GPU-accelerated Model-Based Drug Development

Chee M Ng, Pharm.D., Ph.D., FCP

Outlines

- What is **model-based drug development**
- **Nonlinear Mixed-effect Model (NLME)** for model-based drug development approach
- **GPU-accelerated EM-based NLME method (MCPEM)**

MCPEM – Monte-Carlo Parametric Expectation Maximization

Global Drug Market

- Global drug sales – USD 707 billion in 2011
- Expected to reach ~ USD 817 billion in 2018

Top-selling drugs in the US

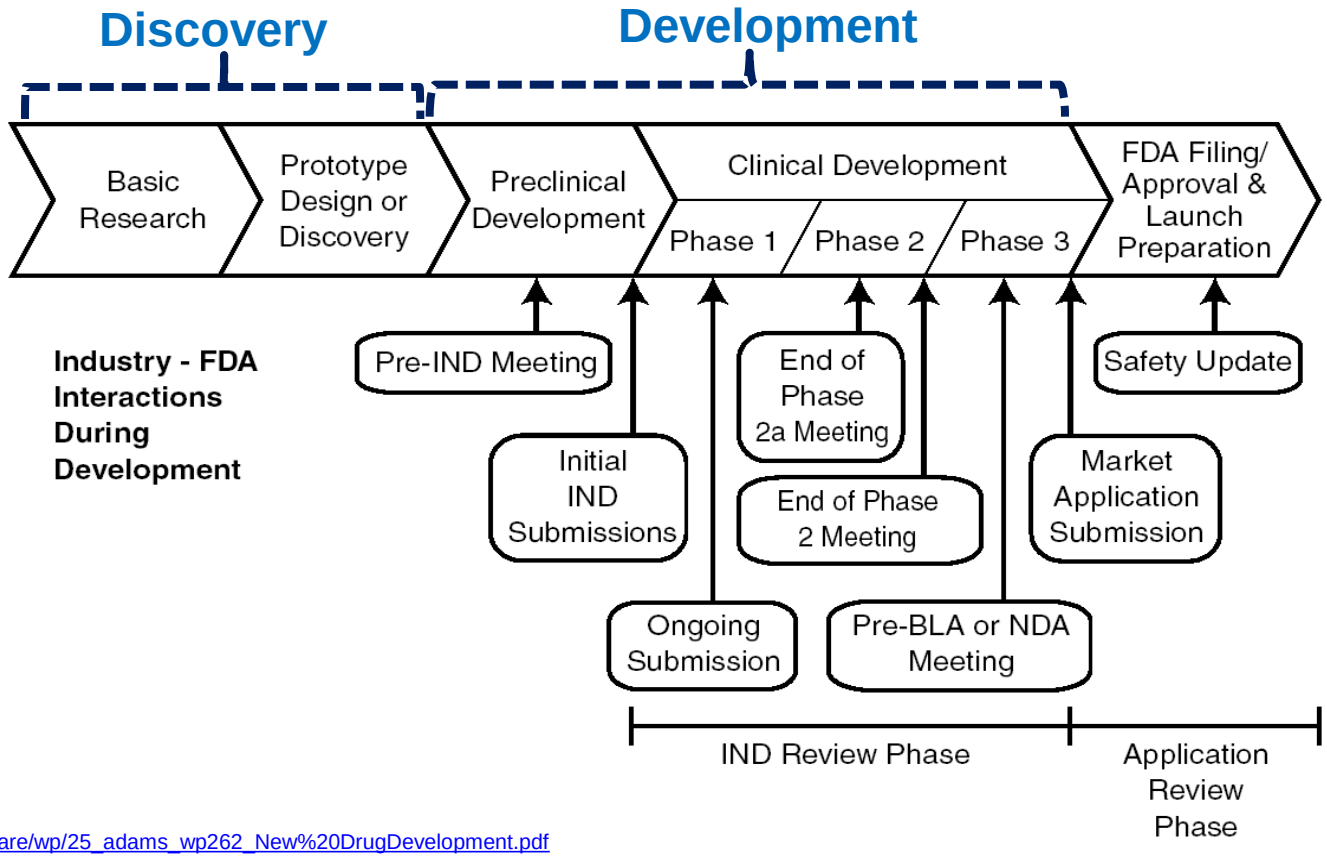
RANK	DRUG	CLASS	2010 SALES (Billion USD)
1	Lipitor	Lipid (Cholesterol) lowering agent	7.2
2	Nexium	Proton-pump inhibitor	6.3
3	Plavix	Anti-platelet agent	6.1

2010 total sales of the add-in graphic video card ~ 17 billion USD
2010 total video game sales ~18.6 billion USD

Sources:
1.http://www.fiercepharma.com/press-releases/positive-currency-effects-help-global-pharmaceutical-market-grow-53-percent
2.http://www.forbes.com/sites/matthewherper/2011/04/19/the-best-selling-drugs-in-america/2/
3.http://www.slashgear.com/jpr-report-finds-graphics-card-add-in-board-sales-totaled-17b-for-2010-04137843/
4.http://www.cnbc.com/id/41062675/Video_Game_Sales_Drop_6_in_2010_Second_Year_of_Declines

