Parameter Estimation with Integral Elimination

Louis Roussel

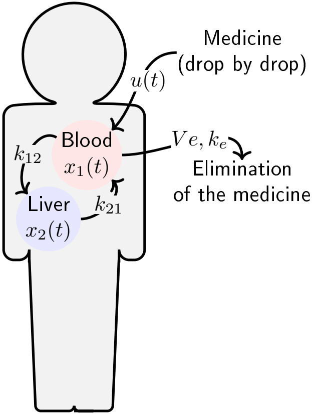
Laboratoire CRIStAL, Université de Lille (France)
2^{nd} year PhD Student
Supervised by François Boulier and François Lemaire

JNCF 2024

March 7,2024

Table of contents

Academic example taken from [Boulier et al., 2014]



$$\begin{cases} \dot{x}_1(t) = & -k_{12}\, x_1(t) + k_{21}\, x_2(t) \\ & -\frac{V_e\, x_1(t)}{k_e + x_1(t)} + u(t) \\ \dot{x}_2(t) = & k_{12}\, x_1(t) - k_{21}\, x_2(t) \\ y(t) = & x_1(t) \end{cases}$$

- $u(t)$: medicine (drop by drop). We simplify by taking $u(t) = 0$.
- $x_1(t)$: amount of medicine in the blood (known and noisy).
- $x_2(t)$: amount of medicine in the liver (unknown).

Eliminate to estimate

An example of **linear** differential system

$$\begin{cases} \dot{x}(t) = y(t) \\ \dot{y}(t) = \theta x(t) \end{cases}$$

- known quantity : $y(t)$
- unknown quantity: $x(t)$
- parameter : θ

To estimate the value of θ :

1 - **Elimination** : obtain the Input/Output equation [Fliess, 1989] : $\ddot{y}(t) = \theta y(t)$ which does not contain unknown quantities

2 - **Estimation** : estimate the parameters using the previous equation and the experimental datas (e.g : least squares)

Differential elimination and parameter estimation

$$\begin{cases} \dot{x}(t) = y(t) \\ \dot{y}(t) = \theta x(t) \end{cases}$$

$x(t)$ unknown

Differential Elimination

↓

$$\ddot{y}(t) = \theta y(t)$$

Parameter Estimation

↓

$$\hat{\theta} = 3$$

1 - Differential elimination :

$$\dot{x}(t) \xrightarrow{(1)} y(t)$$

$$\theta x(t) \xrightarrow{(2)} \dot{y}(t)$$

With $\theta(1)$ et $(2)'$: $\ddot{y}(t) = \theta y(t)$

2 - Parameter estimation :

$\ddot{y}$ is estimated numerically

$$\begin{cases} \ddot{y}(t_0) - \theta y(t_0) = 0 \\ \ddot{y}(t_1) - \theta y(t_1) = 0 \\ \vdots \\ \ddot{y}(t_n) - \theta y(t_n) = 0 \end{cases}$$

Why using integrals ?

By using integral equations, we hope to reduce :

- Noise: the numerical computation of the derivatives in the I/O differential equation amplifies the measurement error

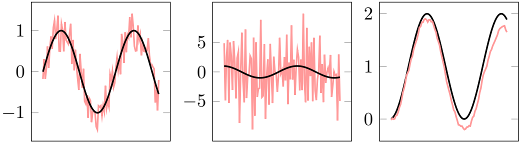


Figure: **A signal (without filtering), its derivative and its integral. In red, the noisy measurement.**

- Size of equations: they can be much shorter
- Integral equations encodes the initial conditions. e^{-t} is coded by $u(t) = 1 - \int_0^t u(\tau)d\tau$ (simply $u = 1 - \int u$)

Two approaches to obtain I/O integral equations

$$\begin{cases} \dot{x} = y \\ \dot{y} = \theta x^2 \end{cases}$$

x unknown

Two approaches to obtain I/O integral equations

$$\begin{cases} \dot{x} = y \\ \dot{y} = \theta x^2 \end{cases} \xrightarrow[]{\substack{\textbf{Differential Elimination} \\ \text{[Boulier, 2023,} \\ \text{DifferentialAlgebra]}}} 4\theta \dot{y} y^2 = \ddot{y}^2$$

x unknown

Two approaches to obtain I/O integral equations

$$\begin{cases} \dot{x} = y \\ \dot{y} = \theta x^2 \end{cases}$$
x unknown

Differential Elimination

[Boulier, 2023, DifferentialAlgebra]

$$\longrightarrow 4\theta\dot{y}y^2 = \ddot{y}^2$$

Integration
($\approx$ 10 steps by hand)
Guessing integrating factors
+ [Boulier et al., 2016, Integrate]
Algorithm

$$y - y_0 = \theta x_0^2 t + 2\theta x_0 \int \left(\int y\right) + 2\theta \int \left(\int y \left(\int y\right)\right)$$

