

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

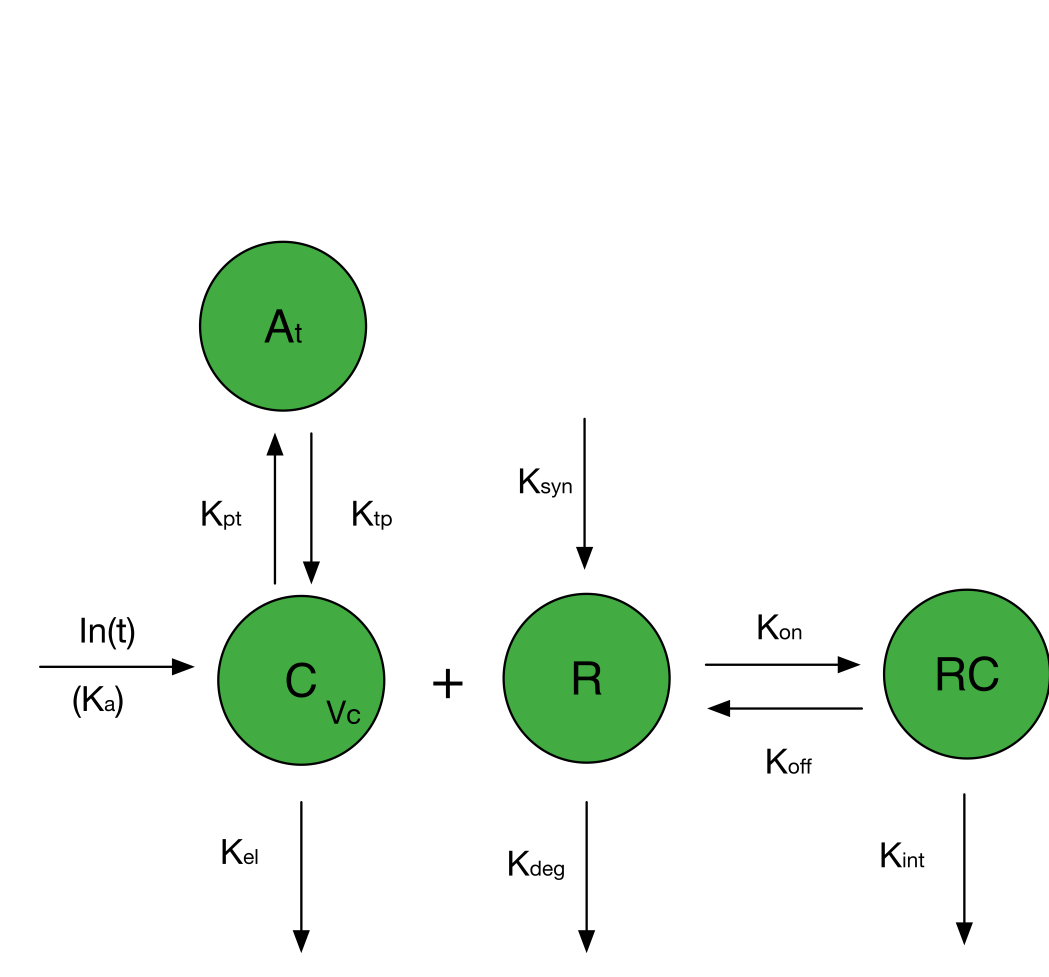


Figure 1: Classic Target-mediated drug disposition model (TMDD)