Drug Development is

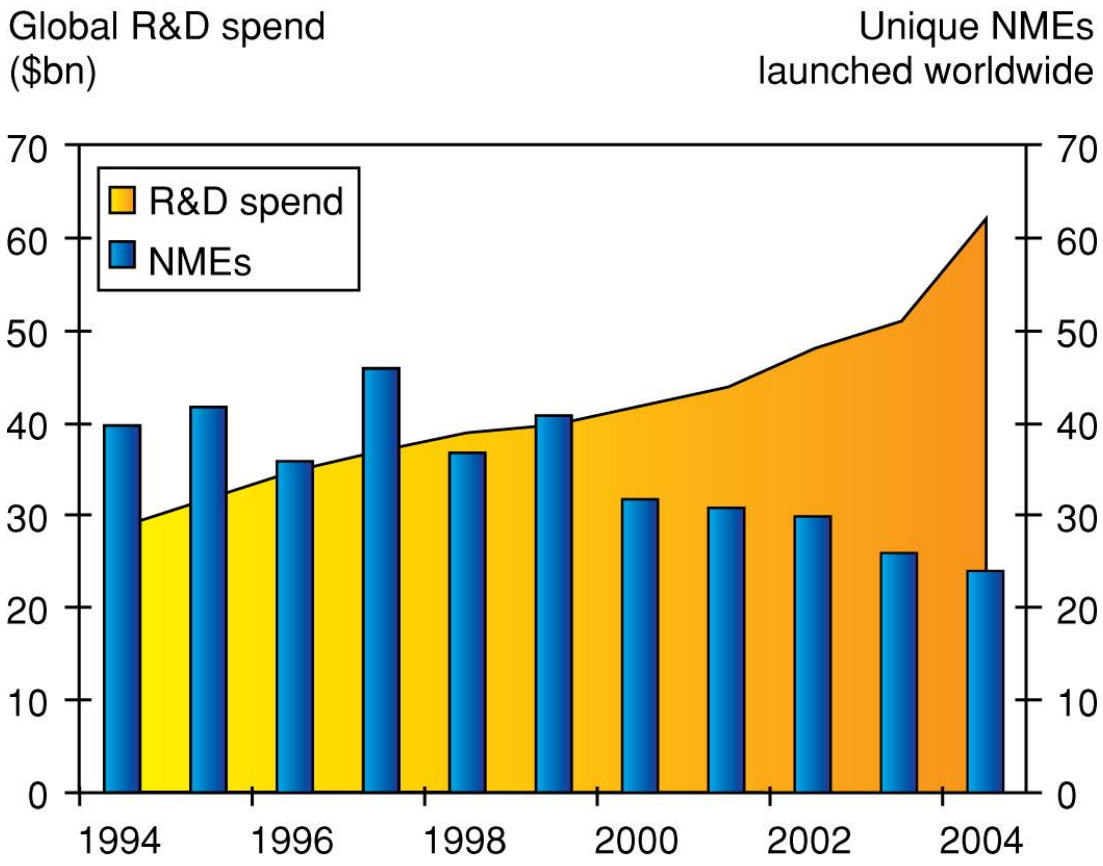
- **Expensive** (~ 0.8 – 1.7 billions USD)
- **Lengthy** (~ 8 years from Phase I to market lunch)
- **Complex**



http://www.ftc.gov/be/healthcare/wp/25_adams_wp262_New%20DrugDevelopment.pdf
http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

