Enhancing the efficiency of animal-alternative in-silico drug cardiotoxicity prediction through CUDA-based parallel processing

CUDA기반 병렬처리를 통한 동물대체 인실리코 약물 심독성 예측 효율성 증대

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Introduction

Background

- Cardiovascular diseases are a leading cause of death globally.
- Current drug discovery methods, which rely heavily on animal testing, face ethical concerns and limitations in accuracy to predict human drug safety.
- In recent years, ***in silico*** **(computer-based)** methods have emerged as a promising **alternative**.
- However, their **efficiency** is often hindered by the complexity of simulating biological processes, and **large samples** that being processed.

Main Objectives

- Develop an efficient *in silico* cardiotoxicity prediction method capable of handling large sample sizes.
- Utilise GPU-based parallel processing with CUDA to accelerate simulations while maintaining accuracy.

CUDA

CUDA (Compute Unified Device Architecture) is a parallel computing platform and programming model developed by NVIDIA. It enables general-purpose computing on NVIDIA graphics processing unit (GPU).

Key Features

1. **Massive Parallelism:**
   - Utilizes thousands of GPU cores to process tasks simultaneously.
   - Ideal for large-scale computations like in silico simulations.
2. **Flexible Programming Model:**
   - Built on **C, C++, and Fortran**, making it accessible for developers.
   - Allows for custom thread and memory management.
3. **Hierarchical Threading:**
   - Threads are grouped into blocks, and blocks form grids.
   - Supports efficient task distribution for high-performance computing.

Why CUDA for This Research?

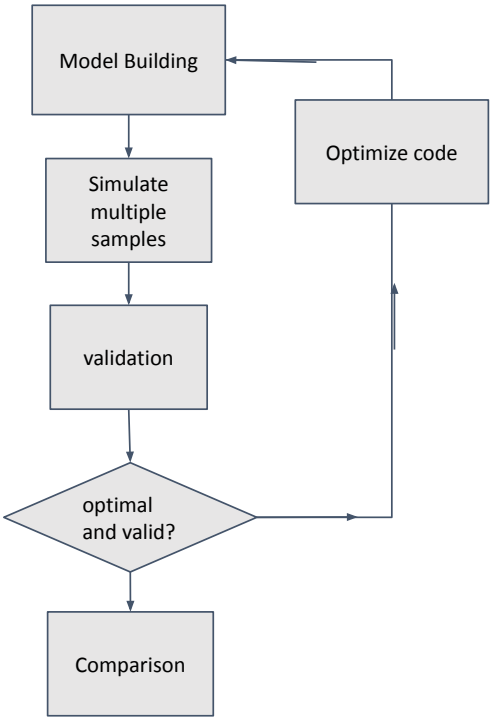
- Accelerates **simulations** by distributing tasks across **multiple threads.**
- Leverages GPU's architecture to handle large datasets efficiently -> Reduces simulation time.

Development Workflow

The simulation process was designed to efficiently model cardiac electrophysiology and predict cardiotoxicity under drug-induced and control conditions. Each step leverages CUDA-based GPU parallelization to accelerate processing.

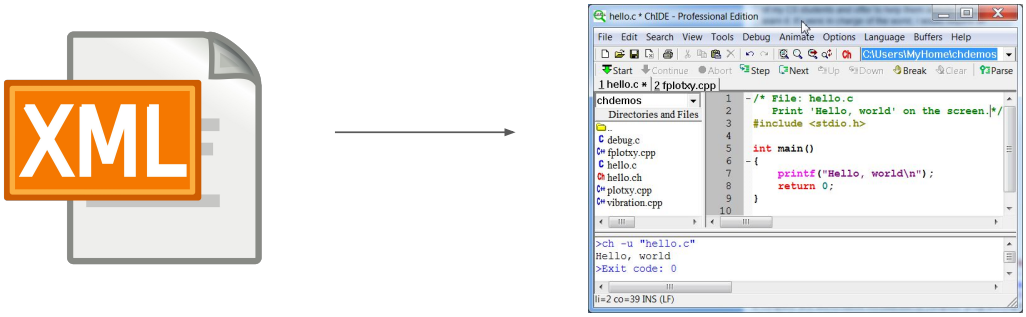
Steps:

1. **Parse CellML models and export to C.**
2. **Format C to CUDA**
3. **Apply Ordinary Differential Equation Solver**
4. Compile and run CUDA-enabled simulations.
5. Simulate for 1000 paces, with and without drug effects.
6. Output time-series data and biomarkers for analysis.



Development Workflow

1. Parse CellML models and export to C.



Model Selection: Three well-established cardiac cell models (ORd 2011*, ORd 2017**, and ToR-ORd***).

* T. O'Hara, L. Virág, A. Varró, and Y. Rudy, "Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation." 2011, PLOS Computational Biology 7(5): e1002061. Available: https://doi.org/10.1371/journal.pcbi.1002061.

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*** Tomek, Jakub et al. "Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block." eLife vol. 8 e48890. Dec 2019, doi:10.7554/eLife.48890.

Development Workflow

Before

```
Cellmodel *p_cell = new mar_cell_MKII();

void do_drug_sim_analytical(const double conc, std::array<double, 14> ic50,
const param_t* p_param, const unsigned short sample_id, Cellmodel *p_cell)
{
```

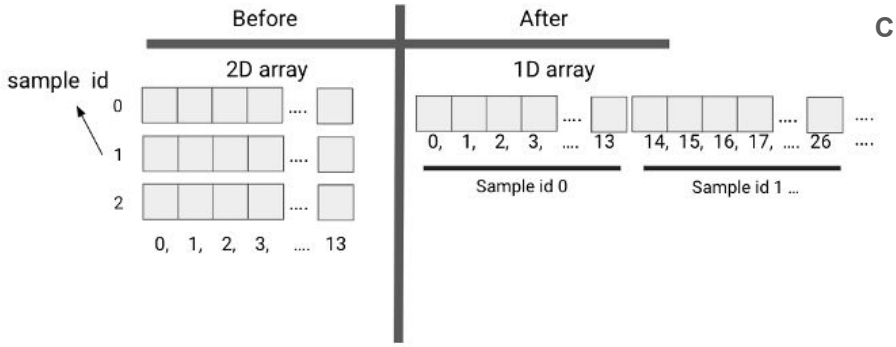
CUDA Implementation:

- **Converted CellML models to C, then simplify to CUDA.**
- Optimized GPU memory allocation (global, shared, constant).
  - Flattened multidimensional data structures for efficiency.

After

```
__global__ void do_drug_sim_analytical(drug_t d_ic50, double *d_CONSTANTS, double *d_STATES, double *d_RATES, double *d_ALGEBRAIC, double *dt_set){
    unsigned short sample_id;
    sample_id = threadIdx.x;
    int num_of_constants = 146;
    int num_of_states = 41;
    int num_of_rates = 41;
```

Development Workflow



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```
There are a total of 223 entries in the algebraic variable array.
There are a total of 43 entries in each of the rate and state variable arrays.
There are a total of 163 entries in the constant variable array.
```

```
ALGEBRAIC[3] = 1.00000/(1.00000+exp((STATES[0]+87.6100)/7.48800))
```

↓

```
ALGEBRAIC[(sample_id * 223) + 3] = 1.00000/(1.00000+exp((STATES[( sample_id * 43) +
0]+87.6100)/7.48800));
```


Development Workflow

Rush-Larsen

$$y(t+\Delta t) = y(t)e^{-B\Delta t} + \frac{A}{B}(1 - e^{-B\Delta t}).$$

Models and ODE Solvers:

1. ORd 2011 (Rush-Larsen solver)
2. ORd 2017 (Forward Euler solver)
3. ToR-ORd (Forward Euler solver)

Forward Euler

$$x_{n+1} = x_n + rate(x_n) \cdot \Delta t$$

↓