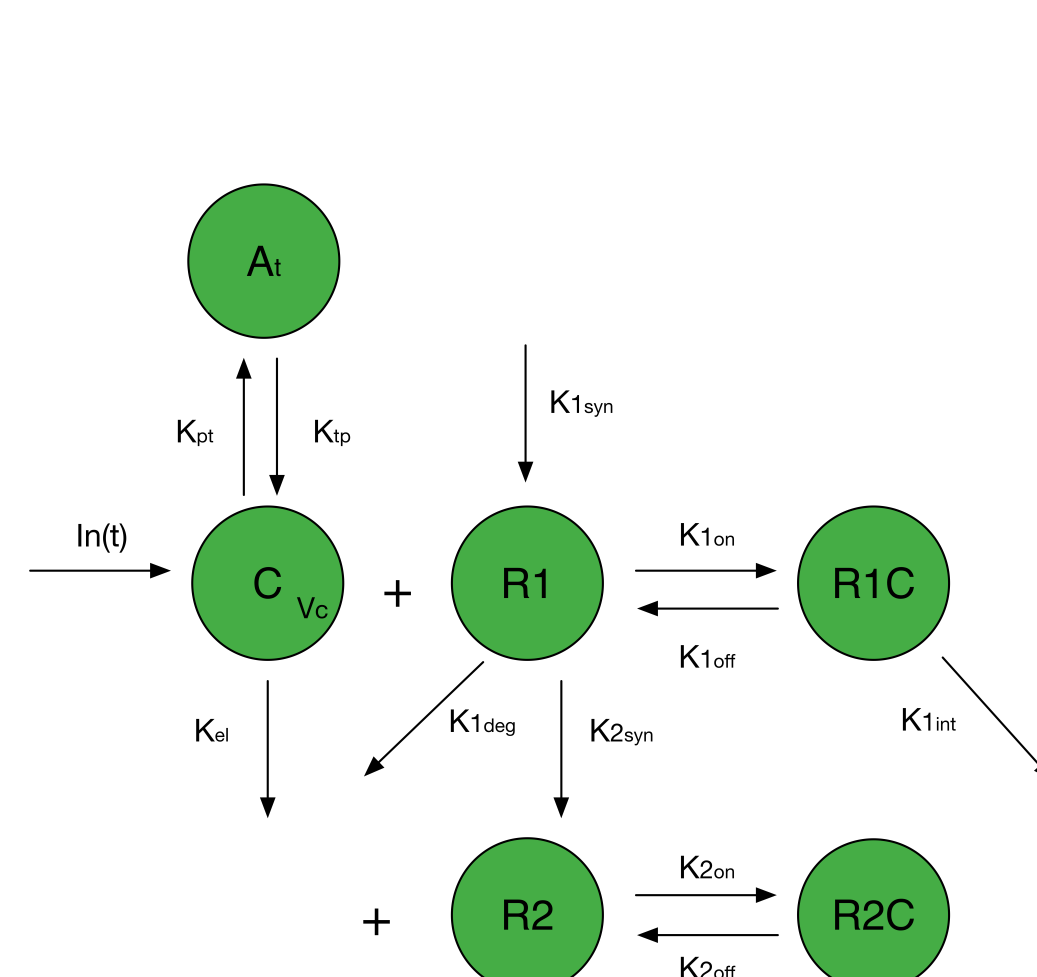


Figure 2: 2-Target TMDD

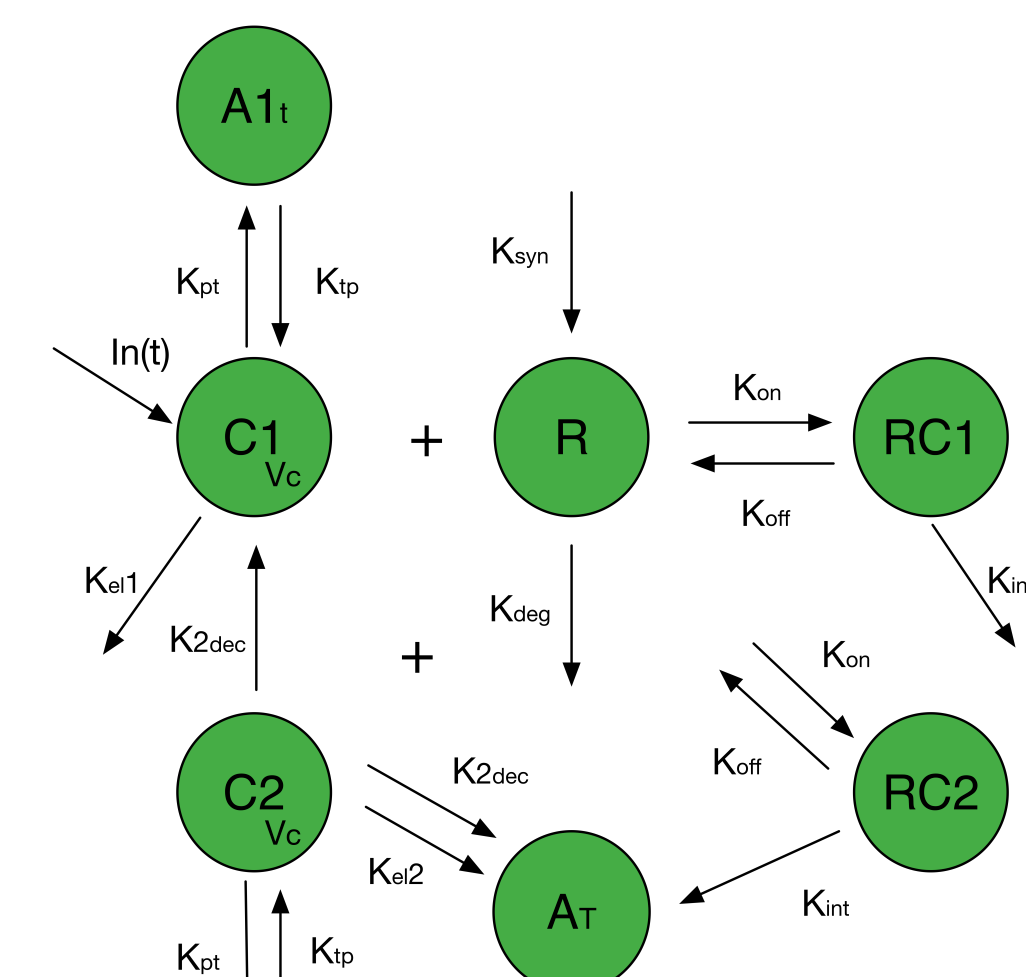


Figure 3: Antibody-drug conjugate model

Descriptions, input requirements and examples for each algorithm are highlighted 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, <i>deg</i> |
| The call "IdentifiabilityAnalysis" and arguments <i>deg</i> , 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.

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.

```
WRITE "IDENTIFIABILITY OF TMDD"
% B is a reserved name used to indicate the vector (non constant) input, output and state variables.
% before [p, x1, y1, L, C=1, R=2, D=3, A2=4]
% B1 is a reserved name used to indicate the vector of unknown parameters.
% before [kon, koff, kel, kpt, ktp, kdeg, kint]
% NC and NT are reserved to indicate the number of states and outputs respectively.
% NC=4
% NT=3
% C is a reserved variable name used to indicate the system of differential polynomials (each rational and int) that describe the model.
% C=1
%Free drug
% Receptor
% Drug-receptor complex
% Output
% Choose an integer value (see 1). The subroutine "randstr" will choose, in a random way in the interval [1, n], the numerical values corresponding to each component (model unknown parameters) of vector B1.
% Include the procedure that calculates characteristic the set.
