Time course simulation replicability of SBML-supporting biochemical network simulation tools

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I certify that all material in this thesis which is not my own work has been identified and that no material is included for which a degree has previously been conferred on me.

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Abstract

Background

Modelling and simulation are important tools for understanding biological systems. Numerous modelling and simulation software tools have been developed for integrating knowledge regarding the behaviour of a dynamic biological system described in mathematical form. The Systems Biology Markup Language (SBML) was created as a standard format for exchanging biochemical network models among tools. However, it is not certain yet whether actual usage and exchange of SBML models among the tools of different purpose and interfaces is assessable. Particularly, it is not clear whether dynamic simulations of SBML models using different modelling and simulation packages are replicable.

Results

Time series simulations of published biological models in SBML format are performed using four modelling and simulation tools which support SBML to evaluate whether the tools correctly replicate the simulation results. Some of the tools do not successfully integrate some models. In the time series output of the successful simulations, there are differences between the tools.

Conclusions

Although SBML is widely supported among biochemical modelling and simulation tools, not all simulators can replicate time-course simulations of SBML models exactly. This incapability of replicating simulation results may harm the peer-review process of biological modelling and simulation activities and should be addressed accordingly, for example by specifying in the SBML model the exact algorithm or simulator used for replicating the simulation result.

Background

Computational modelling and simulation of biological systems

Past and recent efforts in the characterization of biological system components, such as complete genome sequencing, have increased our knowledge about the corresponding biological systems. However, in order to understand how a biological system functions as a whole, it is required to integrate our understanding of the system's parts and to see whether or to what extent those pieces of understanding will predict the system's behaviours [1, 2]. Biological modelling can be defined as such an integration effort.

A model can be defined as any representation of a system [3]. There are several approaches in biological modelling, including the simplest directed graphs or pathway models (in which molecules are vertices and the reactions are the edges), Boolean models (in which a biological object is in an on or off state), differential equation models (in which chemical kinetics rate equations are used to represent molecule concentrations deterministically and continuously over time), and stochastic models (in which the number of molecules is considered as a discrete quantity and the change occuring to them is probabilistic) [4, 5].

On the other hand, simulation can be defined as a representation which embodies information contained in a model, and which provides access to the model by allowing computation of system behaviour [3]. The simulation of biological models serves to check the consistency of the postulated model with a set of experimental measurements; it can explore the possible behaviours of the model, help to postulate new hypotheses, support wet experiments, and even test experimentally unfeasible scenarios [2, 6–9]. Modelling and simulation of biological system is an important tool in the emerging field of systems biology [9–12].

Variety of software tools

There has been a variety of computational software implemented or developed for quantitative modelling and simulation of biological systems. The software can be divided into two broad groups [2, 13]: general-purpose mathematical software (for example, MATLAB [14]), and specialised modelling and simulation tools (for example, Gepasi [6]). In the tools, the cellular reactions are typically described by sets of differential equations that are solved using numerical integration methods, presuming that all the model parameters possess predefined values [15].

Standard format of models

There have also been efforts to define standards for representing biological models. The Systems Biology Markup Language (SBML) [16, 17] and CellML [18, 19] are two different computer-readable XML-based formats for representing biological models. Both formats are designed for the exchange of biological models. Nevertheless, SBML seems to gain more popularity among software tools; it is now supported by over 90 software systems [17], compared to less than ten applications supporting CellML [19].

Necessity for evaluation of existing platforms in biological modelling and simulation

Since the importance of biological modelling and simulation is realized more and more and many platforms of modelling and simulation, such as tools and standards as mentioned above, are emerging, there is a need to evaluate the variety of platforms to help the scientific community choose the right platform to use or to improve if necessary. Knowledge of interoperability between platforms is also of importance to make use of the available tools efficiently.

However, there have been very few studies on evaluating the variety of tools for modelling and simulation of biological systems and evaluating aspects of SBML. Nordling [20] investigated the available cellular network modelling software in order to evaluate their usability in modelling of large-scale cellular regulatory networks, but did not take into account the SBML features of the tools. Pettinen et al. [15] evaluated the properties of several simulation tools by actually performing time series simulations using the tools, but the study includes SBML evaluation in only one of the tools. While one study [21] compared SBML to other standards for representation of biological pathways, it did not take into account SBML's capacity in representing quantitative biological models.

The widely available tools supporting SBML are not accompanied with studies of how well SBML can be used as intended to exchange models between tools. Particularly, it is not clear whether dynamic simulation of SBML models using different modelling and simulation packages is replicable. A model in SBML format might be saved and reopened using different tools, but it is not clear whether the tool can replicate the simulation result.

This study tries to evaluate several biochemical network modelling and simulation tools that claim to support SBML in their ability to replicate dynamic simulation of models in SBML format. Time series simulations of biological models in SBML are performed using the tools and the differences in the resulting simulations are investigated.

Results and Discussion

Time course simulations of biological models in SBML format were performed using four biochemical modelling and simulation software packages. These packages are

CellDesigner version 3.0 [22], Jarnac version 2.16g [23]—which is used via JDesigner in the Systems Biology Workbench (SBW) environment version 2.5.0 [24], Copasi (*Co*mplex *Pa*thway *Si*mulator) 4.0 Build 15 [25] which is the successor of Gepasi [6], and the web-based SBML ODE Solver version 1.5 that uses libSBML version 2.3.2 (C. Flamm, personal communications) at the SBML Model Integration Server [26, 27]. A detailed description of the research approach can be found in the Methods section of this manuscript.

Pairwise tool comparisons

Out of 44 models from the BioModels Database [28], only 16 can produce complete time course simulations with no error messages by using all the four tools. Time course simulations for the other models may be performed by only some of the tools. Therefore, comparative analysis was done only for the time course simulations of those 16 models. Out of 238 chemical species from those 16 SBML models, 38 have constant values and so are excluded from the analysis. The score of difference between each tool pair were calculated using the formula shown in the Methods section of this manuscript.

The comparative analysis of the simulation result shows that there are differences between the tools. This is shown by the score of differences which are not zero. Out of 1200 comparisons from 200 species, only 5 have a score of zero, meaning that only 5 pairs of time course simulation data are perfectly equal. The other pairs have non-zero scores, indicating that most of the simulation data are not perfectly replicable. The score of differences between each pair for each species are shown in Additional File 1. The average score of difference per time step (that is, the total score of difference for all species divided by the number of analysed species,

200, divided by the number of time steps, 1000) between the tool pairs as shown in Table 1 ranges from approximately 0.1 to 1×10^8.

Table 1 - Average score of difference per time step between each tool-pair

	Jarnac	Copasi	CellDesigner
Copasi	1.24565675×10^8		
CellDesigner	1.24565503×10^8	0.1044503	
SBML ODE Solver	1.24565522×10^8	0.6174724	0.72375788

Table 1 also shows that the tool pair CellDesigner-Copasi has the most similarity among the tool pairs, with the lowest value of average difference of 0.10445 per time step. Furthermore, the scores for the tool pair are the lowest for 180 out of 200 analysed species, as shown in Additional File 1. On the other hand, the pair Jarnac-SBML ODE Solver has the highest score for 147 out of 200 species.

The high average scores of difference between the pairs Jarnac-Copasi, Jarnac-SBML ODE Solver, and Jarnac-CellDesigner in a magnitude of 10^8 indicate that the difference between the pairs is caused by the tool Jarnac. The score difference is very noticeable particularly for the model BIOMD0000000041. For some species in the model, the score difference between the three tool pairs and the other pairs can reach a magnitude of 1×10^9 (see Additional File 1). This difference seems to be caused by an error in SBML to Jarnac script translation; it did not initialize the compartment volume values from the SBML model and leave the parameters to have the default value of 1.

The Pearson product moment correlation coefficients of time-series data between each tool pair for each species as shown in Additional File 2 also show that the simulation results are not perfectly equal. This is shown by the values of the coefficients which are not 1. The coefficient value of 1 must be retrieved if two time-series data between each tool pair for each species have a perfectly linear relationship.