```
void solveEuler( double *STATES, double *RATES, double dt, int sample_id)
{
      for(int i=0;i<43;i++){
      STATES[(43 * sample_id) + i] = STATES[(43 * sample_id) + i] + RATES[(43 * sample_id) + i] * dt;
      }
}
```

Methodology

Development Overview

The study focuses on implementing GPU-based parallel computing for in silico cardiotoxicity prediction. This involves:

- **CUDA Parallelization**: Efficiently utilizing GPU resources for simulation.
- **Comparison**: Validation against CPU-based OpenCOR results.

Models and ODE Solvers:

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Validation: Results compared with CPU-based OpenCOR simulations.

Simulation Results

Parameters Overview

Accuracy Validation

- Ensure GPU-based simulations replicate physiological outputs of CPU-based simulations.
- **Key Metrics**:
  - **Action Potential Duration (APD).**
  - **Simulation time (seconds)**
  - Ionic currents: INa, ICaL, IKs, IKr, Ito.
  - Calcium transients (Cal).
- **Validation Process**:
  - Compare GPU results with OpenCOR (CPU-based) benchmarks.
  - Visual alignment of action potentials confirms fidelity.
- **Common Parameters**
  - 1000 paces
  - 1000ms per pace

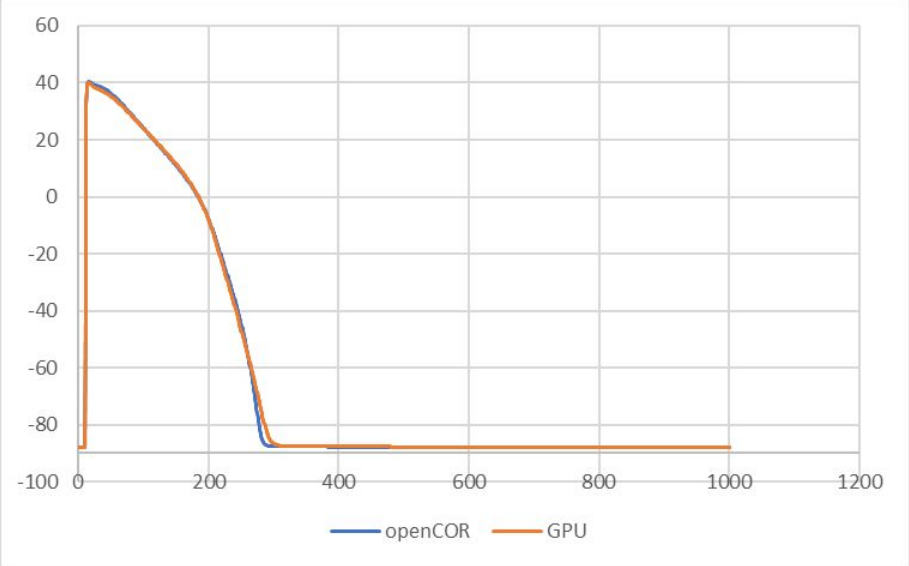
Performance Metrics

- **Hardware Used**:
  - **GPU**: NVIDIA RTX 4090.
