9th International Work-Conference on Bioinformatics and Biomedical Engineering

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A 3D Multicellular Simulation Layer for the Synthetic Biology CAD Infobiotics Workbench Suite

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Background

- **Synthetic Biology** is the **technological use of Biology**.
  - **Genetic** and hence **metabolic manipulations** (operons, synthetic genetic sequences, parts).
- Our main objective was the integration of Synthetic Biology CAD with a multicellular simulation layer.
- Potential Utility:
  - CAD design for **medicine/industry**.
  - **Experimental prototyping**.
  - **Educational** resources.
  - **Pure research** (Biophysics/Biochemistry/Morphogenesis etc.).
  - **Archiving of information**.
- Synthetic Biology CAD suites proved to have **limited** or **absent multicellular capabilities**:
  - **Tinkercell** (Chandran et al. 2010).
  - **lBW** (Konur et al.).
  - **iBioSim 3** (Wantanabe et al. 2019).
- Multicellular simulators also possessed limitations:
  - **Gro** (Gutiérrez et al. 2017) -> 2D, lack of parallelization.
  - **Simbiotics** (Naylor et al. 2017) -> antiquated graphics, limited to real-time.
  - **NUFEB/PhysiCell/iDynoMiCS/Biocellion** (Li, B. et al. 2019, Ghaffarizadeh, A. et al. 2018, Lardon, L.A., et al. 2011, Kang, S., et al. 2014) -> morphological limitations, no real-time, accessibility, physical rather than biochemical focus.
  - **CompuCell3D** (Swat et al. 2009) -> Restricted to lattice, performance limitations.

Aims

- **Spatiotemporal extension of Synthetic Biology** CAD systems, hence:
- **Characterization of** multicellular simulation **methodologies**.
  - **Interdisciplinary challenge** (biophysics, computer science, biochemistry, histology etc.).
  - A comparison of **real-time versus batch-processed** solutions.
- Integration of the **NGSS stochastic biochemical simulator** from IBW.
  - Concurrent executions.
- **Addressing limitations** in multicellular and Synthetic Biology software.

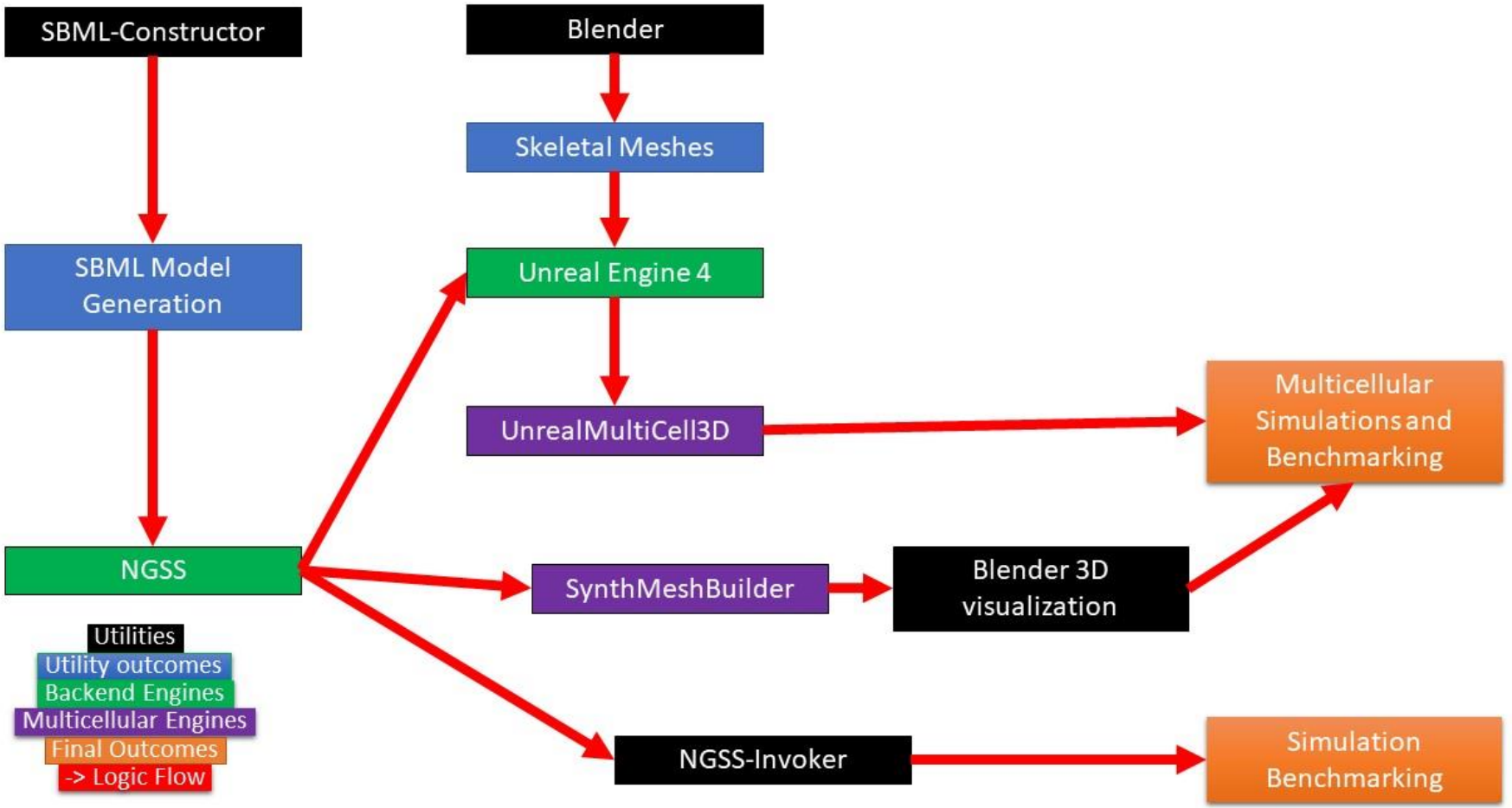
Methodology – Interdisciplinary Elucidation #1