Two approaches to obtain I/O integral equations

$$\begin{cases} \dot{x} = y \\ \dot{y} = \theta x^2 \end{cases}$$

x unknown

Differential Elimination

[Boulier, 2023, DifferentialAlgebra]

$$4\theta \dot{y} y^2 = \ddot{y}^2$$

Integration

($\approx$ 10 steps by hand)

Guessing integrating factors

+ [Boulier et al., 2016, Integrate]

Algorithm

Integral Elimination

(3 steps by hand)

Handled by my prototype

$$y - y_0 = \theta x_0^2 t + 2\theta x_0 \int \left(\int y\right) + 2\theta \int \left(\int y \left(\int y\right)\right)$$

Partial techniques of integral elimination

$$\begin{cases} x = x_0 + \int y \\ y = y_0 + \theta \int x^2 \end{cases}$$

Partial techniques of integral elimination

$$\begin{cases} x = x_0 + \int y \\ y = y_0 + \theta \int x^2 \end{cases}$$

$$x \xrightarrow{(1)} x_0 + \int y$$

$$\theta \int x^2 \xrightarrow{(2)} y - y_0$$

Partial techniques of integral elimination

$$\begin{cases} x = x_0 + \int y \\ y = y_0 + \theta \int x^2 \end{cases}$$

$$x \xrightarrow{(1)} x_0 + \int y$$

$$\theta \int x^2 \xrightarrow{(2)} y - y_0$$

"Critical pair" between (1) and (2), compute $\theta \int (1)^2$ minus (2):

$$-\ \theta x_0^2 \int 1 \ -\ 2\theta x_0 \int (\int y) \ -\ 2\theta \int (\int (y \int y)) \ -\ y_0 \ +\ y \ =\ 0$$

Integral equations containing exponentials

- By hand or with my elimination prototype, we can produce I/O integral equations involving exponentials. An example from another system:

$$y - y_0 - \dot{y}_0 \int \left(e^{\boldsymbol{\theta}(y-y_0)}\right) - \int \left(e^{\boldsymbol{\theta}(y-y_0)} \int \left(y e^{-\boldsymbol{\theta}(y-y_0)}\right)\right) = 0$$

Integral equations containing exponentials

- By hand or with my elimination prototype, we can produce I/O integral equations involving exponentials. An example from another system:

$$y - y_0 - \dot{y}_0 \int \left(e^{\boldsymbol{\theta}(y-y_0)}\right) - \int \left(e^{\boldsymbol{\theta}(y-y_0)} \int \left(ye^{-\boldsymbol{\theta}(y-y_0)}\right)\right) = 0$$

- Can we avoid the exponentials ? Not really

$$\begin{cases} \dot{x} = \theta x \\ \dot{y} = xy \end{cases}$$

1. $y - y_0 - x_0 \int e^{-\theta t} y = 0$
2. $y - y_0 e^{\frac{-x_0 + x_0 e^{\theta t}}{\theta}} = 0$

$\rightarrow$ This short example admits exponential I/O integral equations in y but no polynomial integral equation in y.

Integral equations containing exponentials

- By hand or with my elimination prototype, we can produce I/O integral equations involving exponentials. An example from another system:

$$y - y_0 - \dot{y}_0 \int \left(e^{\boldsymbol{\theta}(y-y_0)}\right) - \int \left(e^{\boldsymbol{\theta}(y-y_0)} \int \left(y e^{-\boldsymbol{\theta}(y-y_0)}\right)\right) = 0$$

- Can we avoid the exponentials ? Not really

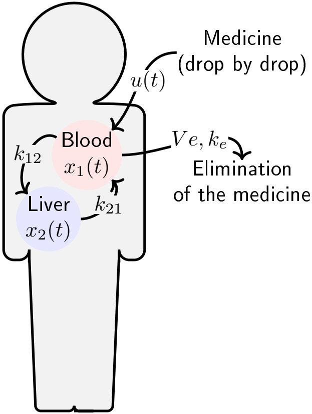
$$\begin{cases} \dot{x} = \theta x \\ \dot{y} = xy \end{cases}$$

1. $y - y_0 - x_0 \int e^{-\theta t} y = 0$
2. $y - y_0 e^{\frac{-x_0 + x_0 e^{\theta t}}{\theta}} = 0$

$\rightarrow$ This short example admits exponential I/O integral equations in y but no polynomial integral equation in y.

