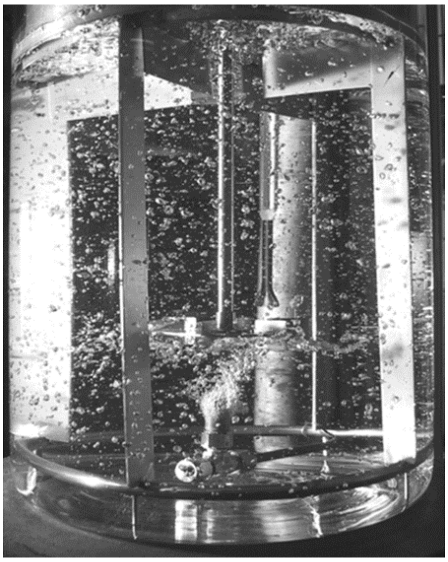
Establishing the Design Space of a Sparged Bioreactor on Microsoft Azure

An UberCloud Experiment



With Support From

UberCloud Case Study 206

http://www.TheUberCloud.com

July 30, 2018

Welcome!

The UberCloud* Experiment started in July 2012, with a discussion about cloud adoption in technical computing and a list of technical and cloud computing challenges and potential solutions. We decided to explore these challenges further, hands-on, and the idea of the UberCloud Experiment was born, also due to the excellent support from INTEL generously sponsoring these experiments!

We found that especially small and medium enterprises in digital manufacturing would strongly benefit from technical computing in HPC centers and in the cloud. By gaining access on demand from their desktop workstations to additional compute resources, their major benefits are: the agility gained by shortening product design cycles through shorter simulation times; the superior quality achieved by simulating more sophisticated geometries and physics and by running many more iterations to look for the best product design; and the cost benefit by only paying for what is really used. These are benefits that increase a company's innovation and competitiveness.

Tangible benefits like these make technical computing - and more specifically technical computing as a service in the cloud - very attractive. But how far away are we from an ideal cloud model for engineers and scientists? In the beginning, we didn't know. We were just facing challenges like security, privacy, and trust; conservative software licensing models; slow data transfer; uncertain cost & ROI; availability of best suited resources; and lack of standardization, transparency, and cloud expertise. However, in the course of this experiment, as we followed each of the 205 teams closely and monitored their challenges and progress, we've got an excellent insight into these roadblocks, how our teams have tackled them, and how we are now able to reduce or even fully resolve them.

Bioreactors are the heart of every pharmaceutical manufacturing process. One goal of a bioreactor is to operate at process conditions that provide sufficient oxygen to the suspended cells. The design space of a bioreactor defines the relationship between the input and output parameters of the cell culture process. This knowledge is used to establish and maintain consistent process (and therefore product) quality. The design space typically relies on a design of experiments (DOE) approach to characterize the interdependencies between tank design and process operating conditions. This can be an expensive and time-consuming exercise to perform in the lab, especially at manufacturing scale. Therefore, the pharmaceutical industry has adopted computational fluid dynamics (CFD) modeling as a cost-saving option that can also reduce the risk associated with scale-up and day-to-day operations. However, the simulation time and compute resources required to explore the relationships between various process parameters can be quite extensive. Therefore, this case study reviews the use of HPC to establish the design space of a production scale sparged bioreactor. The simulation framework is developed and executed on Azure Cloud resources running the ANSYS Fluent UberCloud container.

We want to thank our main UberCloud Experiment **sponsors INTEL and HPE** for generously supporting all 205 UberCloud Experiments.

Now, enjoy reading!
Sravan Kumar Nallamothu, Marc Horner, Shital Joshi, Wolfgang Gentzsch, and Burak Yenier

**) UberCloud is the online community and marketplace where engineers and scientists discover, try, and buy Computing Power as a Service, on demand. Engineers and scientists can explore and discuss how to use this computing power to solve their demanding problems, and to identify the roadblocks and solutions, with a crowd-sourcing approach, jointly with our engineering and scientific community. Learn more about the UberCloud at: http://www.TheUberCloud.com.*

Team 206

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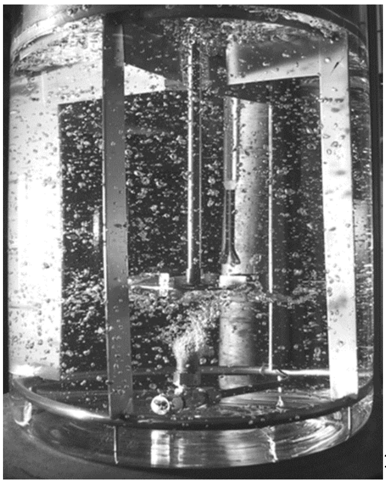

[1])

"The combination of Microsoft Azure with UberCloud ANSYS FLUENT Container provided a strong platform to develop an accurate virtual simulation model that involved complex multi-phase flow and tank geometries."