- **Key biological concepts**:
  - **Phenomenological approach** (Swat et al. 2009) to multicellularity, with **multiscale implications** (Li et al. 2019).
    - **Cellular phenomena:** e.g. motility, secretions, morphology, adhesion, signaling, biochemistry.
    - **Extracellular phenomena:** e.g. surfaces, hydrodynamics, nutrients, diffusion, extracellular matrix.
  - Population level **emergent effects** from **phenotypes**.
    - e.g. Fitness, attachment, patterning, morphogenesis, differentiation.
  - Local **biochemical microenvironment** (Ghaffarizadeh et al. 2018), (Karimian and Motamedian 2020) influences phenotype.
- **Genetics** determines **expression levels**, key to determining **phenotypes**.
  - Hence, **Synthetic Biology CAD extension to multicellularity**.

Methodology – Interdisciplinary Elucidation #2

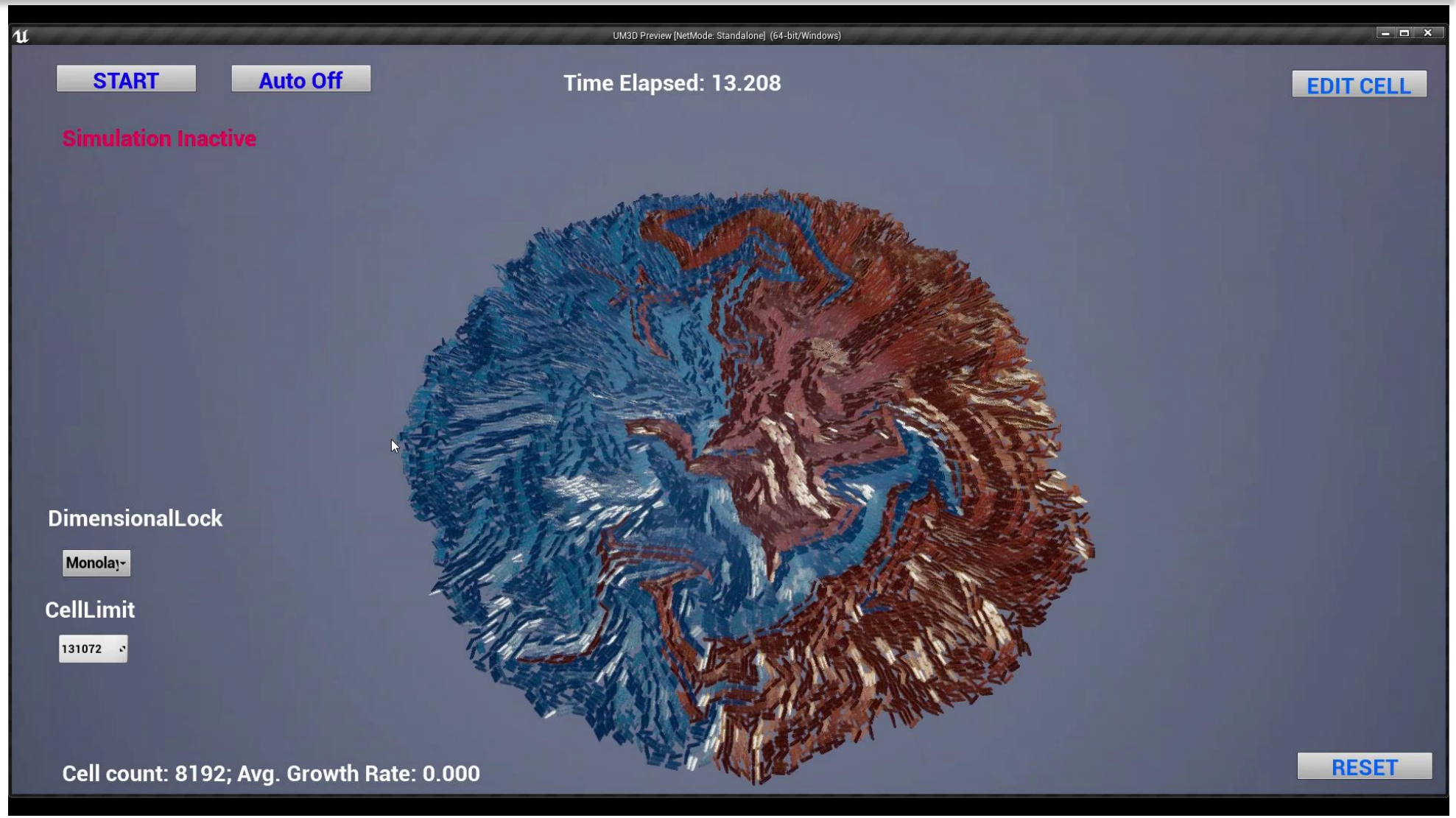
- **Key computational concepts:**
  - Domain-based computing (domain decomposition, voxels)
  - Clustering of computations (e.g. phenotypes)
  - Batch processing
  - State outputs
  - Graphical simplifications
  - Parallelization and HPC

