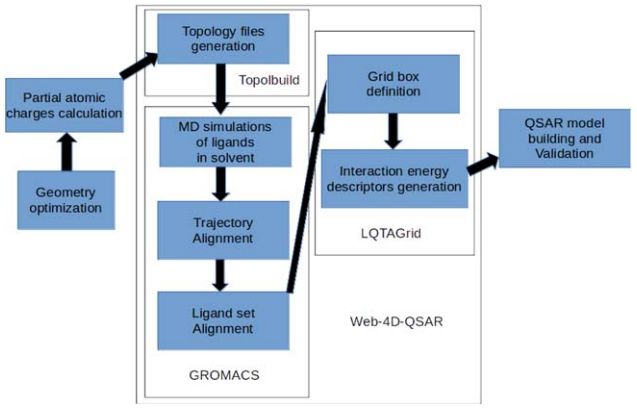


**Figure 5**. Flowchart of all processes involved in a 4D-LQTA-QSAR study. [Color figure can be viewed at wileyonlinelibrary.com]

Each probe selected by the user runs over the grid, and the electrostatic and steric 3D properties are computed for each individual grid point, based on the Coulombic (1) and Lennard-Jones potential functions (2), respectively.

$$E_{ele} = \frac{1}{n}\frac{q_i q_j}{4\pi\ _0 r_{ij}} \quad (1)$$

$$E_{vdW} = \frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^{6}}, \quad (2)$$

with

$$C_{ij}^{(12)} = \sqrt{\frac{1}{n} C_{ii}^{(12)} C_{jj}^{(12)}} \quad (3)$$

$$C_{ij}^{(6)} = \sqrt{\frac{1}{n} C_{ii}^{(6)} C_{jj}^{(6)}}, \quad (4)$$

where $q_i$ is the charge of the $i$th probe; $q_j$ is the charge of the $j$th atom from CEP; $\epsilon_0$ is vacuum permittivity; $C_{ii}^{(12)}$, $C_{ii}^{(6)}$, $C_{jj}^{(12)}$, and $C_{jj}^{(6)}$ are parameters for the probes and the atoms in the CEP, respectively; $n$ indicates the number of frames aligned in the CEP; and $r_{ij}$ represents the distances between the $i$th probe and the $j$th atom of CEP.

If the user does not fill in the coordinates and dimensions of the grid, Web-4D-QSAR generates a grid automatically with a 5 Å distance from the extreme atoms to the walls of the grid. Figure 4 shows the options presented to the user in the LQTAGrid step and the probes available to be selected.

The output of an LQTAgrid analysis is a matrix with columns representing the descriptors, which are the energies calculated for each grid point (according to 1 and 2). The rows represent the molecules of the investigated set. This matrix is used in a multivariate regression, for example, an MLR, principal components regression (PCR), or PLS regression, with the biological activity as the dependent variable, to construct the QSAR model. The columns in the matrix are tab-separated and are ready to be used in a multivariate analysis program, such as QSAR modeling,[31] QSARINS,[32] or R,[33] for model building and validation.

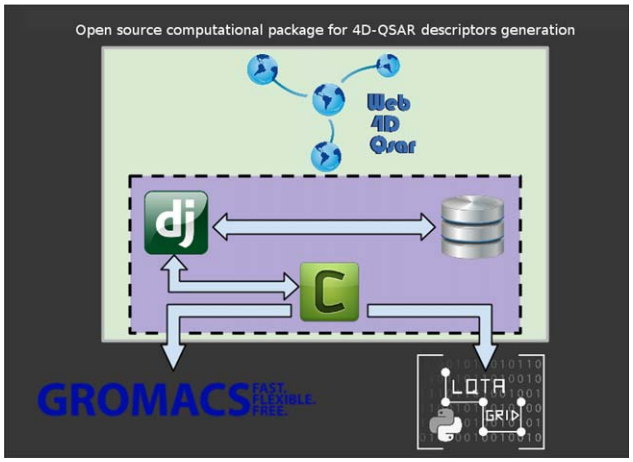


**Figure 6**. Macro architecture of the system. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 5 shows all steps necessary to perform a complete 4D-LQTA-QSAR study, including those carried out by Web-4D-QSAR.