MEET THE TEAM

End-User/CFD Expert: Sravan Kumar Nallamothu, Sr. Application Engineer, and Marc Horner, PhD, Technical Lead, Healthcare, ANSYS, Inc.
Software Provider: ANSYS, Inc. and UberCloud Fluent Container
Resource Provider: Microsoft Azure
HPC Expert: Shitalkumar Joshi, ANSYS, and Wolfgang Gentzsch, UberCloud.

USE CASE

The scale-up of pharmaceutical laboratory mixers to a production tank is not a trivial task as it requires a thorough understanding of complex turbulent and multiphase processes impacting oxygen mass transfer. The interplay between the geometric design of the tank and tank operating parameters are critical to achieving good mixing, esp. at (larger) production scales. In an effort to improve process understanding, international regulators suggest a Quality by Design (QbD) approach to process development and process control. In the Quality by Design (QbD) framework, significant emphasis is placed on the robust characterization of the manufacturing processes by identifying the engineering design space that ensures product quality. There are various geometry and operating parameters influencing oxygen mass transfer scale-up from lab scale to production scale. Understanding the effect of these parameters can lead to robust design and optimization of bioreactor processes.

The main objective of this study is to understand the impact of agitation speed and gas flow rate on the gas holdup and mass transfer coefficient, which are two critical parameters that help process engineers understand mass transfer performance. The general-purpose CFD tool ANSYS Fluent is used for the simulations and the simulation framework is developed and executed on Azure Cloud resources running the ANSYS Fluent UberCloud container. This solution provided a scalable platform for achieving sufficient accuracy while optimizing the solution time and resource utilization.

[1] Picture from Marko Laakkonen (reference see next page)

PROCESS OVERVIEW

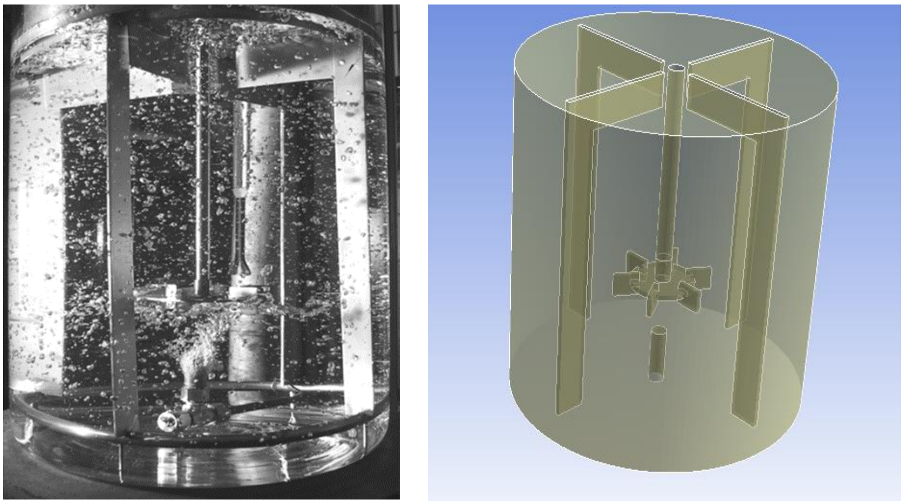

Figure 1: 194L Tank used for experiments[1] and representative CFD Model

The stirred tank is agitated by a 6-bladed Rushton turbine blade for dispersing the air bubbles generated by the sparger. Four custom baffles are included to prevent vortex formation. Experimental conditions and results are taken from the extensive study performed by Laakkonen[2].