- **Do equations with exponentials give good results for estimating parameters ?**

Academic example taken from [Boulier et al., 2014]



$$\begin{cases} \dot{x}_1(t) = & -k_{12}\,x_1(t) + k_{21}\,x_2(t) \\ & -\frac{V_e\,x_1(t)}{k_e + x_1(t)} + u(t) \\ \dot{x}_2(t) = & k_{12}\,x_1(t) - k_{21}\,x_2(t) \\ y(t) = & x_1(t) \end{cases}$$

- $u(t)$: medicine (drop by drop). We simplify by taking $u(t) = 0$.
- $x_1(t)$: amount of medicine in the blood (known and noisy).
- $x_2(t)$: amount of medicine in the liver (unknown).

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Method

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Method

1. Generate noisy solution $y(t)$ from chosen parameter values

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Method

1. Generate noisy solution $y(t)$ from chosen parameter values
2. Consider 5 different I/O equations

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Method

1. Generate noisy solution $y(t)$ from chosen parameter values
2. Consider 5 different I/O equations
3. For each I/O equation p:

Experiment

Goal

Compare the quality of estimation between integral (with exponentials) I/O equations and differential I/O equations on the academical example

Method

1. Generate noisy solution $y(t)$ from chosen parameter values
2. Consider 5 different I/O equations
3. For each I/O equation p:
   Estimate the parameter values by minimizing the following error using CMA-ES [Hansen et al., 2019] optimization algorithm.

$$E(k_{12}, k_{21}, k_e, V_e) = \frac{1}{N} \sum_{i=0}^{N-1} p(t_i)^2$$

We used a 4 points scheme to estimate the signal derivatives and the Simpson rule for estimating integrals.

Different Input/Output equations

Different Input/Output equations

1. $Vek_{21}k_e y + Vek_{21}y^2 + Vek_e\dot{y} + k_{12}k_e^2\dot{y} + 2k_{12}k_e y\dot{y} + k_{12}y^2\dot{y} + k_{21}k_e^2\dot{y} + 2k_{21}k_e y\dot{y} + k_{21}y^2\dot{y} + k_e^2\ddot{y} + 2k_e y\ddot{y} + y^2\ddot{y}$

Different Input/Output equations

1. $Vek_{21}k_e y + Vek_{21}y^2 + Vek_e\dot{y} + k_{12}k_e^2\dot{y} + 2k_{12}k_e y\dot{y} + k_{12}y^2\dot{y} + k_{21}k_e^2\dot{y} + 2k_{21}k_e y\dot{y} + k_{21}y^2\dot{y} + k_e^2\ddot{y} + 2k_e y\ddot{y} + y^2\ddot{y}$

2. $k_{21}V_e \int\int \frac{y}{\boldsymbol{k_e}+y} + (k_{12}+k_{21})\int(y-y_0) - V_e\int(\frac{y}{\boldsymbol{k_e}+y} - \frac{y_0}{\boldsymbol{k_e}+y_0}) - \dot{y}_0 t + y - y_0$

Different Input/Output equations

1. $Vek_{21}k_e y + Vek_{21}y^2 + Vek_e\dot{y} + k_{12}k_e^2\dot{y} + 2k_{12}k_e y\dot{y} + k_{12}y^2\dot{y} + k_{21}k_e^2\dot{y} + 2k_{21}k_e y\dot{y} + k_{21}y^2\dot{y} + k_e^2\ddot{y} + 2k_e y\ddot{y} + y^2\ddot{y}$

2. $k_{21}V_e \int\int \frac{y}{\boldsymbol{k_e}+y} + (k_{12}+k_{21})\int(y-y_0) - V_e\int(\frac{y}{\boldsymbol{k_e}+y} - \frac{y_0}{\boldsymbol{k_e}+y_0}) - \dot{y}_0 t + y - y_0$

3. $-y + y_0 - k_{12}\int y - \int \frac{V_e y}{\boldsymbol{k_e}+y} + (\frac{V_e y_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{-\boldsymbol{k_{21}}t} + k_{21}k_{12}\int(e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$