## Computational Details

The front end of the system is developed using the Python programming language.[23] The choice of programming language was based on the fact that Python is one of the most commonly used programming languages, and has been used successfully in several programs in computational chemistry.

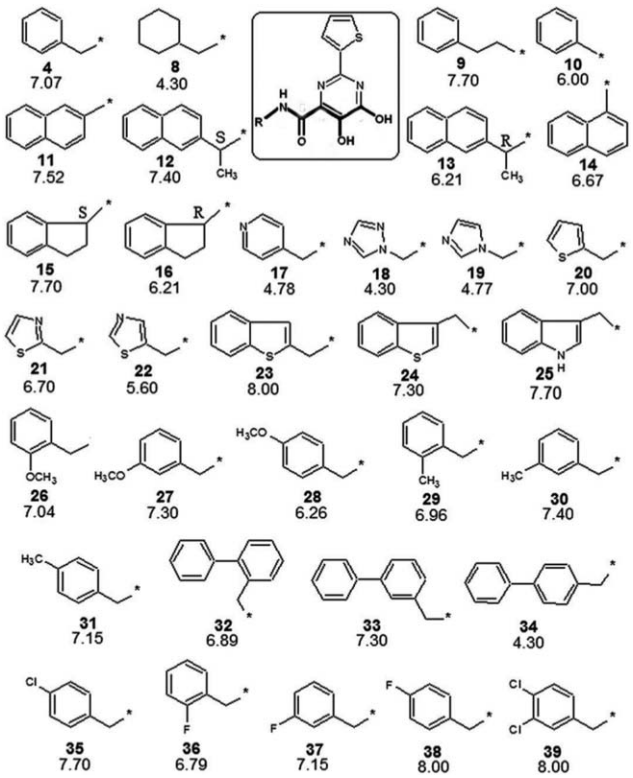


**Figure 7**. Data set of thirty-three 4,5-dihydroxypyrimidine carboxamides adapted from de Melo and Ferreira.[36]

**Table 1.** Statistical parameters obtained for internal validation of the QSAR models.

| | 4D-QSAR | 2D-QSAR [36] | Expected result[37] |
|---|---|---|---|
| Number of molecules | 28 | 25 | – |
| Number of variables | 11 | 4 | – |
| Number of latent variables | 1 | 2 | – |
| $R^2$ | 0.77 | 0.66 | >0.6 |
| SEC | 0.55 | 0.61 | Low as possible |
| $Q^2$ | 0.70 | 0.53 | >0.5 |
| SEV | 0.64 | 0.68 | Low as possible |

Django is a web framework for web development, written in Python, that uses MTV pattern (*model–template–view*). In addition, it embodies the principle of code reuse. Another advantage of Django is the relational object mapping that converts objects defined by the programer into persistent tables in a database.

Celery is an asynchronous task queue/job queue based on distributed message passing. It is focused on real-time operation, but supports scheduling as well. The execution units, called tasks, are executed concurrently on one single or more worker servers using multiprocessing. Tasks can execute asynchronously (in the background) or synchronously (wait until ready).[34]

Figure 6 represents the computational package of the solution, showing a general view of Web-4D-QSAR organization. The role of Django is to manage the users' requests and the dynamics of the view layer. The molecular dynamics simulation can be carried out for *n* molecules added by the user. That is, for each requested dynamic, there must be at least one molecule, which is represented by a data file.

Because the system can treat several requests to execute molecular dynamics, molecular alignment, and descriptor-generation tasks, Celery manages the tasks queues in the most efficient way, diminishing possible processing bottlenecks.

