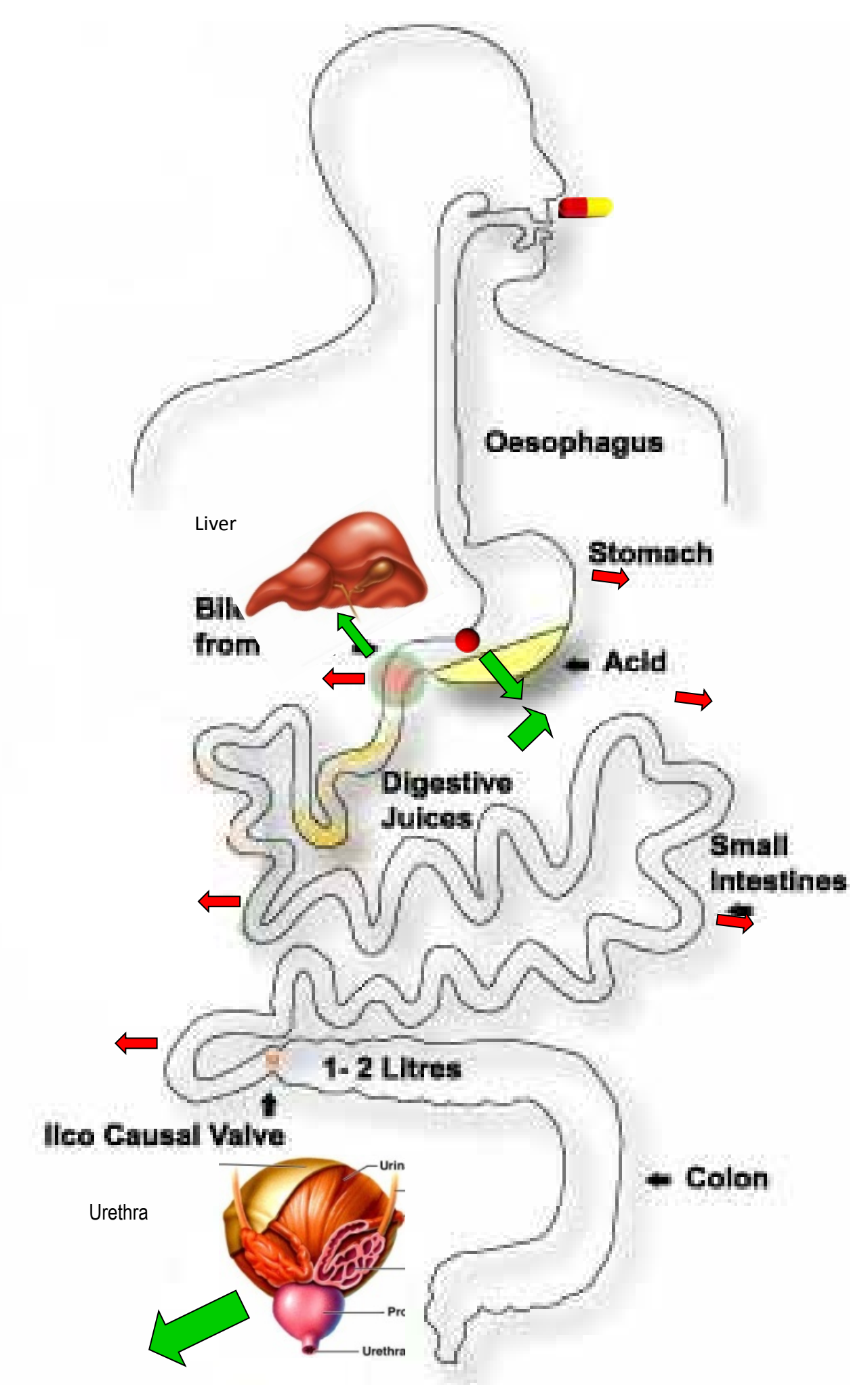# Application Of Parallelized Grid Search Method For Parameter Estimation Using PK-PD Models

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PK-PD Modeling

▪ Pharmacokinetic (PK) and Pharmacodynamic (PD) modeling and simulation are well recognized tools in drug development.

