Introduction to Structural & Practical Identifiability

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Identifiability

- Identifiability—Is it possible to uniquely determine the parameters from the data?

- Important problem in parameter estimation

- Many different approaches - statistics, applied math, engineering/systems theory

IDENTIFIABILITY OF A LINEAR RELATION BETWEEN VARIABLES WHICH ARE SUBJECT TO ERROR

MATHEMATICAL BIO SCIENCES

On Structural Identifiability

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Identifiability

- Practical vs. Structural
- Broad, sometimes overlapping categories
- Noisy vs. perfect data
- Example: \( y = (m_1 + m_2)x + b \)
- Unidentifiability - can cause serious problems when estimating parameters
- Identifiable combinations
Structural Identifiability

• Assumes best case scenario - data is known perfectly at all times

• Unrealistic!

• But, necessary condition for practical identifiability with real, noisy data
Structural Identifiability

- Reveals identifiable combinations and how to restructure the model so that it is identifiable
- Can give a priori information, help direct experiment design
Identifiability

Local

Global

Analytical Methods

Numerical Methods

Structural

Practical
Key Concepts

- Identifiability vs. unidentifiability
- Practical vs. structural, local vs. global
- Can be in between, e.g. quasi-identifiable
- Identifiable Combinations
- Reparameterization
- Related questions: observability, distinguishability & model selection
Reparameterization

• Identifiable combinations - parameter combinations that can be estimated

• Once you know those, why reparameterize?

• Estimation issues - reparameterization provides a model that is input-output equivalent to the original but identifiable

• Often the reparameterized model has ‘sensible’ biological meaning (e.g. nondimensionalized, etc.)
Methods we’ll talk about today

- Differential Algebra Approach - structural identifiability, global, analytical method
- Fisher information matrix - structural or practical, local, analytical or numerical method
- Profile likelihood - structural or practical, local, numerical method
Simple Methods

- Simulated data approach

- If you have a small system, you can even plot the likelihood surface (typically can’t though—more on this with profile likelihoods)
Analytical Methods for Structural Identifiability
Methods for Structural Identifiability

- **Laplace transform** - linear models only

- **Taylor series approach** - more broad application, but only local info & may not terminate

- **Similarity transform approach** - difficult to make algorithmic, can be difficult to assess conditions for applying theorem

- **Differential algebra approach** - rational function ODE models, global info

Methods for Structural Identifiability

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Structural Identifiability Analysis

• Basic idea: use substitution & differentiation to eliminate all variables except for observed output \( y \)

• Clear (divide by) the coefficient for highest derivative term(s)

• This is called the **input-output equation(s)**

• Contains all structural identifiability info for the model
Structural Identifiability Analysis

- Use the coefficients to solve for identifiability of the model

- If unidentifiable, determine identifiable combinations

- Find identifiable reparameterization of the model?

- Easier to see with an example—
2-Compartment Example

- Linear 2-Comp Model

\[
\begin{align*}
\dot{x}_1 &= u + k_{12}x_2 - (k_{01} + k_{21})x_1 \\
\dot{x}_2 &= k_{21}x_1 - (k_{02} + k_{12})x_2 \\
y &= \frac{x_1}{V}
\end{align*}
\]

- state variables (x)

- measurements (y)

- known input (u) (e.g. IV injection)
2-Compartment Example

\[
\begin{align*}
\dot{x}_1 &= u + k_{12}x_2 - (k_{01} + k_{21})x_1 \\
\dot{x}_2 &= k_{21}x_1 - (k_{02} + k_{12})x_2 \\
y &= x_1 / V
\end{align*}
\]
2-Compartment Example

\[
\begin{align*}
\dot{y}V &= u + k_{12}x_2 - \left(k_{01} + k_{21}\right)yV \\
\dot{x}_2 &= k_{21}x_1 - \left(k_{02} + k_{12}\right)x_2
\end{align*}
\]
2-Compartment Example

