Establishing *A Priori* Identifiability of Target Mediated Drug Disposition Models

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Abstract

A priori global identifiability of nonlinear systems assures that in an input/output experiment under ideal conditions, all unknown parameters have only one unique solution. Algorithms differential identifiability of systems (DAISY) and exact arithmetic rank (EAR) have been developed to systematically determine identifiability of a given system and experimental design.

Many biologics exhibit target mediated drug disposition (TMDD). In practice, TMDD models are over-parameterized or do not converge because it is difficult to describe the system with sparse clinical data, or when only the drug concentration is available. DAISY and EAR were used to test the *a priori* identifiability of a TMDD model as well as the quasi-steady state (QSS), quasi-equilibrium/rapid binding (QE/RB), Michaelis-Menten (MM) approximations and two extensions of the TMDD model. Surprisingly, the full TMDD is still *a priori* identifiable even if the drug concentration (free or total) is the only output of the system.

Methods

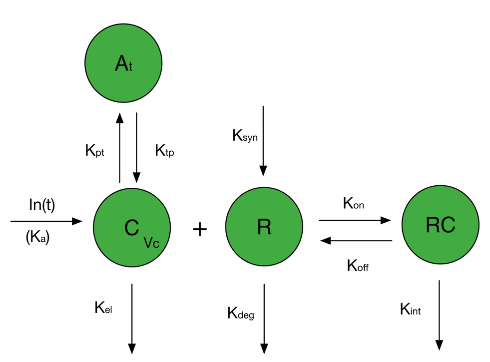

Figure 1: Classic Target-mediated drug dispostion model (TMDD)

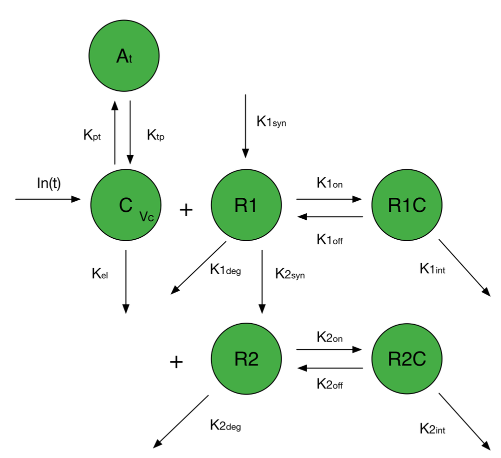

Figure 2: 2-Target TMDD

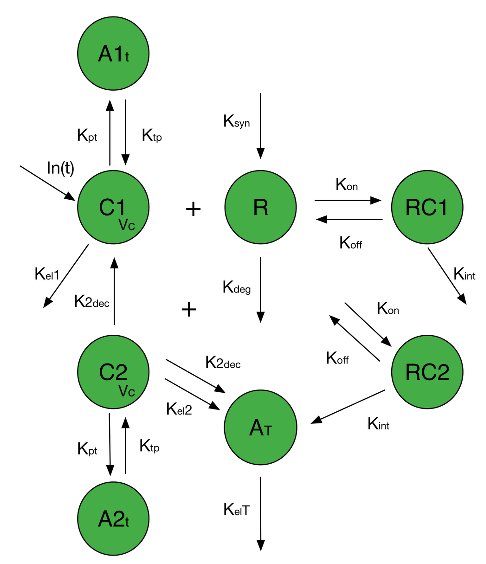

Figure 3: Antibody-drug conjugate model

Descriptions, input requirements and examples for each algorithm are highlighed below.

DAISY
A vector, **B** of inputs, outputs, and state variables
A vector, **B1**, of parameters
A set, **C**, of differential and output equations vector
A vector **IC**, of initial conditions

Table 1: Input requirements for DAISY

EAR
A set of differential equations and the initial condition for each assigned to variable, *deq*
The call "IdentifiabilityAnalysis" and arguments *deq*, vector of variables, independent variable, inputs and outputs

Table 2: Input requirements for EAR

DAISY was run as a package within REDUCE (v3.8) software [1]. The approach involves iterations of dividing the set of differentials by ranked input variables until a reduced set of minimum rank is reached. A test set of pseudorandom parameter values is evaluated within the reduced system to determine if a unique solution exists.

