

# Chemically Aware Model Builder (camb): An R package for bioactivity and property modeling of small molecules and proteins

Daniel S. Murrell<sup>1,\*</sup>, Isidro Cortes-Ciriano<sup>2,\*</sup>, Gerard J.P. van Westen<sup>3</sup>,  
Andreas Bender<sup>1,†</sup>, Thérèse E. Malliavin<sup>2,†</sup>, Robert C. Glen<sup>1,†</sup>

<sup>1</sup>Unilever Centre for Molecular Science Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

<sup>2</sup>Unité de Bioinformatique Structurale, Institut Pasteur and CNRS UMR 3825, Structural Biology and Chemistry Department, 2528, rue Dr. Roux, 75 724 Paris, France.

<sup>3</sup>European Molecular Biology Laboratory European Bioinformatics Institute Wellcome Trust Genome Campus, Hinxton, United Kingdom.

Received on XXXXX; revised on XXXXX; accepted on XXXXX

Associate Editor: XXXXXXXX

## ABSTRACT

**Summary:** *camb* is an R package that can be used for the rapid generation of quantitative predictive models in the area of medicinal chemistry (QSAR, QSPR, QSAM, proteochemometrics and chemogenomics). It is aimed at both advanced and beginner R users. Its capabilities include the standardisation and representation of chemical structures, computation of 905 two-dimensional and 14 fingerprint type descriptors for small molecules, the computation of 8 types of amino acid descriptors and 13 different whole protein sequence descriptors, filter methods for feature selection, generation of predictive models (R package *caret*), as well as techniques to ensemble these models (R package *caretEnsemble*). Results can be visualised through high-quality, customisable plots (R package *ggplot2*).

**Availability:** *camb* is written in R, C++, Python and Java and is available open source at <https://github.com/cambDI/camb>. Two tutorials are also included.

**Contact:** Therese Malliavin [terez@pasteur.fr](mailto:terez@pasteur.fr) or Robert Glen [rrog28@cam.ac.uk](mailto:rrog28@cam.ac.uk)

## 1 INTRODUCTION

The advent of high-throughput technologies over the last two decades has led to a vast increase of compound, bioactivity and genomic databases (Bender, 2010) [TBD: cite other databases]. This rampant increase in the amount of chemical and biological information has been exploited by emergent fields in drug discovery such as quantitative structure activity relationships (QSAR), quantitative structure property relationships (QSPR), quantitative sequence-activity modelling (QSAM), or proteochemometric modelling (PCM) (van Westen *et al.*, 2011).

The R programming language provides a flexible platform for statistical analyses (R Core Team, 2013), and its applicability in medicinal chemistry has been reviewed elsewhere (Mente and Kuhn, 2012). Although R is extensively used in diverse biological domains, *e.g.* genomics (Gentleman *et al.*, 2004), the availability of R packages for cheminformatics and medicinal chemistry is limited. Nonetheless, R still constitutes the most frequent choice in the medicinal chemistry literature for compounds bioactivity and property modelling (Mente and Kuhn, 2012). In general, these studies share a common algorithmic structure, which can be summarised in 4 model generation steps: (i) compound standardisation, (ii) descriptor calculation, (iii) preprocessing, feature selection, model training and validation, and (iv) bioactivity/property prediction for new molecules.

Currently available R packages provide the capability for a subset of the previous steps. For instance, R packages *chemmineR* (Cao *et al.*, 2008) and *rcdk* (Guha, 2007) enable the manipulation of SDF and SMILES files, the calculation of physicochemical descriptors, the clustering of molecules, and the retrieval of compounds from PubChem (Wang *et al.*, 2012). On the machine learning side, the *caret* package provides a unified platform for the training of machine learning models (Kuhn, 2008).

Here, we present the R package *camb*: Chemically Aware Model Builder, which aims to address the current lack of an R framework encompassing all four steps mentioned above. The package has been conceived in a way that users with minimal programming skill are able to generate competitive predictive models and high-quality plots under default operation. However, each function can be utilised to fulfil the more versatile needs of more experienced users.

