From Personalized Medicine to Clean Energy Production:

Accelerating Multicellular Biological System Simulation Using BioCellion

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Interactions drive multicellular biological system behavior

BACTERIAL BIOFILMS: FROM THE NATURAL ENVIRONMENT TO INFECTIOUS DISEASES

Luanne Hall-Stoodley[*1§], *J. William Costerton*[§] *and Paul Stoodley*[||]

"The complex interaction between the biofilm pathogens and the host inflammatory response modifies the environment, and successful biofilm parasites respond accordingly by altering their phenotype to the biofilm mode of growth"

Placing microalgae on the biofuels priority list: a review of the technological challenges

H. C. Greenwell, L. M. L. Laurens, R. J. Shields, R. W. Lovitt and K. J. Flynn

J. R. Soc. Interface 2010 **7**, doi: 10.1098/rsif.2009.0322 first published online 23 December 2009

"At the heart of any attempt to commercially exploit microalgae is the need to identify the optimal combination of microalgal strain and growth conditions."

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

Genetically engineered bacteria: An emerging tool for environmental remediation and future research perspectives

Jay Shankar Singh [a,*], P.C. Abhilash [b], H.B. Singh [c], Rana P. Singh [a], D.P. Singh [a]

[a] Department of Environmental Science, BB Ambedkar (Central) University, Lucknow-226025, India
[b] Agrotechnology and Soil Science Division, Central Institute of Medicinal and Aromatic Plants, Lucknow 226 015, Uttar Pradesh, India
[c] Department of Mycology and Plant Pathology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi-221005, India

"A major difficulty with in situ bioremediation by using transgenic bacteria is the unpredictable end result on account of various environmental factors that may interfere."

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The New York Times

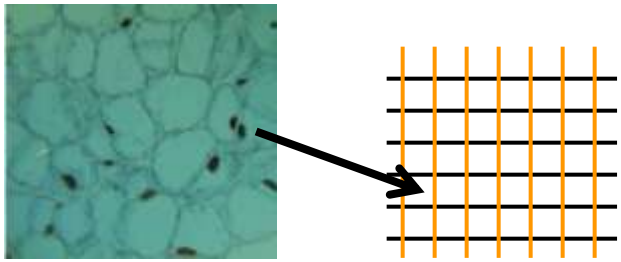
“Nearly half of women who had lumpectomies for breast cancer had second operations they may not have needed because surgeons have been unable to agree on guidelines for the most common operation for breast cancer, a new study finds. It also hints that some women who might benefit from further surgery may be missing out on it.”

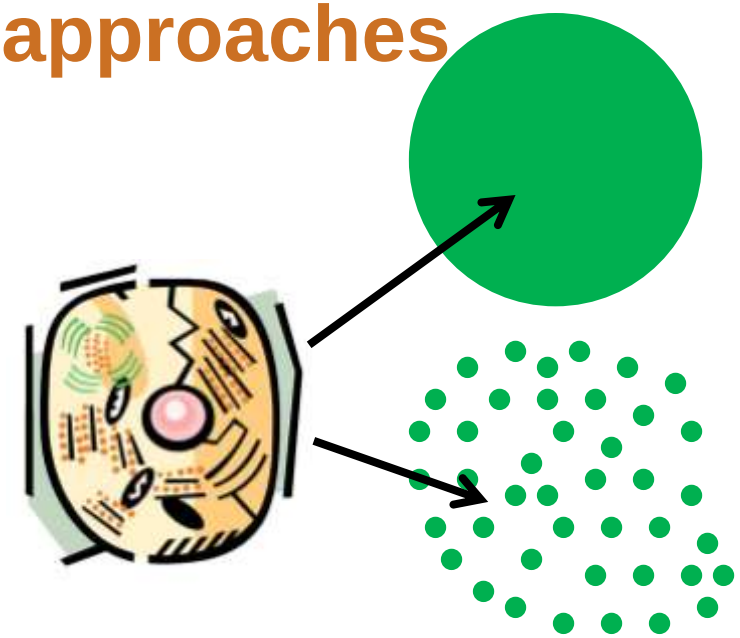
Source: http://www.nytimes.com/2012/02/01/health/repeat-breast-cancer-surgery-guidelines-found-unclear.html