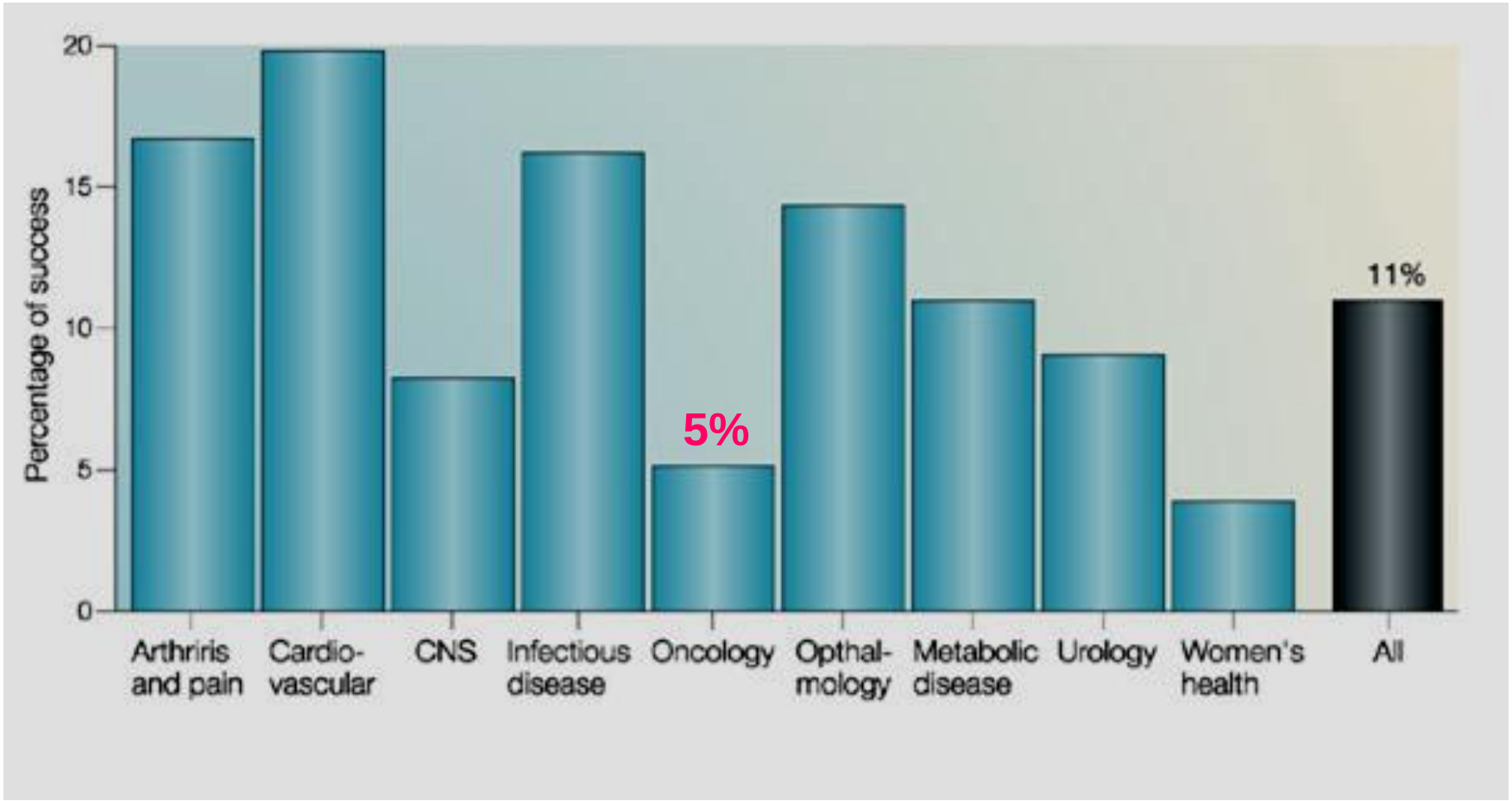
Problems in Drug Development

Science advances, research and development Investment Increases…. but successful drug development is slowing



Woodcock J, Woosley R. 2008.
Annu. Rev. Med. 59:1–12

Low Success Rates from First in Human to Registration



From 1) Kola et al. Nature Rev Drug Discov 2004;3:711-15 and 2) Kola et al. Clin Pharmcol Ther 2008

How Did This Happen?

… The **science of drug development** is lagging behind the recent basic science achievement….

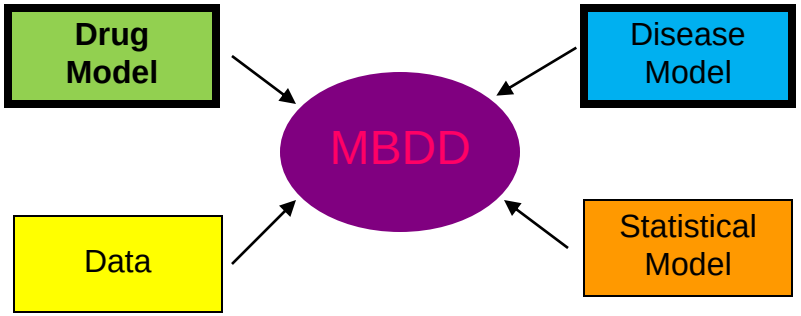
Often, drug developer are forced to use the tools of the last century to evaluate this century's advances…

The standard modeling and simulation software for drug development is > 30 years-old FORTRAN program (with part of the program upgraded to FORTRAN 95 in 2010)

The single enterprise license is 95000 USD!

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

FDA Critical Path
Model-based Drug Development (MBDD)



By making better use of data to improve knowledge of product development, a model-based development program could

1. **Reduce uncertainty** about dose selection, and other key safety and efficacy issue…
2. **Reduce the risk and cost** of human testing by making more informed decision on how to proceed with drug product testing and when to remove a product from further development..

http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf

Pharmacokinetics and Pharmacodynamics

Our Knowledge About Drugs in Development Process

- **Pharmacokinetics (PK)** – **What the body does to the drug**

  Absorption/**D**ispostion/**M**etabolism/

  Excretion

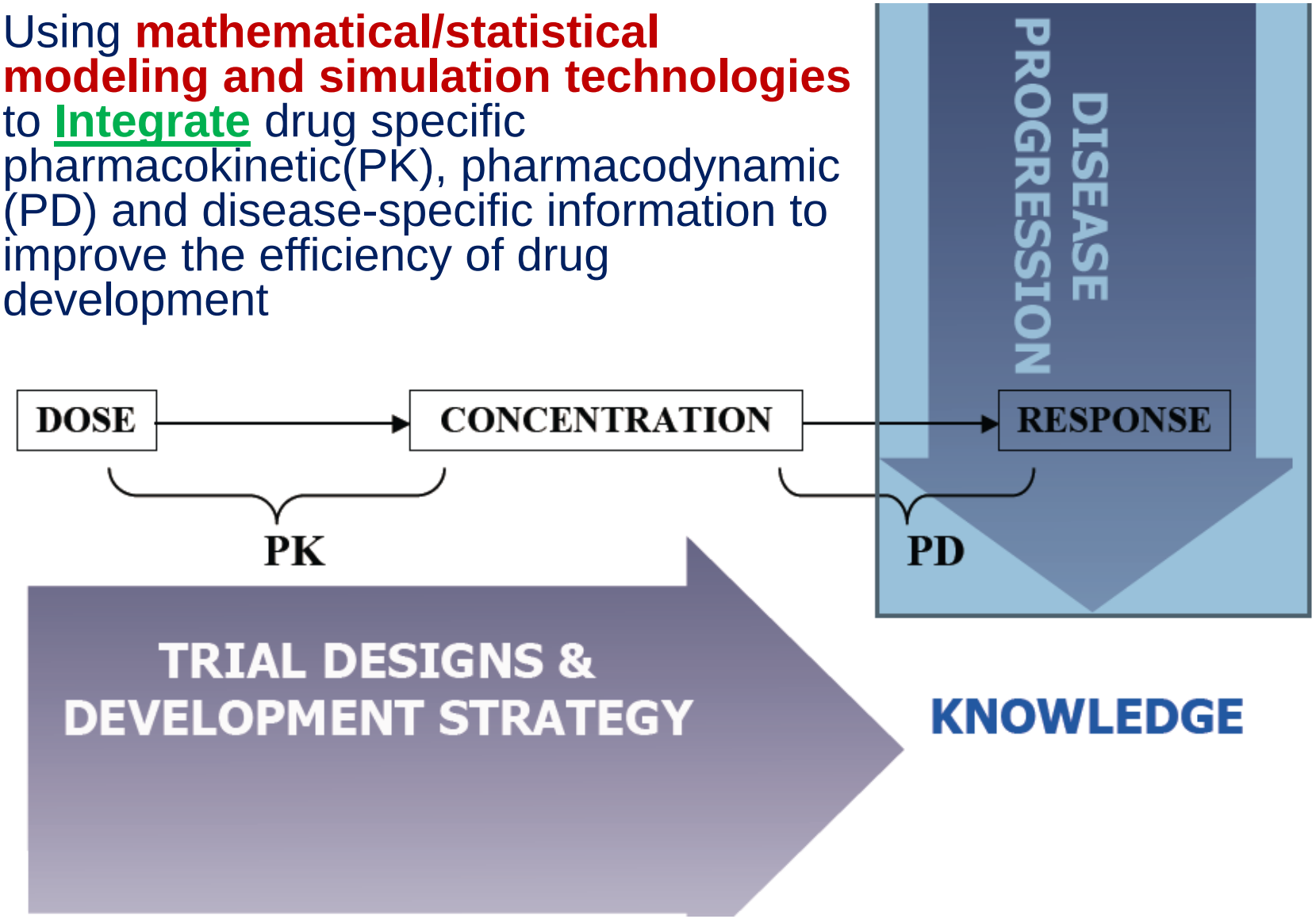
- **Pharmacodynamics (PD)** – **What the drug does to the body**