Tasks from Django are directed to GROMACS or LQTAGrid, with Celery responsible for the intermediation between *Front-End* and *Back-End*.

Web-4D-QSAR is open source software and can be executed in a server where users submit their tasks to generate 4D-LQTA-QSAR descriptors. However, it can also run on a local machine. Instructions to download, install, and execute Web-4D-QSAR are available at https://github.com/rougeth/Web-4D-QSAR, and as a supplementary material.

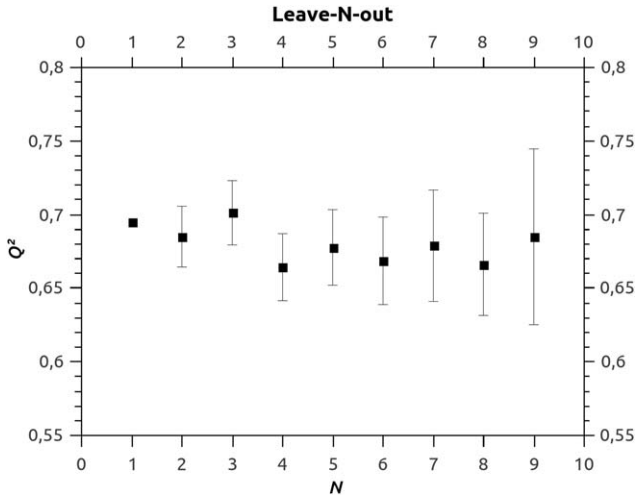


**Figure 9**. Leave-N-out test for the training set. $Q^2$ values are stable until leave-9-out (32% of the samples in the training set).

## Case Study

To illustrate the operation of the Web-4D-QSAR program, a 4D-LQTA-QSAR study is carried out for a data set of thirty three 4,5-dihydroxypyrimidine carboxamide derivatives acting as HIV-1 integrase (HIV-1 IN) inhibitors[35] (Fig. 7), for which there is already a 2D QSAR study described in the literature.[36]

The molecules in this data set are submitted to Web-4D-QSAR and all steps of the LQTA-QSAR methodology are executed. Molecular dynamics is performed using the default parameters described in the Methodology section. The CEPs are generated using the atoms present in the benzene ring common to all structures (Fig. 7) for the alignment. Then, the LQTAGrid module of the program generates a grid with dimensions 30 Å × 26 Å × 28 Å, and a step of 1 Å is selected for the chosen probe, $NH_3^+$, to run the grid. Interaction descriptors