\[
\dot{y} + \left( k_{01} + k_{21} + k_{12} + k_{02} \right) \dot{y} - \\
\left( k_{12} k_{21} - (k_{02} + k_{12})(k_{01} + k_{21}) \right) y - u \left( k_{12} + k_{02} \right) / V - \dot{u} / V = 0
\]
2-Compartment Example

\[ \frac{1}{V} = a_1 \]

\[ \left( k_{12} + k_{02} \right) / V = a_2 \]

\[ \left( k_{01} + k_{21} + k_{12} + k_{02} \right) = a_3 \]

\[ \left( k_{12}k_{21} - \left( k_{02} + k_{12} \right)\left( k_{01} + k_{21} \right) \right) = a_4 \]
2-Compartment Example

\[
\frac{1}{V} = a_1 \implies V = \frac{1}{a_1}
\]

\[
\frac{(k_{12} + k_{02})}{V} = a_2
\]

\[
\left( k_{01} + k_{21} \right) - k_{12} + k_{02} = a_3
\]

\[
\left( k_{12}k_{21} - (k_{02} + k_{12})(k_{01} + k_{21}) \right) = a_4
\]
2-Compartment Example

\[ \dot{x}_1 = u + k_{12} x_2 - (k_{01} + k_{21}) x_1 \]
\[ \dot{x}_2 = k_{21} x_1 - (k_{02} + k_{12}) x_2 \]
\[ y = \frac{x_1}{V} \]

Let \( x_2 = k_{12} x_2 \)

\[ \dot{x}_1 = u + x_2 - (k_{01} + k_{21}) x_1 \]
\[ \dot{x}_2 = k_{12} k_{21} x_1 - (k_{02} + k_{12}) x_2 \]
\[ y = \frac{x_1}{V} \]

Or add information about one of the parameters
Differential Algebra Approach

- View model & measurement equations as differential polynomials
- Reduce the equations using Gröbner bases, characteristic sets, etc. to eliminate unmeasured variables (x)
- Yields input-output equation(s) only in terms of known variables (y, u)
- Use coefficients to test model identifiability

Differential Algebra Approach

- From the coefficients, can often determine:
  - Simpler forms for identifiable combinations
  - Identifiable reparameterizations for model
  - Not always easy by eye—use Gröbner bases & other methods to simplify
Differential Algebra Approach

• Convenient as a way to prove identifiability results for relatively broad classes of models
  
  • Linear compartmental models & graph structure (with Nikki Meshkat & Seth Sullivant)
  
  • SIR-type models (with Tony Nance)
  
  • Hodgkin-Huxley-type models (with Olivia Walch)
Numerical Methods for Identifiability Analysis
Numerical Approaches to Identifiability

- Analytical approaches can be slow, sometimes have limited applicability
- Wide range of numerical approaches
  - Sensitivities/Fisher Information Matrix
  - Profile Likelihood
- Many others (e.g. Bayesian approaches, etc.)
Numerical Approaches to Identifiability

- Most can do both structural & practical identifiability
- Wide range of applicable models, often (relatively) fast
- Typically only local
Simple Simulation Approach

• Simulate data using a single set of ‘true’ parameter values
  • Without noise for structural identifiability
  • With noise for practical identifiability (in this case generate multiple realizations of the data)
Simple Simulation Approach

- Fit your simulated data from multiple starting points and see where your estimates land.
- If they all return to the ‘true’ parameters, likely identifiable, if they do not, examine the relationships between the parameters.
- Note—unidentifiability when estimating with ‘perfect’, noise-free simulated data is most likely structural.
As previously, we simulated 100 data sets for each distribution and to assess the efficacy of different intervention strategies. This fundamental quantity such as the basic reproduction number, $R_0$, is particularly relevant for waterborne disease models because of the introduction pathways, which are often quite difficult to measure directly. From a given data set will determine the ability to estimate fundamental quantities such as the basic reproduction number, $R_0$. Based on the pathogen shedding rate, which was not available using case measurements in the water also gives additional information on water data was added. The inclusion of a second series of data measurements alone.