Different Input/Output equations

1. $Vek_{21}k_ey + Vek_{21}y^2 + Vek_e\dot{y} + k_{12}k_e^2\dot{y} + 2k_{12}k_ey\dot{y} + k_{12}y^2\dot{y} + k_{21}k_e^2\dot{y} + 2k_{21}k_ey\dot{y} + k_{21}y^2\dot{y} + k_e^2\ddot{y} + 2k_ey\ddot{y} + y^2\ddot{y}$
2. $k_{21}V_e \int\int \frac{y}{\boldsymbol{k_e}+y} + (k_{12}+k_{21})\int(y-y_0) - V_e\int(\frac{y}{\boldsymbol{k_e}+y} - \frac{y_0}{\boldsymbol{k_e}+y_0}) - \dot{y}_0t + y - y_0$
3. $-y + y_0 - k_{12}\int y - \int\frac{V_ey}{\boldsymbol{k_e}+y} + (\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{-\boldsymbol{k_{21}}t} + k_{21}k_{12}\int(e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$
4. $-y^2 + y_0^2 - 2k_ey + 2k_ey_0 - 2k_ek_{12}\int y - 2k_{12}\int y^2 - 2V_e\int y + 2k_e(\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{-\boldsymbol{k_{21}}t} + 2(\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int ye^{-\boldsymbol{k_{21}}t} + 2k_ek_{21}k_{12}\int(e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y) + 2k_{21}k_{12}\int(ye^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$

Different Input/Output equations

1. $Vek_{21}k_ey + Vek_{21}y^2 + Vek_e\dot{y} + k_{12}k_e^2\dot{y} + 2k_{12}k_ey\dot{y} + k_{12}y^2\dot{y} + k_{21}k_e^2\dot{y} + 2k_{21}k_ey\dot{y} + k_{21}y^2\dot{y} + k_e^2\ddot{y} + 2k_ey\ddot{y} + y^2\ddot{y}$

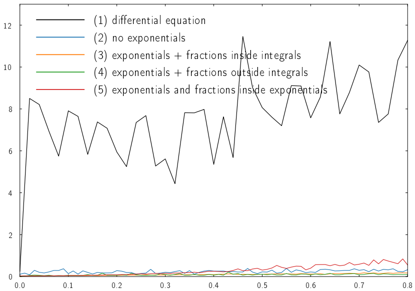
2. $k_{21}V_e\int\int\frac{y}{\boldsymbol{k_e}+y}+(k_{12}+k_{21})\int(y-y_0)-V_e\int(\frac{y}{\boldsymbol{k_e}+y}-\frac{y_0}{\boldsymbol{k_e}+y_0})-\dot{y}_0t+y-y_0$

3. $-y + y_0 - k_{12}\int y - \int\frac{V_ey}{\boldsymbol{k_e}+y} + (\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{-\boldsymbol{k_{21}}t} + k_{21}k_{12}\int(e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$

4. $-y^2 + y_0^2 - 2k_ey + 2k_ey_0 - 2k_ek_{12}\int y - 2k_{12}\int y^2 - 2V_e\int y + 2k_e(\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{-\boldsymbol{k_{21}}t} + 2(\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int ye^{-\boldsymbol{k_{21}}t} + 2k_ek_{21}k_{12}\int(e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y) + 2k_{21}k_{12}\int(ye^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$

5. $-ye^{\int(\boldsymbol{k_{12}}+\frac{\boldsymbol{V_e}}{\boldsymbol{k_e}+y})} + y_0 + (\frac{V_ey_0}{\boldsymbol{k_e}+y_0} + \dot{y}_0 + k_{12}y_0)\int e^{\int(\boldsymbol{k_{12}}+\frac{\boldsymbol{V_e}}{\boldsymbol{k_e}+y})}e^{-\boldsymbol{k_{21}}t} + k_{12}k_{21}\int(e^{\int(\boldsymbol{k_{12}}+\frac{\boldsymbol{V_e}}{\boldsymbol{k_e}+y})}e^{-\boldsymbol{k_{21}}t}\int e^{\boldsymbol{k_{21}}t}y)$

Quality of the parameter estimation - 4 parameters



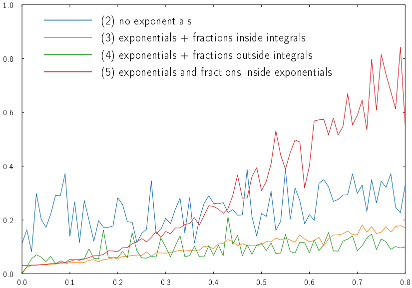


Figure: Estimation of parameters k_{12}, k_{21}, V_e, k_e and $\dot{y}_0$ (for integral equations). In x-axis, the standard deviation σ used to produce the white gaussian noise added to the signal $y(t)$. In y-axis, the average value, for 50 different simulations, of the relative error.

Integral equations have better results for the parameter estimation.
Among them, the two best involves exponentials.