Table 2 shows that the datasets from the tool pair CellDesigner-Copasi have perfect linearity for 158 out of 200 species, while the tool pair Jarnac-SBML ODE Solver has the least linearity of 8 out of 200 species. This is in accordance with the results indicated by the score of differences.

The difference in the simulation result might be due to different numerical methods the tools use for solving differential equations [15]. The version of Jarnac in this study uses CVODE [29] as the default integrator to solve differential equations, though LSODA [30] is also available. SBML ODE Solver also implements CVODE (hence CellDesigner, which uses SBML ODE Solver as its simulator). Copasi uses LSODA as its integrator. It is interesting that the closest pair in this study is CellDesigner-Copasi, while each of them uses different integrator.

Other possible sources of difference in the simulation results are the difference in rounding off the decimals in the integration or calculations and the difference in the decimal place in the time course simulation output. For example, in Copasi, for reactions which involve only metabolites from one compartment, the rate law imported from SBML is multiplied with the volume of that compartment. The rounding off of the result of this calculation might cause differences in the integration result.

The differences in the simulation results between the tools need to be considered carefully. The differences indicate that the simulation results are not perfectly replicable and this might hinder the process of peer review of biological modelling and simulation in a sense that someone cannot replicate simulation results of someone else's model. Science is an iterative process and replication of previous works in the peer review process is needed as a means of quality control. The purpose of modelling is to as much as possible mimic natural phenomena, and modellers try to

make sure that the simulation results of the model replicate the data obtained from wet experiments. One way to check the validity of a model is by replicating the simulation results. If we cannot replicate the simulation results of a model developed by others, we cannot be sure that the model is valid.

The small differences in the simulation result might be a reason for one to say that the differences are not significant. However, how small the difference is and how much the difference can be tolerated is relative. "Gold standard" as a guidance for tolerating the small differences that can be accepted should be agreed on by the community of biological modelling and simulation discipline.

Unsuccessful simulations

None of the tools were capable of performing time course simulation of all the 44 models. Some models could not be opened (or imported) by some of the tools, some models could be opened but then simulation could not be started, and some tools even crashed when opening some model files. Out of 44 models, the tool CellDesigner retrieved 40 time course simulations, Jarnac got 28, Copasi got 21, and SBML ODE Solver got 39. Table 3 summarises the unsuccessful time course simulations encountered by the tools.

While all the tools support SBML Level 2 Version 1 (L2V1), not all of them fully support the specification. SBML ODE Solver's implementation of "events" is not fully SBML conformant. CellDesigner uses SBML ODE Solver as its simulator, so this applies as well, although that is not indicated in the simulation results (no error or warning messages). The version of Jarnac used in this study does not support events. Copasi does not support events either, and it might explain the failure in importing the SBML files containing events. Copasi does not fully support the SBML

feature of “rules” either, as also indicated by simulation error messages generated by the tool.

Many of the simulation failures cannot be explained only by referring to the error message the tools generate. Some failures are not even accompanied with any error messages. This happens for CellDesigner in simulating the model with BioModels ID BIOMD0000000001 and for Copasi in simulating models BIOMD0000000009 and BIOMD0000000042. The former case happens as the simulation is executed; the simulation panel of CellDesigner does not show any progress in simulation. In the latter case, Copasi crashes after the import of the SBML files. The lack of documentation regarding error messages and the tools not having logging systems makes it very difficult to explain the simulation failures.

A particular model with BioModels ID BIOMD0000000020 does not include species or reactions. CellDesigner, Jarnac, and Copasi cannot generate any time series simulation of the model, while SBML ODE Solver manages to produce the simulation of the model’s parameter values. The model is taken from the Hodgkin-Huxley squid-axon model which concerned the flow of electric current through the surface membrane of a giant nerve fibre [31]. In the SBML model, the variables are not chemical species but, for example, transmembrane voltage and electrical currents. Therefore, they are not defined as species (with the corresponding processes as reactions), but as parameters (with the corresponding processes as equations in the rules). The web-based SBML ODE Solver by default includes time series simulation of all the species and parameter values in the output; therefore time series data of the model are still retrievable using the tool. On the other hand, although CellDesigner by default also includes all species and parameter values, the time course simulation cannot be run without having any species in the model. The error message generated

by Jarnac while trying to perform the time course simulation of the model stated that the tool does not recognise the type of rule(s) used in the model. This might be caused by incomplete support of Jarnac to the “rule” feature of SBML. Copasi cannot import the model, probably because this tool does not support rules either.

The incapability of the tools to perform time course simulations does not seem to depend on the size of the model. The model BIOMD0000000014, which describes a Mitogen Activated Protein Kinase (MAPK) cascade with scaffold protein [32], includes 86 species and 300 reactions. Nevertheless, time course simulation data from the model are obtainable using all the four tools.

Conclusions

Evaluation of SBML simulation replication capability of four different tools in biochemical modelling and simulation has been done in this study. SBML is widely supported among biochemical modelling and simulation tools. Nevertheless, not all simulators can replicate exactly time-course simulation of SBML models.

Since SBML was developed for exchanging biological models between tools, the incapability of simulators to replicate the simulation results of SBML models may harm the peer-review process of biological modelling and simulation activities. While models in SBML may be used in different tools, the interpretation and integration of the models into dynamic simulation must be repeatable among the tools in order to make possible the replication of previous works in the scientific process. Therefore, the irreplicability of the simulation results of SBML models should be addressed accordingly.

An example of how to address the problem is by including in the SBML model the specification which explains how to obtain replicable simulation, such as

stating the exact simulator or algorithm used for simulating the SBML model. Such clear statements will help to ensure that simulation replicability is testable in the peer-review processes.

To avoid problems of replicability due to software not fully supporting SBML features, informative documentation specifically regarding SBML conformance of tools is also required.

Methods

Overview

In this study, time series simulations of biological models in SBML format were performed using four different applications that support SBML. The differences in time course simulation datasets between each pair of tools are calculated as the score of difference between the tool pair and as the Pearson product moment correlation coefficient.

Simulation tools and models compared

The biochemical simulation tools being compared in this study are CellDesigner 3.0 [22], Jarnac 2.16g used via JDesigner in the Systems Biology Workbench (SBW) environment version 2.5.0 [23, 24], Copasi (*Co*mplex *Pa*thway *Si*mulator) 4.0 Build 15 [25], and the web-based SBML ODE Solver version 1.5 that uses libSBML version 2.3.2 at the SBML Model Integration Server [26, 27].

The models in SBML format are taken from the BioModels Database [28], particularly the third release (July 28, 2005). The database is chosen since it is the largest publicly accessible SBML model repository. All the models have been published in peer-review publications and verified by the BioModels Database curators. The 44 models from the third release of the database (BioModels ID

BIOMD0000000001–BIOMD0000000045; BIOMD0000000019 does not exist) were downloaded in SBML Level 2 Version 1 format.

Time course simulation

Time course simulations of all 44 models are performed using the four different tools. Each SBML model file is opened (CellDesigner, JDesigner), imported (Copasi), or uploaded (SBML ODE Solver) to each tool manually and time course simulation is done using the simulation feature of the tool. The simulations are ended at the time point where the system is assumed to reach a steady state; that is when all values of species are visually observed to reach a constant or, in case of oscillatory result, when (three or four periods of) stable oscillations have occurred. The simulation end time point is set the same for the same model simulated in the different tools. The simulation time is divided into 1000 time steps for all the models (that is, “number of points” in CellDesigner, “intervals” in Copasi, and “print step” in SBML ODE Solver are set to 1000, while “number of points” in Jarnac/JDesigner is set to 1001). All simulations using the standalone tools (CellDesigner, Jarnac/JDesigner, and Copasi) are done on an ordinary desktop PC with a 730 MHz processor and 256 MB RAM on Microsoft Windows platform. The simulation result is time series data, showing the value of the magnitude (in this case, the concentration) of each species in a model for each time step of the simulation.

