Programming MATLAB Symbolic Math Toolbox for Speed: Experience from the GenSSI Version 2 Project

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<Ligon>
Systems biology

GenSSI 2.0: multi-experiment structural identifiability analysis of SBML models

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The structurally *globally identifiable* parameters are: $[K_3, k_1, k_2]$

The structurally *locally identifiable* parameters are: $[]$

The structurally *non-identifiable* parameters are: $[s]$
GenSSI Version 1

- GenSSI written in MATLAB with the Maple toolbox
- In 2008, Mathworks acquired MuPAD
- MuPAD developed by University of Paderborn and sold to SciFace
- MuPAD became MATLAB Symbolic Math Toolbox, replacing Maple

GenSSI Version 2

- Convert Code to run in newer version of MATLAB
- Calculation of Jacobian matrix required change
- Many performance problems required change
- New functions, such as multi-experiment model created
- Performance (R2016a) better than Version 1 (R2008a)
Thomas Ligon: MATLAB Symbolic Math Speed

(b) Computation time relative to GenSSI (R2008a)

- Arabidopsis: 2-fold speedup
- Glycolysis: 4-fold speedup
- Goodwin: 8-fold speedup
- HighDim nonlinear model: 2-fold speedup
- NFKB: 4-fold speedup
- Pharmacokinetics: 8-fold speedup

GenSSI 2.0 Performance

28.04.2018
Maple can calculate Jacobian of a matrix
MATLAB only calculates Jacobian of a vector
Possible solution:

\[ \text{df} = \text{sym}(\text{zeros}([\text{size}(f,1),\text{size}(f,2),\text{length}(v)]) \]) 
\]
for iRow = 1:size(f,1)
    \[ \text{df}(\text{iRow},:,:) = \text{jacobian}(f(\text{iRow},:),v) \]
end

This **does not work** for GenSSI, because Maple and MATLAB order the result differently
% Original code:
rank(LDer); % LDer is matrix of Lie derivatives
JacParamC = jacobian(LDer, Par); % Par is vector of parameters

% Final code:
% calculate 2D jacobian the way Maple does it
JacParam = jacobian(reshape(LDer,[numel(LDer),1]),model.sym.Par);

That works, but then we had big performance problems!
Memory management can be very dangerous

Example of a very efficient system:

• Call the operating system rarely...
• ... and manage that buffer internally
• Allocate many pieces of memory (internally)...
• ... and manipulate pointers instead of data

But that’s low-level code, and we are using MATLAB
Numeric matrices have a fixed size

- Number of cells times size of (double precision) number
- Pre-allocation is effective

Symbolic matrices have a variable size

- Cells can be long expressions or polynomials
- Pre-allocation is still not enough
Mathworks highly recommends **Pre-allocation** and **Vectorization**

1. `rowN = zeros(numCols,1);` **pre-allocate** `rowN`
2. `for iCol = 1:numCols`
3. `rowN(iCol) = matrix(n,iCol) % elementwise (loop)`
4. `end`

% alternate code
5. `rowN = matrix(n,:); % vectorized`

Without line 1, line 3 changes size of `rowN`
Line 5 puts all the logic inside of MATLAB
Performance numbers later (in GenSSI code)
Remove Zero Rows - Old

1 remove_Lie_index=[];
2 for iRow=JacParamx:-1:1
3     if JacParam(iRow,:)==0;
4         JacParam(iRow,:)=[];
5     remove_Lie_index=[remove_Lie_index iRow];
6     end
7 end

Line 4 changes the size of JacParam
  • Causes memory management

Line 5 also changes size
1 \[\text{JacParam,tilde,useful\_Lie\_index} = \text{genssiRemoveZeroRows(JacParam)};\]
3 \[\text{results.useful\_Lie\_index} = \text{useful\_Lie\_index};\]

4 function \[\text{[matrixOut,keepBoolean,keepIndex]}=\text{genssiRemoveZeroRows(matrixIn)}\]
5 \[\text{keepBoolean=any(matrixIn}==0,2);\]
6 \[\text{matrixOut=matrixIn(keepBoolean,:)};\]
7 \[\text{keepIndex=find(keepBoolean)’};\]
8 end

**Line 5 contains all logic, no “for” loop, no “if”**

- “any” creates a Boolean array
- Line 6 returns rows with 1 in keepBoolean
Remove Zero Rows - Results

![Bar chart showing runtime for different versions of MATLAB Symbolic Math]

- Thomas Ligon: MATLAB Symbolic Math Speed
Test Performance of Rank

1 load('JacParamC1.mat');
2 A=JacParamC1;
3 tic;
4 R1=rank(A); % MATLAB Rank
5 disp(['rank1=',num2str(R1),', time=',num2str(toc)]);
6 tic;
7 R2=feval(symengine,'linalg::rank',A); % MuPAD Rank
8 disp(['rank2=',char(R2),', time=',num2str(toc)]);
9 disp('end');
MuPAD Rank – Results

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28.04.2018
Convert Jacobian (symbolic) to Tableau (Boolean)

**Old code (vectorized single line)**

```matlab
% JacParam01=zeros(sizeJacParam);
JacParam01=double(JacParam~=0);
```

**New code**

```matlab
JacParam01=zeros(size(JacParam));
JacParam01(find(JacParam))=1;
```
Symbolic to Numeric - Results

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MATLAB solve

- In some cases, it cannot find a solution
- Warning: Explicit solution could not be found
- Limits information returned