  Any efficacy (clinical response, biomarkers, surrogate markers) and safety endpoints related to drugs

Ratain MJ, Mick R. In Schilsky et al. Principles of antineoplastic drug development 1996
Takimoto CH, Ng CM. In Devita et al. Cancer: Principles & Practice of Oncology 2007

Model-based Drug Development

Using **mathematical/statistical modeling and simulation technologies** to **Integrate** drug specific pharmacokinetic(PK), pharmacodynamic (PD) and disease-specific information to improve the efficiency of drug development



Takimoto CH and Ng CM. 2007; Gastonguay M 2008

Challenges in Model-based Drug Development

Integration of the Highly Complicated/Heterogeneous Preclinical/Clinical Data From Different Studies

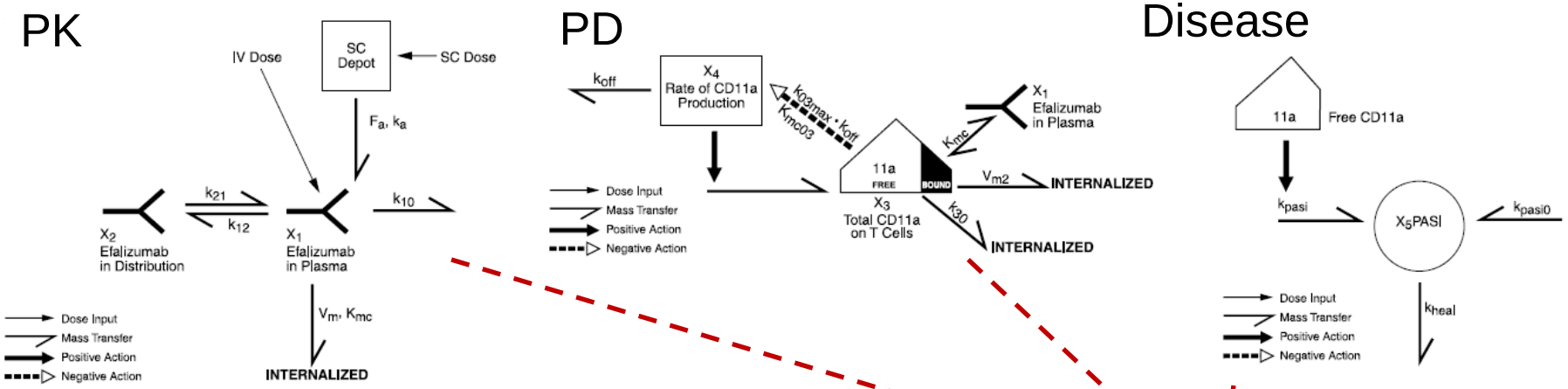
- **However,** the data from these different studied population shared certain degree of similarity (+ difference)
- **Nonlinear mixed-effect model (NLME) is used to integrate information** from highly complicated/heterogeneous studied population → **POPULATION DATA ANALYSIS**

Challenges in Model-based Drug Development

Complex Population PK/PD/Disease Model

Mechanism-based Population Model of Efalizumab in Psoriasis Patients

Mathematical Model



Statistical Model (Nonlinear Mixed Effect Model)