A full 3D model of the 194 L tank is considered for this CFD study, which is meshed using polyhedral elements. The Eulerian multiphase model is used for simulating the two phases: water and air. The population balance model with quadrature method of moments (QMOM) is used to simulate bubble coalescence and breakup processes. The Ishii-Zuber drag model is used to account for momentum exchange between water and air bubbles. For bubble coalescence, a model based on the Coulaloglou-Tavlarides model is used and the breakup model is based on the work of Laakkonen. It was observed that non-drag forces did not significantly impact gas holdup and mass transfer. A zero-shear boundary condition was applied for the water phase at the upper free surface, and a degassing boundary condition is used to remove the air bubbles.

The steady-state solver is used for running the simulations. Each simulation is solved until gas holdup and mass transfer coefficient reach steady values. The mass transfer coefficient is calculated using a custom field function, formulated based on a correlation derived from penetration theory[3]. A volume-averaged mass transfer coefficient is defined as an output parameter of the simulations to facilitate comparison of the various process conditions. Specifically, a design of experiments (DOE) study is performed with agitation speed and gas flow rate as input parameters and volume-averaged mass transfer coefficient as the output parameter. ANSYS Workbench with DesignXplorer is used to run the DOE and study the bioreactor design space.

RESULTS

As shown in Figure 2, air bubbles undergo breakup near the impeller blades and coalesce in the circulation regions with low turbulent dissipation rates. This leads to bubble size varying throughout the tank. Since interfacial area depends on bubble size, bubble size distribution plays a critical role in oxygen mass transfer.

[1,2] Marko Laakkonen, Development and validation of mass transfer models for the design of agitated gas-liquid reactors, https://pdfs.semanticscholar.org/c6bd/d98a364a73fecb84468da9352659e475344d.pdf

[3] J.C. Lamont, D. S. Scott, An eddy cell model of mass transfer into the surface of a turbulent liquid, AIChE J. 16 (1970) 513-519

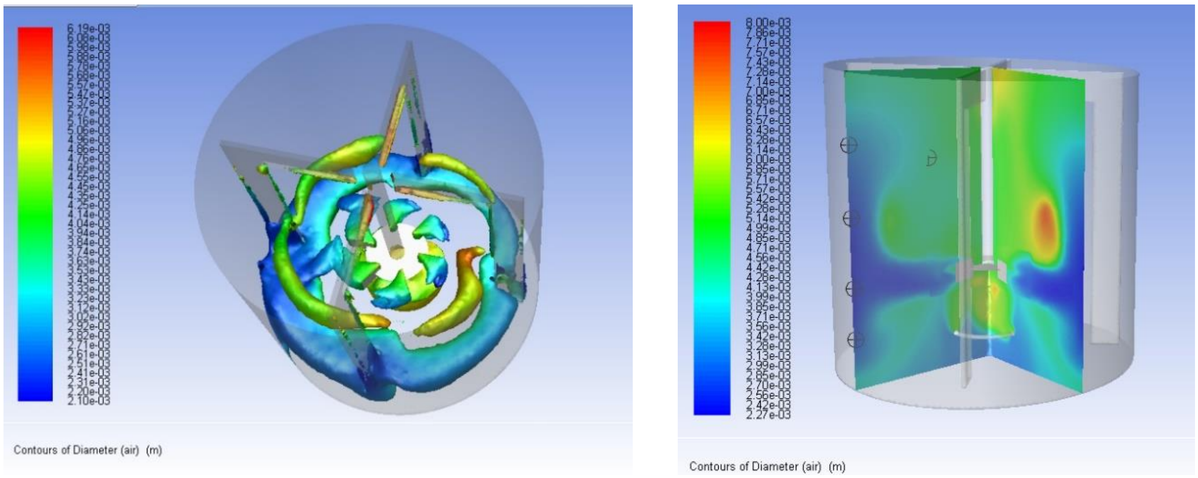

Figure 2: a) Iso-surface of gas volume fraction colored with bubble diameter b) Contour plot of bubble size distribution.

To study the design space of the bioreactor, a DOE study has been performed to generate the response surface for the average mass transfer coefficient. From the response surface shown in Figure 3, we can see that agitation speed has a greater impact on the mass transfer coefficient versus gas flow rate. Even though we can increase the agitation speed to increase the mass transfer coefficient, there is a limit on maximum speed since some processes involve mammalian cells that are sensitive to hydrodynamic shear. Therefore, studying the design space with several input parameters provides an opportunity to optimize the operating conditions to identify a safe operational range for the bioreactor.