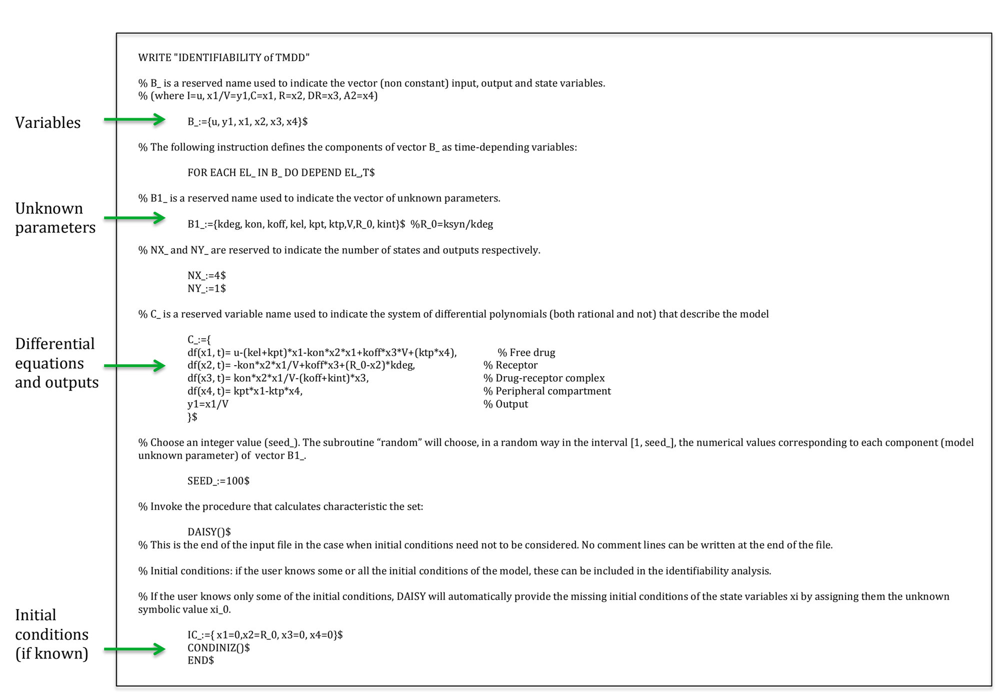

Figure 4: Example of DAISY input for TMDD

EAR is a package within Mathematica (v9.0) software [2]. EAR was used as an alternative approach for systems with complex rational constants or limited outputs, which DAISY could not resolve. EAR is designed to handle larger systems with more generally parameterized initial conditions. This algorithm constructs a Jacobian matrix of partial derivatives and performs rank testing to determine local identifiability.