Examples of simulated data set using least squares estimation with four noise distributions (left to right): Poisson, Gaussian, negative binomial with variance equal to 50 times the mean, and negative binomial with variance equal to 5 times the mean, and negative binomial with variance equal to 5 times the mean. To determine how this value, we calculated the parameters, particularly those involved in the waterborne transmission pathway.

Date et al., 2011; Koopman, 2004; Chick et al., 2003; Abrams et al., 2012; and more specifically has been recently used in the cholera epidemic in Haiti (Tuite et al., 2011; Temime et al., 2008; Halloran and Lipsitch, 2005), making the issue of parameter identifiability an important and commonly encountered problem in public health. Mathematical modeling and parameter estimation has increasingly been used to help guide public health practice (Temime et al., 2008; Halloran and Lipsitch, 2005), and to assess the efficacy of different intervention strategies. This is particularly relevant for waterborne disease models because of the introduction pathways, which are often quite difficult to measure directly. From a given data set will determine the ability to estimate fundamental quantities such as the basic reproduction number, $R_0$. Based on the pathogen shedding rate, which was not available using case measurements in the water also gives additional information on water data was added. The inclusion of a second series of data measurements alone.

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Parameter Sensitivities

- Design matrix/output sensitivity matrix
- Closely related to identifiability
- Insensitive parameters
- Dependencies between columns

\[ X = \begin{pmatrix}
\frac{\partial y(t_1)}{\partial p_1} & \ldots & \frac{\partial y(t_1)}{\partial p_n} \\
\vdots & \ddots & \vdots \\
\frac{\partial y(t_m)}{\partial p_1} & \ldots & \frac{\partial y(t_m)}{\partial p_n}
\end{pmatrix} \]
Fisher Information Matrix

- FIM - \( N_p \times N_p \) matrix
- Usefull in testing practical & structural ID - represents amount of information that the output \( y \) contains about parameters \( p \)
- Cramer-Rao Bound: \( \text{FIM}^{-1} \leq \text{Cov}(p) \)
- \( \text{Rank(FIM)} = \text{number of identifiable parameters/combinations} \)
- Identifiable Combinations
Fisher Information Matrix

- Special case when errors are normally distributed

\[ F = X^T W X \]

\[ W = \text{weighting matrix} \]

\[ X = \begin{pmatrix}
\frac{\partial y(t_1)}{\partial p_1} & \cdots & \frac{\partial y(t_1)}{\partial p_n} \\
\vdots & \ddots & \vdots \\
\frac{\partial y(t_m)}{\partial p_1} & \cdots & \frac{\partial y(t_m)}{\partial p_n}
\end{pmatrix} \]

Design Matrix
Fisher Information Matrix

- For looking at structural ID, often just use

\[
F = X^T X
\]

Design Matrix

\[
X = \begin{pmatrix}
\frac{\partial y(t_1)}{\partial p_1} & \ldots & \frac{\partial y(t_1)}{\partial p_n} \\
\vdots & \ddots & \vdots \\
\frac{\partial y(t_m)}{\partial p_1} & \ldots & \frac{\partial y(t_m)}{\partial p_n}
\end{pmatrix}
\]
Identifiability & the FIM

- Covariance matrix/confidence interval estimates from Cramér-Rao bound: \( \text{Cov} \geq \text{FIM}^{-1} \)
- e.g. large confidence interval \( \Rightarrow \) probably unID
- Often can detect structural unID as ‘near-infinite’ (gigantic) variances in \( \text{Cov} \sim \text{FIM}^{-1} \)
Identifiability & the FIM

- **Rank of the FIM** is number of identifiable combinations/parameters - can do a lot by testing sub-FIMs and versions of the FIM

- Use FIM to find blocks of related parameters & how many to fix (not estimate)