Simulation Components

- Individual Cell Behavior
- Cell-cell interaction
  1. Physical contact
  2. Via diffusible molecules
- Cell-environment interaction
  1. Molecule consumption and production
  2. Limit or promote cell movement
  3. Affect molecule transport
  4. …

Two principal modeling approaches



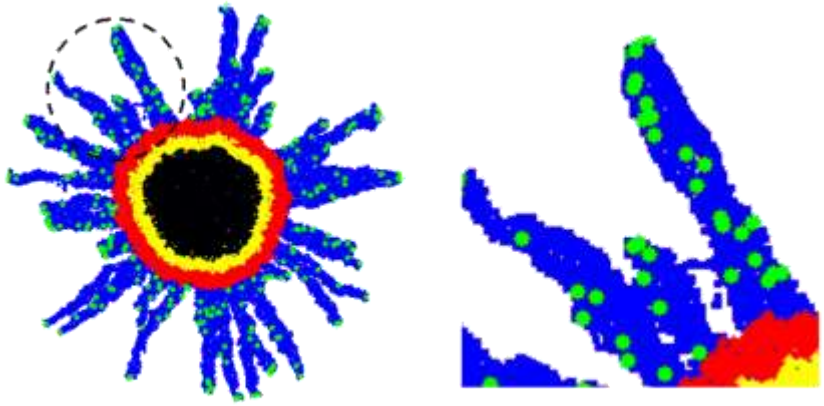


- Population based approach
  - Computationally inexpensive (with coarse grid spacing)
  - Difficult to model individual cell level events
  - Inappropriate for multicellular systems with high spatial heterogeneity
- Discrete agent based approach
  - Computationally demanding to model large biological systems (> 10^6 cells)

OPEN ACCESS Freely available online PLoS COMPUTATIONAL BIOLOGY

Emergent Behaviors from a Cellular Automaton Model for Invasive Tumor Growth in Heterogeneous Microenvironments