MATLAB jacobian, rank, solve

- can be slow
- support for parallel processing would help

Memory

- every new derivative increases the size of the jacobain by a factor of Npar (number of parameters)
- Memory usage grows exponentially
Beware of things that require memory management
Pre-allocation is good
Vectorization is good
Special functions including “any” and “find” are good
  • but might require a version check

Thanks to Mathworks for support cases
  • provided quick help and workarounds
  • fixed bugs and improved code in future versions

General recommendations
  • Support: Always provide a clear and concise test program and description.
  • Change requests: Include a business case.
GenSSI Teams

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Appendix
Dynamical systems, especially in systems biology, are often modeled by systems of ordinary differential equations (ODEs) and we want to know if it is possible to infer the parameters of these equations (e.g. reaction rates) from experimental data, in a process called parameter estimation or “the inverse problem”. If this is possible in principle, i.e. based on optimal data, the parameters are called “structurally identifiable”. GenSSI (Generating Series for testing Structural Identifiability) uses generating series of Lie derivatives to analyze the structural identifiability of parameters of a set of ODEs based on arbitrary analytical functions. We converted GenSSI from version 1, which uses the Maple toolbox and runs on MATLAB version R2008a and older, to version 2, which uses the MATLAB Symbolic Math toolbox (based on MuPAD) and runs on MATLAB version R2008b and newer. As part of this, we corrected some very significant performance issues with the Symbolic Math toolbox, ultimately achieving better performance than the original version. This talk addresses those performance aspects.
Table S1. Implementation and availability of different toolboxes for structural identifiability analysis.

<table>
<thead>
<tr>
<th></th>
<th>COMBOS</th>
<th>DAISY</th>
<th>EAR</th>
<th>GenSSI 1.0 and 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Differential algebra</td>
<td>Differential algebra</td>
<td>Semi-numerical probabilistic differential algebra</td>
<td>Generating series</td>
</tr>
<tr>
<td>Software base</td>
<td>Maxima</td>
<td>REDUCE</td>
<td>Mathematica</td>
<td>MATLAB</td>
</tr>
<tr>
<td>Availability</td>
<td>Web</td>
<td>Object Code</td>
<td>Object Code</td>
<td>Source Code</td>
</tr>
<tr>
<td>Operating system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Windows</td>
<td></td>
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<td>✓</td>
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<tr>
<td>Linux</td>
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<td>✓</td>
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<tr>
<td>Mac OS</td>
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</tr>
<tr>
<td>Web</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table S2. Features of structural identifiability toolboxes.

<table>
<thead>
<tr>
<th>Model and experimental setup</th>
<th>COMBOS</th>
<th>DAISY</th>
<th>EAR</th>
<th>GenSSI 1.0</th>
<th>GenSSI 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBML import</td>
<td>x</td>
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<tr>
<td>rational kinetic laws</td>
<td>x¹</td>
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<td>✓</td>
<td>✓</td>
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<td>Parameter-dependent initial conditions</td>
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<td>✓</td>
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<tr>
<td>Control inputs</td>
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<tr>
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<td>x</td>
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<td>Transformation to polynomial form</td>
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<td>Identifiability analysis</td>
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<td>Local structural identifiability</td>
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<td>State transformation</td>
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<tr>
<td>Parameter transformation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
</tr>
</tbody>
</table>

¹ COMBOS only supports polynomial kinetics, i.e. mass-action kinetics.
² COMBOS and DAISY do not support the usage of parameters that are not included in the vector field of the ODE model. Removing these parameters from our existing models changes them, making a comparison less meaningful.

Paper of first slide, supporting information
Global Identifiability of Differential Models

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https://arxiv.org/abs/1801.08112
Single-cell mRNA transfection studies:
Delivery, kinetics and statistics by numbers

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Figure 1. Comparison of mRNA and pDNA Vectors (both gene vectors encoding for the same eGFP protein) and their respective uptake pathways. (A) Linearized RNA (1192 bases) furnished with a stabilizing CAP sequence, an enhancing UTR sequence, and poly-(A) tail. (B) pDNA (4733 base pairs) under the control of the CMV promoter. The vector transfer under identical transfection protocols differs because mRNA is translated after endosomal escape, while plasmid DNA must be transferred into the nucleus for the initiation of transcription.
mRNA transfection model

\[ \frac{d}{dt} G = k_{TL} \cdot m - \beta \cdot G \]
\[ \frac{d}{dt} m = -\delta \cdot m \]

Solution

\[ G_{mRNA}(t) = \frac{k_{TL} \cdot m_0}{\delta - \beta} \left( 1 - e^{-(\delta - \beta)(t-t_0)} \right) \cdot e^{-\beta(t-t_0)} \]

Problems

- \( k_{TL} \cdot m_0 \) cannot be separated (identified).
- Solution is symmetric in \( \beta \) and \( \delta \).
- 2 equation for 4 parameters.
Reduced identifiability tableau of order 2
GenSSI: Nothing is identifiable

--> WARNING: The number of parameters is Larger than the number of relations!
An explicit solution cannot be given for this subset of parameters.
   PLEASE CONSIDER AN EXTRA DERIVATIVE!

Structurally globally identifiable parameters:
[]
Structurally locally identifiable parameters:
[]
Structurally non-identifiable parameters:
[]
Experimental solutions

Measure not only GFP, but also mRNA

• ...but that is difficult in living cells

Perform multiple experiments

• GFP with different degradation rate (eGFP)
• mRNA with different degradation rate (poly-A-tail)
• antibiotic that inhibits translation (different rate)

-> Multi-experiment models