- Identifiable combinations - can often see what parameters are related, but don’t know form

- Interaction of combinations
Identifiability & the FIM

- But, be careful—FIM is local & asymptotic
- Local approximation of the curvature of the likelihood

Raue et al. 2010
Profile Likelihood

- Want to examine likelihood surface, but often high-dimensional

- Basic Idea: ‘profile’ one parameter at a time, by fixing it to a range of values & fitting the rest of the parameters

- Gives best fit at each point

- Evaluate curvature of likelihood to determine confidence bounds on parameter (and to evaluate parameter uncertainty)
Profile Likelihood

- Choose a range of values for parameter $p_i$
- For each value, fix $p_i$ to that value, and fit the rest of the parameters
- Report the best likelihood/RSS/cost function value for that $p_i$ value
- Plot the best likelihood values for each value of $p_i$—this is the profile likelihood
Profile Likelihood

\[-\text{LL} \quad p\]

\[-\text{LL} \quad p\]

\[-\text{LL} \quad p\]
Profile Likelihood & ID

- Can generate confidence bounds based on the curvature of the profile likelihood
- Flat or nearly flat regions indicate identifiability issues
- Can generate simulated ‘perfect’ data to test structural identifiability
Profile Likelihood

- Can also help reveal the form of identifiable combinations
- Look at relationships between parameters when profiling
- However, can be problematic when too many degrees of freedom
2-Compartment Example

\[ \frac{1}{V} = a_1 \implies V = \frac{1}{a_1} \]

\[ \frac{k_{12} + k_{02}}{V} = a_2 \]

\[ \left( k_{01} + k_{21} \right) - k_{12} + k_{02} = a_3 \]

\[ \left( k_{12} k_{21} \right) - \left( k_{02} + k_{12} \right) \left( k_{01} + k_{21} \right) = a_4 \]
Profile Likelihoods
Parameter Relationships
Parameter Relationships
### Likelihood Profiling Example

\[ \begin{align*}
\dot{x}_1 &= k_1 x_2 - (k_2 + k_3 + k_4) x_1 \\
\dot{x}_2 &= k_4 x_1 - (k_5 + k_1) x_2 \\
y &= x_1 / V
\end{align*} \]

A diagram of these combinations is given as the bottom combination. The results for \(k_1, k_2, k_4\), and \(k_5\) satisfy our criteria. These subsets form a single component of the example in Figure 1. Based on these combinations, note that one of the subsets of parameters is greater than the number of combinations plus one, thus resulting in 10 distinct parameter relationships from the likelihood profile (as there are 3 combinations + 1 that maintain all parameters). When we consider the subsets of parameters, we find that one of the subsets is not fully constrained, i.e., they both may take on any values in order to yield an identifiable model (as there are 3 combinations + 1 that maintain all parameters). To illustrate the necessity of the remaining equation in Eq. (8), we see that these expressions that our identifiable combinations are most likely to test against the true values in each step of the profile, but the specific form of the relationship is flat in this region. We note that the general trends of the relationships are similar for a range of parameter pairs pairwise relationships. That is, assuming parameters in sub-results in 10 distinct parameter relationships from the likelihood profile. Likelihood Profiling Example.
FIM Subset Approach

- Basic idea - evaluate the rank of the FIM for subsets of parameters to elucidate the structure of the identifiable combinations

- Can then combine this with profile likelihood approach by Raue et al. to determine the form of the combinations
FIM Subset Approach

• Use the FIM rank to select subsets of parameters which are *nearly full rank* (i.e. which become full rank if any single parameter is fixed)

• Use these subsets when likelihood profiling to determine all parameter relationships

