Structural and Practical Identifiability Analysis of Models for Syncytia Growth

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Background

- Syncytia are multi-nucleated cells that can occur due to virus infections.
- To better understand viral dynamics it is important to understand how syncytia populations evolve during an infection.
- Syncytia can be cultured in vitro to obtain data about their growth over time.
- Ordinary Differential Equation (ODE) models can be used to model the growth of syncytia both in vivo and in vitro.
- Before actual experimentation it is essential to ensure we acquire the correct amount and type of data to parameterize the model.

Structural and Practical Identifiability Analysis

- **Structural Identifiability** of an ODE model refers to the ability to estimate a model's parameters from its outputs. If a model is structurally identifiable, we can estimate parameter values from a given output measurement. Structural Identifiability Analysis refers to determining if a model is structurally identifiable, and it is a prerequisite before trying to fit a model to experiment data.
- **Practical Identifiability** of a model refers to the ability to determine the parameter values of a model under experimental conditions. Practical Identifiability analysis incorporates noise in output measurements and limited data sampling to replicate experimental conditions.

Cell-Cell Fusion Assay

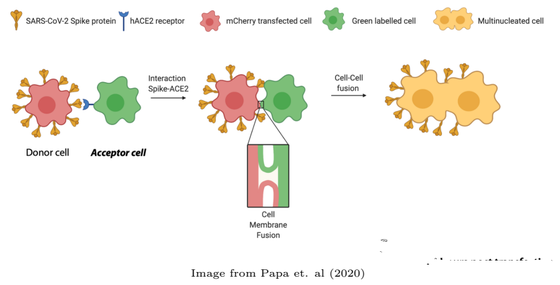


Image from Papa et. al (2020)

- One group of cells (donor cells) expresses the virus surface protein and is stained with one dye.
- A second group of cells (acceptor cells) expresses the cell surface receptor and is stained with a second dye.
- When the cells fuse, the syncytia will fluoresce with both dyes.
- Experiments typically measure the area covered by syncytia as a function of time.

Model Overview

- We can write ODEs relating the donor cells (D), acceptor cells (A), and syncytia (S) that can predict the evolution of syncytia over time.
- We propose 3 models for syncytia growth to be analyzed.
- The models include the following parameters that need to be determined from the data.

Parameter	Name
γ	Syncytia Formation Rate
N	Max Population
k	Fusion Rate
D_0	Initial Number of Donors
δ	Syncytia Death Rate

Asymmetric & Symmetric Models

The asymmetric model is a simple model for syncytia fusion consisting of only acceptors, donors, and syncytia cells. The transition to syncytia is proportional to parameter γ.

$$\begin{aligned}\frac{dD}{dt} &= -\gamma DA \\ \frac{dA}{dt} &= -\gamma DA - \gamma SA \\ \frac{dS}{dt} &= 2\gamma DA + \gamma SA\end{aligned}$$

The symmetric model adds a term to account for the fusion of donor cells into existing syncytia.

$$\begin{aligned}\frac{dD}{dt} &= -\gamma DA - \gamma SD \\ \frac{dA}{dt} &= -\gamma DA - \gamma SA \\ \frac{dS}{dt} &= 2\gamma DA + \gamma SA + \gamma SD \\ N &= D + A + S\end{aligned}$$

Model With Death and Fusion

In this model, syncytia can die, and before syncytia can fuse there is a transitory fusing phase. The rate of fusion and death are represented by the parameters k and δ respectively.

$$\begin{aligned}\frac{dD}{dt} &= -\gamma DA \\ \frac{dA}{dt} &= -\gamma DA - \gamma SA \\ \frac{dF_1}{dt} &= 2\gamma DA + \gamma SA - kF_1 \\ \frac{dF_2}{dt} &= kF_1 - kF_2 \\ \frac{dS}{dt} &= kF_2 - \delta S\end{aligned}$$

Structural Identifiability of Models

We can analyze the identifiability of a system Using software called Differential Algebra for Identifiability of Systems(DAISY).

- The Asymmetric Model is globally identifiable for all parameters.
- The Symmetric Model is globally identifiable for all parameters.
- The model with Death and Fusion is identifiable for all parameters when 2 outputs are measured.

Practical Identifiability of Models

Monte Carlo Simulation

Monte Carlo simulations involve creating surrogate data with noise using set parameters and fitting our model to it. We can then estimate the parameter values from this surrogate data and compare them to actual parameter values. To do this we compute the average relative estimation error (ARE). θ_0 is the actual parameter value, and θ_i is the estimated parameter value from our simulated data set.

$$\text{ARE} = 100\% \times \sum_{i=1}^{N} \frac{|\theta_0 - \theta_i|}{|\theta_0|}$$

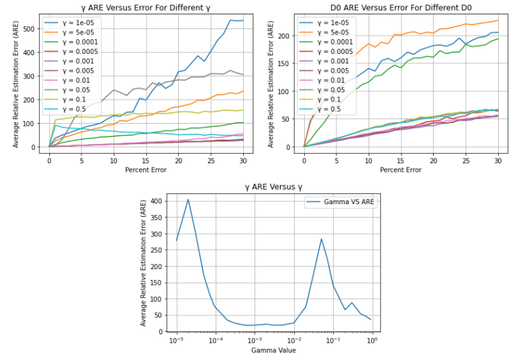
Likelihood Profiling

Likelihood profiling involves measuring how the SSR, which we assume to be analogous to the likelihood of the parameter, changes in response to changes to the parameter. The shape of this curve can help us determine local identifiability.

Monte Carlo Simulations

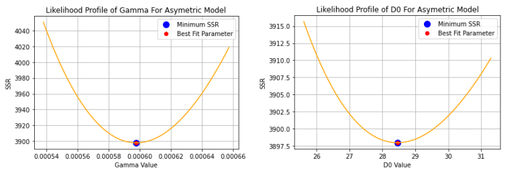
When doing Monte Carlo Simulations for practical identifiability 3 primary factors can affect parameter estimation.

- Sampling time and frequency
- Actual Parameter Value
- Measurement Noise



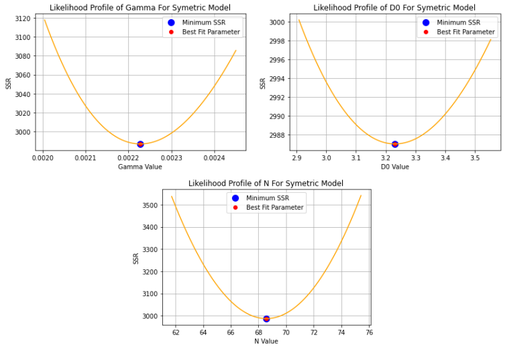
Likelihood Profiles (Asymmetric)

Below are likelihood profiles for the asymmetric model which can help us determine the identifiability of parameters.



Likelihood Profiles (Symmetric)

Below are likelihood profiles for the symmetric model which can help us determine the identifiability of parameters.



The parabolic shape of the likelihood profiles indicates that the parameters they are plotting are identifiable.

Conclusions

- Using DAISY analysis, we were able to determine the structural identifiability of novel ODE models for syncytia growth.
- Practical identifiability analysis provides data on how parameter estimation is affected by experimental details and limitations.
- Knowledge of practical identifiability can inform experimental design so we may accurately parameterize our models.
- In these models, practical identifiability depended on sampling frequency, parameter value, and measurement error.
- The most practical way to decrease ARE is to increase sampling frequency.