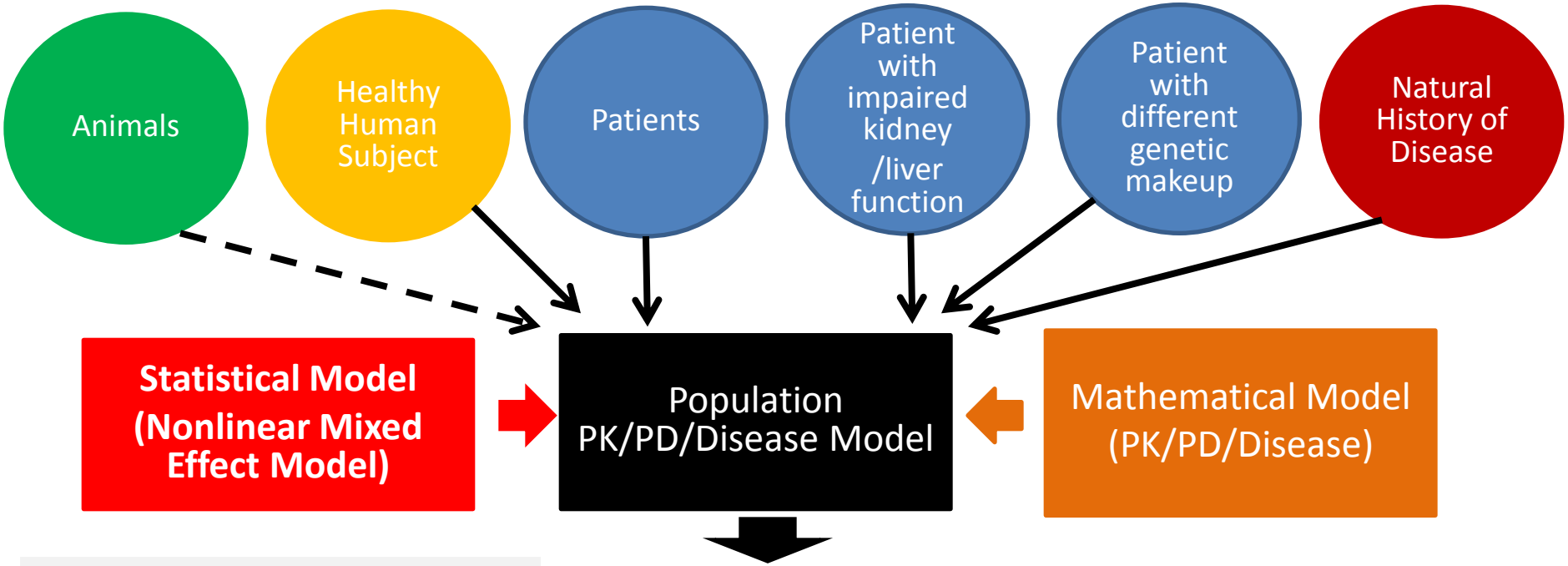
$$-\log(l(yi|\theta i,\sigma)=\frac{1}{2}\sum_{j=1}^{mj}[\frac{(y_{ij}-f(t_{ij},\theta_i))^2}{g_{ij}}+\ln(g_{ij})]$$

$$L=-2\sum_{i=1}^{n}\log(\int_{-\infty}^{+\infty}l(y_i\,|\,\theta_i,\sigma)h(\theta_i\,|\,\mu,\Omega,\sigma)d\theta_i)$$

Nonlinearity → no closed form solution and computationally expensive

From Ng CM et al. 2005

Model-based Drug Development



HOWEVER…..

Numerical intensive/time consuming model development process (weeks or months) → Decision is often made before the model is completed!

Modeling and Simulation

Support Decision Making and Optimal Dose/Patient Selection

Using GPU-Computing Technology to Accelerate the Performance of EM-based NLME Algorithm (MCPEM) in Population Data Analysis For Model-based Drug Development

MCPEM – Monte-Carlo Parametric Expectation Maximization

What is MCPEM and Why MCPEM for GPU Computing?

MCPEM – Monte-Carlo Parametric Expectation Maximization

Nonlinear Mixed Effect Model for Population Data Analysis

$$L = -2\sum_{i=1}^{n} \log\left(\int_{-\infty}^{+\infty} l(y_i \mid \theta_i, \sigma) h(\theta_i \mid \mu, \Omega, \sigma) d\theta_i \right)$$

Nonlinearity → **no closed form solution** and computationally expensive

- **Approximate Methods** (Fast but approximation)
  - FO/FOCE and ITS
- **Exact "Likelihood" Methods** (No Approximation but computational intensive)

  EM – MCPEM, and SAEM

MCPEM – Monte-Carlo Parametric EM;
FO – First-order; FOCE – First-order Conditional Estimation; ITS – Iterative 2-stages
SAEM - Stochastic Approximation EM;

MCPEM (Exact "Likelihood") Method Has Better Performances and Been Used Successfully in Developing Population PK/PD/Disease Model for Drug Development

The AAPS Journal 2007; 9 (1) Article 7 (http://www.aapsj.org).

Themed Issue: Bioinformatics and Computational Advances in the Pharmaceutical Sciences
Guest Editor - Murali Ramanathan

A Survey of Population Analysis Methods and Software for Complex Pharmacokinetic and Pharmacodynamic Models with Examples

Submitted: November 9, 2006; Accepted: January 13, 2007; Published: March 2, 2007

Robert J. Bauer,[1] Serge Guzy,[1] and Chee Ng[2]

[1]Pharmacokinetics, Pharmacodynamics, and Bioinformatics, XOMA (US) LLC, Berkeley, CA
[2]Institute for Drug Development/Cancer Research and Therapy Center, San Antonio, TX

Pharmaceutical Research, Vol. 22, No. 7, July 2005 (© 2005)
DOI: 10.1007/s11095-005-5642-4