Overall, *camb* enables the generation of predictive models (QSAR, QSPR, QSAM and PCM) starting with: chemical structure files, protein sequences (if required), and the associated properties or bioactivities. Moreover, *camb* is the first R package that enables the manipulation of chemical structures utilising Indigo's C API (Indigo, 2013), and the calculation of: (i) molecular

\*Equal contributors

†to whom correspondence should be addressed

fingerprints and descriptors calculated using the PaDEL-Descriptor Java library (v2.16) (Yap, 2011), (ii) hashed and unhashed Morgan fingerprints (Rogers and Hahn, 2010), and (iii) 8 types of amino acid descriptors [TBD: are these implemented here for the first time?]. Two case studies illustrating the application of *camb* for QSPR modelling (solubility prediction) and PCM are available in the online supplementary information. In the following section we detail the main functionalities provided by *camb*.

## 2 DESCRIPTION

This section describes the tools provided by *camb* for (i) compound standardisation, (ii) molecular descriptor calculation, (iii) preprocessing and feature selection, model training, visualisation and validation, and (iv) bioactivity/property prediction for new molecules.

### 2.1 Compound standardization

In order to represent all molecules in a given dataset in the same way (compound standardisation), *camb* provides the function *StandardiseMolecules* which utilises Indigo's C API (Indigo, 2013). SDF and SMILES formats are provided as molecule input options. The maximum number of fluorines, chlorines, bromines and iodines that a compound can include in order to pass the standardisation process can be defined by the user. Additional arguments of this function include the removal of inorganic molecules or those compounds with a molecular mass above or below a given thresholds. *camb* makes use of Indigo's InChI [TBD: cite] InChI plugin to standardise tautomers to the same SMILES representation by converting to InChI, discarding tautomeric information, and converting back to SMILES.

### 2.2 Descriptor calculation

Currently, *camb* supports the calculation of compound descriptors and fingerprints via PaDEL-Descriptor (Yap, 2011), and extended connectivity circular fingerprints (Rogers and Hahn, 2010) as implemented in the RDKit (Landrum, 2006). The function *GeneratePaDelDescriptors* permits the calculation of 905 2-dimensional descriptors and 10 PaDEL fingerprints [TBD: mention fingerprints].

Morgan fingerprints can be computed with the function *MorganFPs* through the python library RDKit (Landrum, 2006). Hashed fingerprints are either binary, recording the presence or absence of each substructure, or count based, recording the number of occurrences of each substructure. Additionally, this function computes unhashed (keyed) fingerprints, where each substructure in the dataset is assigned a unique position in a binary fingerprint of length equal to the number of substructures existing in the dataset.

Since the positions of substructures in the unhashed fingerprint depend on the dataset, the function *MorganFPs* allows calculation of unhashed fingerprints for new compounds using a basis defined by the substructures present in the training dataset. This ensures that substructures in new compounds map to the same locations on the fingerprint.

*camb* also enables the calculation of 13 types of whole protein sequence descriptors from UniProt identifiers (Xiao and Xu, 2014),

as well as the calculation of 8 types of amino acid descriptors (van Westen *et al.*, 2013).

### 2.3 Model training and validation

Prior to model training, descriptors often need to be statistically preprocessed (Andersson *et al.*, 2011). To this end, several functions (see package documentation and tutorials) are provided, *e.g.* the removal of non-informative predictors or their conversion to z-scores.

*camb* invokes the R package *caret* to train individual machine learning models. *caret* provides a common interface to the most popular machine learning package that exist in R. These include learning methods in Bagging, Bayesian Methods, Boosting, Boosted Trees, Elastic Net, MARS, Gaussian Processes, K Nearest Neighbour, Principal Component Regression, Radial Basis Function Networks, Random Forests, Relevance Vector Machines, Support Vector Machines among others. Additionally, two ensemble modelling approaches, namely: greedy and stacking optimisation, have been integrated from the R package *caretEnsemble* (Mayer, 2013). Statistical metrics for model validation have also been included (Golbraikh and Tropsha, 2002).

### 2.4 Visualization

All plots are generated using the R package *ggplot2* (Wickham, 2009). Default options for plotting functions allow the generation of high-quality plots, however, the layer-based structure of *ggplot* objects allows for further tweaking by the addition of customisation layers. Visual depiction of compounds is also possible with the function *PlotMolecules*, utilises Indigo's C API. Visualization functions are explained in the tutorials.