• Polynomial interpolation to recover identifiable combinations
Example Model

\[
\begin{align*}
\dot{x}_1 &= k_1 x_2 - (k_2 + k_3 + k_4) x_1 \\
\dot{x}_2 &= k_4 x_1 - (k_5 + k_1) x_2 \\
y &= x_1 / V
\end{align*}
\]
Example Model

\[
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y &= x_1 / V
\end{align*}
\]
Example Model

\[ p_1 p_2 \]

\[ p_2 + p_3 + p_4 \]

\[ p_4 + p_5 \]

\[ p_6 + p_7 \]

\[ p_7 + p_8 \]

Eisenberg & Hayashi, Math Biosciences 2014
Conclusions

• Many related questions and potential issues when connecting models to data: observability, distinguishability & model selection, reparameterization & model/parameter reduction, and more

• Many other methods! (eigenvalues of FIM, sloppy models, active subspaces, Bayesian methods, & more)

• Depending on amount of data, model complexity, model type, and more, different approaches may work in different circumstances
Conclusions

- Identifiability—an important question to address when estimating model parameters
- Common problem in math bio (identifiability-robustness tradeoff)
- Many approaches, both numerical and analytical
Identifiability of Hodgkin-Huxley Models

Joint work with Olivia Walch (UM)
Hodgkin-Huxley Model

- Hodgkin & Huxley - Nobel 1963
- Classic model of neuronal firing & dynamics
- The basis for many modern neuronal models
- Treats each component of cell as an electrical element
Hodgkin-Huxley Equations

\[ I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_Na m^3 h (V_m - V_{Na}) + \bar{g}_L (V_m - V_L) \]

\[
\begin{align*}
\frac{dn}{dt} &= \frac{n_\infty - n}{\tau_n} \\
\frac{dm}{dt} &= \frac{m_\infty - m}{\tau_m} \\
\frac{dh}{dt} &= \frac{h_\infty - h}{\tau_h}
\end{align*}
\]
Retinal subconscious vision cells

\[ C_m \frac{dV}{dt} = -g_{Na}m^3h(V - E_{Na}) - g_Kn^4(V - E_K) - g_{Ca}rP(V - E_{Ca}) - g_L(V - E_L) + I_{app} \]

\[ \frac{dw}{dt} = \frac{w_\infty - w}{\tau_w} \]

\[ m_\infty = \frac{1}{e^{0.126582(24.8 - 2(V + 30))} + 1} \]
\[ h_\infty = \frac{1}{78647.2e^{0.363636V} + 1} \]
\[ r_\infty = \frac{1}{0.035674e^{-0.266667V} + 1} \]
\[ f_\infty = \frac{1}{e^{265} + 1} \]
\[ n_\infty = \frac{1}{\sqrt{e^{-\frac{1}{17}(V-7)} + 1}} \]

\[ m_\infty = \frac{1}{0.0336138e^{-0.12383V} + 1} \]
\[ h_\infty = \frac{1}{17086.4e^{0.177865V} + 1} \]
\[ r_\infty = \frac{1}{0.109289e^{-0.130435V} + 1} \]
\[ f_\infty = \frac{1}{e^{396.12589} + 1} \]
\[ n_\infty = \frac{1}{\sqrt{e^{4131.1850} + 1}} \]

\[ \tau_m = \frac{5}{21}e^{\frac{1}{80}(-V-143)} \]
\[ \tau_h = 0.121429 + 0.00561921e^{-0.28169V} \]
\[ \tau_r = 0.738 \]
\[ \tau_f = 1.79158e^{-V/110} \]
\[ \tau_n = \frac{5}{21}e^{\frac{1}{68}(67-2V)} \]

\[ \tau_m = 0.0112252e^{-9V/1472} \]
\[ \tau_h = 0.0324545 + 0.00490052e^{-0.137783V} \]
\[ \tau_r = 0.1973 \]
\[ \tau_f = 0.547216e^{-9V/2024} \]
\[ \tau_n = 0.4821e^{-45V/3128} \]
The What and Where of Adding Channel Noise to the Hodgkin-Huxley Equations

Joshua H. Goldwyn, Eric Shea-Brown

Published: November 17, 2011. DOI: 10.1074/jci112307.1
Hodgkin-Huxley-Katz Prize Lecture

Analysis and Simulation of Neuron Reparation

A quantitative description of membrane current and its application to conduction and excitation in nerve
The nature of the permeability change. At present the thickness and composition of the excitable membrane are unknown. Our experiments are therefore unlikely to give any certain information about the nature of the molecular events underlying changes in permeability.