Comparative analysis

The difference between time course simulation data of two different tools is checked using the score of difference and the Pearson product moment correlation coefficient between the two datasets. The score of difference is used to see how different the simulation results are by checking the differences between the magnitudes of the

species for each time steps. The Pearson product moment correlation coefficient is used to see how linear the relationship between the pair of datasets is.

The score of difference between a pair of tools for a species is calculated by using the following equation:

$$\text{Score of difference} = \sum (x - y)^2 ,$$

where x is the magnitude of the simulated species of one tool at a particular time step, while y is the magnitude of the simulated species of the other tool at the same particular time step.

The Pearson product moment correlation coefficient between datasets of time course simulation of a chemical species using two different tools is calculated using the following equation:

$$r = \frac{n\left(\sum xy\right) - \left(\sum x\right)\left(\sum y\right)}{\sqrt{\left[n\sum x^2 - \left(\sum x\right)^2\right]\left[n\sum y^2 - \left(\sum y\right)^2\right]}},$$

where r is the Pearson product moment correlation coefficient, n is the number of time steps in the simulation (1000), x is the magnitude of the simulated species of one tool, while y is the magnitude of the simulated species of the other tool.

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Tables

Table 2 - Perfect linearity of time course simulation datasets between each tool pair for each species for 200 species

	Jarnac	Copasi	CellDesigner
Copasi	12		
CellDesigner	19	158	
SBML ODE Solver	8	16	16

Table 3 - SBML components of models and failure in time course simulation

BioModels ID	SBML components					Tools			
	Comp.	Species	React.	Rules	Events	CellDes	JDesigner	Copasi	SOS
BIOMD0000000001	1	12	17	0	2	Us?	Ume	Um9	Use
BIOMD0000000002	1	13	17	0	0			Um9	
BIOMD0000000003	1	3	7	2	0		Um34	Usr	
BIOMD0000000004	1	5	7	2	0		Us4	Usr	
BIOMD0000000005	1	7	9	0	0				
BIOMD0000000006	1	3	3	0	0				
BIOMD0000000007	1	22	25	15	2		Umr	Um10	Use
BIOMD0000000008	1	6	13	0	0				
BIOMD0000000009	1	22	20	0	0			Um?	
BIOMD0000000010	1	8	10	0	0				
BIOMD0000000011	1	22	30	0	0			Usi	
BIOMD0000000012	1	7	12	0	0				
BIOMD0000000013	1	27	21	0	0		Usi	Usi	Usi
BIOMD0000000014	1	86	300	0	0				
BIOMD0000000015	1	18	37	0	0	Um1			
BIOMD0000000016	3	7	10	1	0			Wmr	
BIOMD0000000017	1	19	14	0	0			Usi	
BIOMD0000000018	2	33	47	2	0		Um5	Wmr	
BIOMD0000000020	1	0	0	16	0	Usx	Umr	Um9	Wsx
BIOMD0000000021	2	10	24	2	0		Us4	Wmr	
BIOMD0000000022	3	13	32	0	0		Us4	Um9	Wsf
BIOMD0000000023	1	13	11	0	0			Um10	
BIOMD0000000024	1	3	4	0	0		Um6	Um9	Wsf
BIOMD0000000025	1	4	4	0	2		Ume	Um9	Use
BIOMD0000000026	1	11	10	0	0		Us7		
BIOMD0000000027	1	5	4	0	0		Us7		
BIOMD0000000028	1	16	17	0	0				
BIOMD0000000029	1	6	7	0	0			Um10	
BIOMD0000000030	1	18	20	0	0				
BIOMD0000000031	1	6	4	0	0		Us7		
BIOMD0000000032	2	37	47	0	0		Um8	Um10	
BIOMD0000000033	1	32	26	0	0				
BIOMD0000000034	2	9	22	6	0		Umr	Um9	Wsf
BIOMD0000000035	1	10	16	0	0				
BIOMD0000000036	2	3	5	0	0				
BIOMD0000000037	1	12	12	0	0	Um2			
BIOMD0000000038	1	17	10	0	0				
BIOMD0000000039	3	5	7	0	0				
BIOMD0000000040	1	5	5	0	0			Um11	
BIOMD0000000041	2	10	9	0	0				

BIOMD0000000042	1	15	25	0	0	Um?
BIOMD0000000043	3	5	7	0	0	Um10
BIOMD0000000044	3	7	8	0	0	Um10
BIOMD0000000045	4	4	8	0	0	

The “SBML components” columns indicate the number of particular SBML components the models have. The “tools” columns indicate the unsuccessful or incomplete time course simulation result (U), complete simulation result with warning message (W), and complete simulation result without warning (no mark); m indicates the error happens when opening or importing the model, s indicates the error happens when executing simulation. Some identified errors are indicated by e (the tool not supporting SBML “events”), f (the tool not supporting user defined functions), i (mathematical integration failed), r (the tool not supporting SBML “rules”), and x (no species in the model). The unidentified error messages are indicated by numbers:

1. CellDesigner error: “String index out of range: -1”;
2. CellDesigner error: “Line=411: cvc-complex-type.2.4.b: The content of element 'listOfParameters' is not complete. One of '{"http://www.sbml.org/sbml/level2":notes, "http://www.sbml.org/sbml/level2":annotation, "http://www.sbml.org/sbml/level2":parameter}' is expected”;
3. JDesigner error: “Error while trying to read SBML file in LoadSBMLFile: Syntax error: expecting number, identifier or left bracket”;
4. JDesigner error: “Method Call Error: Error while initializing and calling model fcn: Outer Exception Handler <EMathError>: Divide by Zero error during model equation evaluation: n=0 d=0 while computing ModelFcn”;
5. JDesigner error: “Method Call Error: Error in loadSBMLFromString”;
6. JDesigner error: “Error while trying to read SBML file in LoadSBMLFile: Syntax error: missing right bracket”;

7. JDesigner error: “Method Call Error: Error while initializing and calling model fcn: Outer Exception Handler <ESymNotInitialsied>: Warning: Symbol [uVol] has not been initialised with a value”;
8. JDesigner error: “Error while trying to read SBML file in LoadSBMLFile: LoadFromStream: Error in ParseXMLDoc: Internal Error in getEdgeType: too many products (UniX)”;
9. Copasi error: “Error while loading file! >EXCEPTION date and time< .\SBMLImporter.cpp (438) compiled: Sep 13 2005 11:55:19”;
10. Copasi error: “Error while loading file! >EXCEPTION date and time< CReaction (7): CMetab object '[species name]' is neither substrate, product nor modifier to the reaction”;
11. Copasi error: “Error while loading file! >EXCEPTION date and time< CReaction (7): SBML(10): Copasi does not support stoichiometric expressions yet”.

The mark “?” indicates failure without any error messages. “Comp.”: compartment; “React.”: reactions; “CellDes”: CellDesigner; “SOS”: SBML ODE Solver.

Additional files

Additional file 1 – Score of difference.xls

The file is a Microsoft Excel file showing the score of differences between each tool pair for each species. The lowest and the highest scores for each species are indicated by different shading. The score of difference shows the difference in the time series data between two tools for the same species; lower score means lower difference and vice versa. See Methods section for detailed explanation for obtaining the values.