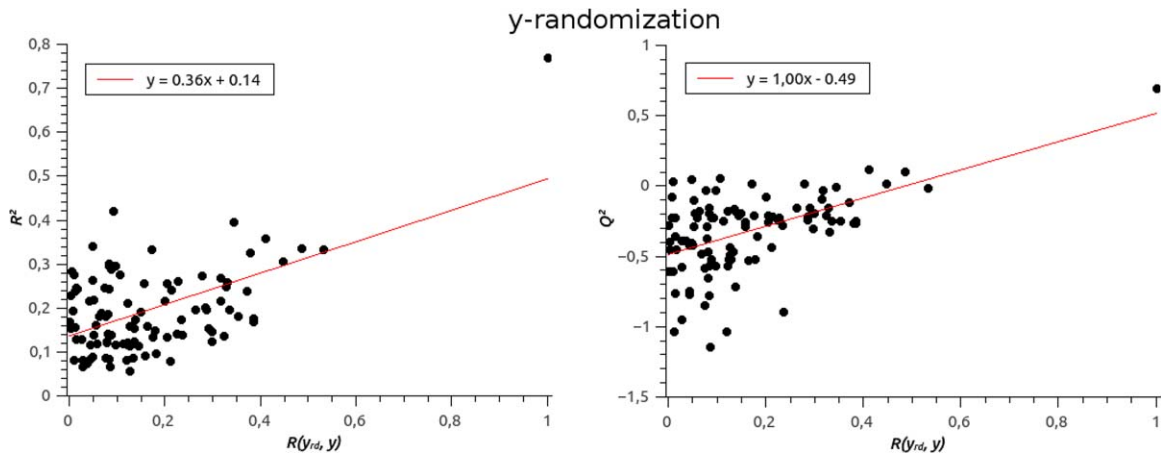


**Figure 8**. *y*-Randomization test for the training set. The intercepts for the $R^2$ and $Q^2$ graphs (0.14 and −0.49, respectively) are in agreement with the limits established by Eriksson et al.[38] [Color figure can be viewed at wileyonlinelibrary.com]

**Table 2.** Statistical parameters obtained for external validation of the QSAR models.

| | 4D-QSAR | 2D-QSAR[36] | Expected result[39] |
|---|---|---|---|
| $R^2_{pred}$ | 0.63 | 0.87 | >0.5 |
| SEP | 0.29 | 0.41 | Low as possible |
| $ARE_{pred}$ | 4.37 | 5.63 | Low as possible |
| $k$ | 0.99 | 0.97 | $0.85 < k < 1.15$ |
| $k'$ | 1.01 | 1.02 | $0.85 < k' < 1.15$ |
| $\lvert R^2_0 - R'^2_0 \rvert$ | 0.18 | 0.016 | <0.3 |

[eqs. [1] and [2]] are calculated and a matrix with 43680 descriptors (21840 Coulomb descriptors and 21840 Lennard-Jones descriptors) is generated.

The descriptors matrix is then submitted to the QSAR modeling program[31] to build and validate the QSAR model. After the variable selection procedure using the OPS algorithm,[19] 11 variables are selected with one latent variable, yielding the following model:

$$\begin{aligned} pIC_{50} = {} & 0.00272687 \times 12.00\_16.00\_20.00\_NH3\_C + 0.00771482 \\ & \times 7.00\_14.00\_19.00_N H3\_C + 0.003819 \\ & \times 7.00\_14.00\_18.00\_NH3\_C + 0.00278558 \\ & \times 13.00\_13.00\_20.00\_NH3\_C + 0.00669941 \\ & \times 14.00\_14.00\_20.00\_NH3\_C + 0.00147442 \\ & \times 12.00\_16.00\_19.00\_NH3\_C + 0.00485688 \\ & \times 8.00\_16.00\_19.00\_NH3\_C + 0.00551685 \\ & \times 8.00\_14.00\_21.00\_NH3\_C + 0.00370068 \\ & \times 7.00\_14.00\_20.00\_NH3\_C + 0.00268853 \\ & \times 8.00\_14.00\_18.00\_NH3\_C + 0.0157205 \\ & \times 13.00\_16.00\_19.00\_NH3\_C + 5.54722 \end{aligned} \quad (5)$$

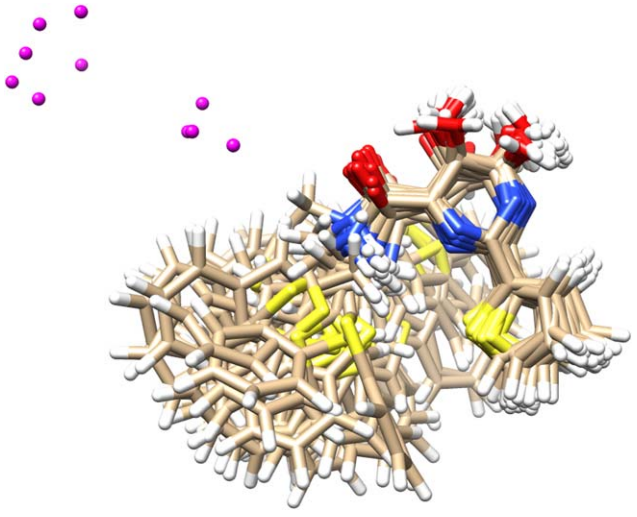

**Figure 10.** CEP for compound 23 with the descriptors selected represented by isolated points. [Color figure can be viewed at wileyonlinelibrary.com]

The numbers in the name of the descriptors are the *x*, *y*, and *z* coordinates, respectively, NH3 refers to the probe ($NH_3^+$) and C is for Coulomb interaction.

