Identification of biological models in cell populations using single-cell data

Andres Mauricio Gonzalez Vargas

Joint work with
Giancarlo Ferrari Trecate (UNIPV),
J. Uhlendorf, J. Schaul, E. Cinquemani, G. Batt (INRIA)

Università degli Studi di Pavia
Outline

Introduction
• Advantages of using single cell data over regular techniques.
• Sources of variability.

Setup:
• The process
• Experimental setup
• The data

Models:
• Mixed Effects Models
• Chemical Master Equations

Results:
• How do the models compare?

Conclusions and Future Work
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**Conclusions and Future Work**
Introduction

- Improvements in time-lapse fluorescence microscopy give rich information, not available with technologies that only capture histograms.
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• The problem of modeling biochemical networks in cell populations has only been addressed in a few works (Munsky et al, 2009. Hasenauer et al, 2011. Zechner et al. 2012) and remains an open question.
Introduction

• Improvements in time-lapse fluorescence microscopy give rich information, not available with technologies that only capture histograms.

• The problem of modeling biochemical networks in cell populations has only been addressed in a few works (Munsky et al, 2009. Hasenauer et al, 2011. Zechnner et al. 2012) and remains an open question.

• We propose Mixed Effects Models as an ideal tool for modeling biochemical networks in cells at individual and population level.
The “Mean Cell” Approach

Traditional approach is to model the average expression of cells, and explain variability as measurement noise.
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Observations

Single cell’s expression over time can’t be modeled with this approach.
The “Mean Cell” Approach

Traditional approach is to model the average expression of cells, and explain variability as measurement noise.

Observations
Variability in Gene Expression

Extrinsic variability: Variations in expression from cell to cell due to external factors that alter their dynamics.

Intrinsic variability: Variations in expression inside one cell due to stochasticity in chemical reactions.

Elowitz et al., Science 2012
Causes of Extrinsic Variability

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Yeast Osmoregulation

- Organism: Budding yeast (Saccharomyces cerevisiae)
- Process: Change in environmental osmolarity activates HOG pathway.
- Osmoresponsive gene: STL1
- Fluorescent protein: yECitrine
- Data acquisition: Fluorescence videomicroscopy.
Case Study

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Experimental Setup

Uhlendorf et al., PNAS, 2012
The Data

Adapted from Uhlendorf et al., PNAS, 2012
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Models

Mixed Effects Models
- Used widely in pharmacokinetics. So far haven’t been used in this context.

CHEMICAL MASTER EQUATION
- Used to model stochasticity of chemical reactions at low concentrations.
Models

**Mixed Effects Models**
- Used widely in pharmacokinetics. So far haven’t been used in this context.
- Estimation can be done via Stochastic Approximation Expectation-Maximization (SAEM)

**CHEMICAL MASTER EQUATION**
- Used to model stochasticity of chemical reactions at low concentrations.
- Estimation can be done via Moment Based Inference
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- Require the use of single cell data.

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- Estimation can be done via Stochastic Approximation Expectation-Maximization (SAEM)
- Require the use of single cell data.
- Best suited for modeling *extrinsic* variability.

**CHEMICAL MASTER EQUATION**
- Used to model stochasticity of chemical reactions at low concentrations.
- Estimation can be done via Moment Based Inference
- Can use population distributions (e.g. flow cytometry)
- Best suited for modeling *intrinsic* variability, but can be adapted to include *extrinsic* variability Zechner et al, 2012.
Mixed Effects Model

Classical statistics

Mixed effects approach

Sales, y

Price, x

Price, x
Mixed Effects Model

Individual Model: \( y_{ij} = f(Z_{ij}, \beta_i) + e_{ij} \), \( j = 1, \ldots, J_i \)

Giltinian and Davidian, 1995
Mixed Effects Model

Individual Model:

\[ y_{ij} = f(Z_{ij}, \beta_i) + e_{ij} , \quad j = 1, \ldots, J_i \]

Datapoint at time \( t_j \) \( \rightarrow \) Regressors \((t,u)\) \( \rightarrow \) Individual Parameters

Measurement Noise

Giltinian and Davidian, 1995
Individual Model:  \[ y_{ij} = f(Z_{ij}, \beta_i) + e_{ij}, \quad j = 1, \ldots, J_i \]

Population Model:  \[ \beta_i = d(\alpha_i, \beta, b_i), \quad i = 1, \ldots, N \quad b_i \sim N(0, C) \]

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Giltinian and Davidian, 1995

Noise Model:
\[ e_{ij} = (e_a + e_b f(x_{ij}, \beta_i)) \eta_{ij}, \quad \eta_i \sim N(0, 1) \]
Mixed Effects Model