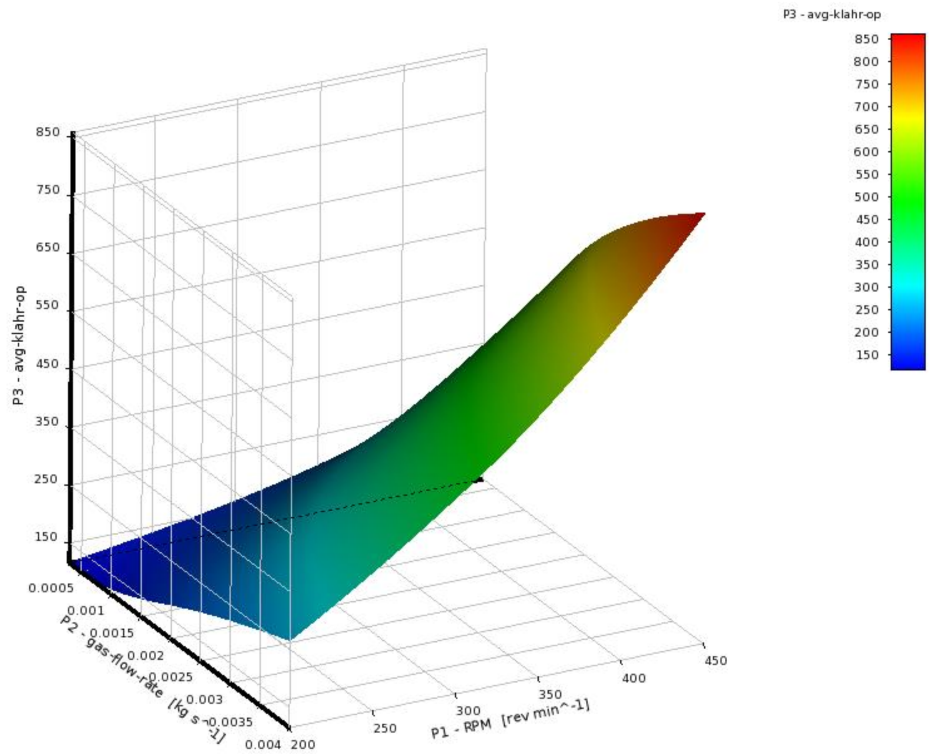

Figure 3: Response surface of average mass transfer coefficient versus gas flow rate and agitation speed

HPC PERFORMANCE BENCHMARKING

We used cloud resources in Microsoft's Singapore data center because this is relatively close to the ANSYS office in Pune, India. The experiment start date was: 2017-12-27, and experiment finish date was: 2018-01-30. Simulations started on 1 node (16 cores) and the last run was on 16 nodes (256 cores). Instance node type: Standard_H16r; FDR InfiniBand (56 Gbps bandwidth); Azure compute instances: 16 CPU cores (Intel(R) Xeon(R) CPU E5-2667 v3 @ 3.20GHz), 112 GB of memory.

The software used to simulate the gas sparging process is ANSYS Workbench with FLUENT in an UberCloud HPC container integrated with the Microsoft Azure cloud platform. The solution methodology is tested with fine and coarse tetrahedral and polyhedral meshes. The time required for solving the model with different mesh densities is captured to benchmark the HPC performance in solving high density mesh models. Boundary conditions, solution algorithm, solver setup and convergence criteria were identical for all models.