BioModels ID	Jarnac-Copasi	Copasi-SBML ODE Solver	SBML ODE Solver-CellDesigner	Jarnac-SBML ODE Solver	Copasi-CellDesigner	Jarnac-CellDesigner	Nr. of species
BIOMD0000000005	8.4109E-11	1.82469E-12	1.78974E-12	8.57685E-11	1.16947E-14	8.43344E-11	6
	1.47524E-06	1.82749E-06	1.79531E-06	2.51776E-06	1.15632E-08	1.62191E-06	
	2.26898E-06	2.72245E-06	2.65622E-06	3.61622E-06	7.39404E-09	2.48304E-06	
	3.73882E-06	4.53895E-06	4.43168E-06	6.16529E-06	1.25109E-08	4.09926E-06	
	7.99308E-11	1.15261E-14	1.13714E-14	7.99486E-11	2.2064E-17	7.99346E-11	
	7.43554E-07	8.43629E-07	8.24945E-07	1.18151E-06	2.41104E-09	8.16189E-07	

BIOMD0000000006	6.47138E-06	9.9227E-06	1.02205E-05	2.83803E-05	4.11355E-09	6.14974E-06	2
	1.09163E-05	1.75748E-05	1.8081E-05	4.89733E-05	6.88631E-09	1.03797E-05	
BIOMD0000000008	6.62736E-05	0.001861819	0.001838153	0.002610229	7.87371E-08	7.08631E-05	5
	0.000754124	0.020803883	0.020533459	0.029202863	9.26239E-07	0.000807307	
	0.000647527	0.018602548	0.018364547	0.025986199	7.96067E-07	0.000693282	
	7.76831E-09	2.95621E-06	2.95329E-06	2.96847E-06	5.37676E-10	7.38273E-09	
	5.39887E-09	1.87166E-06	1.87121E-06	1.98041E-06	3.23491E-11	5.77831E-09	
BIOMD0000000010	0.226262883	0.04822703	0.050428978	0.091379926	4.84812E-05	0.232165836	8
	0.226260559	0.0482244	0.050426775	0.091383801	4.81094E-05	0.232165836	
	6.451968219	0.858253996	0.901377692	2.991485791	0.0008753	6.582792812	
	1.620472904	0.22205987	0.233112195	0.830635394	0.000199263	1.65484801	
	3.222787896	0.516179749	0.536187371	1.545136472	0.000386892	3.283461714	
	4.70922967	1.142792923	1.171747954	2.183713466	0.001246243	4.836887742	
	0.836827313	0.415566086	0.421243593	0.387868299	0.000386894	0.860105987	
	6.952714103	1.805243579	1.86360837	2.635749955	0.001733692	7.136570297	
BIOMD0000000012	0.080587069	1238.534171	1238.735861	1257.366353	0.006202824	0.089455448	6
	0.0602335	1032.703835	1033.301137	1046.64167	0.009911666	0.055527554	
	0.055180496	1209.161541	1209.063329	1224.5915	0.006259026	0.064260728	
	0.084854814	1319.079433	1319.295065	1339.127064	0.006493156	0.093795392	
	0.063024758	1098.627525	1099.316508	1113.48127	0.010189888	0.057889081	
	0.060044618	1353.156214	1352.973963	1370.320338	0.006684903	0.070163258	
BIOMD0000000014	5.538E-09	3.379E-09	3.32019E-09	1.3459E-08	8.2836E-11	5.45439E-09	86
	4.63E-10	4.88E-10	3.70751E-10	1.245E-09	9.31225E-11	4.52381E-10	
	2.1703E-10	7.982E-11	7.85308E-11	3.2453E-10	8.53515E-13	2.17552E-10	
	2.56E-10	2.82E-10	1.93237E-10	6.22E-10	7.8626E-11	2.65059E-10	
	1.96E-08	1.1778E-08	1.17007E-08	4.7742E-08	8.68881E-11	1.94046E-08	
	8.57554E-10	4.51408E-10	4.49813E-10	1.97844E-09	7.24366E-13	8.56524E-10	
	1.52533E-10	5.18048E-11	5.19814E-11	2.69863E-10	9.85691E-15	1.52264E-10	
	7.0465E-10	3.1344E-10	3.06441E-10	1.56503E-09	4.36426E-12	7.11547E-10	
	8.27096E-11	1.22943E-11	1.17746E-11	9.86314E-11	8.112E-13	8.14745E-11	
	2.20606E-10	8.62242E-11	8.5739E-11	4.22512E-10	1.14577E-14	2.207E-10	
	2.05748E-09	1.81238E-09	1.78545E-09	6.3047E-09	7.36945E-12	2.06583E-09	
	3.96526E-09	2.44483E-09	2.33553E-09	9.86911E-09	7.9393E-11	3.99575E-09	
	1.04462E-09	4.57438E-10	4.51676E-10	2.16675E-09	7.70315E-13	1.04592E-09	
	2.93727E-10	1.38322E-10	1.38035E-10	6.36882E-10	1.17218E-14	2.93523E-10	
	2.58753E-10	8.02723E-11	7.86903E-11	4.43462E-10	7.68985E-13	2.57139E-10	
	1.02842E-10	4.08342E-11	3.99254E-11	1.79864E-10	6.41028E-13	1.01628E-10	
	3.09199E-09	1.68003E-09	1.67881E-09	7.2543E-09	8.42056E-13	3.08739E-09	
	4.22397E-10	2.52471E-10	2.54036E-10	9.7345E-10	2.33808E-14	4.20679E-10	
	1.05275E-10	3.42606E-11	3.33855E-11	1.54431E-10	7.9626E-13	1.04562E-10	
	5.15906E-10	2.40344E-10	2.36661E-10	1.08071E-09	7.44141E-13	5.14694E-10	
	1.39754E-10	4.80431E-11	4.79363E-11	2.18589E-10	6.7587E-14	1.40019E-10	
	2.65682E-10	1.0182E-10	9.99711E-11	5.3945E-10	7.42847E-13	2.65059E-10	
	9.53696E-11	4.36373E-11	4.33997E-11	1.93213E-10	2.01207E-14	9.54306E-11	
	5.64507E-11	4.77954E-13	4.36368E-13	5.73089E-11	1.46419E-15	5.64733E-11	
	1.7035E-10	6.51454E-11	6.53202E-11	2.89455E-10	9.79475E-15	1.70094E-10	
	1.11016E-10	9.39732E-12	9.39345E-12	1.14443E-10	1.43259E-15	1.10991E-10	
	1.05352E-10	1.1486E-13	1.15123E-13	1.05469E-10	1.7427E-16	1.05348E-10	
	8.52875E-11	2.07657E-12	2.06892E-12	8.13588E-11	7.50561E-15	8.51754E-11	
	7.65384E-11	2.10676E-13	2.10636E-13	7.93315E-11	7.8116E-17	7.65399E-11	
	1.57889E-10	1.77567E-16	1.77586E-16	1.57873E-10	1.50488E-19	1.57889E-10	

