

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

Table S1: Summary of features of systems biology dynamic modelling related toolboxes

	AMIGO2	COPASI	Data2Dynamics	SBtoolbox2/IQM
Programming Environment	MATLAB plus MEX	Stand-alone	MATLAB plus MEX	MATLAB plus MEX
Types of models	ODEs	General non-linear ODEs	Biochemical reaction equation based models	Biochemical reaction equation based models
	PDEs / DDEs	Link to external simulators (blackbox)	N.A.	N.A.
Model simulation	Runge-Kutta; Adams; BDF methods; CVODES	LSODAR; Gillespi and hybrids for stochastic simulation	CVODES	CVODES
Sensitivity analysis	Local / Global sensitivities (parameters and initial/boundary conditions); Finite differences with several formulae; CVODES	Local sensitivities; Metabolic control analysis; Finite differences	Local sensitivities; CVODES	Local and global sensitivities; Metabolic control analysis; CVODES
Identifiability analysis	Asymptotic (Fisher Information Matrix, Local sensitivities); cost plots; robust Monte-Carlo	Asymptotic (Fisher Information Matrix, local sensitivities)	Asymptotic (Fisher Information Matrix, local sensitivities); Profile likelihood	Asymptotic (Fisher Information Matrix, local sensitivities); Monte-Carlo
Parameter estimation	Multi-experiment; local and global parameters and initial conditions; several cost functions; several noise models; multiple local and global optimizers; sequential hybrid optimizers; general constraints; PE Cost in C or Full C code for PE	Multi-experiment; several cost functions; several noise models; several local and global optimizers	Multi-experiment; local and global unknowns; several cost functions; several noise models; several local and global optimizers	Multi-experiment; local and global unknowns; several cost functions; several noise models; several local and global optimizers
Best fit Post-Analysis	Several best-fit analyses; analysis of residuals	Several best-fit analyses; analysis of residuals	Several best-fit analyses; analysis of residuals	Several best-fit analyses; analysis of residuals
Regularization techniques	Tikhonov regularization with fixe regularization parameter or L-Shape Pareto curve; exact Jacobians	N.A.	N.A.	N.A.
Optimal experimental design	Multi-experiment; several cost functions; several noise models; Designs observables; Number and location of sampling times; Stimulation and initial conditions; Experiment(s) duration(s); experimental constraints	N.A.	N.A.	N.A.

(Multi-objective) Optimal control / design / Dynamic flux balance analysis	Non-linear constrained optimization; flexible cost functions; path and point constraints; single- or multi-objective	N.A.	N.A.	N.A.
Other features	Test your own optimizer; Network visualization with Cytoscape	Stoichiometric analysis of the reaction network; Time scale separation analysis; Lyapunov exponents; Network visualization	Some distributed computing facilities; Network visualization	Stoichiometric analysis of the reaction network; Steady-state and stability analysis; Pharmacology tools; Network visualization

N.A.: Not available

Table S2: Comparison between AMIGO and AMIGO2 - Summary of novelties in AMIGO2

Model simulation	CVODES
Sensitivity analysis	New finite differences schemes; CVODES
Parameter estimation	New experimental noise models
	New PE cost functions (more weighted least squares possibilities)
	New enhanced optimizers - exact Jacobian
	New asymptotic confidence analysis in parameters and observables
	Nonlinear constraints
	C enhancements: PE Cost in C or Full C code for PE
Identifiability analysis	Updated for new noise models
Best fit Post-Analysis	N.A. in AMIGO
Regularization techniques	N.A. in AMIGO
Optimal experimental design	Desing of observables
	Simultaneous desing of number and location of sampling times
	Updated stimulation design
	Nonlinear constraints
(Multi-objective) Optimal control / design / Dynamic flux balance analysis	N.A. in AMIGO
Other features (above)	N.A. in AMIGO
Other improvements	Bugs corrected