The obtained model presents a $Q^2$ value superior to that obtained in the 2D QSAR model for the same data set (Table 1) and did not present an outlier. Then, as in the 2D QSAR model, the 4D-QSAR model obtained here is submitted to *y*-randomization and leave-N-out tests. These tests show that it is robust according to the criteria established by Kiralj and Ferreira,[37] and free from chance correlation, according to the criteria established by Eriksson et al.,[38] as shown in Figures 8 and 9.

The same compounds chosen by de Melo and Ferreira[36] for the test set in their 2D QSAR model are selected in this case study. The statistical parameters obtained in the external validation are presented in Table 2. Although the obtained values for the external validation parameters are worse than those of the 2D QSAR model, all values are acceptable according to the literature.[39]

Figure 10 shows the CEP obtained for one of the most active molecules (compound 23), with the isolated points representing the selected descriptors. The obtained model may help future interpretations of the selected descriptors and serve as a basis for the design of new compounds.

## Conclusions

QSAR is an important research field in theoretical medicinal chemistry that helps to predict and understand the relationship between molecular structures and biological activity. LQTA-QSAR is an important 4D-QSAR methodology that generates interaction energy descriptors with a physical meaning that are relatively easy to interpret. However, the diversity of programs necessary to carry out an LQTA-QSAR study makes it a difficult methodology to use.

Web-4D-QSAR is a user-friendly web-based open-source application that integrates all software used in an LQTA-QSAR analysis. Developed using the Python programming language and Django web framework, it is easily configurable and adaptable. Available at https://github.com/rougeth/Web-4D-QSAR, it can be downloaded to be used on a local machine or configured to run on a server to be accessed remotely by users who want to perform LQTA-QSAR studies, because it uses Celery to manage queues/jobs submitted by users. A case study was conducted to illustrate the use of the program. The descriptors generated resulted in a model with good predictability and robustness. To the best of our knowledge, this is the first free software that generates descriptors for a 4D-QSAR study.

## *Acknowledgment*

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**Keywords:** 4D-QSAR · molecular dynamics · interaction energy descriptors · web software · Python

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Additional Supporting Information may be found in the online version of this article.