▪ Effective PK-PD modeling is expected to provide opportunities to accelerate the drug development process.

▪ This research includes Parallelized Grid search method, Nelder-Mead method, Gauss-Newton method, Algebraic and Differential equation PK-PD Models.

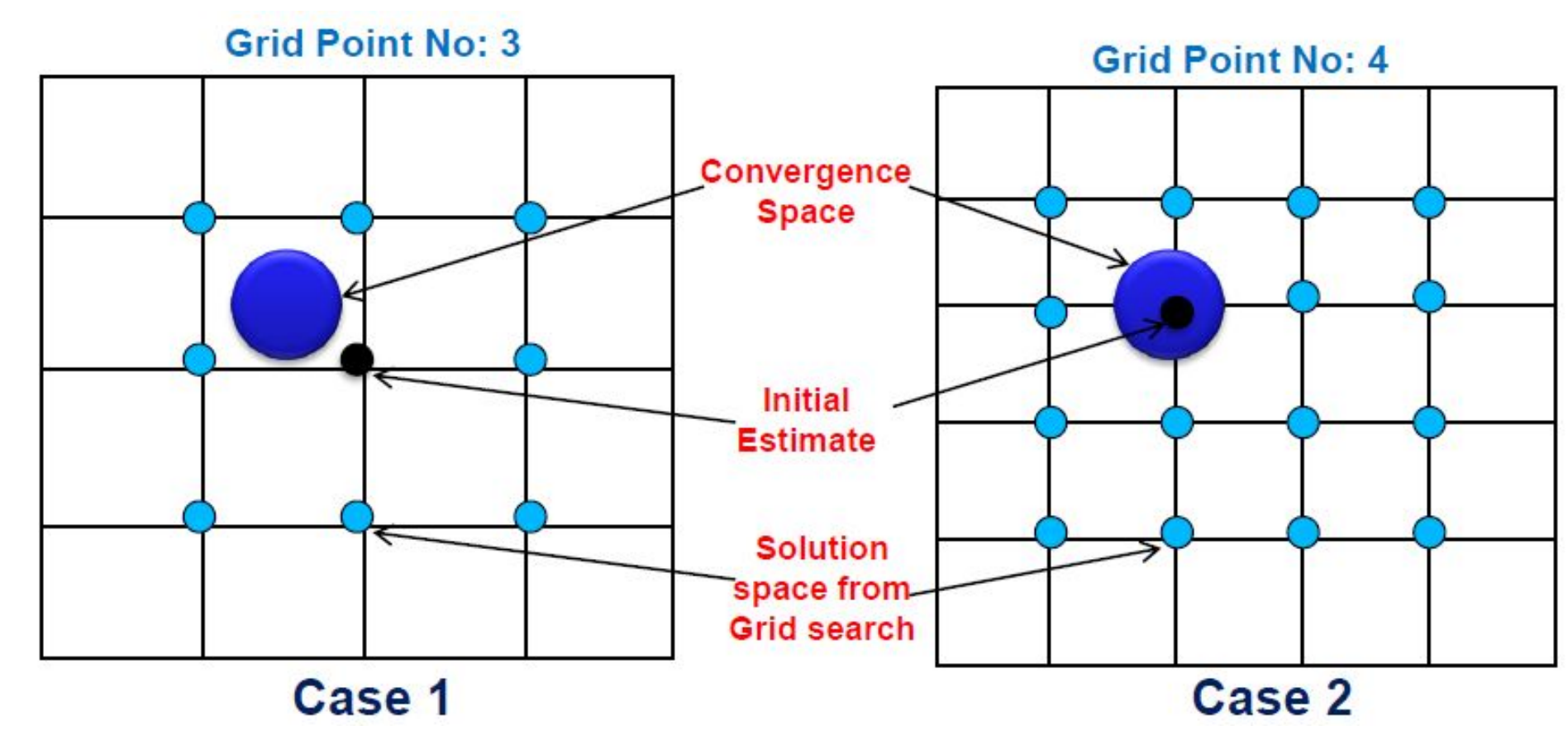## Role of PK-PD Modeling in Drug Discovery &Development
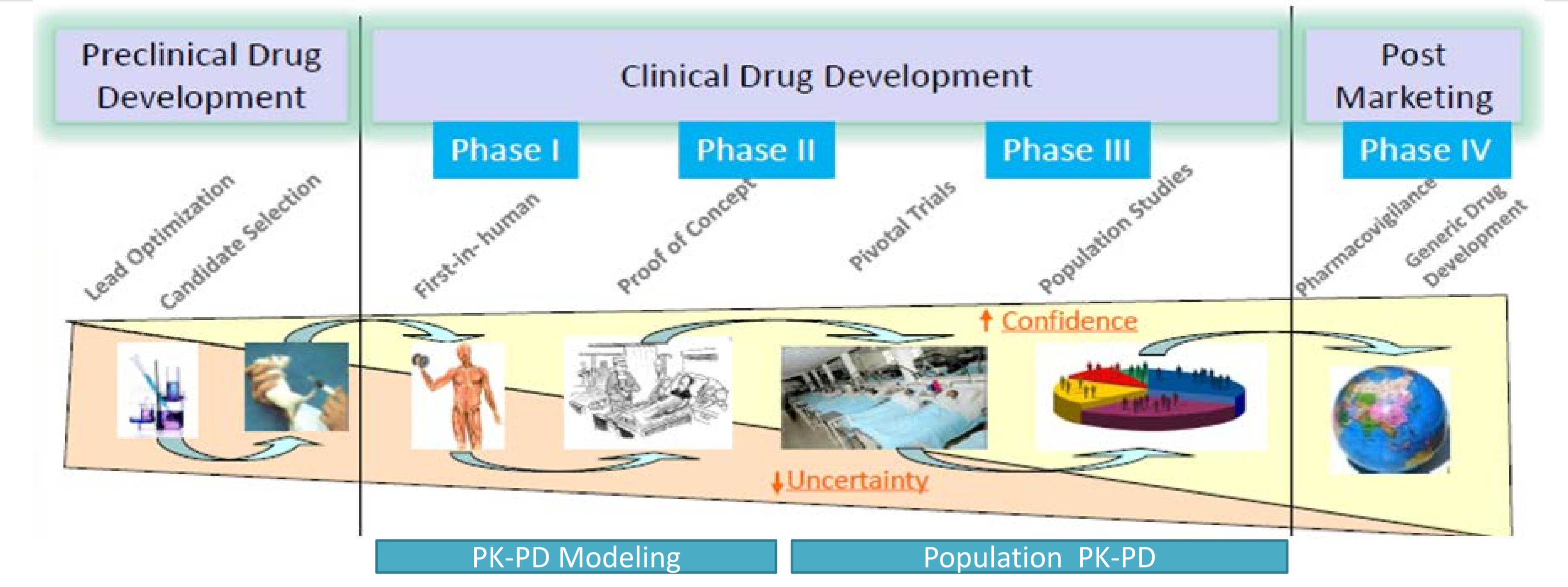
