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Applications Note

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AMIGO2, a toolbox for dynamic modeling, optimization and control in systems biology

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Abstract

Motivation: Many problems of interest in dynamic modeling and control of biological systems can be posed as non-linear optimization problems subject to algebraic and dynamic constraints. In the context of modeling, this is the case of, e.g. parameter estimation, optimal experimental design and dynamic flux balance analysis. In the context of control, model-based metabolic engineering or drug dose optimization problems can be formulated as (multi-objective) optimal control problems. Finding a solution to those problems is a very challenging task which requires advanced numerical methods.

Results: This work presents the AMIGO2 toolbox: the first multiplatform software tool that automatizes the solution of all those problems, offering a suite of state-of-the-art (multi-objective) global optimizers and advanced simulation approaches.

Availability and Implementation: The toolbox and its documentation are available at: sites.google.com/site/amigo2toolbox.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Optimization is at the core of many problems related to the modeling and design of biological systems (Banga, 2008). For example, **model parametric identification** involves two types of optimization problems (Balsa-Canto *et al.*, 2010): parameter estimation, to compute unknown parameters by data fitting and optimal experimental design, to design the best experimental dynamic scheme for model identification.

The organization and behavior of biological systems can also be described based on optimality principles. This is the case in, e.g. (dynamic) flux balance analysis (Kauffman *et al.*, 2003) or in the analysis of activation of metabolic pathways (Klipp *et al.*, 2002). In this context, **model-based dynamic optimization** aims the computation of time-varying fluxes or enzyme concentrations and expression rates that minimize (or maximize) a given objective function (biomass production) or the best trade-off between various objectives (de Hijas-Liste *et al.*, 2014).

Models can be used to confirm hypotheses, to draw predictions and to find those (time varying) stimulation conditions that result in a particular desired behavior via (**multi-objective**) **optimal control**. This is the case in, e.g. model-based metabolic engineering (Villaverde *et al.*, 2016), pattern formation (Vilas *et al.*, 2012) or drug dose optimization (Jayachandran *et al.*, 2015).

All these problems can be stated as—or transformed to—(multi-objective) non-linear programming problems with algebraic and dynamic constraints. Their solution requires the combination of the control vector parameterization approach, a simulation method and a global optimizer.

AMIGO2 is the first multi-platform (MATLAB-based) environment that automatizes the solution of all these problems (see Fig. 1 and Supplementary Tables S1 and S2). It fully covers the iterative identification of dynamic models, it allows using optimality principles for predicting biological behavior and it deals with the

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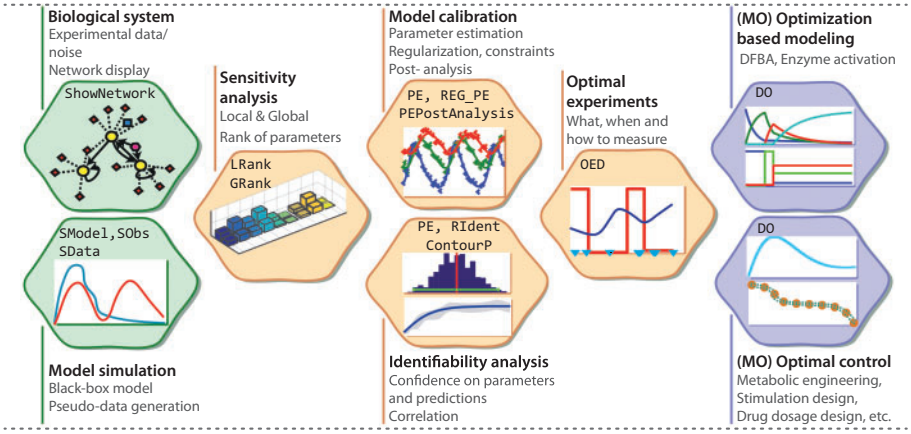

Fig. 1. AMIGO2 features and tasks (Color version of this figure is available at *Bioinformatics* online.)

optimal control of biological systems using constrained multi-objective dynamic optimization.

2 Summary of features

2.1 Models

The tool supports general non-linear deterministic dynamic models and black-box simulators, dealing with ordinary, partial or delay differential equations. Biological networks can be visualized linking to Cytoscape (Shannon *et al.*, 2003).

2.2 Experimental scheme and data

Users can define multi-experiment schemes with maximum flexibility and several types of Gaussian experimental noise with known or unknown observable dependent variance.

2.3 Parameter estimation with regularization

It is possible to estimate parameters and initial conditions which may depend on the experiment using weighted least squares or log-likelihood functions. Ill-conditioned problems can be handled using Tikhonov regularization. Users may fix the regularization parameter or let the tool to automatically compute the most appropriate using the L-shaped Pareto curve (Gábor and Banga, 2015).

2.4 Identifiability and best fit post-analysis

The tool offers various methods to analyze model identifiability: (i) local and global parametric sensitivities; (ii) the Fisher Information Matrix for an asymptotic analysis; (iii) cost contour plots and (iv) a robust Monte-Carlo sampling approach. Results can be used to define and solve optimal experimental design problems aimed at improving identifiability. Besides, the validity of models along with the significance and determinability of their parameters are assessed using the χ^2 goodness of fit and Pearsons χ^2 tests, the autocorrelation of residuals, and the Akaike and Bayesian information criteria.

2.5 Optimal experimental design

To improve identifiability, users may automatically design simultaneous or sequential experiments optimizing observables, initial and stimulation conditions, number and location of sampling times and experiment durations. The tool allows for different design objectives and experimental error descriptions.

2.6 (Multi-objective) Optimal control

AMIGO2 solves optimal control problems with flexibility in the objective functional, stimuli interpolation, and path and point constraints. The aim is to find time varying stimulation conditions to maximize or minimize a given objective related to cell performance or to a desired behavior. The control vector parameterization method with mesh refining allow the efficient solution for smooth control profiles. Pareto fronts with best trade-offs for multi-objective cases can be obtained with the weighted sum method, the ϵ-constraint approach or the multi-objective genetic algorithm NSGA-II (Deb *et al.*, 2002).

2.7 C based enhancements

The tool generates C code to offer the following modes of operation: (i) C based simulation, compatible with all tasks; (ii) C based cost function and (iii) stand-alone C code for parameter estimation.

2.8 Numerical methods

AMIGO2 incorporates the MATLAB-based initial value problem solvers as well as CVODES (Hindmarsh *et al.*, 2005) to cover stiff, non-stiff and sparse dynamic systems. Parametric sensitivities can be computed by either direct methods or various finite differences schemes. Also, exact Jacobians can be obtained using symbolic manipulation. Regarding the optimizers, AMIGO2 interfaces to a suite of state-of-the-art solvers to cover constrained convex and non-convex, multi-objective non-linear optimization problems. Users can also test their optimizers within the toolbox.

2.9 Documentation

Descriptions of tool underlying theory, numerical methods, and usage are provided on the web page. Users can access HTML documentation from the MATLAB Help menu. Step by step examples illustrate the usage of the tool and serve as templates for new problems.

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Conflict of Interest: none declared.

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