8.46511E-11	5.78301E-13	5.81136E-13	8.82602E-11	7.82523E-15	8.458E-11
6.84692E-11	1.3198E-13	1.30627E-13	6.95069E-11	1.11547E-16	6.84751E-11
8.70358E-11	1.8475E-16	1.85739E-16	8.70277E-11	1.63832E-19	8.70362E-11
7.44073E-11	8.03016E-13	8.02067E-13	7.55006E-11	7.95195E-15	7.44142E-11
2.22816E-10	3.21307E-10	3.20297E-10	8.17277E-10	2.25401E-14	2.23239E-10
5.9511E-11	2.5048E-13	2.68485E-13	6.00585E-11	8.61126E-16	5.9511E-11
2.12404E-10	3.3217E-10	3.3486E-10	8.64815E-10	8.19078E-13	2.09237E-10
7.5874E-11	2.9606E-11	2.96445E-11	1.10944E-10	1.15378E-14	7.58365E-11
5.42648E-11	1.41709E-12	1.37412E-12	5.54303E-11	2.05095E-15	5.42805E-11
1.47733E-10	3.15696E-11	3.13549E-11	1.68492E-10	1.18226E-13	1.47919E-10
6.92169E-11	1.83098E-12	1.8315E-12	7.32995E-11	1.62468E-16	6.92084E-11
3.8771E-11	8.25522E-15	8.26011E-15	3.87784E-11	2.82489E-18	3.87712E-11
1.203E-10	1.91089E-11	1.91476E-11	1.47462E-10	7.1012E-14	1.19911E-10
6.17763E-11	8.78825E-13	8.77778E-13	6.57528E-11	3.3201E-16	6.17694E-11
1.07288E-10	9.2987E-15	9.31825E-15	1.0712E-10	1.35294E-18	1.07289E-10
1.60756E-10	2.90778E-11	2.92258E-11	2.24442E-10	1.18203E-14	1.6073E-10
1.03076E-10	1.41848E-12	1.41164E-12	1.06328E-10	2.4487E-16	1.03066E-10
6.74448E-11	4.98148E-15	4.99486E-15	6.75362E-11	2.9569E-19	6.74434E-11
8.14864E-11	2.14586E-12	2.19215E-12	8.93584E-11	8.40253E-15	8.14026E-11
1.11408E-10	6.77178E-13	6.77058E-13	1.12863E-10	4.04421E-17	1.11412E-10
1.51235E-10	4.05819E-15	4.05853E-15	1.51279E-10	3.59456E-20	1.51236E-10
1.01227E-10	3.36739E-13	3.42463E-13	1.03726E-10	1.27402E-16	1.01195E-10
8.70274E-11	1.70707E-15	1.73652E-15	8.72476E-11	1.74025E-18	8.70226E-11
9.48965E-11	1.32921E-17	1.33592E-17	9.4914E-11	2.91887E-21	9.48964E-11
8.78784E-11	1.06437E-13	1.08402E-13	8.91745E-11	9.97974E-17	8.78627E-11
5.54256E-11	3.27649E-13	3.26504E-13	5.64879E-11	2.01569E-16	5.5424E-11
7.95739E-11	1.52375E-15	1.52971E-15	7.96435E-11	8.26607E-19	7.95735E-11
1.22994E-10	1.02811E-11	1.03705E-11	1.58171E-10	8.97438E-15	1.22734E-10
7.94121E-11	1.6783E-12	1.66574E-12	8.27922E-11	3.30143E-16	7.94178E-11
1.28278E-10	3.63189E-15	3.63594E-15	1.28138E-10	4.39822E-19	1.2828E-10
9.81359E-11	5.22708E-12	5.31601E-12	1.12283E-10	8.71674E-15	9.79134E-11
9.38417E-11	5.30618E-13	5.3046E-13	9.45826E-11	9.1587E-17	9.38146E-11
8.38021E-11	2.98716E-15	2.9875E-15	8.37884E-11	3.43745E-20	8.38018E-11
9.1247E-11	3.24883E-13	3.32112E-13	9.14203E-11	1.45099E-16	9.12574E-11
7.0037E-11	4.43383E-15	4.45075E-15	7.00519E-11	1.763E-18	7.00391E-11
7.2738E-11	1.32723E-17	1.33036E-17	7.27551E-11	2.40591E-21	7.27377E-11
7.1678E-11	8.47154E-14	8.64608E-14	7.21316E-11	8.95072E-17	7.16686E-11
9.59217E-11	6.87816E-13	6.85466E-13	9.49397E-11	5.03134E-16	9.5848E-11
1.41293E-10	1.98253E-15	1.99662E-15	1.4121E-10	9.90689E-19	1.41295E-10
1.24297E-10	1.33374E-11	1.36063E-11	1.66398E-10	1.10069E-14	1.23885E-10
1.5258E-10	5.66263E-11	5.66439E-11	2.25081E-10	3.29242E-14	1.52342E-10
1.09979E-10	1.71492E-11	1.70297E-11	1.17401E-10	1.06847E-14	1.0963E-10
6.65561E-11	3.85735E-13	3.9045E-13	6.69289E-11	2.0393E-16	6.65481E-11
1.09242E-10	3.51004E-13	3.56536E-13	1.10483E-10	1.23295E-16	1.09221E-10
1.80862E-10	1.46756E-10	1.47718E-10	4.77096E-10	6.69083E-13	1.79355E-10
1.30868E-10	3.34292E-11	3.37968E-11	1.30711E-10	7.91073E-14	1.31035E-10
1.07516E-10	1.52596E-11	1.5399E-11	1.29535E-10	1.21575E-14	1.07482E-10
8.94279E-11	9.47275E-12	9.53064E-12	1.19584E-10	7.73163E-15	8.95351E-11
8.13417E-11	2.78104E-12	2.7994E-12	8.17926E-11	4.33212E-16	8.13243E-11
8.99834E-11	1.75805E-12	1.76289E-12	9.23507E-11	1.18677E-16	8.99591E-11
6.81292E-11	3.21816E-14	3.2779E-14	6.78488E-11	1.85592E-17	6.8133E-11

	7.22238E-11	3.60341E-12	3.6474E-12	8.32579E-11	2.81312E-15	7.21354E-11	
	8.47592E-11	3.924E-12	3.9526E-12	9.08138E-11	6.54296E-16	8.46775E-11	
	8.92537E-11	1.44417E-12	1.45234E-12	9.23731E-11	1.19244E-16	8.92267E-11	
	7.76659E-11	1.67782E-14	1.69633E-14	7.82037E-11	5.35712E-18	7.7658E-11	
	9.90638E-11	4.27815E-12	4.37921E-12	1.10518E-10	4.1043E-15	9.89637E-11	
BIOMD0000000028	0.055178596	0.021666	0.021511564	0.028309716	0.000106132	0.054625775	16
	0.015643125	0.00764731	0.007600389	0.019098135	9.54214E-05	0.015385819	
	0.008879958	0.003520802	0.003495793	0.004602087	3.3279E-06	0.008782931	
	0.072276412	0.020298872	0.020316263	0.053905927	6.39712E-05	0.071660462	
	0.000174705	3.59732E-05	3.59381E-05	0.000111123	8.55276E-07	0.000173675	
	3.8934E-06	5.35884E-05	5.35951E-05	5.38562E-05	1.91526E-08	3.84951E-06	
	0.001778999	0.0009818	0.000979372	0.000979191	1.79758E-06	0.001773293	
	5.25961E-05	1.10316E-05	1.09334E-05	3.04148E-05	2.17673E-08	5.19935E-05	
	8.2639E-06	3.3641E-06	3.32543E-06	4.5496E-06	1.19592E-08	8.19143E-06	
	0.003549218	0.00140319	0.001377546	0.001884714	7.92149E-06	0.003498821	
	0.002373214	0.002756597	0.002754428	0.003389306	1.45813E-06	0.002349447	
	5.56007E-05	0.000133763	0.000133953	0.000157206	4.30147E-08	5.50427E-05	
	6.34243E-05	0.000134649	0.000134422	0.000135667	2.88874E-08	6.25988E-05	
	5.41687E-06	2.3463E-05	2.34173E-05	2.1846E-05	1.06507E-08	5.33038E-06	
	4.53928E-05	0.00017477	0.000175719	0.000194063	9.15648E-07	4.42191E-05	
	0.001969838	0.00250618	0.002498369	0.002879596	1.48314E-06	0.001946394	
BIOMD0000000033	19936.40359	0	19936.36663	19936.40359	19936.36663	1.71125E-08	28
	137.5189166	51	147.7386833	216.9243366	113.2520178	20.32635459	
	3.483E-07	3.483E-07	1.69615E-08	0	3.69957E-07	1.69446E-08	
	1.2236004	0	1.223888547	1.2236004	1.223888547	1.69451E-08	
	20.89834915	34.2386	34.82975602	104.5555951	0.017799619	20.32635444	
	20.89833355	34.2386	34.8297404	104.5555795	0.017783999	20.32635443	
	2548.647997	2352.909723	2372.331295	7589.652454	1.712015425	2544.12751	
	2550.543052	2354.26	2372.215568	7589.343088	3.38743001	2544.12751	
	42216.79479	28928.48212	29343.90919	132490.7507	5.471460191	41786.85907	
	42281.31476	29131.7902	29493.55386	132727.7828	63.02179085	41786.85907	
	185.5662897	207	167.8236384	358.7963697	80.29014592	95.81668167	
	95.85618127	91.2849	91.93922901	288.7716681	0.103431319	95.81668194	
	87.42909685	11	87.63652422	88.05277685	87.21594467	0.165479039	
	0.165611329	0.41616806	0.41536792	0.697128865	0.000453098	0.165479046	
	11.86547544	0	11.8672995	11.86547544	11.8672995	8.46228E-07	
	3.24754E-05	0.00017301	0.000179222	0.000200079	3.5232E-05	8.46223E-07	
	426.6259097	724	655.9648655	1305.79143	80.66635691	344.7733775	
	426.1830867	724.0301	655.667842	1305.288215	80.35753363	344.7733784	
	341.2386755	440.04	397.1915249	934.3930415	79.35405219	259.0834499	
	342.6570211	449.0104	399.6587716	938.0611275	82.35138281	259.0834501	
	0.001480938	0.010011765	0.004367041	0.005277325	0.001182684	0.000718521	
	0.45401062	0.01	0.476088618	0.45779862	0.472915756	0.000718521	
	41127.66578	17008.77982	17199.41918	106748.9523	5.959832237	40845.88544	
	41219.83408	17128.61	17282.9406	106876.2394	55.36818235	40845.88544	
	0.020377443	0.941012657	0.950343306	0.949439827	0.014886575	0.001923227	
	0.092423855	1	1.582843039	1.580103855	0.088574935	0.001923227	
	140.7001822	0	140.7025763	140.7001822	140.7025763	2.64332E-05	
	0.597473173	0.250004	0.791476853	0.792656893	0.597629551	2.64332E-05	
BIOMD0000000035	37.95095057	342.4040167	340.5531594	607.9691477	0.006507194	38.55682491	9
	48.58919252	459.4997979	456.8621928	806.368147	0.008475295	49.4266327	