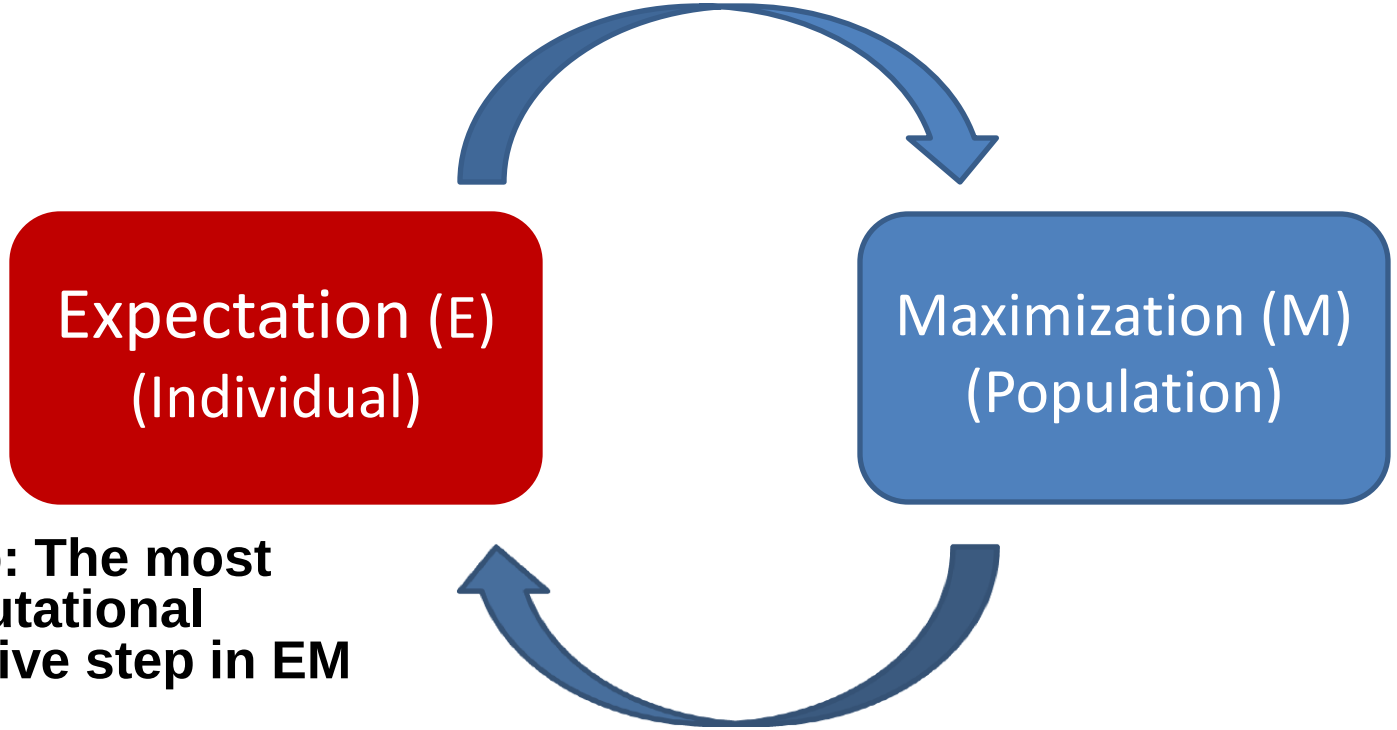
Research Paper

Pharmacokinetic–Pharmacodynamic–Efficacy Analysis of Efalizumab in Patients with Moderate to Severe Psoriasis

Chee M. Ng,[1,3] Amita Joshi,[1] Russell L. Dedrick,[2] Marvin R. Garovoy,[2] and Robert J. Bauer[2]

Expectation Maximization (EM) Estimation Method for Population Data Analysis

- Iterative optimization process



E-step: The most computational intensive step in EM

Repeat E and M steps until population parameters no longer change (Maximum Likelihood is reached)

MCPEM Algorithm and GPU Computing

- The MCPEM algorithm is suitable for GPU computing because in the most computational intensive **E step**:
  - The conditional mean and variance of each subject
  - Generated random samples used to obtain the conditional mean and variance-covariance matrix for each individual

Individual Conditional Mean $\overline{\theta_i} = \dfrac{\int_{-\infty}^{+\infty} \theta p(y_i, \theta \mid \mu, \Omega) d\theta}{\int_{-\infty}^{+\infty} p(y_i, \theta \mid \mu, \Omega) d\theta}$

- ***Are independent from each others***, and therefore can be evaluated separately!