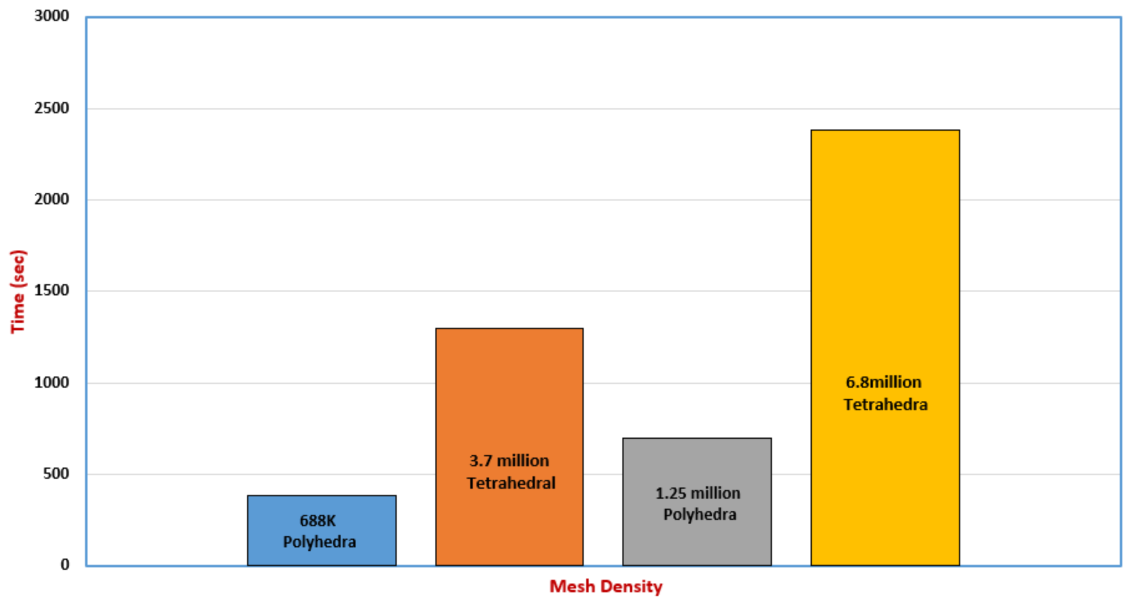

Figure 4: Run time comparison for different mesh densities using 24 CPU cores

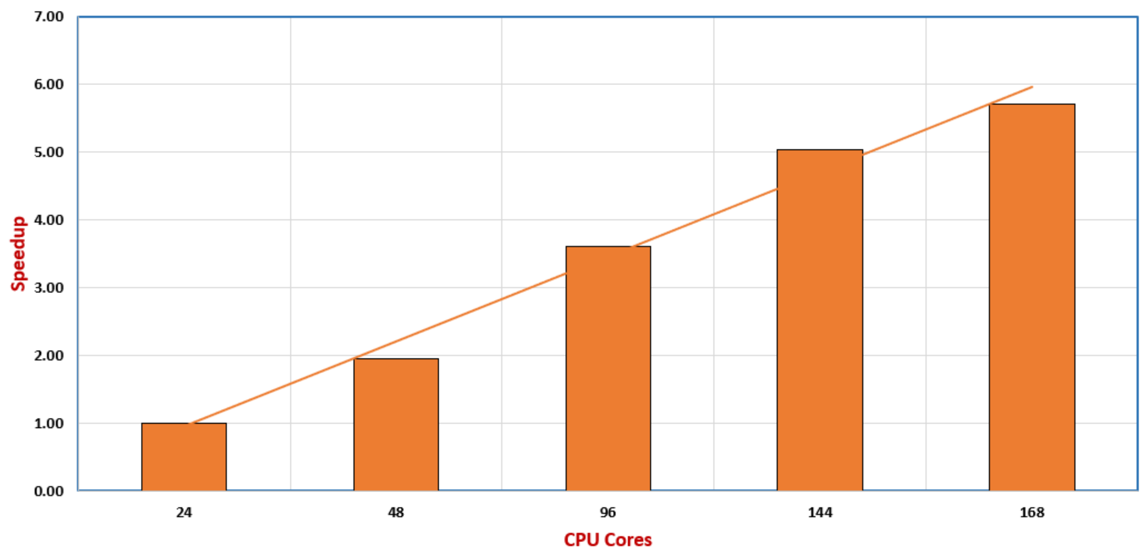

Figure 5: Speedup of 688K polyhedral mesh at different CPU cores

Figures 4 compares the time required to run 200 iterations for different mesh densities with 24 CPU cores. The comparison of the solution time shows a significant reduction in the solution time when converting the meshes from tetrahedral to polyhedral. This is primarily due to the lower number of mesh elements with minimal impact on solution accuracy. Figures 5 summarizes the scalability study, which was based on the 688K polyhedral mesh. As can be seen from the figure, that the solution speed scales close to linear up to 168 CPU cores. Figure 6 shows the decrease of simulation run time as the number of cores is increased. When using 168 cores, each simulation takes less than an hour, making it possible to run the entire design space of the bioreactor in less than 24 hours.