  - **CPU**: 10-core Intel Xeon @ 2.50 GHz.

Drug-Induced Simulation Parameters

- **Test Drug**: Bepridil, simulated at cmax 1 (33 mMol), cmax 2 (66 mMol), and cmax 4 (132 mMol).
- **Key Observations**:
  - Action potentials altered predictably with drug effects.
  - Compare GPU results with OpenCOR (CPU-based) benchmarks.

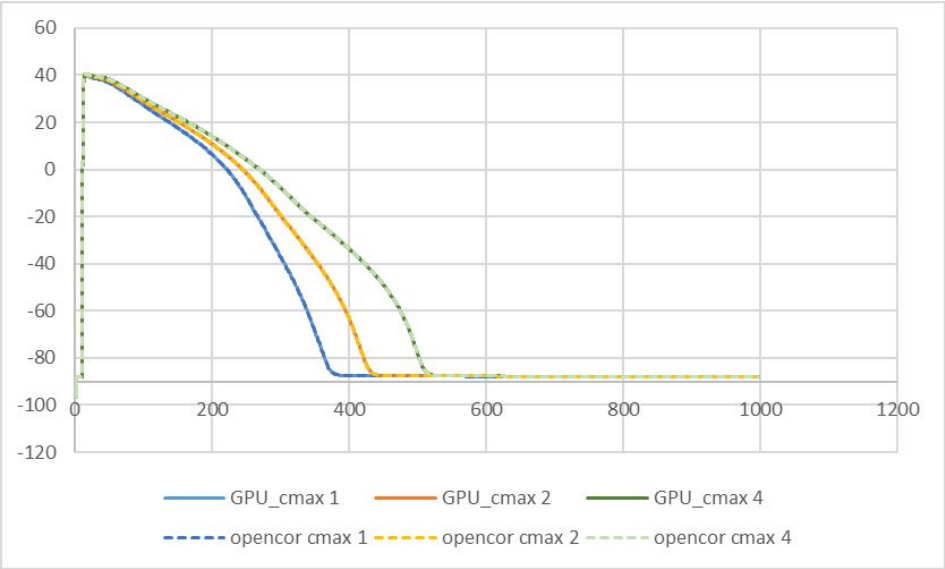
Drug-Free ORd 2011 Result Validation



Action Potential (mV) Shape of both CPU (blue) and GPU (orange) Result Using ORd 2011

The GPU-based simulation for the ORd 2011 model was validated against CPU (OpenCOR) results by comparing action potential plots and key biomarkers like APD under no-drug conditions. The findings showed near-identical outputs, confirming the GPU's accuracy in replicating physiological dynamics.

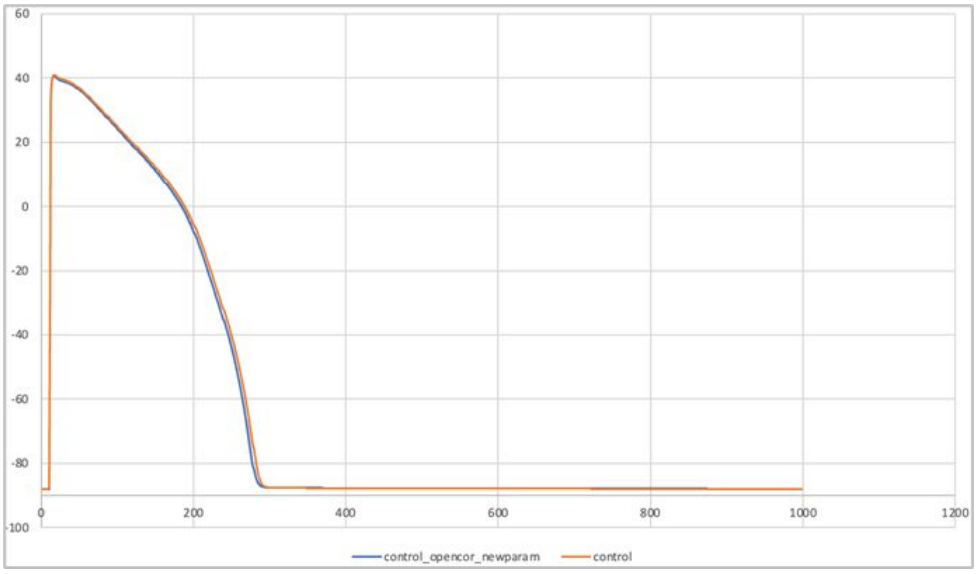
Drug-Induced ORd 2011 Result Validation



Action Potential Shape (mV) of both CPU (dashed) and GPU under drug effect Using ORd 2011

To validate our GPU-based simulation of the ORd 2011 model, we compared its action potential traces and key biomarkers to those generated by a CPU-based simulation (OpenCOR). We consistently applied drug effects to both platforms by adjusting ionic current parameters using IC50 and Hill coefficients. The results demonstrated that the GPU simulation accurately replicated the CPU's output, confirming its reliability in simulating both normal physiological and drug-induced responses.