GPU-based MCPEM Heterogeneous Computing

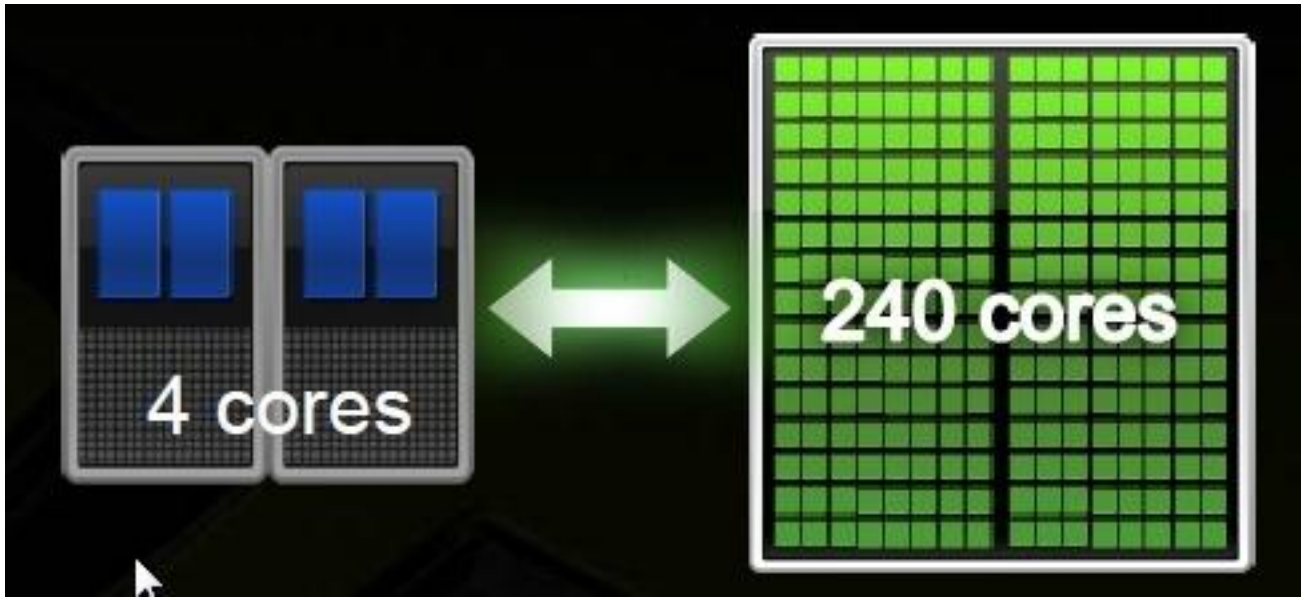
- Computing with CPU and GPU

CPU

M Step

GPU

E steps + partial derivatives of the intra-individual variance matrix



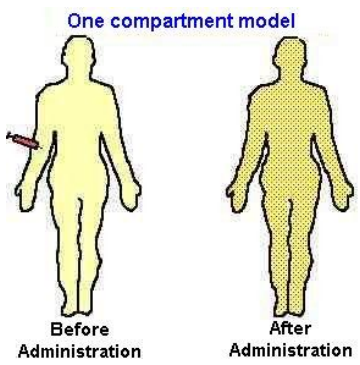
GPU-Based MCPEM

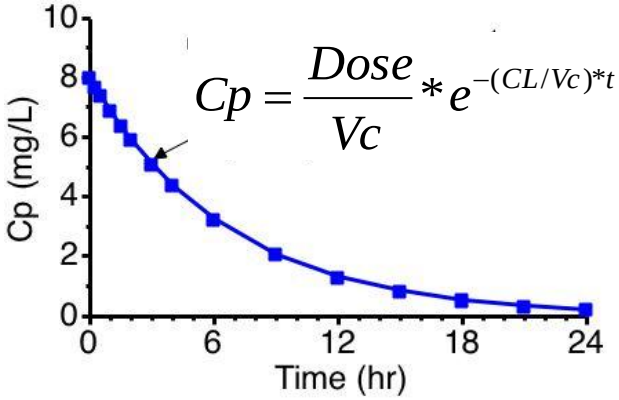
- **Computing Environment**

  * Windows 7 64-bit Workstation + Dual Intel Xeon X5690 6-cores CPU (3.46GHz) + a NVIDIA Tesla C2070 GPU [448 GPU-cores/6GB RAM] + 48GB RAM
  * Matlab 2009b/Jacket 1.8/CUDA 4.0