	6.52384E-05	0.000592119	0.000589278	0.001050024	7.34589E-09	6.61697E-05	
	6.52389E-05	0.00059213	0.000589291	0.001050042	7.30056E-09	6.61697E-05	
	5.18217E-05	0.000468419	0.000466222	0.000831527	5.73835E-09	5.25451E-05	
	5.18221E-05	0.000468396	0.0004662	0.0008315	5.69402E-09	5.25451E-05	
	0.104779206	0.946630439	0.942048363	1.680716118	1.16379E-05	0.106287447	
	0.07054953	0.653316896	0.650041043	1.152234307	9.31421E-06	0.071589986	
	47.7235962	442.0726601	439.7407415	779.4463075	0.008444374	48.47173875	
BIOMD0000000036	1.18188E-05	0.011810849	0.011456777	0.012437509	3.88095E-06	2.68358E-05	2
	3.44275E-05	0.026133007	0.025552198	0.027383759	6.28741E-06	6.42237E-05	
BIOMD0000000038	7.305E-11	4.1E-11	8.19538E-11	8.205E-11	7.15161E-11	1.43158E-12	13
	1.36485E-08	1.04E-08	1.59993E-08	1.58685E-08	1.21945E-08	1.14756E-09	
	1.71458E-08	3.4523E-08	3.46768E-08	3.09378E-08	8.5751E-09	7.87954E-09	
	2.02132E-06	6.9107E-06	6.93206E-06	5.91087E-06	1.26765E-08	1.96165E-06	
	1.52113E-08	5.1902E-08	5.16023E-08	4.52815E-08	1.48065E-10	1.47614E-08	
	0.000125063	0.00043199	0.000429062	0.000355524	9.31444E-07	0.000120326	
	3.56244E-07	7.08729E-06	7.11695E-06	6.65104E-06	1.07191E-09	3.47462E-07	
	9.24656E-05	0.00032551	0.000323148	0.000266505	7.23458E-07	8.94982E-05	
	9.4293E-05	0.000326258	0.000324775	0.000267161	7.68232E-07	9.17913E-05	
	1.11576E-06	3.5973E-06	3.56886E-06	3.02141E-06	8.77177E-09	1.09443E-06	
	4.79329E-07	2.24306E-06	2.24481E-06	2.08412E-06	1.01029E-08	4.63953E-07	
	3.4948E-10	2.63212E-08	2.64246E-08	2.50092E-08	6.92209E-11	2.6604E-10	
	2.88386E-07	8.454E-07	8.38511E-07	9.58266E-07	8.16153E-09	2.78738E-07	
BIOMD0000000039	0.003787758	0.591352648	0.581769327	0.643949635	0.000621948	0.006793278	5
	0.001039417	0.303317035	0.300536112	0.323992326	0.000146637	0.001762349	
	0.000453095	0.127257768	0.126174824	0.135849054	5.05571E-05	0.000726981	
	0.003325512	0.84454348	0.835489225	0.900045186	0.000520229	0.005089907	
	0.003325512	0.84454348	0.835489225	0.900045186	0.000520229	0.005089907	
BIOMD0000000041	2.57632E+12	1555.800004	1533.971864	2.57626E+12	1.253922863	2.57632E+12	10
	11421241.59	0.123378	0.121788488	11420685.78	0.000147817	11421217.93	
	1.94093E+13	12035.37	12129.94709	1.94093E+13	56.35607319	1.94093E+13	
	5104.087999	0.000785577	0.000791937	5101.86207	1.10944E-07	5104.0791	
	6523.599038	1.74475E-06	1.77315E-06	6523.462248	6.03056E-10	6523.599243	
	395.1286928	10.9433	10.77966364	472.110719	0.010711589	396.6535393	
	460.0328086	0.01441237	0.014480252	460.0533222	0.000146454	460.0417799	
	6570.008483	83.82	83.76066222	6870.977511	1.369066028	6431.581545	
	2.724E+12	1617.61	1648.621609	2.72404E+12	1.088296191	2.724E+12	
	2.03491E+11	11.3436	11.51548724	2.03491E+11	0.009399168	2.03491E+11	
BIOMD0000000045	4.64606E-07	0.003265079	0.003066966	0.005219189	3.36585E-06	1.42634E-06	4
	0.000216671	0.581378069	0.553469958	1.398486734	0.001842513	0.000807803	
	0.000244873	0.673149983	0.637331572	1.682268246	0.002097905	0.000922591	
	1.81786E-05	0.142681461	0.134070702	0.250483037	0.000145751	6.33238E-05	
Total	2.49131E+13	123494.4783	144751.5764	2.49131E+13	20890.05136	2.49131E+13	200
Average score	1.24566E+11	617.4723916	723.7578822	1.24566E+11	104.4502568	1.24566E+11	

Color legend: lowest score for a species

highest score for a species

Additional file 2 – Pearson correlation.xls

The file is a Microsoft Excel file showing the Pearson product moment correlation coefficient of time-series data between each tool pair for each species. The coefficient reflects the extent of a linear relationship between two time-series data sets of two tools for the same species; coefficient of 1 means that the two data sets are perfectly linear. A dash ("-") indicates that the coefficient is not available for the particular time-series data pair due to mathematical constraint.

