Multi-scale simulations of whole yeast cells

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NCSA Blue Waters Symposium for Petascale Science and Beyond: June 6, 2018
Chemical kinetic simulations

Chemical kinetic simulations

Chemical kinetic simulations

\[ c(t), \quad c(x, t) \]

- **CME** (Chemical Master Equation)
- **ODE** (Ordinary Differential Equations)
- **PDE** (Partial Differential Equations)
- **RDME** (Reactive Diffusion Master Equation)

**Single molecule resolution**

**Spatial resolution**

**Diffusion rate**

**Concentration**

Chemical kinetic simulations

$P(n, t)$

$C(t)$

$P(x, t)$

Chemical kinetic simulations

\[ P(n, t) \]

\[ P(n, x, t) \]

\[ c(t) \]

\[ c(x, t) \]
CME/ODE — Well mixed chemical kinetics
**Saccharomyces cerevisiae — Characteristic scales**

<table>
<thead>
<tr>
<th></th>
<th>Conc. [µM]</th>
<th>Diff. coeff. [µm²/s]</th>
<th>Diff. time [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar</td>
<td>~1,000</td>
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<td>0.013</td>
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Concentration/time scales do not overlap!
Yeast galactose switch

Ramsey et al. Nat Genet. 2006 10.1038/ng1869
Yeast galactose switch

10⁷ reactions per second
over 6 hours

Ramsey et al. Nat Genet. 2006 10.1038/ng1869
Yeast galactose switch

10^7 reactions per second over 6 hours

Ramsey et al. Nat Genet. 2006 10.1038/ng1869
Hybrid CME/ODE simulations
Hybrid CME/ODE simulations

Chemical master equation: *Gillespie algorithm*

Hybrid CME/ODE simulations

Chemical rate equation: **LSODA**

Chemical master equation: **Gillespie algorithm**

---

Hybrid CME/ODE simulations

Chemical rate equation: \textit{LSODA}

Chemical master equation: \textit{Gillespie algorithm}

Results: 40x speed up with limited impact on accuracy

Wall time to simulate 750 min

<table>
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<tr>
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<th>External galactose</th>
<th>0.055 mM</th>
<th>2.0 mM</th>
</tr>
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<tbody>
<tr>
<td>CME (hr)</td>
<td>2.1</td>
<td>47.4</td>
<td></td>
</tr>
<tr>
<td>Hybrid (10 s)</td>
<td>0.4 (5.2)</td>
<td>1.1 (43.1)</td>
<td></td>
</tr>
<tr>
<td>Hybrid (1s)</td>
<td>0.8 (2.6)</td>
<td>1.8 (26.3)</td>
<td></td>
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![Graphs showing simulation results and protein counts]
RDME/ODE — Spatial resolution
Reaction-Diffusion Master Equation
Reaction-Diffusion Master Equation
Reaction-Diffusion Master Equation

Discretize to lattice
Reaction-Diffusion Master Equation

Discretize to lattice

Particles:
- React within subvolumes
- Diffuse between subvolumes
Reaction-Diffusion Master Equation

Discretize to lattice

Particles:
  *React within subvolumes*
  *Diffuse between subvolumes*

System state described by particle count of each type at each subvolume
Whole-cell modeling with Lattice Microbes

Designed for CUDA

Multiple levels of parallelism
- GPGPU
  - Roberts et al. IPDPS (2009)
  - 10.1109/ipdps.2009.5160930
- Multi-GPU
  - 10.1016/j.parco.2014.03.009
- MPI
  - (w.i.p.)

Extensible through Python
  - Peterson et al. PyHPC 2013
  - 10.13140/2.1.3207.7440
  - Hybrid solvers
Yeast galactose switch — Initial geometry

Cryo-electron tomography

2.04 × 1.91 × 0.242 μm³
section of yeast cell

2% of total volume

Use tomogram as template to build whole cell geometry
Use tomogram as template for cell geometry
Use tomogram as template for cell geometry
Use tomogram as template for cell geometry
Use tomogram as template for cell geometry
G80 is sequestered from nucleus
New transporters are localized near nucleus

\( t=0.0 \text{ min} \)
New transporters are localized near nucleus
Outlook

**Demonstrated**
- CME $\leftrightarrow$ ODE
- RDME $\leftrightarrow$ ODE

**Planning**
- RDME $\leftrightarrow$ PDE

**In progress**
- RDME $\leftrightarrow$ Brownian dynamics
Outlook

**Demonstrated**
- CME $\leftrightarrow$ ODE
- RDME $\leftrightarrow$ ODE

**Planning**
- RDME $\leftrightarrow$ PDE

**In progress**
- RDME $\leftrightarrow$ Brownian dynamics
Outlook

Goal
Whole-cell physico-chemical model of minimal cell

JCVI-syn3A
- 400 nm diameter
- 453 protein coding genes
- 2 hr doubling time

Multi-scale modeling
- ODE — Metabolism
- RDME — Gene expression
- BD — Ribosomes, DNA, cytoskeleton

1Huchison et al. Science 2016 10.1126/science.aad6253
2Breuer, TME, …, ZLS 2018 submitted
3TME, …, ZLS. BPJ 2016 10.1016/j.bpj.2015.07.030
Acknowledgements

Zan Luthey-Schulten
David Bianchi
Mike Hallock
Joe Peterson
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