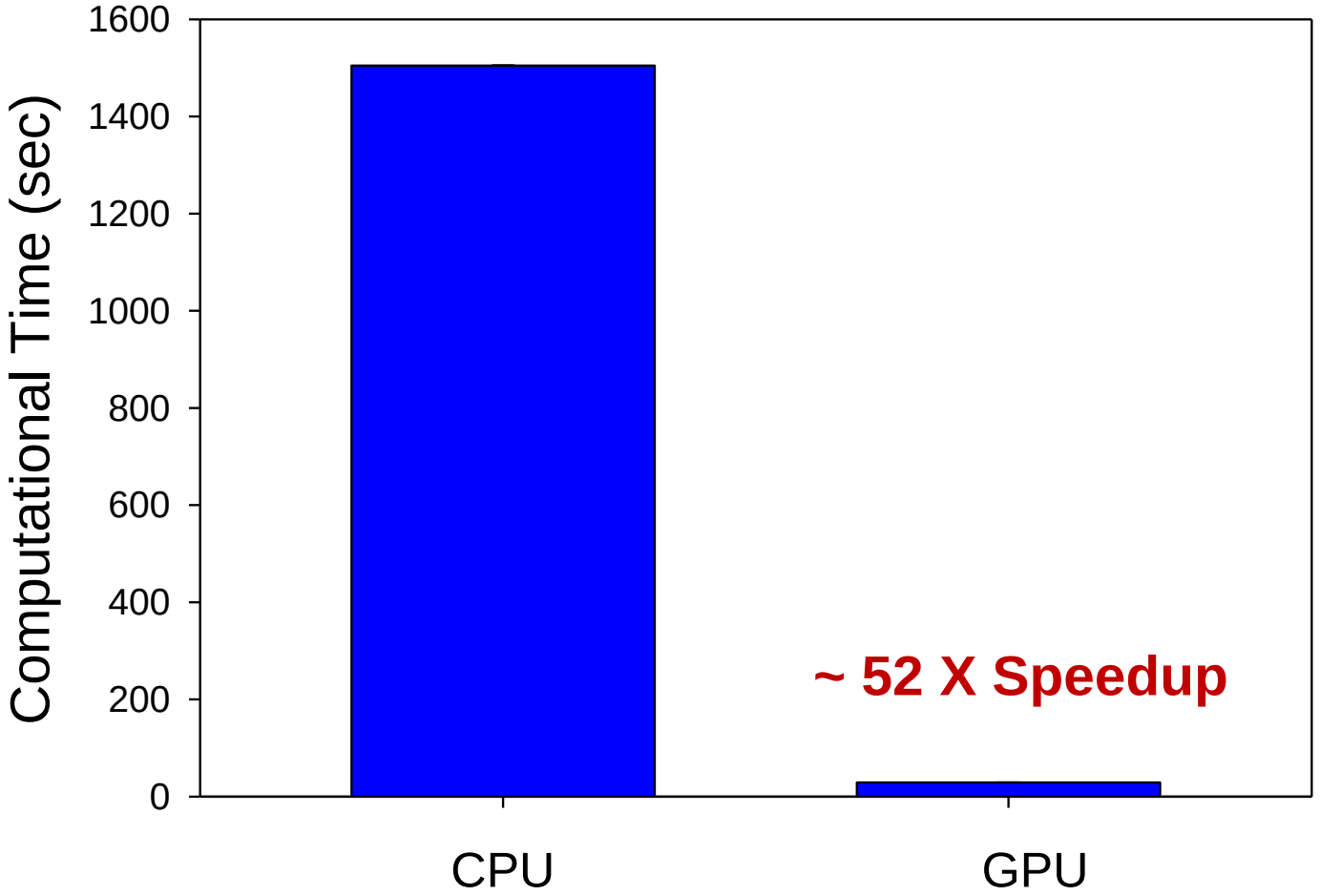
- **Data**

  Number of studied subject=100





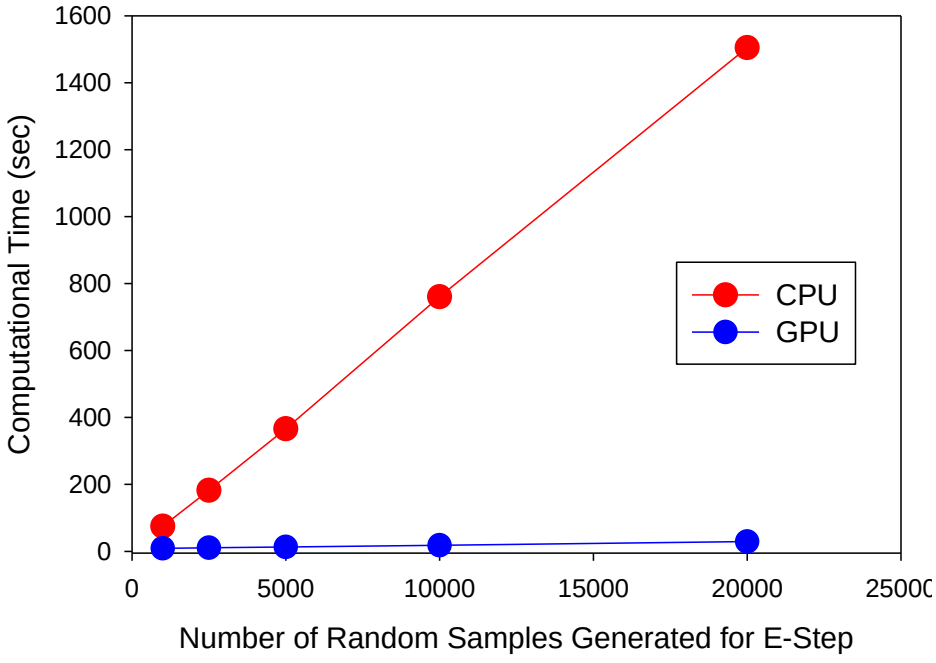
GPU-based MCPEM Computed Much Faster Than the CPU-MCPEM

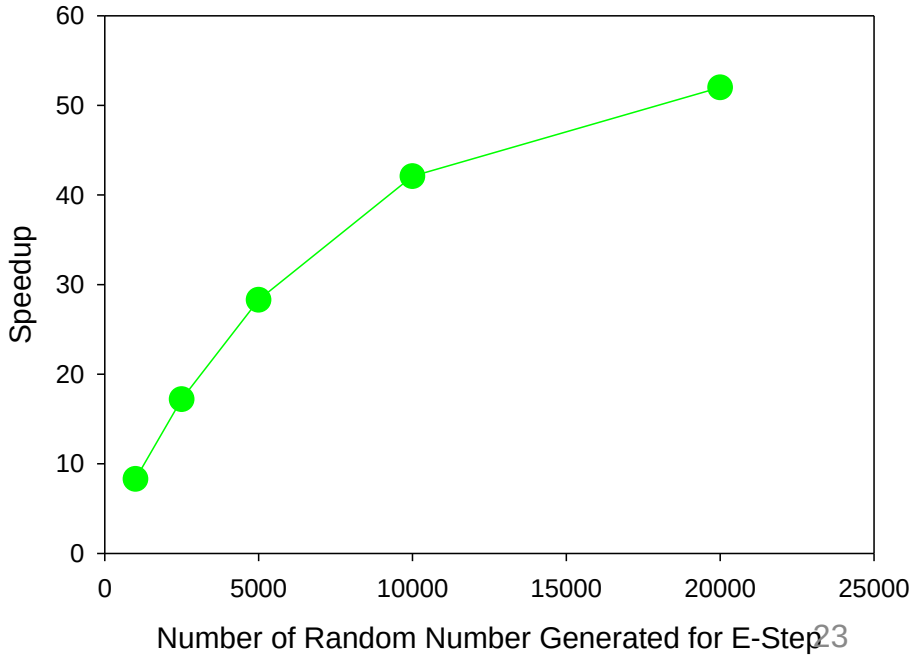


Number of studied subject =100; Number of random samples for E-step = 20,000; Number of run =100

GPU-based MCPEM Computed Much Faster Than the CPU-MCPEM

- GPU-based MCPEMhas a better scaling relationships between mean computational times and number of random samples generated for E-step
- Speedup of GPU-based MCPEM ↑ as the number of random number generated for E-step ↑





Conclusions

- **First** reported GPU-based parallelized MCPEM prototype was developed for population PK data analysis
- Innovative, GPU-oriented approaches can lead to vast speed-up, and reduce data analysis and model development times for model-based drug development

Future Works

- A study is ongoing to
  - expand the capability of the GPU-based MCPEM in using parallel differential equation solver to develop complex population PK/PD/disease model ; Multiple doses
  - improve the efficiency of the algorithm either through further parallelization of the program codes or with multiple GPU processors

Children Hospital of Philadelphia/University of Pennsylvania NVIDIA CUDA Research Center

- GPU-based NLME Estimation method for population data analysis in Mode-based Drug Development
- Medical imaging analysis (DCE-MRI) in assessing the pharmacodynamic of the anti-vascular drugs in preclinical/clinical studies
- GPU-based global optimization algorithm (GA/pattern-search) for complex PK/PD data analysis (Ng CM. ACOP 2010)
- Machine learning/Artificial intelligent/Rule-based PK/PD/disease model development and decision makings
- Others