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Cameo: A Python Library for Computer Aided Metabolic Engineering and Optimization of Cell Factories

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**ABSTRACT:** Computational systems biology methods enable rational design of cell factories on a genome-scale and thus accelerate the engineering of cells for the production of valuable chemicals and proteins. Unfortunately, the majority of these methods' implementations are either not published, rely on proprietary software, or do not provide documented interfaces, which has precluded their mainstream adoption in the field. In this work we present cameo, a platform-independent software that enables in silico design of cell factories and targets both experienced modelers as well as users new to the field. It is written in Python and implements state-of-the-art methods for enumerating and prioritizing knockout, knock-in, overexpression, and down-regulation strategies and combinations thereof. Cameo is an open source software project and is freely available under the Apache License 2.0. A dedicated Web site including documentation, examples, and installation instructions can be found at http://cameo.bio. Users can also give cameo a try at http://try.cameo.bio.

**KEYWORDS:** metabolic engineering, genome-scale metabolic models, heterologous pathway predictions, computer-aided design, software, Python

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The engineering of cells for the production of chemicals and proteins affects all areas of our modern lives. Beer, yogurt, flavoring, detergents, and insulin represent just a few products that are unimaginable without biotechnology. Engineered cells may further provide solutions to many of mankind's greatest challenges like global climate, multiple drug resistance, and overpopulation, by producing fuels, novel antibiotics, and food from renewable feedstocks. Manipulating cells to perform tasks that they did not evolve for, however, is challenging and requires significant investments and personnel in order to reach economically viable production of target molecules.  

A central task in developing biotechnological production processes is to reroute metabolic fluxes toward desired products in cells. This task is particularly prone to failure due to our limited understanding of the underlying biology and the complexity of the metabolic networks in even the simplest of organisms. In line with other recent technological advancements, like high-fidelity genome editing through CRISPR/Cas9 and DNA synthesis costs dropping, modeling methods are increasingly used to accelerate cell factory engineering, helping to reduce development time and cost.4

Genome-scale models of metabolism (GEMs)5 are of particular interest in this context as they predict phenotypic consequences of genetic and environmental perturbations affecting cellular metabolism.6 These models have been developed throughout the past 15 years for the majority of potential cell factory host organisms ranging from bacteria to mammalian cells. A large repertoire of algorithms has been published that utilize GEMs to compute cell factory engineering strategies composed of overexpression, down-regulation, deletion, and addition of genes.7,8 Unfortunately, most of these algorithms are not easily accessible to users as they have either been published without implementation (e.g., using pseudo code or mathematical equations to describe the method) or the implementation provided by the authors is undocumented or hard to install. These problems significantly limit the ability of metabolic engineers to utilize computational design tools as part of their workflow.

**RESULTS**

Cameo is open source software written in Python that alleviates these problems and aims to make in silico cell factory design broadly accessible. On the one hand it enables cell factory engineers to enumerate and prioritize designs without having to be experts in metabolic modeling themselves. On the other hand it aims to become a comprehensive library of published methods by providing method developers with a library that simplifies the implementation of new cell factory design methods.

Cameo provides a high-level interface that can be used without knowing any metabolic modeling or how different algorithms are implemented (see Supplementary Notebook 8 [v0.11.4, current]). In fact, the most minimal form of input that cameo requires is simply the desired product, for example vanillin.

from cameo import api

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api.design(product='vanillin')

This function call will run the workflow depicted in Figure 1. It is also possible to call the same functionality from the command line. First, it enumerates native and heterologous production pathways for a series of commonly used host organisms and carbon sources. Then it runs a whole suite of design algorithms available in cameo to generate a list of metabolic engineering strategies, which can then be ranked by different criteria (maximum theoretical yield, number of genetic modifications, etc.).

More advanced users can easily customize this workflow by providing models for other host organisms, changing parameters and algorithms, and of course by including their own methods.

In order to become a community project and attract further developers, cameo has been developed as a modular Python package that has been extensively documented and tested using modern software engineering practices like test-driven development and continuous integration/deployment on Travis-ci.org (Figure 2 shows an overview of the package organization).

To avoid duplication of effort, cameo is based on the constraint-based modeling tool cobrapy¹³ thus providing its users with already familiar objects and methods (see also Figure 2a). Furthermore, cameo takes advantage of other popular tools of the scientific Python stack, like for example Jupyter notebooks for providing an interactive modeling environment and pandas for the representation, querying, and visualization of results.¹⁵

Accessing published GEMs can be a challenging task as they are often made available in formats that are not supported by existing modeling software.¹¹ Cameo provides programmatic access to collections of models (Figure 2b) hosted by BiGG¹⁶ and the University of Minho darwin.di.uminho.pt/models. Furthermore, by relying on the common namespace for reaction and metabolite identifiers provided by the MetaNetX.org project¹⁷ that covers commonly used pathway databases like KEGG,¹⁸ RHEA¹⁹ and BRENDA²⁰, a universal reaction database can be used to predict heterologous pathways (see Supplementary Notebooks 5 [v0.11.4, current] and 6 [v0.11.4, current]). In the end, the computed designs can be sorted using different criteria relevant to the actual implementation in the lab and economic considerations such as the number of genetic modifications needed and maximum theoretical product yield. Furthermore, a number of results can be further visualized using the pathway visualization tool Escher.¹⁰

With this broad overview of capabilities, we would like to emphasize the role of cameo as a useful resource to the modeling community and wish to support its development as a

Figure 1. Cell factory design workflow with cameo. The first step is to import a metabolic model from a file or using a web service. Next, the user needs to select a target product. If the target product is a non-native chemical, shortest heterologous production pathways can be enumerated to determine a suitable route to the product.⁹ Potential production pathways can then be compared using production envelopes, i.e., visualizations of the trade-off between production rate and organism growth rate (see Supplementary Notebooks 5 [v0.11.4, current] and 6 [v0.11.4, current]). After a production pathway has been chosen, a number of different design methods are used to compute the genetic modifications (designs) necessary to achieve the production goal (see Supplementary Notebooks 5 [v0.11.4, current] and 6 [v0.11.4, current]). In the end, the computed designs can be sorted using different criteria relevant to the actual implementation in the lab and economic considerations such as the number of genetic modifications needed and maximum theoretical product yield. Furthermore, a number of results can be further visualized using the pathway visualization tool Escher.¹⁰
The majority of published strain design algorithms have not been experimentally validated and we believe that their inaccessibility to users is a major factor for the lack of validation. With cameo we hope to counteract this problem by making these methods accessible to the entire metabolic engineering community and also providing a platform for modelers to implement and publish novel methods.

CONCLUSIONS

With cameo version 0.11.4 we release a tool that is ready to be used in metabolic engineering projects. It is under active development, and future work will include interfacing cameo with genome-editing tools to streamline the translation of computed strain designs into laboratory protocols, modeling of fermentation processes to get estimates on titers and productivities, and include pathway predictions based on retrobiosynthesis including hypothetical biochemical conversions.

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Notes
The authors declare no competing financial interest.

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Figure 2. Package organization and functionality overview. The cameo package is organized into a number of subpackages: core extends cobrapy’s own core package11 to use optlang12 as interface to a number of optimization solvers. models enables programmatic access to models hosted on the Internet. parallel provides tools for the parallelization of design methods. visualization provides a number of high-level visualization functions, e.g., production envelopes. flux_analysis implements many basic simulation and analysis methods needed for higher-level design methods and the evaluation of production goals etc. strain_design provides a collection of in silico design methods and is subdivided into methods that use deterministic and heuristic optimization approaches. At last, api provides a high-level interface for computing designs.