Integral Elimination Prototype

- Rewriting system
- Elimination ordering

$$1 < y < \int y < y^2 < y \int y < \int y^2 < xy < \int xy < x^2 y$$

- No concept of confluence or termination yet
- Incomplete reduction and critical pairs
- Written in Python using `SymPy` library : arround 1500 lines of code
- Give promising results on non-trivial examples

Example (1/2): Intra-host model of Malaria

$$\begin{cases} \dot{x} = 1 - x - \boldsymbol{\beta} x m \\ \dot{y} = \boldsymbol{\beta} x m - y \\ \dot{m} = y - m - \boldsymbol{\beta} x m \end{cases} \qquad x,\ m \text{ unknown, } y \text{ known}$$

Taken from [Anderson et al., 1989]

Example (1/2): Intra-host model of Malaria

$$\begin{cases} \dot{x} = 1 - x - \beta x m \\ \dot{y} = \beta x m - y \\ \dot{m} = y - m - \beta x m \end{cases}$$

x, m unknown, y known

Taken from [Anderson et al., 1989]

Differential I/O equation:

$$\begin{aligned}
& 4\beta^2 y^3 \dot{y}^3 + 12\beta^2 y^2 \dot{y}^4 + 12\beta^2 y \dot{y}^5 + 4\beta^2 \dot{y}^6 - 12\beta^2 y^2 \dot{y}^3 - 24\beta^2 y \dot{y}^4 \\
& + 12\beta^2 y \dot{y}^3 + 12\beta^2 \dot{y}^4 - 8\beta y^3 \dot{y}^2 + 4\beta y^3 \dot{y}\ddot{y} + \beta y^3 \ddot{y}^2 - 32\beta y^2 \dot{y}^3 \\
& - 4\beta y^2 \dot{y}^2 \dddot{y} + 3\beta y^2 \dot{y}\ddot{y}^2 - 37\beta y \dot{y}^4 - 6\beta y \dot{y}^3 \ddot{y} - 8\beta y \dot{y}^3 \dddot{y} + 6\beta y \dot{y}^2 \ddot{y}^2 \\
& - 13\beta \dot{y}^5 - 2\beta \dot{y}^4 \ddot{y} - 4\beta \dot{y}^4 \dddot{y} + 4\beta \dot{y}^3 \ddot{y}^2 - 4\beta^2 \dot{y}^3 + 16\beta y^2 \dot{y}^2 - 8\beta y^2 \dot{y}\ddot{y} \\
& - 2\beta y^2 \ddot{y}^2 + 52\beta y \dot{y}^3 + 10\beta y \dot{y}^2 \ddot{y} + 8\beta y \dot{y}^2 \dddot{y} - 6\beta y \dot{y}\ddot{y}^2 + 34\beta \dot{y}^4 \\
& + 14\beta \dot{y}^3 \ddot{y} + 8\beta \dot{y}^3 \dddot{y} - 6\beta \dot{y}^2 \ddot{y}^2 - 8\beta y \dot{y}^2 + 4\beta y \dot{y}\ddot{y} + \beta y \ddot{y}^2 - 20\beta \dot{y}^3 \\
& - 10\beta \dot{y}^2 \ddot{y} - 4\beta \dot{y}^2 \dddot{y} + 3\beta \dot{y}\ddot{y}^2 + 4y^3 \dot{y} - 4y^3 \ddot{y} + 20y^2 \dot{y}^2 - 4y^2 \dot{y}\ddot{y} + 4y^2 \dot{y}\dddot{y} \\
& - 6y^2 \ddot{y}^2 - 2y^2 \ddot{y}\dddot{y} + 29y \dot{y}^3 + 11y \dot{y}^2 \ddot{y} + 12y \dot{y}^2 \dddot{y} - 5y \dot{y}\ddot{y}^2 + y \dot{y}\ddot{y}\dddot{y} \\
& + y \dot{y}\dddot{y}^2 - y \ddot{y}^2 \dddot{y} + 10\dot{y}^4 + 2\dot{y}^3 \ddot{y} + 7\dot{y}^3 \dddot{y} - 7\dot{y}^2 \ddot{y}^2 + \dot{y}^2 \ddot{y}\dddot{y} \\
& + \dot{y}^2 \dddot{y}^2 - \dot{y}\ddot{y}^3 - 2\dot{y}\ddot{y}^2 \dddot{y} + \ddot{y}^4 - 4y^2 \dot{y} + 4y^2 \ddot{y} - 20y \dot{y}^2 - 4y \dot{y}\dddot{y} + 10y \ddot{y}^2 \\
& + 2y \ddot{y}\dddot{y} - 25\dot{y}^3 - 25\dot{y}^2 \ddot{y} - 10\dot{y}^2 \dddot{y} + \dot{y}\ddot{y}^2 - 5\dot{y}\ddot{y}\dddot{y} - \dot{y}\dddot{y}^2 + 4\ddot{y}^3 + \ddot{y}^2 \dddot{y} \\
& = 0
\end{aligned}$$