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Ghostbursting: A Novel Neuronal Burst Mechanism

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Action Editor: John Rinzel

Hodgkin and Huxley and the basis for electrical signalling: a remarkable legacy still going strong

Jamie I. Vandenberg1,2
and Stephen G. Waxman3,4

1Mark Good, Liddle Prize Lecture
Voltage Clamp

• Common method for collecting current data from neurons & other excitable cells (e.g. cardiac cells)

• Uses electrodes to maintain constant voltage, then can measure the resulting current dynamics

• Often do multiple runs with different voltage levels

• Can measure individual channel currents by blocking channels
Parameter Estimation for HH-Type Models

- Estimate parameters for HH-type model using voltage clamp data
- Break down estimation by each type of ion current
- Wide range of models use this formalism & data type
- Are the parameters identifiable?
Generalized HH for One Channel

\[ I(t) = g(V - E)m_{1}^{p_1} \cdots m_{n}^{p_n} \]

\[ m'_i(t) = \frac{m_{i,\infty}(V) - m_i}{\tau_i(V)} \]
Generalized HH Identifiability

• Theorem. The time constants for the gating variable kinetics, $\tau_i$, are identifiable from voltage clamp data.

• Approach: re-scale the system s.t. we can rewrite derivatives of $I(t)$ using a Vandermonde matrix

\[
\begin{pmatrix}
1 & 1 & \ldots & 1 \\
\lambda_1 & \lambda_2 & \ldots & \lambda_{2n-1} \\
\lambda_1^2 & \lambda_2^2 & \ldots & \lambda_{2n-1}^2 \\
\vdots & \vdots & \ddots & \vdots \\
\lambda_1^{2n-2} & \lambda_2^{2n-2} & \ldots & \lambda_{2n-1}^{2n-2}
\end{pmatrix}
\begin{pmatrix}
-\tau_1 \dot{z}_1 \\
\vdots \\
(-1)^k \tau_1 \tau_j \dot{z}_j \\
(-1)^n \tau_1 \tau_n \dot{z}_1 \ldots \dot{z}_n
\end{pmatrix}
= 
\begin{pmatrix}
\tilde{I} \\
\hat{I}'(t) \\
\vdots \\
\hat{I}^{(p)}(t) \\
\hat{I}^{(2n-1)}(t)
\end{pmatrix}
\]
Generalized HH Identifiability

- Theorem. The conductance term $g$ and the steady state parameters $m_{i,\infty}$ are not identifiable from voltage clamp data

$$g \prod_{i=1}^{n} m_{i,\infty}^{p_i}$$

- The product $g \prod_{i=1}^{n} m_{i,\infty}^{p_i}$ is an identifiable combination

- But! if initial conditions $m_{i}(0)$ are known, then the $m_{i,\infty}$ become identifiable
Examples

A

Simulated current

\[ m_\infty = 0.15 \text{ and } h_\infty = 0.6 \]

\[ m_\infty = 0.9 \text{ and } h_\infty = 0.1 \]

Time

B

V (mV)

Time (ms)
Generalized HH Conclusions

• HH models unidentifiable from voltage clamp data

• However, can estimate time constants $\tau_i$, and identifiability is resolved if gating variable initial conditions are known

• May help to explain some observed issues with HH model parameter estimation

• Also seen in biological data—‘experimental evidence suggests that biological neurons can achieve similar firing patterns with a continuum of different membrane conductances’ (Prinz et al. 2003)
Questions?

comic by Olivia Walch (UM):
http://imogenquest.net