Individual Model: \[ y_{ij} = f(Z_{ij}, \beta_i) + e_{ij}, \quad j = 1, \ldots, J_i \]

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Giltinan and Davidian, 1995
ME inference of HOG pathway

\[
pSTL^{\text{off}} \xrightleftharpoons[c_1 c_2]{c_1 u(t - \tau)} pSTL^{\text{on}} \]

\[
pSTL^{\text{on}} + CR \xrightarrow[c_3 c_4]{c_3} CR \cdot pSTL^{\text{on}} \]

\[
CR \cdot pSTL^{\text{on}} \xrightarrow[c_5]{c_5} CR \cdot pSTL^{\text{on}} + \text{mRNA} \]

\[
\text{mRNA} \xrightarrow[c_6]{c_6} \text{mRNA} + yECitrine \]

\[
yECitrine \xrightarrow[c_7]{c_7} \emptyset \]

\[
\text{mRNA} \xrightarrow[c_8]{c_8} \emptyset \]
ME inference of HOG pathway

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p_{STL1}^{off} \xrightarrow{c_1 u(t - \tau)} p_{STL1}^{on}
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mRNA \xrightarrow{c_6} mRNA + yECitrine
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yECitrine \xrightarrow{c_7} \emptyset
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mRNA \xrightarrow{c_8} \emptyset
\]

Laws of mass action

6-dimensional ODE system
ME inference of HOG pathway

\[ p_{STL1}^{\text{off}} \xrightleftharpoons[c_1 u(t - \tau)]{c_2} p_{STL1}^{\text{on}} \]

\[ p_{STL1}^{\text{on}} + CR \xrightarrow{c_3} CR \cdot p_{STL1}^{\text{on}} \]

\[ CR \cdot p_{STL1}^{\text{on}} \xrightarrow{c_5} CR \cdot p_{STL1}^{\text{on}} + \text{mRNA} \]

\[ \text{mRNA} \xrightarrow{c_6} \text{mRNA} + yECitrine \]

\[ yECitrine \xrightarrow{c_7} \emptyset \]

\[ \text{mRNA} \xrightarrow{c_8} \emptyset \]

\[ \text{Cell } i : \ y_i = yECitrine|_{\beta_i} + (e_a + e_b yECitrine|_{\beta_i}) \eta_i \]
ME inference of HOG pathway

\[ p_{STL1}^{\text{off}} \xleftrightarrow{c_1 u(t - \tau)} c_2 p_{STL1}^{\text{on}} \]

\[ p_{STL1}^{\text{on}} + CR \xrightarrow{c_3} c_4 CR \cdot p_{STL1}^{\text{on}} \]

\[ CR \cdot p_{STL1}^{\text{on}} \xrightarrow{c_5} c_6 CR \cdot p_{STL1}^{\text{on}} + \text{mRNA} \]

\[ \text{mRNA} \xrightarrow{c_6} \text{mRNA} + yECitrine \]

\[ yECitrine \xrightarrow{c_7} \emptyset \]

\[ \text{mRNA} \xrightarrow{c_8} \emptyset \]

Cell \( i \):

\[ y_i = yECitrine|_{\beta_i} + (e_a + e_b yECitrine|_{\beta_i}) \eta_i \]

\[ \beta_i = e^{{\beta + b_i}} \]
ME inference of HOG pathway

\[ pSTL1^{off} \overset{c1}{\underset{c2}{\rightleftharpoons}} pSTL1^{on} \]
\[ pSTL1^{on} + CR \overset{c3}{\rightarrow} CR \cdot pSTL1^{on} \]
\[ CR \cdot pSTL1^{on} \overset{c5}{\rightarrow} CR \cdot pSTL1^{on} + mRNA \]
\[ mRNA \overset{c6}{\rightarrow} mRNA + yECitrine \]
\[ yECitrine \overset{c7}{\rightarrow} \emptyset \]
\[ mRNA \overset{c8}{\rightarrow} \emptyset \]

Cell \( i \): \( y_i = yECitrine|_{\beta_i} + (e_a + e_byECitrine|_{\beta_i})\eta_i \)

Identification problem
- Inferred parameters: \( \beta, \text{cov} (\beta), e_a, e_b \).
- Method: marginal likelihood maximization, e.g. the SAEM algorithm (Deylon et al, Ann Stat, 99)

Simulation:
- ODE with random parameters extracted from \( N(\beta, C) \)

Laws of mass action
6-dimensional ODE system
CME + Moment Based Inference
(as proposed in Zechner et al, PNAS, 2012)