BioModels ID	Jarnac-Copasi	Copasi-SBML ODE Solver	SBML ODE Solver-CellDesigner	Jarnac-SBML ODE Solver	Copasi-CellDesigner	Jarnac-CellDesigner	Nr. of species
BIOMD0000000005	0.999996083	0.999999904	0.999999906	0.999995491	0.999999999	0.999995574	6
	0.999999923	0.999999904	0.999999906	0.999999869	0.999999999	0.999999915	
	0.999998923	0.999998709	0.999998741	0.999998283	0.999999996	0.999998822	
	0.999999822	0.999999784	0.999999789	0.999999708	0.999999999	0.999999805	
	0.99892253	0.999999844	0.999999846	0.998922187	1	0.998922484	
	0.999999751	0.999999717	0.999999723	0.999999603	0.999999999	0.999999726	
BIOMD0000000006	0.999995261	0.999992745	0.999992527	0.999979217	0.999999997	0.999995497	2
	0.999999421	0.999999066	0.999999039	0.999997388	1	0.999999449	
BIOMD0000000008	0.999997085	0.999917926	0.99991897	0.999884976	0.999999997	0.999996883	5
	0.999994194	0.999839838	0.999841921	0.99977517	0.999999993	0.999993785	
	0.999992569	0.999786686	0.999789417	0.999701984	0.999999991	0.999992044	
	1	0.999999994	0.999999994	0.999999994	1	1	
	1	0.999999915	0.999999915	0.99999991	1	1	
BIOMD0000000010	0.999999786	0.999999952	0.99999995	0.999999916	1	0.99999978	8
	0.999999786	0.999999952	0.99999995	0.999999916	1	0.99999978	
	0.999999696	0.999999956	0.999999954	0.999999863	1	0.999999689	
	0.999999098	0.999999878	0.999999871	0.999999529	1	0.999999078	
	0.999999787	0.999999961	0.999999959	0.999999904	1	0.999999782	
	0.999999629	0.999999911	0.999999909	0.999999824	1	0.999999619	
	0.999999381	0.999999681	0.999999678	0.999999708	1	0.999999365	
	0.999999657	0.999999911	0.999999908	0.999999867	1	0.999999647	
BIOMD0000000012	0.999999984	0.999708539	0.999708411	0.999704373	0.999999999	0.999999983	6
	0.99999999	0.999777857	0.999777767	0.999774974	0.999999998	0.999999989	
	0.999999987	0.999647719	0.999647651	0.999643496	0.999999998	0.999999985	
	0.999999984	0.999696979	0.999696849	0.999692624	0.999999999	0.999999983	
	0.999999989	0.999770729	0.999770623	0.999767739	0.999999998	0.999999989	
	0.999999985	0.999611441	0.999611416	0.999606734	0.999999998	0.999999983	
BIOMD0000000014	0.999999994	0.999999997	0.999999997	0.999999988	1	0.999999995	86
	0.999999998	0.999999998	0.999999999	0.999999996	0.999999999	0.999999998	
	0.999999998	1	1	0.999999998	1	0.999999998	
	0.999999998	0.999999998	0.999999999	0.999999997	0.999999999	0.999999998	
	0.999999996	0.999999998	0.999999998	0.999999992	1	0.999999996	
	0.999999994	0.999999997	0.999999997	0.999999987	1	0.999999994	
	0.999999952	0.999999987	0.999999987	0.999999925	1	0.999999952	
	1	1	1	0.999999999	1	1	
	0.999999994	0.999999999	1	0.999999993	1	0.999999994	
	0.999999989	0.999999997	0.999999997	0.999999983	1	0.999999989	
	0.999999999	1	1	0.999999999	1	0.999999999	
	0.999999999	1	1	0.999999998	1	0.999999999	
	0.999999998	0.999999999	0.999999999	0.999999997	1	0.999999998	
	0.999999978	0.999999991	0.999999991	0.999999959	1	0.999999978	

0.999999989	0.999999997	0.999999997	0.999999983	1	0.999999989
0.999999995	0.999999999	0.999999999	0.999999994	1	0.999999995
0.999999996	0.999999998	0.999999998	0.999999992	1	0.999999996
0.999999977	0.999999989	0.999999989	0.999999954	1	0.999999977
0.999999997	0.999999999	0.999999999	0.999999997	1	0.999999997
0.999999992	0.999999997	0.999999997	0.999999987	1	0.999999992
0.999999991	1	1	0.99999999	1	0.999999991
0.999999998	1	1	0.999999998	1	0.999999998
0.999999919	0.999999982	0.999999983	0.999999895	1	0.999999919
0.999997039	0.999999989	0.999999989	0.999997026	1	0.99999704
0.999999967	0.999999996	0.999999996	0.999999956	1	0.999999967
0.999998901	0.999999916	0.999999916	0.999998828	1	0.999998901
0.999995797	0.999999995	0.999999995	0.999995782	1	0.999995797
0.999999727	0.999999998	0.999999998	0.999999726	1	0.999999727
0.999990963	0.999999998	0.999999998	0.999990975	1	0.999990963
0.995162907	0.999999987	0.999999987	0.995165976	1	0.995162888
0.999999204	0.999999996	0.999999996	0.999999187	1	0.999999204
0.999992638	0.999999995	0.999999995	0.999992644	1	0.999992638
0.991445902	0.999999976	0.999999976	0.991440183	1	0.991445886
0.999999454	0.999999994	0.999999994	0.999999446	1	0.999999454
0.999999982	0.999999995	0.999999995	0.999999972	1	0.999999982
0.999999604	0.999999998	0.999999998	0.999999601	1	0.999999604
0.999999996	0.999999999	0.999999999	0.999999994	1	0.999999996
0.999999895	0.99999998	0.99999998	0.99999988	1	0.999999895
0.999999864	0.999999999	0.999999999	0.999999863	1	0.999999864
0.999999995	0.999999999	0.999999999	0.999999994	1	0.999999995
0.999998693	0.999999994	0.999999994	0.999998687	1	0.999998693
0.999955706	0.99999999	0.99999999	0.999955668	1	0.999955705
0.999999986	0.999999998	0.999999998	0.999999982	1	0.999999986
0.99999913	0.999999993	0.999999993	0.999999112	1	0.99999913
0.999709455	0.999999967	0.999999967	0.999709258	1	0.999709454
0.999999968	0.999999994	0.999999994	0.999999959	1	0.999999968
0.999996091	0.999999959	0.999999959	0.999996012	1	0.999996092
0.995989247	0.999999661	0.99999966	0.995988202	1	0.995989287
0.999999728	0.999999994	0.999999994	0.999999709	1	0.999999728
0.999938281	0.999999629	0.99999963	0.999937423	1	0.999938282
0.958673506	0.999998554	0.999998554	0.958653272	1	0.958673394
0.999997529	0.999999994	0.999999994	0.999997507	1	0.99999753
0.999526978	0.999999991	0.99999999	0.999525599	1	0.999526993
0.85709066	0.999999966	0.999999966	0.857094368	1	0.85709069
0.999990845	0.999999992	0.999999991	0.999990805	1	0.999990846
0.999998141	0.999999994	0.999999994	0.999998122	1	0.999998141
0.999180756	0.99999998	0.99999998	0.999181443	1	0.999180749
0.999999925	0.999999992	0.999999992	0.999999909	1	0.999999925
0.999997862	0.999999966	0.999999966	0.999997798	1	0.999997862
0.994137698	0.999999831	0.999999831	0.994143203	1	0.994137602
0.999999766	0.999999988	0.999999988	0.999999736	1	0.999999766
0.999966526	0.9999998	0.9999998	0.999966272	1	0.999966533
0.969910169	0.999998566	0.999998566	0.969906773	1	0.969910165
0.999997062	0.999999992	0.999999992	0.999997061	1	0.999997061
0.999674315	0.999999982	0.999999982	0.999674542	1	0.999674314
0.657344985	0.999999938	0.999999938	0.657310333	1	0.657345894
0.999989926	0.999999991	0.999999991	0.99998989	1	0.999989927
0.999998425	0.999999992	0.999999992	0.999998393	1	0.999998425
0.997504384	0.999999968	0.999999968	0.997505268	1	0.99750435