Methodology - Software Implementations



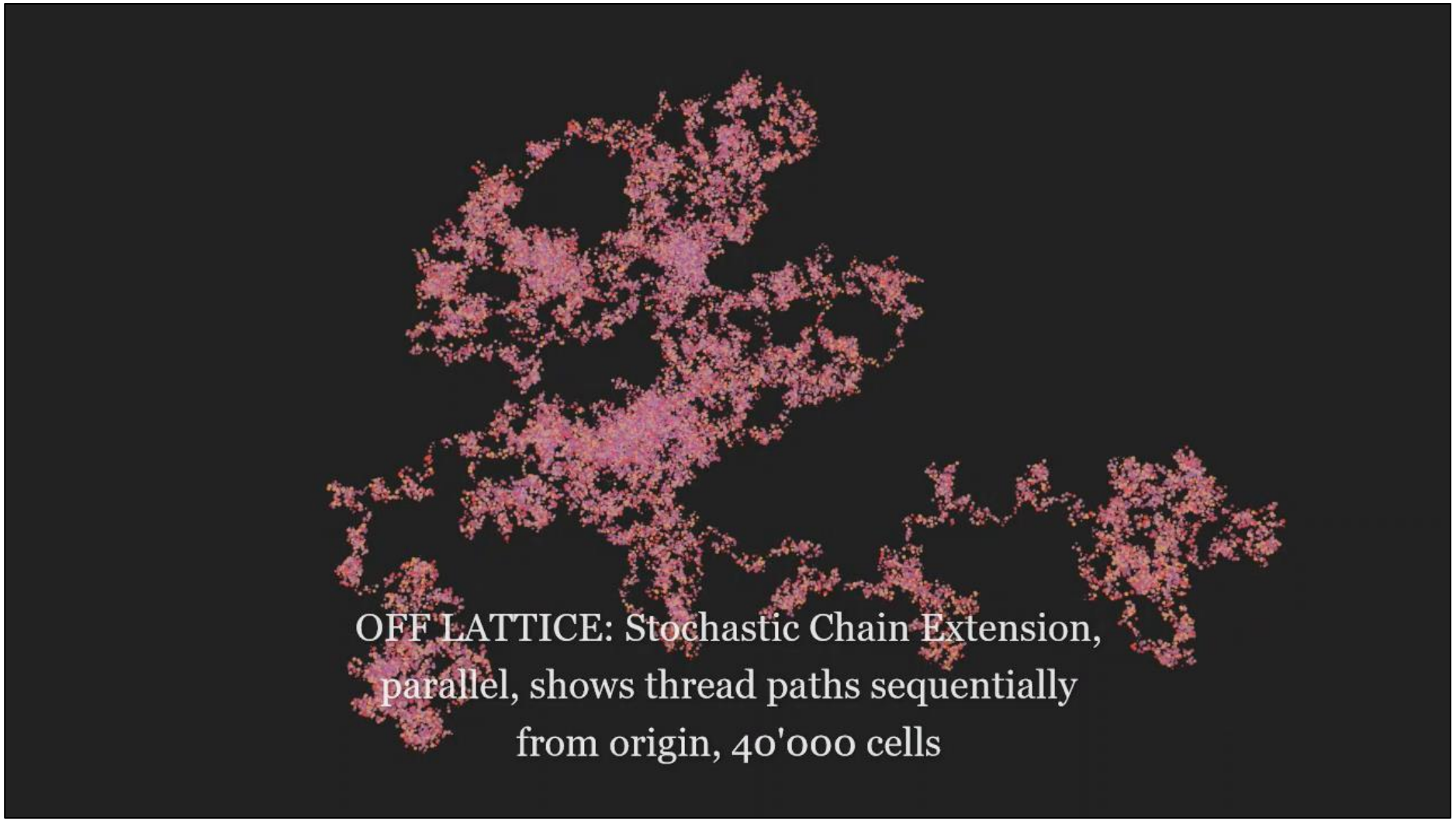
Results – UM3D (Unreal Multicell 3D)

- Agent-Based
- Off-Lattice
- UE4, 3D