Our PK-PD application is demonstrated to provide optimal solution in the case of multiple PK/PD models of varying complexity. We have employed known PK-PD models that fall into different classes such as a) single and multi-compartmental models b) algebraic and seven differential equations models c) Pharmacokinetic and Pharmacodynamics models and d) models with five to seven parameters. Here is an example of one such model:
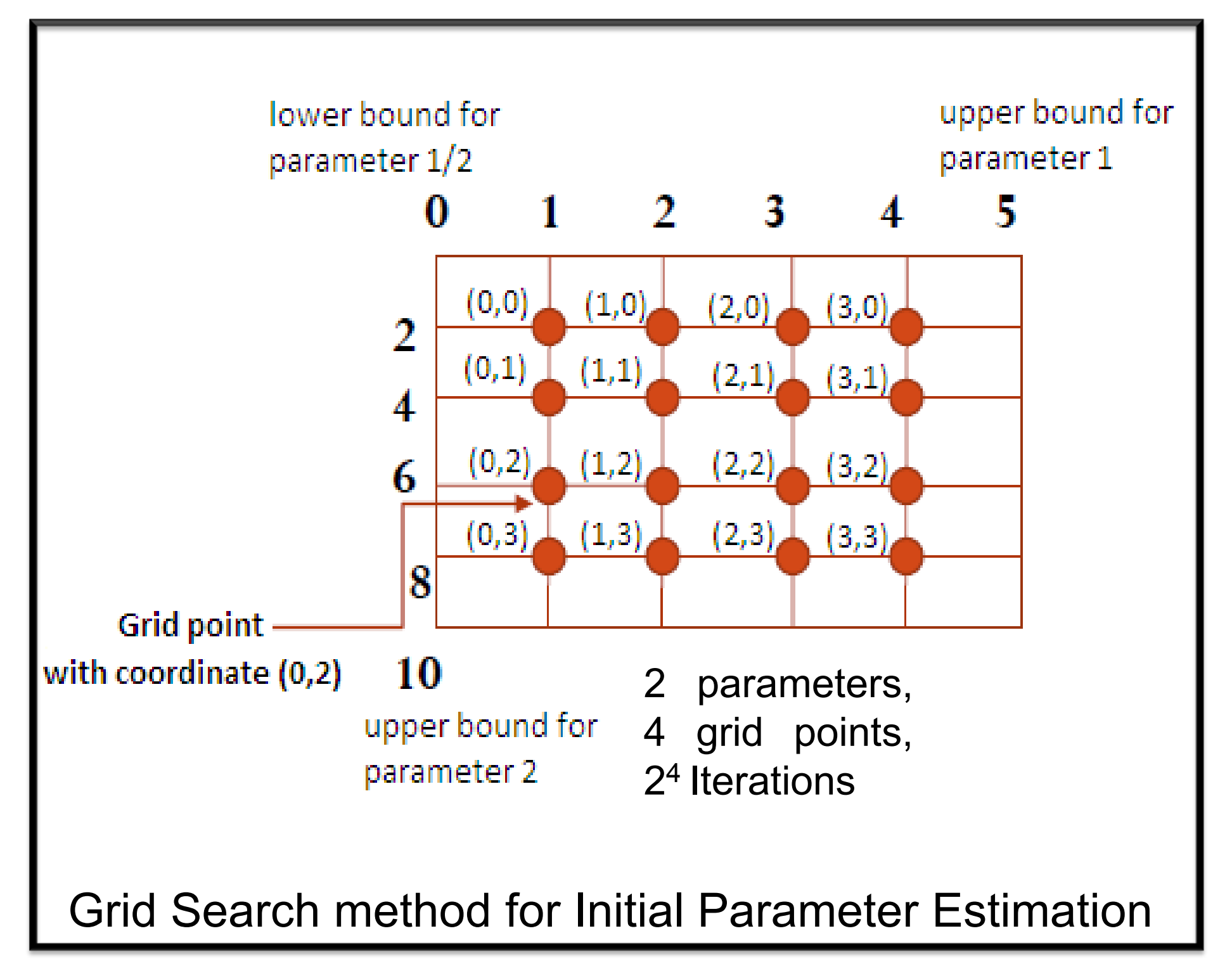
$$C(T) = Ae^{-Alpha \cdot T} + Be^{-Beta \cdot T} + Ce^{-Gamma \cdot T}$$
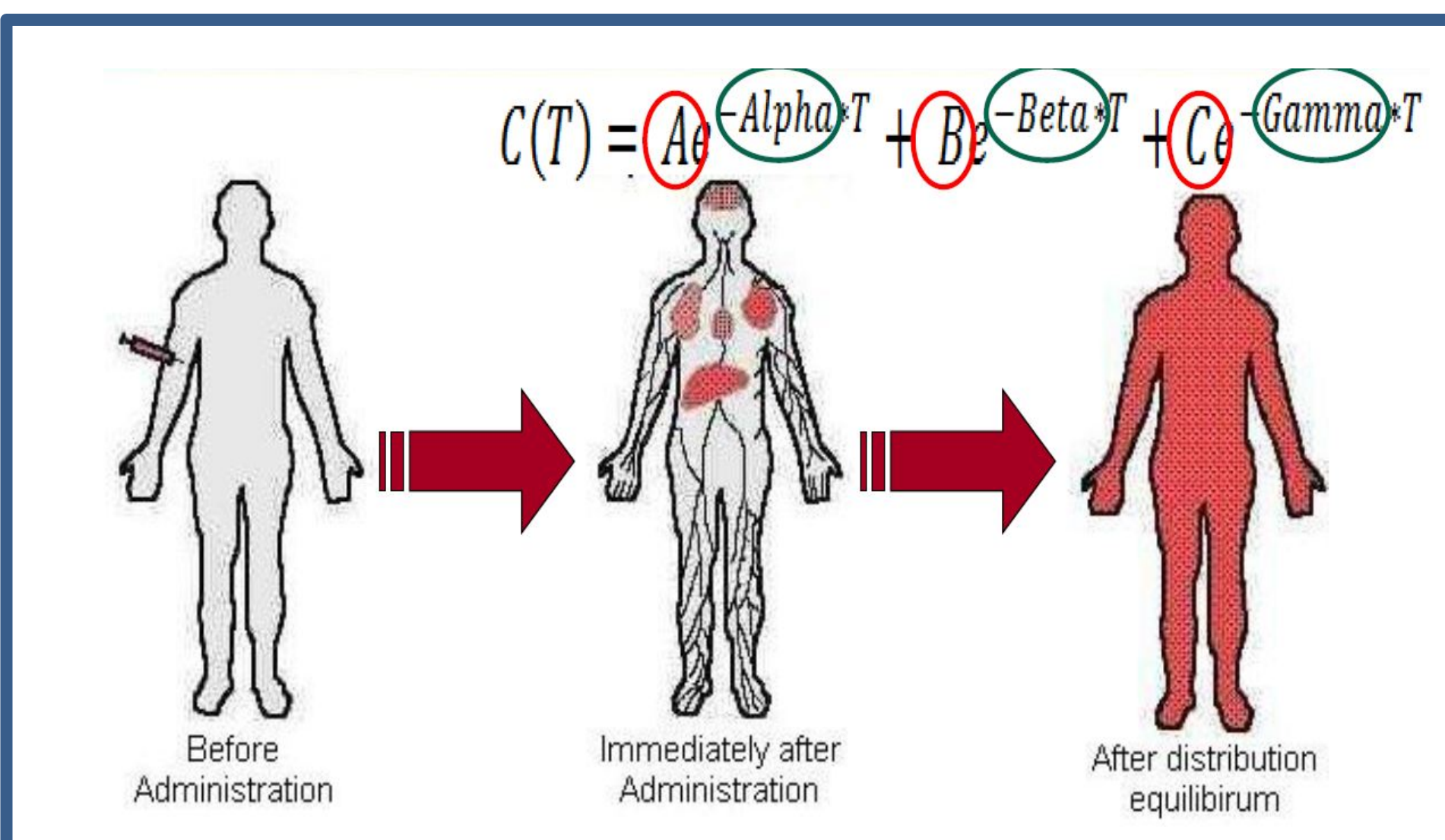
▪ The figure represents a multi-compartment model used in our case-study.
▪ Here, A, B, C, Alpha, Beta, Gamma are the parameters.
▪ **The goal is to find such parameters for this model which best fits the data available.**