Example (1/2): Intra-host model of Malaria

$$\begin{cases} \dot{x} = 1 - x - \beta x m \\ \dot{y} = \beta x m - y \\ \dot{m} = y - m - \beta x m \end{cases} \qquad x,\ m \text{ unknown, } y \text{ known}$$

Taken from [Anderson et al., 1989]

Differential I/O equation:

$$\begin{aligned}
&4\beta^2y^3\dot{y}^3 + 12\beta^2y^2\dot{y}^4 + 12\beta^2y\dot{y}^5 + 4\beta^2\dot{y}^6 - 12\beta^2y^2\dot{y}^3 - 24\beta^2y\dot{y}^4 \\
&+ 12\beta^2y\dot{y}^3 + 12\beta^2\dot{y}^4 - 8\beta y^3\dot{y}^2 + 4\beta y^3\dot{y}\ddot{y} + \beta y^3\ddot{y}^2 - 32\beta y^2\dot{y}^3 \\
&- 4\beta y^2\dot{y}^2\dddot{y} + 3\beta y^2\dot{y}\ddot{y}^2 - 37\beta y\dot{y}^4 - 6\beta y\dot{y}^3\ddot{y} - 8\beta y\dot{y}^3\dddot{y} + 6\beta y\dot{y}^2\ddot{y}^2 \\
&- 13\beta\dot{y}^5 - 2\beta\dot{y}^4\ddot{y} - 4\beta\dot{y}^4\dddot{y} + 4\beta\dot{y}^3\ddot{y}^2 - 4\beta^2\dot{y}^3 + 16\beta y^2\dot{y}^2 - 8\beta y^2\dot{y}\ddot{y} \\
&- 2\beta y^2\ddot{y}^2 + 52\beta y\dot{y}^3 + 10\beta y\dot{y}^2\ddot{y} + 8\beta y\dot{y}^2\dddot{y} - 6\beta y\dot{y}\ddot{y}^2 + 34\beta\dot{y}^4 \\
&+ 14\beta\dot{y}^3\ddot{y} + 8\beta\dot{y}^3\dddot{y} - 6\beta\dot{y}^2\ddot{y}^2 - 8\beta y\dot{y}^2 + 4\beta y\dot{y}\ddot{y} + \beta y\ddot{y}^2 - 20\beta\dot{y}^3 \\
&- 10\beta\dot{y}^2\ddot{y} - 4\beta\dot{y}^2\dddot{y} + 3\beta\dot{y}\ddot{y}^2 + 4y^3\dot{y} - 4y^3\ddot{y} + 20y^2\dot{y}^2 - 4y^2\dot{y}\ddot{y} + 4y^2\dot{y}\dddot{y} \\
&- 6y^2\ddot{y}^2 - 2y^2\ddot{y}\dddot{y} + 29y\dot{y}^3 + 11y\dot{y}^2\ddot{y} + 12y\dot{y}^2\dddot{y} - 5y\dot{y}\ddot{y}^2 + y\dot{y}\ddot{y}\dddot{y} \\
&+ y\dot{y}\dddot{y}^2 - y\ddot{y}^2\dddot{y} + 10\dot{y}^4 + 2\dot{y}^3\ddot{y} + 7\dot{y}^3\dddot{y} - 7\dot{y}^2\ddot{y}^2 + \dot{y}^2\ddot{y}\dddot{y} \\
&+ \dot{y}^2\dddot{y}^2 - \dot{y}\ddot{y}^3 - 2\dot{y}\ddot{y}^2\dddot{y} + \ddot{y}^4 - 4y^2\dot{y} + 4y^2\ddot{y} - 20y\dot{y}^2 - 4y\dot{y}\dddot{y} + 10y\ddot{y}^2 \\
&+ 2y\ddot{y}\dddot{y} - 25\dot{y}^3 - 25\dot{y}^2\ddot{y} - 10\dot{y}^2\dddot{y} + \dot{y}\ddot{y}^2 - 5\dot{y}\ddot{y}\dddot{y} - \dot{y}\dddot{y}^2 + 4\ddot{y}^3 + \ddot{y}^2\dddot{y} \\
&= 0
\end{aligned}$$