- Accessible GUI
- GPGPU Physics
  - PhysX
- Colony growth
- NGSS
- Real-Time



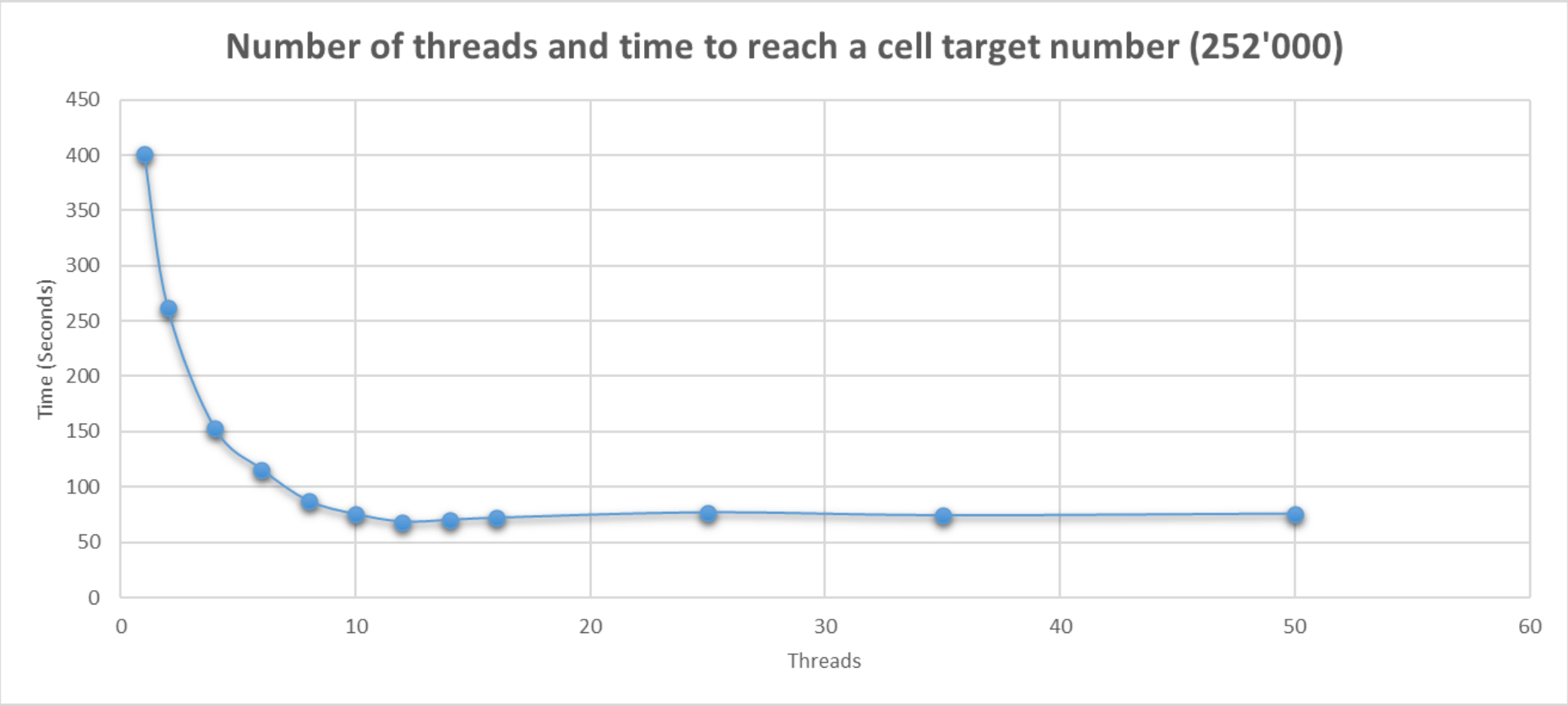
Results – SMB (SynthMeshBuilder)