Before Administration
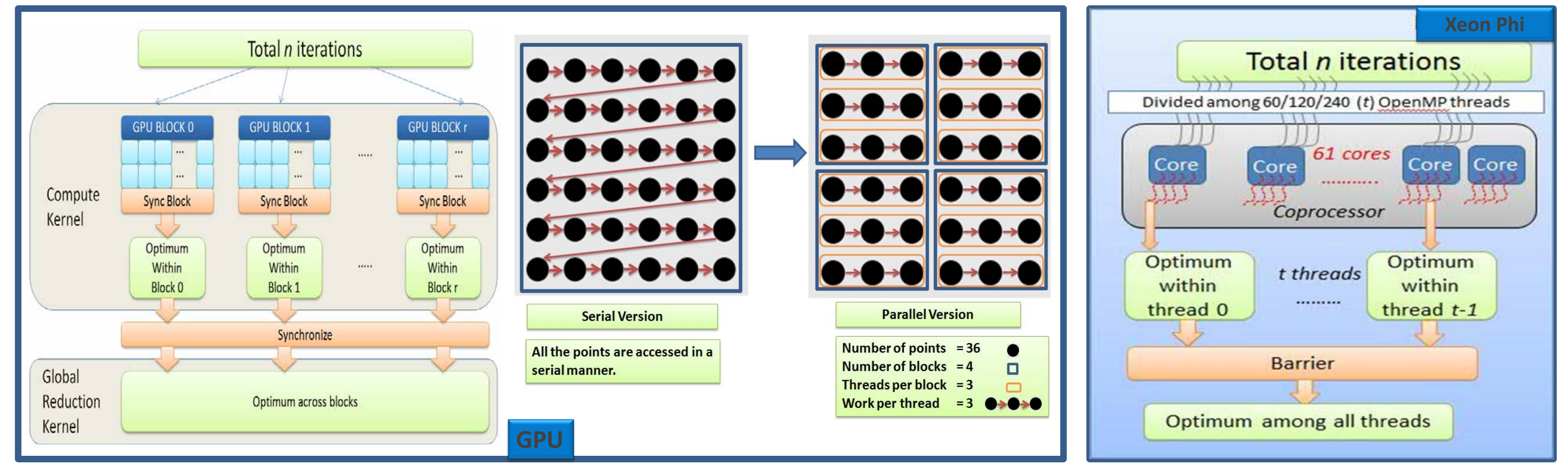Immediately after Administration
After distribution equilibrum