	0.999999893	0.999999991	0.99999999	0.999999865	1	0.999999893	
	0.999999979	0.999999995	0.999999995	0.999999973	1	0.999999979	
	0.99999996	0.999999995	0.999999995	0.999999955	1	0.99999996	
	0.999997676	0.999999988	0.999999988	0.999997679	1	0.999997676	
	0.999996369	0.999999992	0.999999992	0.999996324	1	0.99999637	
	0.999999985	0.999999996	0.999999996	0.99999998	1	0.999999985	
	0.999999996	0.999999999	0.999999999	0.999999996	1	0.999999996	
	0.999999939	0.999999992	0.999999992	0.999999929	1	0.999999939	
	0.999999911	0.999999991	0.999999991	0.999999893	1	0.999999911	
	0.99999902	0.999999976	0.999999976	0.999999014	1	0.999999021	
	0.999992866	0.999999883	0.999999882	0.999992601	1	0.999992867	
	0.999948408	0.999999982	0.999999982	0.999948516	1	0.999948407	
	0.999999726	0.999999988	0.999999988	0.9999997	1	0.999999726	
	0.999999294	0.999999969	0.999999969	0.999999252	1	0.999999295	
	0.999991709	0.999999897	0.999999897	0.999991382	1	0.999991711	
	0.999918181	0.999999988	0.999999987	0.999917867	1	0.999918188	
	0.999999618	0.999999987	0.999999987	0.999999583	1	0.999999619	
BIOMD0000000028	0.999999999	0.999999997	0.999999997	0.999999998	1	0.999999999	16
	0.999999994	0.999999991	0.999999991	0.99999999	1	0.999999994	
	0.999999996	0.999999991	0.999999991	0.999999995	1	0.999999996	
	0.999999995	0.999999986	0.999999986	0.999999989	1	0.999999995	
	0.999999996	0.999999992	0.999999992	0.999999995	1	0.999999995	
	0.999999997	0.999999676	0.999999676	0.999999674	1	0.999999997	
	0.999999999	0.999999997	0.999999997	0.999999998	1	0.999999999	
	0.999999995	0.999999991	0.999999991	0.999999995	1	0.999999994	
	0.999999999	0.999999996	0.999999996	0.999999997	1	0.999999999	
	0.999999999	0.999999996	0.999999996	0.999999998	1	0.999999999	
	0.999999996	0.999999946	0.999999946	0.999999951	1	0.999999996	
	0.999999988	0.999999885	0.999999885	0.999999886	1	0.999999988	
	0.999999997	0.999999932	0.999999932	0.999999938	1	0.999999996	
	0.999999997	0.999999906	0.999999906	0.999999911	1	0.999999997	
	0.999999999	0.999999985	0.999999985	0.999999985	1	0.999999999	
	0.999999994	0.999999929	0.999999929	0.999999936	1	0.999999993	
BIOMD0000000033	-	-	-	-	-	-1	28
	0.999999953	0.999999977	0.999999948	0.999999907	0.999999975	0.999999992	
	1.71878E-09	1.71878E-09	1	1	1.71878E-09	1	
	-	-	-	-	-	1	
	0.999999992	0.999999985	0.999999985	0.999999957	1	0.999999992	
	0.999999992	0.999999985	0.999999985	0.999999957	1	0.999999992	
	0.999999998	0.999999997	0.999999997	0.999999994	1	0.999999998	
	0.999999998	0.999999997	0.999999997	0.999999994	1	0.999999998	
	0.999999991	0.999999992	0.999999992	0.99999997	1	0.999999991	
	0.999999991	0.999999992	0.999999991	0.999999969	1	0.999999991	
	0.999999994	0.999999991	0.999999993	0.99999999	0.999999996	0.999999998	
	0.999999998	0.999999997	0.999999997	0.999999994	1	0.999999998	
	0.999999755	0.999999969	0.999999755	0.999999755	0.999999754	1	
	1	0.999999999	0.999999999	0.999999999	1	1	
	0.999999761	1	0.999999761	0.999999761	0.999999761	1	
	1	1	1	1	1	1	
	0.999999999	0.999999998	0.999999998	0.999999997	1	0.999999999	
	0.999999999	0.999999998	0.999999998	0.999999997	1	0.999999999	
	1	1	1	1	1	1	
	1	1	1	1	1	1	
	1	1	1	1	1	1	

	0.999999999	1	0.999999999	0.999999999	0.999999999	1	
	0.999999995	0.999999996	0.999999996	0.999999984	1	0.999999995	
	0.999999995	0.999999996	0.999999996	0.999999984	1	0.999999995	
	1	1	1	1	1	1	
	1	1	1	1	1	1	
	0.999999999	1	0.999999999	0.999999999	0.999999999	1	
	1	1	1	1	1	1	
BIOMD0000000035	0.999999914	0.999999224	0.999999228	0.999998622	1	0.999999913	9
	0.999999906	0.999999111	0.999999116	0.99999844	1	0.999999904	
	0.999999791	0.999998102	0.999998112	0.999996635	1	0.999999788	
	0.999999791	0.999998102	0.999998112	0.999996635	1	0.999999788	
	0.999999815	0.999998331	0.999998339	0.999997037	1	0.999999813	
	0.999999815	0.999998331	0.999998339	0.999997037	1	0.999999813	
	0.999999833	0.999998492	0.9999985	0.999997323	1	0.999999831	
	0.999999959	0.999999623	0.999999624	0.999999334	1	0.999999959	
	0.999999925	0.999999307	0.999999311	0.999998778	1	0.999999924	
BIOMD0000000036	0.999999989	0.999986702	0.999987101	0.999985977	0.999999996	0.999999972	2
	0.999999992	0.999988937	0.99998918	0.999988437	0.999999997	0.999999982	
BIOMD0000000038	0.999999965	0.999999976	0.999999955	0.999999957	0.999999964	0.999999999	13
	0.999999991	0.999999993	0.999999994	0.999999992	0.999999994	1	
	0.999999995	0.999999991	0.999999993	0.999999991	0.999999998	0.999999999	
	0.999999999	0.999999996	0.999999996	0.999999995	1	0.999999999	
	0.999999999	0.999999996	0.999999996	0.999999995	1	0.999999999	
	0.999999995	0.999999979	0.999999979	0.999999976	1	0.999999995	
	0.999999998	0.999999944	0.999999944	0.999999944	1	0.999999998	
	0.999999993	0.999999969	0.999999969	0.999999966	1	0.999999993	
	0.999999991	0.999999963	0.999999963	0.999999959	1	0.999999991	
	0.999999998	0.999999994	0.999999994	0.999999993	1	0.999999998	
	0.999999999	0.999999996	0.999999996	0.999999995	1	0.999999999	
	1	0.999999992	0.999999992	0.999999992	1	1	
	0.999999994	0.999999977	0.999999977	0.99999997	1	0.999999994	
BIOMD0000000039	0.999779652	0.965565307	0.966114504	0.962510351	0.999963821	0.999604676	5
	0.999953693	0.986441418	0.986560038	0.985515375	0.999993533	0.999921465	
	0.999970588	0.990455929	0.99053473	0.98984105	0.999996244	0.999950991	
	0.999991269	0.996695333	0.99673015	0.996496448	0.999997964	0.999984498	
	0.999991269	0.996695333	0.99673015	0.996496448	0.999997964	0.999984498	
BIOMD0000000041	0.998375843	0.999999993	0.999999993	0.998377322	1	0.998375863	10
	0.999000991	0.999999995	0.999999995	0.99899982	1	0.999000949	
	0.999999812	0.999999984	0.999999984	0.999999858	1	0.999999813	
	0.450705107	0.999997481	0.999997473	0.450739622	0.999999999	0.45073167	
	-0.630211393	0.999999847	0.999999847	-0.630053511	1	-0.630207337	
	0.99999998	0.999999993	0.999999993	0.999999968	1	0.99999998	
	0.998173762	0.999999992	1	0.998173202	0.999999992	0.998173627	
	0.999999858	0.999999984	0.999999984	0.999999788	1	0.999999863	
	-0.99898364	0.999999966	0.999999965	-0.998974703	1	-0.998983731	
	-0.999602523	0.999999966	0.999999965	-0.999607414	1	-0.999602489	
BIOMD0000000045	0.999999947	0.999623851	0.999646669	0.003194424	0.999999612	0.999999836	4
	0.999977597	0.938469193	0.941563175	0.571461867	0.999810201	0.999916962	
	0.999998436	0.995695774	0.995925702	0.660588277	0.999986598	0.999994107	
	0.999999818	0.998570585	0.998656856	0.139694407	0.99999854	0.999999366	