- C# .NET
- CPU Multithreaded
- High scalability
- Mesh generator, 3D
- On and Off Lattice
- Random update
- NGSS
- Batch processed
- Blender visualized

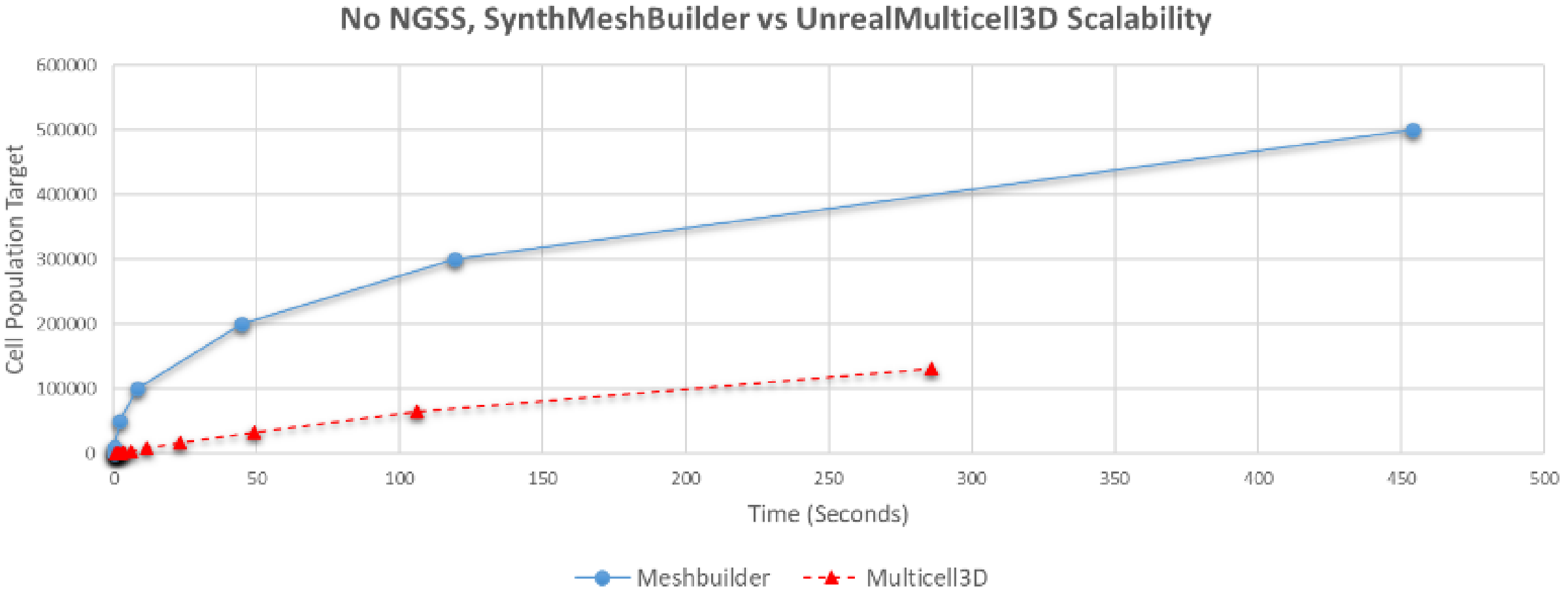


Results – SMB parallelization was successful to CPU saturation

- Critical for future HPC efforts (viable for CPU and GPGPU implementations).

