High Performance Systems Biology Tools

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Outline and goals:

• (Brief) NREL introduction
• (Brief) Metabolic modeling/Systems Biology introduction
• (Main) Report ongoing case study--application of HPC to metabolic modeling at kinetic level--of many links in chain necessary to formulate mathematically and solve numerically real science problems
• (Brief) Simulation Optimization Exploration
National Renewable Energy Laboratory

- A DOE national laboratory dedicated to renewable energy and energy efficiency R&D
- Fundamental science to technology
- Collaboration with industry and university partners
- Aspirations to market relevance
High Performance Systems Biology: Whole Cell Metabolic Modeling of Fuel Producing Algae

Fuel producing green algae *Chlamydomonas reinhardtii*

Systems biology: system level understanding enabled by in-depth knowledge of the molecular nature of biological systems

Project goals:
• Build high performance tools for resolving model uncertainties in large biological models
• Fill knowledge gaps and develop full metabolic model of *C. reinhardtii*. 
**HPC applied to Systems Biology - existing tools**

**Grid Cellware** - Grid based simulation and parameter estimation.

**SBaddon** - Extension package for Systems Biology Toolbox within MatLab, includes compiled simulation functions.

**HiBi09** - Workshop planned for Fall 09, “a forum to link researchers in the areas of parallel computing and computational systems biology.”

**Systems Biology Workbench (SBW)** - Plug in interface, model translation/simulation tools.

...  

No existing truly HPC Systems Biology tools.

Our SciDAC project:

**HiPerSBTK - High Performance Systems Biology Toolkit**

- high performance simulation and sensitivity,
- (hierarchically) parallel optimization and parameter scanning.
Summary of steps in HPC kinetic level metabolic simulation and optimization

\[
\frac{dy}{dt} = f(y, k)
\]

Automatic differentiation

**model.xml**

**y(t;k)**

Local Optimization

Global Optimization

\[ F(k) \text{ for } k \in \Omega \]

Psampler

\[ \min F(k) \text{ such that } k \in \Omega \]

\[ \text{opt}_k \]

Implicit solver

Gradients

Sensitivity

Objective functions ("jobs") \( F(k) \)

\[ \frac{df}{dy}, \frac{df}{dk} \]

\[ \text{model.cpp} \]
Model formulation in SBML

A hierarchical approach

*Nothing* fully known. Proceed in order:
- **C. rheinhardtii**
- Analogs with other species
  - in order of *genetic* similarity
- High performance computing

Sources of uncertainty:
- form of equations
- constants
- transferability of analogs

Systems Biology Markup Language (SBML):
- An xml variant/schema
- Metabolism consists (roughly) of *species, parameters, reactions*
Model equations

Michaelis-Menten Kinetics:

\[
\frac{d[DGP]}{dt} = \frac{K_{1\text{cat}} \cdot [GK][ATP][D]}{K_{1\text{Ki}} + K_{1\text{ATP}}[D] + K_{1\text{D}}[ATP] + [ATP][D]} - \frac{K_{2\text{cat}} \cdot [GPI][DGP]}{K_{2\text{KM}} + [DGP]}
\]

- The vector \( y \) contains *species concentrations*
- \( k \) contains *kinetic parameters*
- \( E \) are *enzyme levels*

Vectors have \( O(100) \) elements today, \( O(1000) \) in future

Goals:
- Resolve uncertainties in \( k \)
- Optimize properties w.r.t. \( E \)
Model translation

The need for translating SBML to a compiled language:

sbml2cpp:
- `Model.cpp/h` generated from `model.xml`.
- Efficient implementation (e.g. hash tables) avoids $O(\text{species } \times \text{parameters } \times \text{reactions})$ ODE construction.
- Jacobians enabled through automatic differentiation.
Simulation and Sensitivity: dfdk

• A model-specific library that performs core simulation and sensitivity calculations.