PK-PD Grid Search method

Higher number of grid points => Better convergence.

Grid Point No: 3   Grid Point No: 4
Convergence Space
Initial Estimate
Solution space from Grid search
Case 1   Case 2

As the number of grid points increases, the computation time increases **exponentially**.

lower bound for parameter 1/2   upper bound for parameter 1

	0	1	2	3	4	5
2	(0,0)	(1,0)	(2,0)	(3,0)		
4	(0,1)	(1,1)	(2,1)	(3,1)		
6	(0,2)	(1,2)	(2,2)	(3,2)		
8	(0,3)	(1,3)	(2,3)	(3,3)		
10						

Grid point with coordinate (0,2)
upper bound for parameter 2

2 parameters, 4 grid points, 2^4 Iterations

Grid Search method for Initial Parameter Estimation

HPC Implementation (GPU and Xeon Phi)

Total n iterations
GPU BLOCK 0   GPU BLOCK 1   GPU BLOCK r
Sync Block   Sync Block   Sync Block
Compute Kernel
Optimum Within Block 0   Optimum Within Block 1   Optimum Within Block r
Synchronize
Global Reduction Kernel   Optimum across blocks
GPU

Serial Version
All the points are accessed in a serial manner.

Parallel Version
Number of points = 36
Number of blocks = 4
Threads per block = 3
Work per thread = 3

Xeon Phi
Total n iterations
Divided among 60/120/240 (t) OpenMP threads
Core Core 61 cores Core Core
Coprocessor
Optimum within thread 0   t threads   Optimum within thread t-1
Barrier
Optimum among all threads

Results and Conclusion

Speedup on GPU and Xeon Phi
(Higher is better)

Speedup

Xeon Phi (7120P)	Symmetric mode (Xeon + Xeon Phi)	GPU (Tesla C2075)	GPU (Kepler K20)	2 GPUs (Kepler K20)
0.38 sec	0.22 sec	0.18 sec	0.14 sec	0.07 sec

Co-processor Architectures

Speedup chart w.r.t. serial version on a single CPU - 77 sec

▪ Parallel implementation facilitates faster solutions to time-consuming Drug Discovery process in the Pharma domain.

▪ HPC can provide much faster and scalable solutions for all combination of grid points and parameters.

▪ The multiple models optimized and parallelized cover a wide range of modeling scenarios and in all the cases, significant improvement is observed on GPUs.