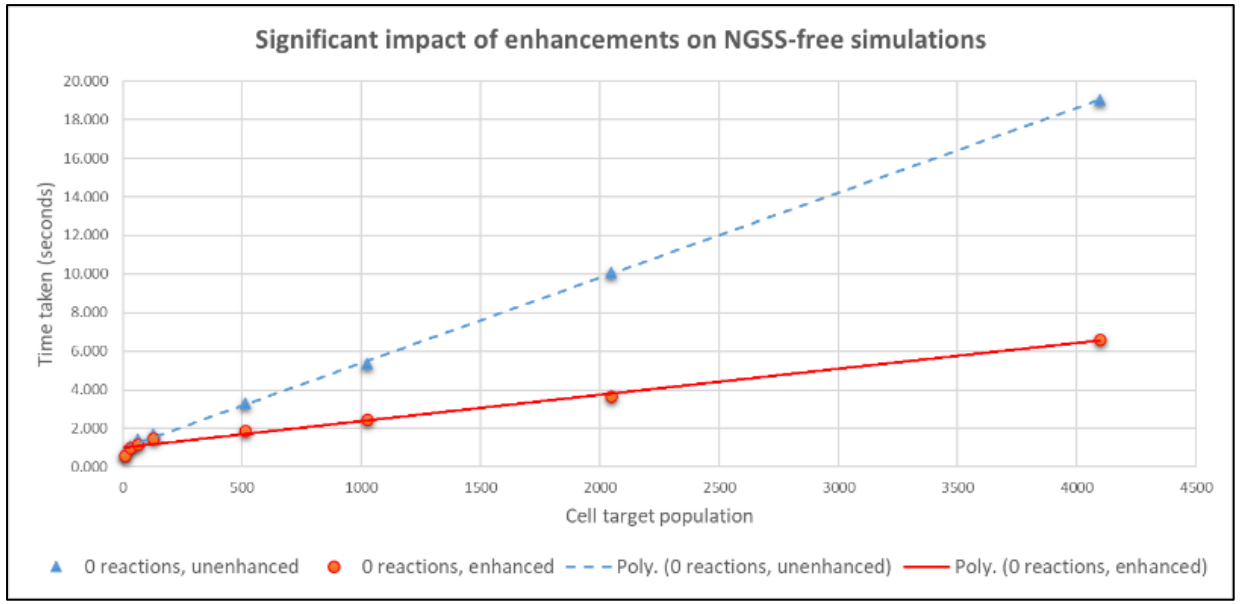


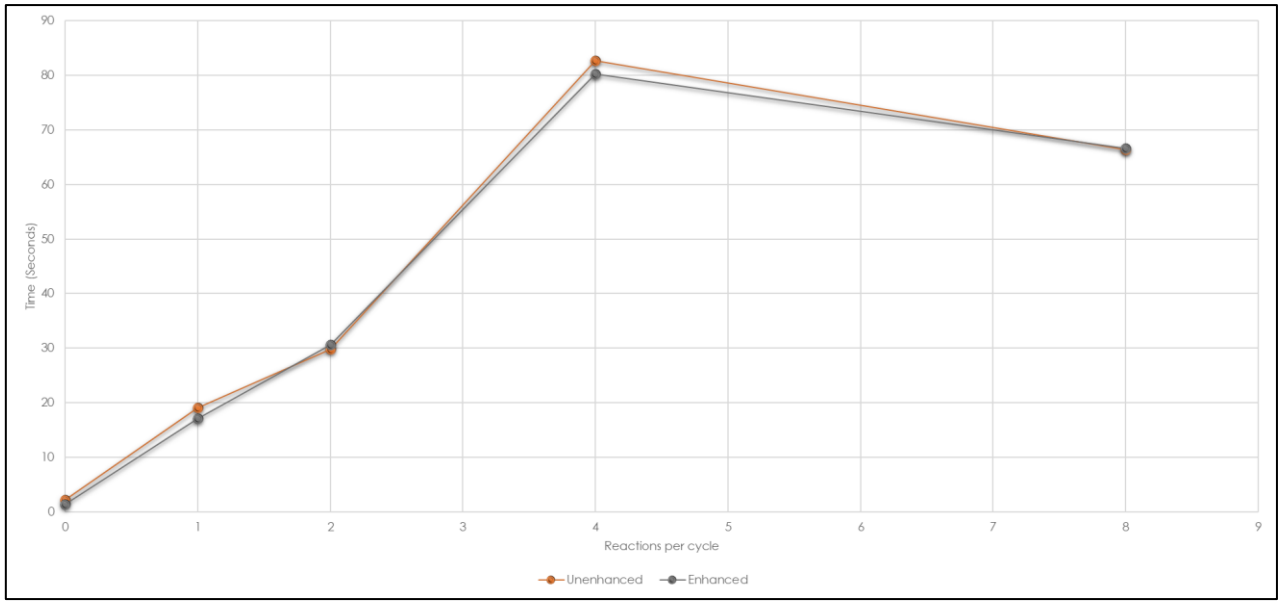
Results – SMB was more scalable, but UM3D offered many features



Results – Benchmarking UM3D with Stochastic Simulation Layer

- **LEFT profile:** Without NGSS a **significant enhancement to the multicellular layer** was made:
  - Camera redirection and mesh simplification **reduced GPU processing costs**.
- **RIGHT profile:** Performance improvements to UM3D were still **limited by NGSS performance**.
- **HPC is implicated** for biochemical simulations and to **enhance GPGPU capabilities**.





Conclusions #1 - Achievements

- A comparison of **real time** and **batch processed** methodologies and **benchmarking**.
- **On-lattice** and **off-lattice** approaches.
- **Parallelization**
  - **Concurrent NGSS activations.**
  - **SynthMeshBuilder processor saturation**.
- Implementation of **Unreal Engine 4** for multicellularity.
  - **GPGPU Physics**; Ease of use, **ergonomic GUI**; **Modern graphics**.
  - **Parametrically adjustable emergent effects** with **heterogeneity**.
- **Stochastic biochemical** network simulator **benchmarking**.
  - Simulator associated with **Synthetic Biology CAD**, use of **SBML standard**.
- **Semi-automated network topology generation** through SBML constructor.

Conclusions #2 - Observations

- **Multicellular systems** are **parametrically complex** to simulate.