• Uses SUNDIALS (LLNL) suite of ODE tools, esp. CVODES

• Command line and script oriented tools, e.g. text file input:

```bash
# defines objective/what to calculate:
job=s
# time to which we simulate:
time=0.001
# species we care about this run: acetate, butyrate, hydrogen
activey_ids = cpd_C00033 cpd_C00246 cpd_C00282
# species target values
activey_expt_vals = 2 10 30
# parameters to optimize
activek_ids = R01196_kcat R00230_kcat R01061_kcat Rpyr_cyto2mito_V R00238_kcat R01512_kcat R00200_kcat R01196_KA
# bounds on selected params (for optimizer)
R01196_kcat_bounds = 0.000000 1000.000000
R00230_kcat_bounds = 0.000000 1000.000000
R01061_kcat_bounds = 0.000000 1000.000000
Rpyr_cyto2mito_V_bounds = 0.00000 1000.000000
R00238_kcat_bounds = 0.000000 1000.000000
```

• Basic tasks enabled

• Provides foundation for HPC model characterization/optimization
dfdk Examples

```
./dfdk --time=1 --job=f --details=1 | grep "^x:" | awk '{for (i=2; i<=NF; i++) printf "%.12f ", $i; printf "\n"}' | xmgrace -nxy -
```

```
./dfdk --job=y; python extract_minimal.py dydk.out
effects of params, in order:
[111, 'R01061CS_KiP', 6903571412765018.0]
[107, 'R01061CS_KiC1', 65996370854907.25]
[83, 'R00756CS_p', 143.12400446157102]
[142, 'ec_4_2_1_11_CS', 5.8202960624527815]
...
effects on species, in order:
[11, 'cpd_C00009_CS', 3039405874122647.0]
[12, 'cpd_C00003_CS', 3039405874122647.0]
[13, 'cpd_C00004_CS', 303944871365413.5]
[17, 'cpd_C00197_CS', 2532305704157037.0]
...
```

python flux_viewer.py
Model optimization / parameter estimation

Criteria for determining $k$: e.g. fit to experimental data

$$g(k) = \sum_{i=1}^{N} |y_i - y_i^{\text{exp}}|^2$$

With this (or any similar) criterion in hand, our model building has been formulated as the global optimization problem

$$\min g(k) \quad \text{for} \quad k_i^{\text{min}} \leq k_i \leq k_i^{\text{max}}$$

The bounds on $k$ are roughly six orders of magnitude, e.g. $k_i$ between 0.001 and 1000.

A hard problem:

• narrow troughs and flat plateaus
• multiple local minima
• multiple “funnels”
• unknown global structure
Gradients

Observation: We can calculate the gradient of least squares objective $g(k)$:

$$
\frac{\partial g}{\partial k_j} = 2\sum_{i=1}^{N} (y_i - y_i^{\text{exp}}) \frac{\partial y_i}{\partial k_j}
$$

The quantity $s = \frac{\partial y}{\partial k}$ is the sensitivity:

In fact, we never explicitly compute it, but instead use adjoint sensitivity analysis to directly compute $\nabla g$. This functionality is built into the CVODES.
Local Optimization

Gradients enable efficient local search. We use TAO’s BLMVM method.

Issues:
- constraints
- extreme sensitivity of gradients
- scaling-large range of spatial and temporal scales
- rootfinding / quasi-steady states
- underdetermination
Global Optimization - Parallel Scatter Search

Local search is not enough. We need global search. **Scatter Search:**
- Population based.
- Diversity systematically maintained.
- Generation of new solutions by interpolation and extrapolation between old ones.
- Includes local search phase--we utilize our existing TAO-based local optimizer

Initial results: This method solves 64 variable problems with 4 orders of magnitude bounds in a matter of minutes, and scales well.
Mixing sampling and fitting. Test model of *C. reinhardtii*. Scan a 2D grid of values of acetoacetyl-CoA thiolase $k_{cat}$ and phosphoglycerate kinase $k_{cat}$; for each value, Fit the rest of the kinetic parameters to synthetic experimental values of acetate and butyrate. Plot the resulting hydrogen flux. x, y units are log (base 10) of parameter values. z-axis (hydrogen flux) units are relative.
The App/Job matrix

Formulation of concepts of interest so far utilizes the following:
• Species concentrations $y(t)$
• Sensitivity $dy/dk$ and its squared Frobenius norm $\|dy/dk\|_F^2$
• Fit to experimental data $|y^e - y^c|^2$

Tasks we might want to do include:
• Simulate the network for any one of the above properties (or, later, functions of them).
• Scan the behavior of the network over a range of kinetic parameters $k$.
• Optimize the network with respect to $k$, where the objective function involves the above quantities.