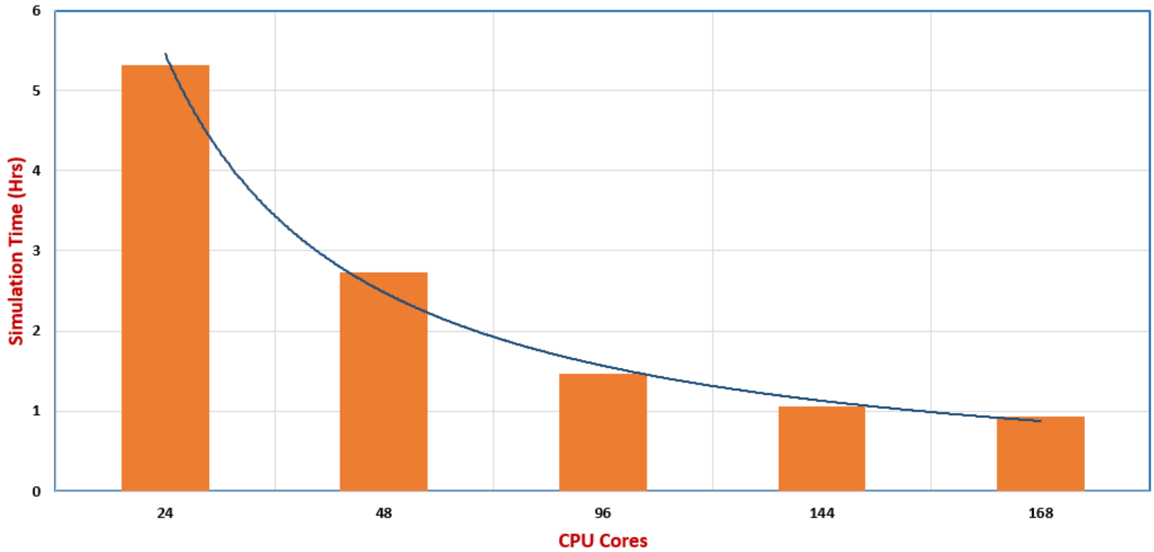

Figure 6: Simulation Run time comparison for 688K polyhedral mesh on different number of CPU cores

A similar speedup study has been performed for the different types of meshes generated for this study. The solution speed scale-up results are plotted and compared with linear scale-up speed to compare the scale-up at different mesh densities. As shown in Figure 7, the solution speed scale-up is observed to move closer to the linear increase in solution speed as the mesh density increases.