- **Stochastic biochemical simulation** integration (NGSS) proved **expensive** on conventional hardware using the CPU.
- **GPGPU** showed **strong potential** using PhysX despite rendering clash (**HPC implicated**).
- **Game Engines** provide powerful frameworks for quickly prototyping sophisticated dynamics.
  - Still involves **considerable person-hours** and **interdisciplinary expertise**.
- **Batch processing** bypasses rendering costs and reliance on real-time progression.
  - HPC applicable.
- **SynthMeshBuilder** demonstrated good parallelization on the CPU.

Further Work

- Refinement of **heterogenous systems** (morphological variability, phenomenological function).
- Integration of a **diffusion layer**.
- Suitable **regulatory models (GRNs** – gene regulatory networks**)**.
- **Regulatory feedback** to alter phenotypes (signaling, e.g. morphogens, growth factors).
- **High performance computing** implementations.
  - Extending SynthMeshBuilder to **GPGPU**.
  - **Further benchmarking** of subsequent solutions.
- Integration with **Infobiotics Workbench** (towards a unified platform).
- **Histological verification** (e.g. specific patterning, cellular and extracellular proportions, expression levels).

Thank you!

- **A 3D Multicellular Simulation Layer for the Synthetic Biology CAD Infobiotics Workbench Suite**
  - https://link.springer.com/chapter/10.1007/978-3-031-07802-6_17 (article and references)
  - Email: rmatzko@bradford.ac.uk, LinkedIn: /richardmatzko