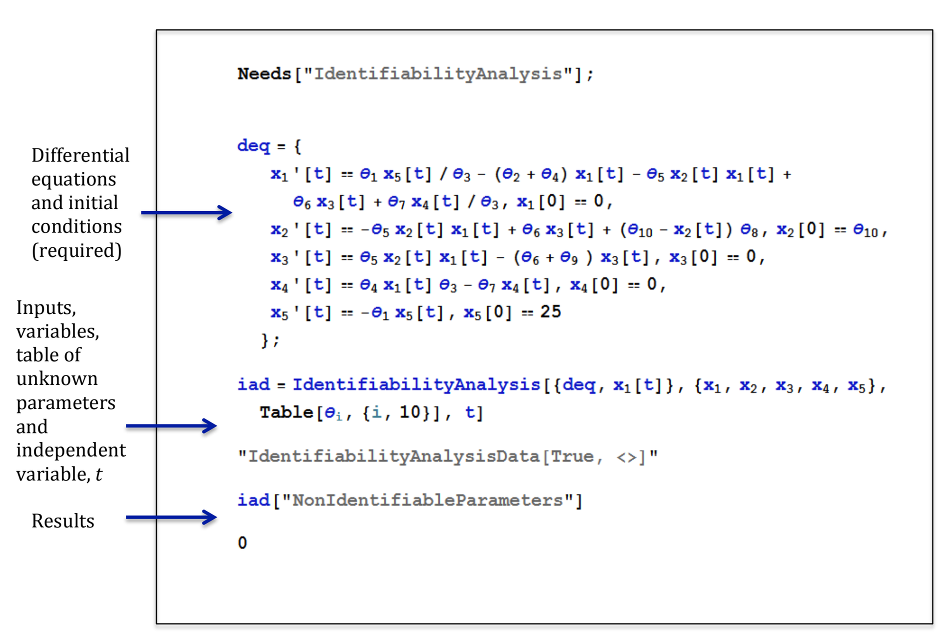

Figure 5: Example of EAR input and results for TMDD with depot compartment

Results

Model	Inputs	Outputs	Parameters	Result
TMDD	iv inf	Free drug	kon, koff, kel, kpt, ktp, Vc, ksyn, kdeg, kint	Globally identifiable
TMDD	iv inf	Target	Same as above	Globally identifiable
TMDD	iv inf	Complex	Same as above	Locally identifiable
TMDD	iv inf	Free drug & free target	Same as above	Globally identifiable
TMDD	iv inf	Free drug & complex	Same as above	Globally identifiable
TMDD	sc dose	Free drug	ka, kon, koff, kel, kpt, ktp, Vc, ksyn, kdeg, kint	Locally identifiable
TMDD	sc dose	Free drug & target	Same as above	Globally identifiable
TMDD	sc dose	Free drug, target, & complex	Same as above	Globally identifiable
QE	iv inf	Total drug	K_D, kel, kpt, ktp, Vc, ksyn, kdeg	Locally identifiable
QE	iv inf	Total target	Same as above	Locally identifiable
QE	iv inf	Total drug & total target	Same as above	Locally identifiable
QSS	iv inf	Total drug & free target	K_{SS}, kel, kpt, ktp, Vc, ksyn, kdeg	Locally identifiable
QSS	iv inf	Total target & complex	Same as above	Locally identifiable
QSS	iv inf	Total drug & total target	Same as above	Locally identifiable
MM	iv inf	Free drug & target	km, kint, kel, kpt, ktp, Vc, ksyn, kdeg	Globally identifiable
MM	iv inf	Total target	Same as above	Globally identifiable
MM	iv inf	Free drug & total target	Same as above	Globally identifiable

Table 3: Results for single target TMDD and approximations

TMDD Model	Inputs	Outputs	Parameters	Result
2-target	iv inf	Free drug	kdeg1, kdeg2, kon1, kon2, koff1, koff2, kel kpt, ktp, Vc, ksyn1, ksyn2, kint1, kint2	Locally identifiable
2-target	iv inf	Targets	Same as above	Globally identifiable
2-target	iv inf	Free drug & targets	Same as above	Globally identifiable
2-target	iv inf	Free drug & complexes	Same as above	Globally identifiable
ADC	iv inf	Drugs & complexes	kdeg, kon, koff, kel1, kel2, kelT, kpt, ktp, Vc, ksyn, kint, k2dec	Non-identifiable: kelT
ADC	iv inf	Drugs & target or complexes & target	Same as above	Non-identifiable: kelT
ADC	iv inf	Drugs & toxins or complexes & toxins	Same as above	Locally identifiable
ADC	iv inf	Drugs, targets, complexes & toxins	Same as above	Globally identifiable

Table 4: Results for TMDD model extensions. In the case of a non-identifiable system, the unidentifiable parameters are indicated

Conclusion

- The single-target TMDD model and model approximations are *a priori* identifiable in all input scenarios evaluated.
- Extension of TMDD model to 2-targets is *a priori* identifiable with any input. With the ADC model, the parameter kelT cannot be identified unless information about the toxin is available.
- Identifiability analyses are an important first step in modeling complex systems, as they immediately rule out efforts that are intractable. Furthermore, they assist in understanding which modifications of the experimental design or simplifications of the model would be necessary to achieve meaningful parameter estimates.

References

1. G. Bellu, M. P. Saccomani, S. Audoly, and L. D'Angió. Daisy: a new software tool to test global identifiability of biological and physiological systems. *Comput Methods Programs Biomed*, 88(1):52-61, Oct 2007.
2. J. Karlsson, M. Anguelova, and M. Jirstrand. 16th IFAC Symposium on System Identification (SYSID 2012), 2012, Brussels, Belgium, July 11-13, 2012.