## 3 CONCLUSIONS

*In silico* predictive models have proved a valuable tool for the optimisation of compounds potency, selectivity and safety profiles. In this context, *camb* provides a complete framework to (i) manipulate compound structures, (ii) generate compound and protein descriptors, and (iii) train and validate QSAR, QSPR, QSAM, PCM and chemogenomic models.

## 4 ACKNOWLEDGEMENTS

ICC thanks the Paris-Pasteur International PhD Programme for funding. ICC and TM thank CNRS, Institut Pasteur and ANR bipbp for funding. DSM and RCG thanks Unilever for funding. GvW thanks EMBL (EIPOD) and Marie Curie (COFUND) for funding. AB thanks Unilever and the European Research Commission (Starting Grant ERC-2013-StG 336159 MIXTURE) for funding.

## REFERENCES

- Andersson, C. R., Gustafsson, M. G., and Strimbergsson, H. (2011). Quantitative chemogenomics: machine-learning models of protein-ligand interaction. *Current topics in medicinal chemistry*, **11**(15), 1978–1993. PMID: 21470169.
- Bender, A. (2010). Databases: Compound bioactivities go public. *Nature Chemical Biology*, **6**(5), 309–309.
- Cao, Y., Charisi, A., Cheng, L. C., Jiang, T., and Girke, T. (2008). Chemminer: a compound mining framework for R. *Bioinformatics*, **24**(15), 1733–1734.

- 
- Gentleman, R. C., Carey, V. J., Bates, D. M., and others (2004). Bioconductor: Open software development for computational biology and bioinformatics. *Genome Biology*, **5**, R80.
- Golbraikh, A. and Tropsha, A. (2002). Beware of q<sup>2</sup>! *Journal of molecular graphics & modelling*, **20**(4), 269–276. PMID: 11858635.
- Guha, R. (2007). Chemical informatics functionality in r. *Journal of Statistical Software*, **18**(6).
- Indigo (2013). Gga software services, indigo cheminformatics library.
- Kuhn, M. (2008). Building predictive models in r using the caret package. *Journal of Statistical Software*, **28**(5), 1–26.
- Landrum, G. (2006). Rdkit: Open-source cheminformatics.
- Mayer, Z. (2013). caretensemble: Framework for combining caret models into ensembles. [r package version 1.0].
- Mente, S. and Kuhn, M. (2012). The use of the r language for medicinal chemistry applications. *Current topics in medicinal chemistry*, **12**(18), 1957–1964. PMID: 23110531.
- R Core Team (2013). R: A language and environment for statistical computing.
- Rogers, D. and Hahn, M. (2010). Extended-connectivity fingerprints. *Journal of chemical information and modeling*, **50**(5), 742–754. PMID: 20426451.
- van Westen, G. J., Swier, R. F., Cortes-Ciriano, I., Wegner, J. K., Overington, J. P., IJzerman, A. P., van Vlijmen, H. W., and Bender, A. (2013). Benchmarking of protein descriptor sets in proteochemometric modeling (part 2): Modeling performance of 13 amino acid descriptor sets. *J. Cheminf.*, **5**(1), 42.
- van Westen, G. J. P., Wegner, J. K., IJzerman, A. P., van Vlijmen, H. W. T., and Bender, A. (2011). Proteochemometric modeling as a tool to design selective compounds and for extrapolating to novel targets. *Med. Chem. Commun.*, **2**, 16–30.
- Wang, Y., Xiao, J., Suzek, T. O., Zhang, J., Wang, J., Zhou, Z., Han, L., Karapetyan, K., Dracheva, S., Shoemaker, B. A., Bolton, E., Gindulyte, A., and Bryant, S. H. (2012). PubChem's BioAssay database. *Nucleic acids research*, **40**(Database issue), D400–412. PMID: 22140110 PMCID: PMC3245056.
- Wickham, H. (2009). ggplot2: elegant graphics for data analysis.
- Xiao, N. and Xu, Q. (2014). protr: Protein sequence descriptor calculation and similarity computation with r. R package version 0.2-1.
- Yap, C. W. (2011). PaDEL-descriptor: an open source software to calculate molecular descriptors and fingerprints. *Journal of Computational Chemistry*, **32**(7), 1466–1474.
-