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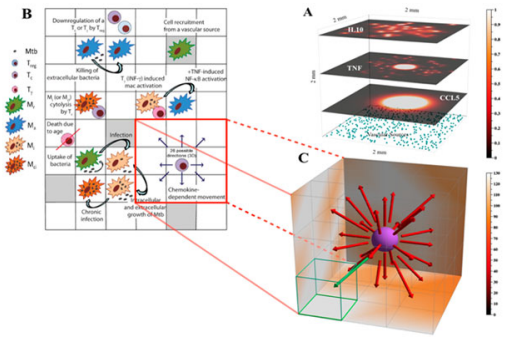
Supercomputer Simulations Help Combat Tuberculosis (TB) Granulomas

University of Michigan Team Uses Comet and Stampede2 to Create TB-Formation Models

The greatest cause of death due to infection globally is tuberculosis (TB). Two supercomputers – *Comet* at the San Diego Supercomputer Center (SDSC) at UC San Diego and *Stampede2* at the Texas Advanced Computer Center (TACC) at the University of Texas at Austin – are being used to help combat this lethal disease.



Comet and Stampede2 enabled researchers to use a program called GranSim to simulate a 3D tuberculosis granuloma in the lung. Three different TB molecules are shown in Panel A, a schematic key describing the GranSim model is illustrated in Panel B, and the zoomed-in 3D granuloma is shown in Panel C. Credit: Denise Kirschner, University of Michigan Computation Tuberculosis Laboratory

Researchers from the University of Michigan relied on *Comet* and *Stampede2* to help them develop detailed models to better understand how TB spreads throughout the lungs. Their most recent findings, published in the January 2019 issue of *Inflammation and Regenerative Medicine* will also be featured in an upcoming special issue of *Computational Modeling in Inflammation and Regenerative Medicine*.

The hallmark of TB infection is the formation of spherical structures in the lungs. These masses of infected tissue, called granulomas, start to form within the first two to four weeks. TB granuloma progression and its final outcome (clearance, containment, or dissemination) depends on an array of factors such as the speed of spread and whether the immune response in the lungs is able to clear the infection. One way that scientists are working to fight this often-fatal disease is by using highly detailed computer-based simulations to determine ways in which to treat the granuloma(s) before the bacteria harbored within them spread to surrounding tissue and organs, preventing any effective treatment.

“For more than 15 years, computer (*in silico*) modeling has been used to provide insight to the lethal disease,” explained Simeone Marino, who is an Associate Research Scientist at the University of Michigan’s Medical School and the first author in the recently published study. “Our recent research looks at the ways in which two-dimensional (2D) and three-dimensional (3D) visualizations differ and offer novel findings for TB researchers to better understand granuloma formation and spread.”

“The current experimental technology does not allow us to track the progression of single granulomas in human and animal hosts; however, the use of *in silico* models offers a viable and scalable alternative to complement long and costly *in vivo* studies in animal models,” explained Marino. “These *in silico* models can help immunologists to simulate intervention protocols (e.g., treatments, vaccines, immunotherapy) and select the most promising ones for clinical trials and experimental validation.”

The mathematical and computational tool used to capture the complex dynamics of TB granuloma formation and progression is called agent-based model (ABM) and referred to as *GranSim* (i.e., Granuloma Simulation). *GranSim* works like a virtual reality environment, where cells, bacteria, and molecules are represented by various agents of different pixel sizes in an abstract 3D cube. The cube captures a section of the lung where granulomas typically form.

Sources in the cube mimic lung vascularization and, depending on certain concentration conditions for the molecules modeled, allow for recruitment of cells upon an initial seed of infection. Cells move around following molecular concentration gradients. Bacteria can infect cells and proliferate inside them. Cells can either kill bacteria or become infected and die if they harbor too many bacteria, setting up a chain reaction for more infection. Granulomas can wall off the spread of infection and generate an environment that limits bacterial growth (see http://malthus.micro.med.umich.edu/lab/movies/Multiscale/3D-GranSim/ for 3D animations).

“*Comet* and *Stampede2* resources were key in the development, calibration and analysis of the 3D simulation of *GranSim*,” said Marino. “Due to the high computational costs of these types of agent-based models, we could not have completed our work without these two supercomputers.”

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