Moment-based inference predicts bimodality in transient gene expression

Christoph Zechner\textsuperscript{a,1}, Jakob Ruess\textsuperscript{a,1}, Peter Krenn\textsuperscript{a}, Serge Pelet\textsuperscript{b}, Matthias Peter\textsuperscript{b}, John Lygeros\textsuperscript{a}, and Heinz Koeppl\textsuperscript{a,2}
CME + Moment Based Inference
(as proposed in Zechner et al, PNAS, 2012)

Chemical Master Equation:
\[
\frac{d}{dt} p(x, t) = \sum_{r=1}^{R} a_r (x - v_r) p(x - v_r, t) - a_r (x) p(x, t)
\]
CME + Moment Based Inference
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Chemical Master Equation:
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\frac{d}{dt} p(x, t) = \sum_{r=1}^{R} a_r (x - v_r)p(x - v_r, t) - a_r(x)p(x, t)
\]

- Probability of being in state \( x \) at time \( t \)
- Propensity Function
- Change in \# of molecules
- \# of molecules

Introduction     Setup     Models     Results     Conclusions
CME + Moment Based Inference

(as proposed in Zechner et al, PNAS, 2012)

Chemical Master Equation: \[ \frac{d}{dt} p(x, t) \] describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \)
CME + Moment Based Inference

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Chemical Master Equation:

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\frac{d}{dt} p(x, t)
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describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \).
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Chemical Master Equation: \[ \frac{d}{dt} p(x, t) \] describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \).

Moment Based Inference:

\[ \dot{\mu} = A(\theta, z)\mu + B(\theta, z)\bar{\mu} \]

Infinite dimensional linear ODE
**CME + Moment Based Inference**

(as proposed in Zechner et al, PNAS, 2012)

Chemical Master Equation: \( \frac{d}{dt} p(x, t) \) describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \)

Moment Based Inference:

- **Moments of Order < L**
  \[ \dot{\mu} = A(\theta, z)\mu + B(\theta, z)\bar{\mu} \]
  - Infinite dimensional linear ODE

- **Moments of Order ≥ L**
  \[ \dot{\bar{\mu}} = A(\theta, z)\bar{\mu} + B(\theta, z)\phi(\bar{\mu}|z) \]
  - Finite-Dimensional non-linear ODE
CME + Moment Based Inference
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Chemical Master Equation: \( \frac{d}{dt} p(x, t) \) describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \).

Moment Based Inference:

- Moments of Order <\( L \): \( \dot{\mu} = A(\theta, z)\mu + B(\theta, z)\bar{\mu} \)
  - Infinite dimensional linear ODE
- Moments of Order \( \geq L \): \( \hat{\mu} = A(\theta, z)\mu + B(\theta, z)\phi(\bar{\mu}|z) \)
  - Finite-Dimensional non-linear ODE

Extrinsic variability: \( z \sim \log N(\gamma, D) \)
CME + Moment Based Inference
(as proposed in Zechner et al, PNAS, 2012)

Chemical Master Equation: \( \frac{d}{dt} p(x, t) \) describes the time evolution of the conditional distribution of the system. The propensity functions \( a_r \) become a vector of kinetic parameters \( \theta \)

Moment Based Inference:

\[ \begin{align*}
\dot{\mu} &= A(\theta, z) \mu + B(\theta, z) \bar{\mu} \\
\text{Infinite dimensional linear ODE}
\end{align*} \quad \rightarrow \quad \begin{align*}
\dot{\hat{\mu}} &= A(\theta, z) \hat{\mu} + B(\theta, z) \phi(\hat{\mu}|z) \\
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\[ z \sim LogN(\gamma, D) \]

Noise Model: Additive + Multiplicative, (same as in ME)
MB inference for the HOG pathway
(as proposed in Zechner et al, PNAS, 2012)

\[ p_{STL1}^{\text{off}} \xrightarrow{\frac{c_1 u(t - \tau)}{c_2}} p_{STL1}^{\text{on}} \]

\[ p_{STL1}^{\text{on}} + CR \xrightarrow{\frac{c_3}{c_4}} CR \cdot p_{STL1}^{\text{on}} \]

\[ CR \cdot p_{STL1}^{\text{on}} \xrightarrow{c_5} CR \cdot p_{STL1}^{\text{on}} + \text{mRNA} \]

\[ \text{mRNA} \xrightarrow{c_6} \text{mRNA} + yECitrine \]

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\text{pSTL1}^{\text{off}} & \xrightarrow{c_1 u(t-t_0)} \text{pSTL1}^{\text{on}} \\
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\text{CR} \cdot \text{pSTL1}^{\text{on}} & \xrightarrow{c_5} \text{CR} \cdot \text{pSTL1}^{\text{on}} + \text{mRNA} \\
\text{mRNA} & \xrightarrow{c_6} \text{mRNA} + \text{yECitrine} \\
\text{yECitrine} & \xrightarrow{c_7} \emptyset \\
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\end{align*} \]