Integral I/O equation:

$$\begin{aligned}
&- \beta m_0 \int (u_{i0}y) - \beta x_0 \int (u_{i0}y) - 2\beta y_0 \int (u_{i0}y) + \beta m_0 x_0 \int (u_{i0}^2) \\
&+ \beta m_0 y_0 \int (u_{i0}^2) + \beta y_0 x_0 \int (u_{i0}^2) + \beta y_0^2 \int (u_{i0}^2) + \beta \int (y^2) \\
&- \beta \int \left(u_{i0}y \int v_{i0}y\right) - \beta \int \left(u_{i0}y \int v_{i0}\right) + \beta x_0 \int \left(u_{i0}^2 \int v_{i0}y\right) \\
&+ \beta y_0 \int \left(u_{i0}^2 \int v_{i0}y\right) + \beta m_0 \int \left(u_{i0}^2 \int v_{i0}\right) \\
&+ \beta y_0 \int \left(u_{i0}^2 \int v_{i0}\right) + \beta \int \left(u_{i0}^2 \int v_{i0}y \int v_{i0}\right) \\
&+ \beta \int \left(u_{i0}^2 \int v_{i0} \int v_{i0}y\right) + y_0 - y - \int y \\
&= 0
\end{aligned}$$

$$\begin{cases} v_{i0} = e^{t} \\ u_{i0} = e^{-t} \end{cases}$$

Example (2/2): SIWR Cholera

$$
\begin{cases}
\dot{S} = \mu - \beta_I SI - \beta_W SW - \mu S + \alpha R \\
\dot{I} = \beta_W SW + \beta_I SI - \gamma I - \mu I \\
\dot{W} = \zeta(I - W) \\
\dot{R} = \gamma I - \mu R - \alpha R \\
y_1 = \kappa I
\end{cases}
$$

Example (2/2): SIWR Cholera

$$\begin{cases} \dot{S} = \mu - \beta_I SI - \beta_W SW - \mu S + \alpha R \\ \dot{I} = \beta_W SW + \beta_I SI - \gamma I - \mu I \\ \dot{W} = \zeta(I - W) \\ \dot{R} = \gamma I - \mu R - \alpha R \\ y_1 = \kappa I \end{cases}$$

Differential I/O equation:

- I/O differential equation and identifiability studied in [Dong et al., 2022] using `StructuralIdentifiability` package in Julia.
- 9Mo: Sum of 209 350 terms
- y_1^{10}, $\dot{y}_1^{10}$, $\ddot{y}_1^{8}$, $\dddot{y}_1^{5}$, $\ddddot{y}_1^{4}$

Example (2/2): SIWR Cholera

$$\begin{cases} \dot{S} = \mu - \beta_I SI - \beta_W SW - \mu S + \alpha R \\ \dot{I} = \beta_W SW + \beta_I SI - \gamma I - \mu I \\ \dot{W} = \zeta(I - W) \\ \dot{R} = \gamma I - \mu R - \alpha R \\ y_1 = \kappa I \end{cases}$$

Differential I/O equation:

- I/O differential equation and identifiability studied in [Dong et al., 2022] using `StructuralIdentifiability` package in Julia.
- 9Mo: Sum of 209 350 terms
- y_1^{10}, $\dot{y}_1^{10}$, $\ddot{y}_1^{8}$, $\dddot{y}_1^{5}$, $\ddddot{y}_1^{4}$

Integral I/O equation:

$$\begin{aligned}
&- \alpha\beta_W\gamma\zeta \int \left(u_{i0}u_{i2} \int v_{i0}y_1 \int u_{i1}v_{i2} \int v_{i1}y_1\right) - \alpha\beta_I\kappa r_0 \int \left(u_{i2}y_1 \int u_{i1}v_{i2}\right) \\
&- \alpha\beta_W\gamma\kappa w_0 \int \left(u_{i0}u_{i2} \int u_{i1}v_{i2} \int v_{i1}y_1\right) - \beta_I\kappa\mu \int \left(u_{i2}y_1 \int v_{i2}\right) \\
&- \alpha\beta_W\gamma\zeta \int \left(u_{i0}u_{i2} \int u_{i1}v_{i2} \int v_{i1}y_1 \int v_{i0}y_1\right) - \beta_W\kappa\zeta s_0 \int \left(u_{i0}u_{i2} \int v_{i0}y_1\right) \\
&- \alpha\beta_W\kappa^2 r_0 w_0 \int \left(u_{i0}u_{i2} \int u_{i1}v_{i2}\right) - \alpha\beta_W\kappa\zeta r_0 \int \left(u_{i0}u_{i2} \int u_{i1}v_{i2} \int v_{i0}y_1\right) \\
&- \alpha\beta_W\kappa\zeta r_0 \int \left(u_{i0}u_{i2} \int v_{i0}y_1 \int u_{i1}v_{i2}\right) - \beta_W\kappa^2 s_0 w_0 \int (u_{i0}u_{i2}) \\
&- \beta_W\kappa^2\mu w_0 \int \left(u_{i0}u_{i2} \int v_{i2}\right) - \beta_W\kappa\mu\zeta \int \left(u_{i0}u_{i2} \int v_{i0}y_1 \int v_{i2}\right) \\
&- \alpha\beta_W\gamma\zeta \int \left(u_{i0}u_{i2} \int u_{i1}v_{i2} \int v_{i0}y_1 \int v_{i1}y_1\right) - \beta_I\kappa s_0 \int (u_{i2}y_1) \\
&- \beta_W\kappa\mu\zeta \int \left(u_{i0}u_{i2} \int v_{i2} \int v_{i0}y_1\right) - \alpha\beta_I\gamma \int \left(u_{i2}y_1 \int u_{i1}v_{i2} \int v_{i1}y_1\right) \\
&+ \gamma\kappa \int (y_1) - \kappa^2 I_0 + \kappa\mu \int (y_1) + \kappa y_1 = 0
\end{aligned}$$