DAISY()
% This is the end of the input file. In the user initial conditions need not to be considered. No comment lines can be written at the end of the file.
% Initial conditions if the user leaves some or all the initial conditions of the model, these can be included in the identifiability analysis.
% If the user knows only some of the initial conditions, DAISY will automatically provide the missing initial conditions of the state variables by assigning them the unknown symbolic value #S.
```

```
Needs["IdentifiabilityAnalysis"];
deg = {
  x1'[t] == theta_1 x2[t] / theta_2 - (theta_1 + theta_2) x1[t] - theta_3 x2[t] x1[t] +
  theta_4 x2[t] + theta_5 x4[t] / theta_6, x1[0] == 0,
  x2'[t] == -theta_5 x2[t] x1[t] + theta_6 x3[t] + (theta_10 - x2[t]) theta_8, x2[0] == theta_10,
  x3'[t] == theta_5 x2[t] x1[t] - (theta_6 + theta_5) x3[t], x3[0] == 0,
  x4'[t] == theta_4 x1[t] theta_5 - theta_5 x4[t], x4[0] == 0,
  x5'[t] == -theta_10 x1[t], x5[0] == 25
};
iad = IdentifiabilityAnalysis[deg, x1[t], {x1, x2, x3, x4, x5},
  Table[theta_i, {i, 10}], t];
IdentifiabilityAnalysisData[True, <>]
iad["NonIdentifiableParameters"]
0
```

Figure 4: Example of DAISY input for TMDD

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

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