2nd order Moment Closure

35-dimensional ODE system describing the MOMENTS of the system
MB inference for the HOG pathway
(as proposed in Zechner et al, PNAS, 2012)

\[ p_{STL1}^{\text{off}} \xrightarrow{\frac{c_1}{c_2}u(t)} p_{STL1}^{\text{on}} \]

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35-dimensional ODE system describing the **MOMENTS** of the system

Extrinsic variability ($Z$):
- \( CR_0 \) (Chromatin Remodeling Factor)
- \( c_6 \) (translation efficiency)
MB inference for the HOG pathway
(as proposed in Zechner et al, PNAS, 2012)

\[ p_{STL1}^{off} \xrightarrow{c_{1u}(t-r)} p_{STL1}^{on} \]
\[ p_{STL1}^{on} + CR \xrightarrow{c_{3}} CR \cdot p_{STL1}^{on} \]
\[ CR \cdot p_{STL1}^{on} \xrightarrow{c_{5}} CR \cdot p_{STL1}^{on} + mRNA \]
\[ mRNA \xrightarrow{c_{6}} mRNA + yECitrine \]
\[ yECitrine \xrightarrow{c_{7}} \emptyset \]
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Identification problem
- Inferred parameters: \( E[Z] \), \( \text{cov}(Z) \), \( \theta \), \( e_a \), \( e_b \)
- Method: Kullback-Liebler divergence minimization.

Simulation:
- SSA simulation with parameters \( \theta \), and \( z \sim \text{LogN}(\gamma, D) \)

Extrinsic variability (\( Z \)):
- \( CR \) (Chromatin Remodeling Factor)
- \( c_6 \) (translation efficiency)

Kinetic Parameters

2nd order Moment Closure

35-dimensional ODE system describing the MOMENTS of the system

ICDS Lab
University of Pavia
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Conclusions and Future Work
Identification vs Validation Set

- Similar spread of identification and validation data (in the figure: mean ±2 sd)
- Different open/close commands to the valve
- Dynamic population: cell are born, die or leave the microscope field of view
Performance measures

At each time instant, compare observed fluorescent protein from a validation dataset vs. 10000 cells simulated using the validation dataset’s input

NRMSE
- Empirical Mean: observations vs and simulations
- Empirical StDev: observations vs and simulations

Kolmogorov-Smirnov (KS) test
- Distance between empirical CDF of two distributions
- Distributions are different with 95% when $p$-Kol < 0.05
- $h$-Kol = success rate
Performance on Identification Set

- Both Models have similar results

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Performance on Identification Set

- Both Models have similar results
- MB has better performance in all indicators

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Performance on Identification Set

Both Models have similar results

MB has better performance in all indicators

MB inference works well even if different from (Zechner, 2012)

- there are much fewer cells
- simpler identification procedure

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Performance on Identification Set

**Mixed Effects**

**CME+MBI**

Population

Single Cell

Fluorescent Protein

Time (min)
Performance on Identification Set

Mixed Effects

CME+MBI

Population

Single Cell

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Performance on Validation Set

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- MB performs better in NRMSE
Performance on Validation Set

- MB performs better in NRMSE
- ME performs better in KS test.

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<td>0.20</td>
<td>0.13</td>
</tr>
<tr>
<td>Avg. p-Kol</td>
<td>0.34</td>
<td>0.32</td>
</tr>
<tr>
<td>h-Kol</td>
<td>87%</td>
<td>74%</td>
</tr>
</tbody>
</table>
Performance on Validation Set

- MB performs better in NRMSE
- ME performs better in KS test.

<table>
<thead>
<tr>
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<th>ME</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRMSE_M</td>
<td>0.08</td>
<td>0.06</td>
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<tr>
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- ME performs better in KS test.
- What is predominant? Intrinsic or extrinsic variability?

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Performance on Identification Set

Mixed Effects

CME+MBI

Population

Introduction     Setup     Models     Results     Conclusions
Conclusions

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• Improvements are needed to separate intrinsic from extrinsic variability.
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CME+MBI Advantages
• Can account for both, intrinsic and extrinsic noise.
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• Tailored to flow-cytometry data (time-course of distributions of fluorescence)
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Future Work
Thanks for your attention!

Acknowledgements

University of Pavia
Giancarlo Ferrari Trecate

INRIA Rhone-Alpes
Eugenio Cinquemani

INRIA Paris-Rocquencourt
Gregory Batt
Jannis Uhlendorf
Joe Schaul
Artemis Llamosi