$$\begin{cases} v_{i0} = & e^{\zeta \int 1} \\ v_{i1} = & e^{(\alpha+\mu) \int 1} \\ v_{i2} = & e^{\left(\mu \int 1 + \frac{\beta_I}{\kappa} \int y_1 + \frac{\beta_W}{\kappa} \int y_1 - \frac{\beta_W}{\kappa} e^{-\zeta \int 1}\left(\int y_1 e^{\zeta \int 1}\right)\right)} \\ & \times e^{\left(\frac{\beta_W w(0)}{\zeta} - \frac{\beta_W w(0)}{\zeta} e^{-\zeta \int 1}\right)} \\ u_{i0}v_{i0} = & u_{i1}v_{i1} = u_{i2}v_{i2} = 1 \end{cases}$$

Other example

$$\begin{cases} \dot{S} = -\boldsymbol{\beta} S(I + J + \boldsymbol{q}A) \\ \dot{E} = \boldsymbol{\beta} S(I + J + \boldsymbol{q}A) - \boldsymbol{k}E \\ \dot{A} = \boldsymbol{k}(1 - \boldsymbol{p})E - \boldsymbol{\gamma_1} A \\ \dot{I} = \boldsymbol{k\rho} E - (\boldsymbol{\alpha} + \boldsymbol{\gamma_1})I \\ \dot{J} = \boldsymbol{\alpha} I - \boldsymbol{\gamma_2} J \\ \dot{C} = \boldsymbol{\alpha} I \\ \dot{R} = \boldsymbol{\gamma_1}(A + I) + \boldsymbol{\gamma_2} J \\ y = C \end{cases}$$

Conclusion

Experimental conclusion

- Modeling with integral equations seems promising
- Even equations involving exponentials can perform well for parameter estimation

Integral Elimination Prototype

- Promising results on non-trivial examples but does not handle:

$$\begin{cases} \dot{x_1} = a(x_2 - x_1) - \frac{k_a V_m x_1}{k_c k_a + k_c \boldsymbol{x_3} + k_a x_1} \\ \dot{x_2} = a(x_1 - x_2) \\ \dot{x_3} = b_1(x_4 - x_3) - \frac{k_c V_m x_3}{k_c k_a + k_c x_3 + k_a x_1} \\ \dot{x_4} = b_2(x_3 - x_4) \\ y = x_1 \end{cases}$$

References

Anderson, R., May, R., and Gupta, S. (1989).
Non-linear phenomena in host–parasite interactions.
Parasitology, 99 Suppl:S59–79.

Boulier, F. (2023).
The DifferentialAlgebra project.

Boulier, F., Korporal, A., Lemaire, F., Perruquetti, W., Poteaux, A., and Ushirobira, R. (2014).
An Algorithm for Converting Nonlinear Differential Equations to Integral Equations with an Application to Parameter Estimation from Noisy Data.
In *Computer Algebra in Scientific Computing*, pages 28 – 43, Warsaw, Poland.

Boulier, F., Lallemand, J., Lemaire, F., Regensburger, G., and Rosenkranz, M. (2016).
Additive Normal Forms and Integration of Differential Fractions.
Journal of Symbolic Computation.

Dong, R., Goodbrake, C., Harrington, H. A., and Pogudin, G. (2022).
Differential elimination for dynamical models via projections with applications to structural identifiability.

Fliess, M. (1989).
Automatique et corps différentiels.
Forum Mathematicum - FORUM MATH, 1:227–238.

Hansen, N., Akimoto, Y., and Baudis, P. (2019).
CMA-ES/pycma on Github.
Zenodo, DOI:10.5281/zenodo.2559634.