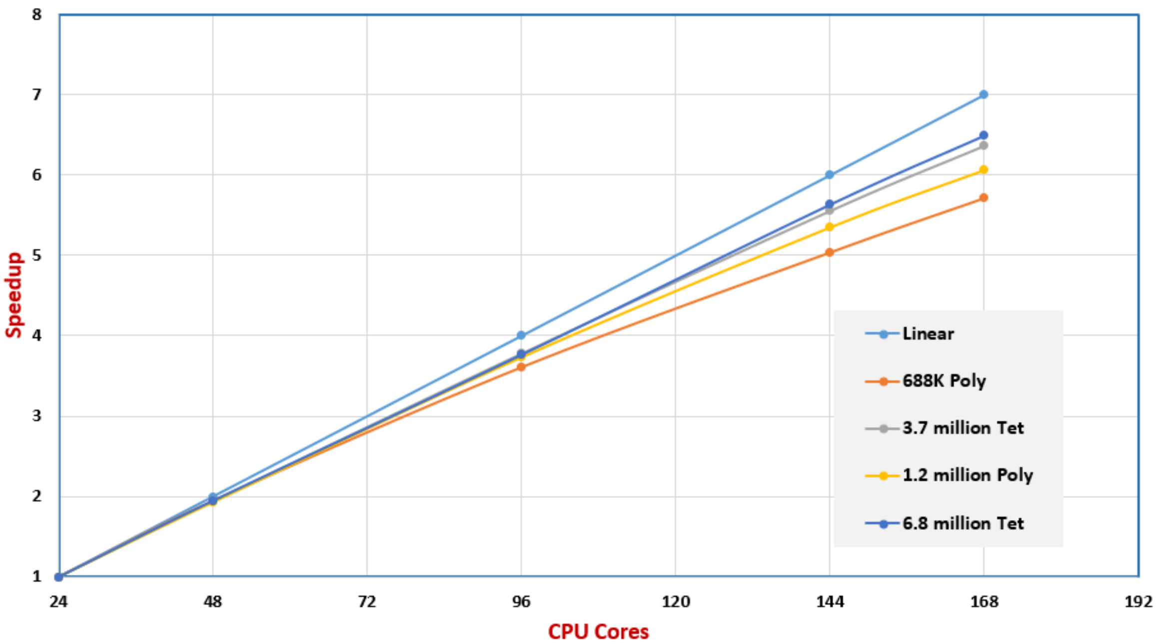

Figure 7: Comparison of solution speed scale-up with different mesh densities

EFFORT INVESTED

End user/Team Expert: 20 hours for simulation setup, technical support, reporting and overall management of the project.
UberCloud support: 4 hours for monitoring & administration of the performance in the host server.
Resources: ~2500 core hours were used for performing design of experiments study using ANSYS workbench**.**

BENEFITS

1. The HPC cloud computing environment with ANSYS Workbench with FLUENT and DesignXplorer streamlined the process of running a DOE with drastically reduced process time.
2. Running the 10 design point simulations and generating the response surface took only 24 hours of run time with 144 CPU cores. This means design engineers can quickly execute DOE analyses to study the scale-up behavior of their bioreactors.
3. With the use of VNC Controls in the web browser, HPC Cloud access was very easy with minimal installation of any pre-requisite software. The entire user experience was similar to accessing a website through the browser.
4. The UberCloud containers helped smooth execution and provide easy access to the server resources. The UberCloud environment integrated with the Microsoft Azure platform proved to be powerful as it facilitates running parallel UberCloud containers, with a dashboard in the Azure environment which helped in viewing the system performance and usage.

CONCLUSION & RECOMMENDATIONS

1. Microsoft Azure with UberCloud HPC resources provided a very good fit for performing advanced computational experiments that involve high technical challenges with complex geometries and multi-phase fluid flow interactions that would not typically be solved on a normal workstation, reducing the time required to establish a two-parameter design space for a bioreactor to a single day.
2. The combination of Microsoft Azure, HPC Cloud resources, UberCloud Containers, and ANSYS Workbench with FLUENT helped to accelerate the simulation trials and also completed the project within the stipulated time frame.

Case Study Author – Sravan Kumar and Marc Horner, ANSYS Inc.

Thank you for your interest in our free and voluntary UberCloud Experiment!

If you, as an end-user, would like to participate in an UberCloud Experiment to explore hands-on the end-to-end process of on-demand Technical Computing as a Service, in the Cloud, for your business then please register at: http://www.theubercloud.com/hpc-experiment/.

If you, as a service provider, are interested in building a SaaS solution and promoting your services on the UberCloud Marketplace then please send us a message at https://www.theubercloud.com/help/.

2013 Compendium of case studies: https://www.theubercloud.com/ubercloud-compendium-2013/
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2018 Compendium of case studies: https://www.theubercloud.com/ubercloud-compendium-2018/

The UberCloud Experiments and Teams received several prestigious international Awards, among other:

- HPCwire Readers Choice Award 2013: http://www.hpcwire.com/off-the-wire/ubercloud-receives-top-honors-2013-hpcwire-readers-choice-awards/
- HPCwire Readers Choice Award 2014: https://www.theubercloud.com/ubercloud-receives-top-honors-2014-hpcwire-readers-choice-award/
- Gartner Cool Vendor Award 2015: http://www.digitaleng.news/de/ubercloud-names-cool-vendor-for-oil-gas-industries/
- HPCwire Editors Award 2017: https://www.hpcwire.com/2017-hpcwire-awards-readers-editors-choice/
- IDC/Hyperion Research Innovation Excellence Award 2017: https://www.hpcwire.com/off-the-wire/hyperion-research-announces-hpc-innovation-excellence-award-winners-2/

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