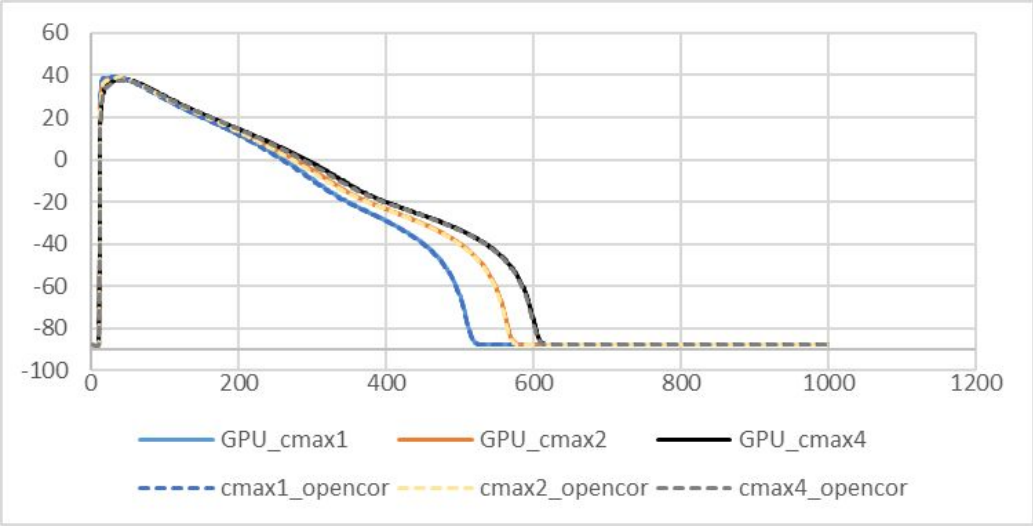
Drug-Free ORd 2017 Result Validation



Action Potential (mV) Shape of both CPU (blue) and GPU (orange) Result Using ORd 2017

The GPU-based ORd 2017 model was validated against a CPU-based reference (OpenCOR). By visually aligning action potential time-series data and analyzing key biomarkers, we confirmed the GPU's accuracy under no-drug conditions. Similar to the ORd 2011 model, the GPU closely replicated the CPU's output, demonstrating its reliability for the ORd 2017 model. Figure 3.4 illustrates the near-identical action potentials from both platforms.

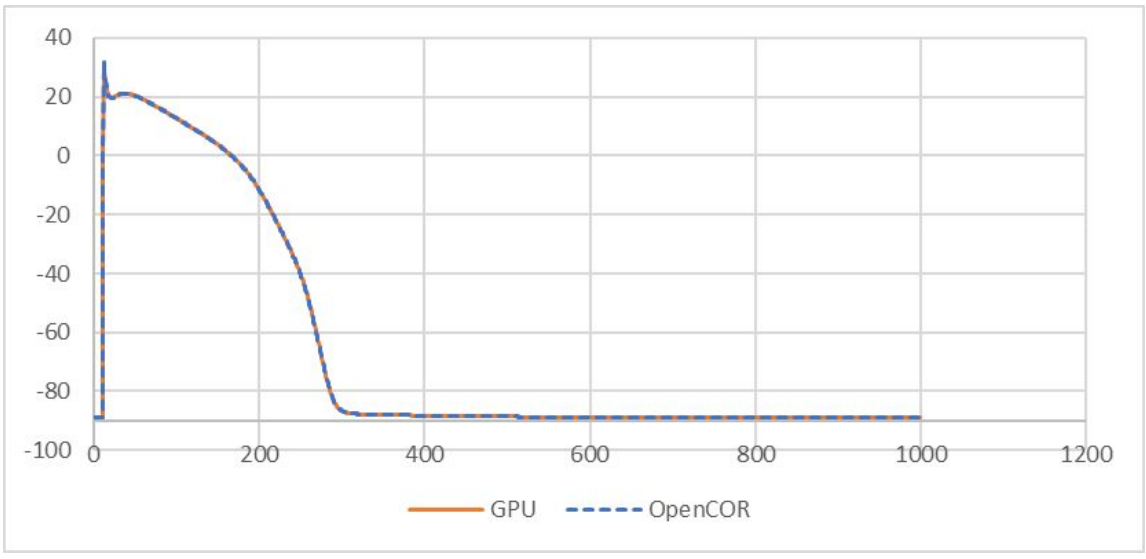
Drug-Induced ORd 2017 Result Validation



Action Potential Shape (mV) of both CPU (dashed) and GPU under drug effect Using ORd 2017

The GPU-based ORd 2017 model was validated under drug conditions by comparing its output to a CPU-based reference (OpenCOR). Drug effects were consistently simulated on both platforms. Analysis of action potential traces and key biomarkers confirmed the GPU's accuracy in replicating physiological and pharmacological responses, even with drug effects.