Thus the following matrix of functionality:

<table>
<thead>
<tr>
<th>app</th>
<th>job</th>
<th>fwd</th>
<th>sens</th>
<th>fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>simulate (dfdk)</td>
<td>$y(t; k, y_0, E)$</td>
<td>$dy/dk$</td>
<td>$</td>
<td>y^e - y^c</td>
</tr>
<tr>
<td>scan (psampler)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>optimize (optk_tao, optk_ss)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

+ = existing functionality, - = in development

In addition, we will implement combinations of these basic tasks, including: treating some of them as constraints, and some of them as objectives; nested combinations of scanning and optimization, over different parameter subsets.
100-way (mostly *embarrassing parallel*) parallelism at each level is possible, could potentially utilize more than 1,000,000 processors (?)
Summary of the HiPerSBTK

• high performance
• utilizing existing HPC tools (SUNDIALS, etc.)
• building blocks
• prototypical scanning and optimization tasks
Simulation Exploration

We think we are doing simulation optimization. In fact, users want simulation exploration.
• Unknown objective functions.
• Unclear parameter spaces.
• More than just optimum is scientifically interesting.
• Experimentalists, theorists, and mathematicians formulate problems w.r.t. different variables.

Examples
• Systems Biology
  “Scan some parameters, fit w.r.t some others, apply selective constraints, then optimize (or maybe just report), certain values.”

• Inverse Material Design
  “What is the PDF of an alloy configuration space?”
  “What is the best $A_xB_yC_{1-x-y}$ alloy?”
Simulation exploration in Inverse Material Design

“What is the PDF of an alloy configuration space?”
“What is the best $A_xB_yC_{1-x-y}$ alloy?”

(Compare to Systems Biology case)
Summary

• NREL is the hub of renewable energy research in the United States.
• Large scale metabolic modeling using HPC is possible.
• Scanning and optimization approach to quantifying and resolving uncertainty.
• Evolution in thinking toward HPC exploration/characterization tools, with optimization as an important sub-component

Outlook

• Testing of 200 species 500 parameter model.
• Use of data versus “physics-based” modeling.
• Rootfinding, explicit calculation of (quasi-)steady states
• More formal treatment of uncertainty
• Allow for logarithmic treatment of all kinetic parameters.
• Parallel I/O. Choose output data format and use it (e.g. parallel HDF5 (?)).
• Implement all possible app/job combinations.
• Constrained optimization. Required to support, for example, "Optimize hydrogen subject to butyrate and acetate fitting experimental values.”
• Take flux seriously. Take distinction between "internal" and "boundary" species seriously. With constrained optimization, required to support, for example, "Optimize hydrogen subject to flux of pyruvate not exceeding $X$.”
• Plug in approach: Combine simulation, scanning, fitting, optimizing [apps], different objective functions [jobs], treatment of them as objectives or constraints, all in user configurable and scalably parallel way.
• Find some users and do what they suggest.
Problems of the Week:

Problem 1:
For $k_1 \in K_1$
Solve:
$$\min F(k_2;k_1) \text{ for } k_2 \in K_2$$
Report $g(k_2^*;k_1)$

E.g. $F = \text{fit to experiment, } g = \text{particular chemical species of interest}$

Problem 2:
For $k_1 \in K_1$
Solve:
$$\max g(k_2;k_1) \text{ s.t. } F(k_2;k_1) = 0, \ k_2 \in K_2$$

E.g. Explore (scan, optimize, ...) parameter space $K_1$ (e.g. uncertain model parameters), for each point maximizing flux of chemical fuel subject to constraint that model fit experimental data, over parameter space $K_2$ (e.g. enzymes).

Goal:

*Modular hierarchically parallel simulation exploration*