[1] M. M. C. Ferreira, *J. Braz. Chem. Soc.* **2002**, *13*, 742.
[2] R. D. Cramer, D. E. Patterson, J. D. Bunce, *J. Am. Chem. Soc.* **1988**, *110*, 5959.
[3] V. Martinez-Merino, H. Cerecetto, *Bioorg. Med. Chem.* **2001**, *9*, 1025.
[4] Z. Wen-Na, Y. Qing-Sen, Z. Jian-Wei, M. Ma, Z. Ke-Wen, *J. Mol. Struct.* **2005**, *723*, 69.
[5] H. Martens, T. Naes, *Multivariate Calibration*; Wiley: Chichester, **1989**.
[6] R. Manne, *Chemometr. Intell. Lab.* **1987**, *1*, 187.
[7] H. Agnar, *J. Chemometr.* **1988**, *2*, 211.
[8] S. de Jong, *Chemometr. Intell. Lab.* **1993**, *18*, 251.
[9] A. J. Hopfinger, S. Wang, J. S. Tokarski, B. Jin, M. Albuquerque, P. J. Madhav, C. Duraiswami, *J. Am. Chem. Soc.* **1997**, *119*, 10509.
[10] J. Polanski, A. Bak, *J. Chem. Inf. Model.* **2003**, *43*, 2081.
[11] J. Polanski, *Adv. Drug. Deliv. Rev.* **2003**, *55*, 1149.
[12] J. Polanski, A. Bak, R. Gieleciak, T. Magdziardz, *Molecules* **2004**, *9*, 1148.
[13] R. Gieleciak, T. Magdziardz, A. Bak, J. Polanski, *J. Chem. Inf. Model.* **2005**, *45*, 1447.
[14] R. Gieleciak, J. Polanski, *J. Chem. Inf. Model.* **2007**, *47*, 547.
[15] A. Bak, J. Polanski, *J. Chem. Inf. Model.* **2007**, *47*, 1469.
[16] A. Bak, V. Kozik, A. Simolinski, J. Jampilek, *RSC Adv.* **2016**, *6*, 76183.
[17] J. P. A. Martins, E. G. Barbosa, K. F. M. Pasqualoto, M. M. C. Ferreira, *J. Chem. Inf. Model.* **2009**, *49*, 1428.
[18] E. Lindahl, B. Hess, D. van der Spoel, *J. Mol. Model.* **2001**, *7*, 306.
[19] R. F. Teófilo, J. P. Martins, M. M. C. Ferreira, *J. Chemometr.* **2009**, *23*, 32.
[20] E. B. de Melo, M. M. C. Ferreira, *J. Chem. Inf. Model.* **2012**, *52*, 1722.
[21] E. G. Barbosa, K. F. M. Pasqualoto, M. M. C. Ferreira, *J. Comput. Aided Mol. Des.* **2012**, *26*, 1055.
[22] J. B. Ghasemi, R. Safavi-Sohi, E. G. Barbosa, *Mol. Divers.* **2012**, *16*, 203.
[23] Python, https://www.python.org/ (accessed September 22, **2017**).
[24] Django: The Web Framework for Perfectionists with Deadlines, https://www.djangoproject.com/ (accessed September 22, **2017**).
[25] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, D. A. Case, *J. Comput. Chem.* **2004**, *25*, 1157.
[26] P. G. Kusalik, I. M. Svishchev, *Science* **1994**, *265*, 1219.
[27] T. Darden, D. York, L. Pedersen, *J. Chem. Phys.* **1993**, *98*, 10089.
[28] B. Hess, H. Bekker, H. J. C. Berendsen, J. G. E. M. Fraaije, *J. Comput. Chem.* **1997**, *18*, 1463.
[29] M. Parrinello, A. Rahman, *Phys. Rev. Lett.* **1980**, *45*, 1196.
[30] H. J. C. Berendsen, J. P. M. Postma, W. F v. Gunsteren, A. DiNola, J. R. Haak, *J. Chem. Phys.* **1984**, *81*, 3684.
[31] J. P. A. Martins, M. M. C. Ferreira, *Quim. Nova* **2013**, *36*, 554.
[32] P. Gramatica, N. Chirico, E. Papa, S. Cassani, S. Kovarich, *J. Comput. Chem.* **2013**, *34*, 2121.
[33] R Core Team, *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, **2013**, URL http://www.R-project.org/
[34] Celery: Distributed Task Queue, http://www.celeryproject.org/ (accessed September 22, **2017**).
[35] A. Petrocchi, U. Koch, V. G. Matassa, B. Pacini, K. A. Stillmock, V. Summa, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 350.
[36] E. B. de Melo, M. M. C. Ferreira, *Eur. J. Med. Chem.* **2009**, *44*, 3577.
[37] R. Kiralj, M. M. C. Ferreira, *J. Braz. Chem. Soc.* **2009**, *20*, 770.
[38] L. Eriksson, J. Jaworska, A. P. Worth, M. T. D. Cronin, R. M. McDowell, P. Gramatica, *Environ. Health Perspect.* **2003**, *111*, 1361.
[39] A. Golbraikh, A. Tropsha, *J. Mol. Graph. Model.* **2002**, *20*, 269.

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