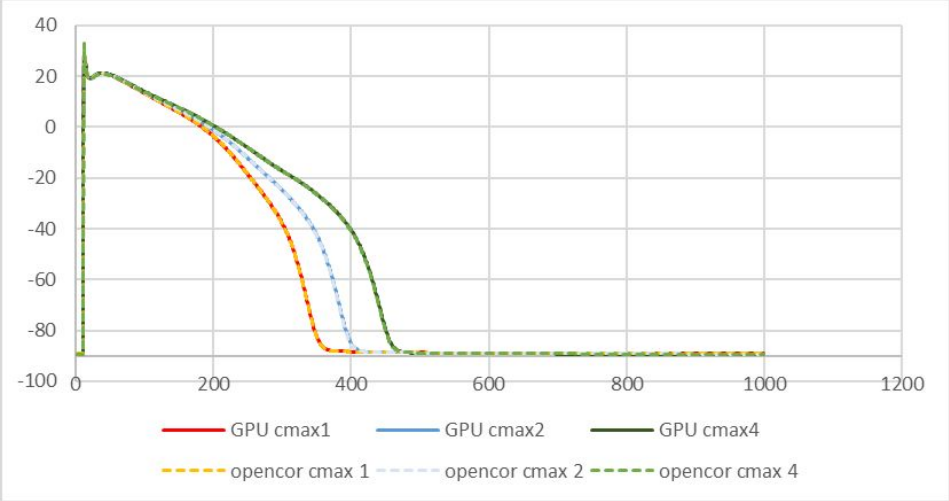
Drug-Free ToR-ORd Result Validation



Action Potential (mV) Shape of both CPU (dashed blue) and GPU (orange) Result Using ToR-ORd

The GPU-based ToR-ORd model was validated by comparing its output to a CPU-based reference (OpenCOR). Time-series plots of action potentials were compared, and key biomarkers were assessed under drug-free conditions. The GPU simulation accurately replicated the CPU results, confirming its reliability for the ToR-ORd model, even with the forward Euler method.

Drug-Induced ORd 2017 Result Validation



Action Potential (mV) Shape of both CPU (dashed) and GPU under drug effect Using ToR-ORd cell model

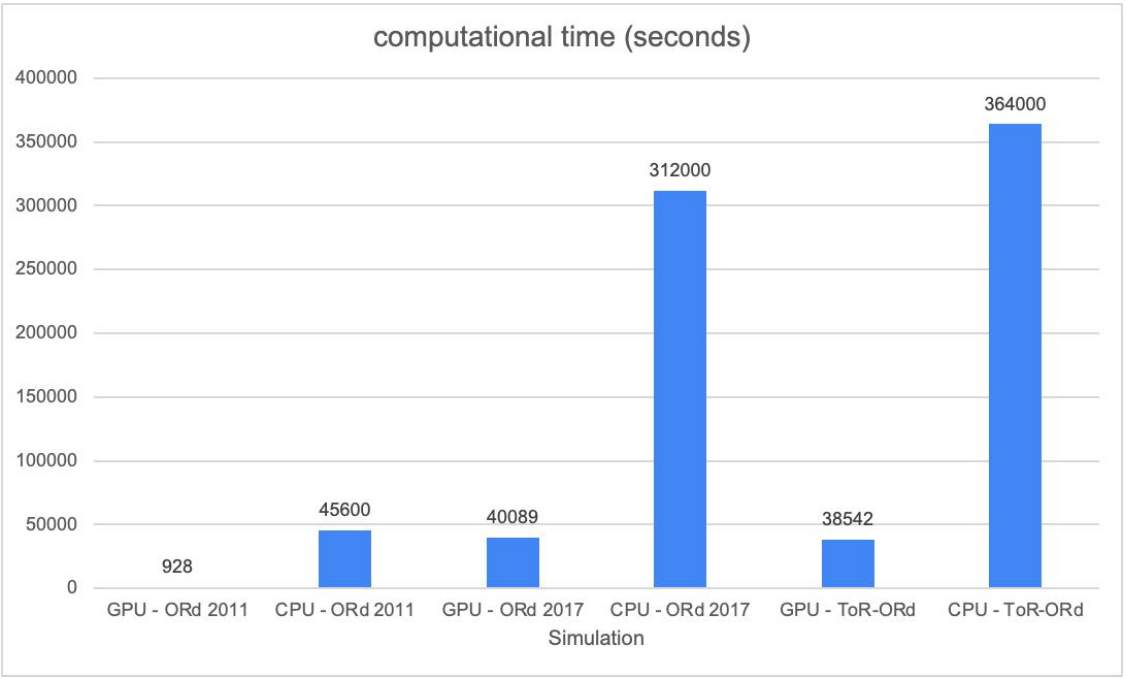
The GPU simulation accurately replicated the CPU-based simulations for the ToR-ORd model, with no significant differences in action potential traces or biomarkers. This confirms the validity of the GPU-based simulation, even under drug-induced perturbations. The successful validation of drug effects highlights the GPU method's capability to reliably simulate complex pharmacological scenarios, reinforcing its utility as a powerful tool for investigating drug-induced cellular behaviors.

Computational Advantages

For the ToR-ORd model, GPUs outperform CPUs when simulating 847 or more samples, for the ORd 2011 model, it is 163 samples, and 1,028 samples for ORd 2017.

Beyond these thresholds, GPUs significantly reduce computation times, handling large-scale simulations without substantial performance loss.

For instance, simulating 8,000 samples with the ORd 2017 model takes 40,089 seconds on the GPU, compared to 312,000 seconds on a 10-core CPU.



Conclusion

- **Key highlights:**
  - Demonstrated the effectiveness of CUDA-based GPU parallelization for in silico drug cardiotoxicity prediction.
  - GPU simulations were up to **40.91x faster (ORd 2011)** than 10-core CPU methods, with runtimes remaining constant regardless of sample size.
  - GPU maintained high similarity in action potentials, biomarkers, and drug-induced effects across all models when compared to CPU.
- **Impact**:
  - Accelerates preclinical testing, reduces reliance on animal models, and lowers complexity in drug discovery processes.

This study positions GPU-based simulations as a transformative tool in the pharmaceutical industry, reducing the time, cost, and ethical concerns associated with traditional methods. With continuous development, it has the potential to revolutionize in silico drug discovery.

Thank you

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