Yang Jiao[1], Salvatore Torquato[1,2]*

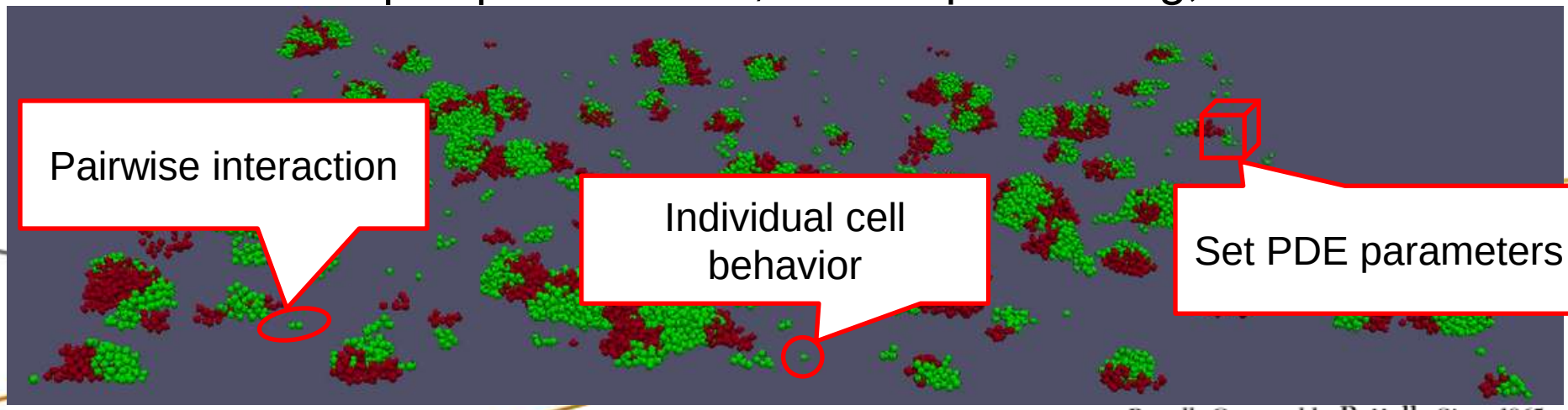


A B

"As currently implemented, a single 2D simulation takes less than 0.5 hours on a 32bit 1.56 GB 1.44 GHz dual core Dell Workstation. We expect that a 3D simulation will take no longer than 24 hours on a supercomputer when a proper parallel implementation is used."

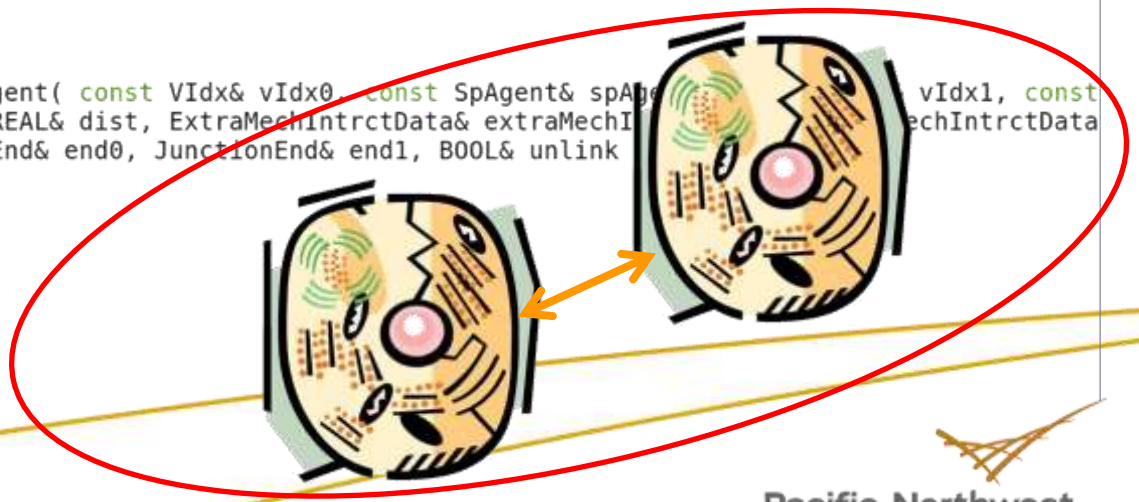
Major Challenge and BioCellion Approach

- No established mathematical models
  - Models vary widely and change over time.
- Users provide model specifics, Biocellion addresses the high-performance parallel computing challenges
  - Model specifics: rules to determine individual cell behvaior, evaluate pairwise interactions, set PDE parameters, …
  - Computing and programming challenges: nested irregular parallelism, multiple time and spatial scales, partitioning, load balancing, adaptive mesh refinement & multi-grid, multi-step implicit method, octtree partitioning, …



```
void ModelRoutine::computeForceSpAgent( const VIdx& vIdx0, const SpAgent& spAgent0, const VIdx& vIdx1, const SpAgent&
spAgent1, const VReal& dir, const REAL& dist, VReal& force ) {
        /* MODEL START */

        REAL R = spAgent0.state.getRadius() + spAgent1.state.getRadius();
        REAL mag;/* + for repulsive force, - for adhesive force */

        if( dist <= R ) {/* shoving */
                mag = 0.5 * ( R - dist );
        }
        else {/* adhesion */
                if( spAgent0.junctionInfo.isLinked( spAgent1.junctionInfo ) == true ) {
                        REAL x = dist / R;
                        mag = -0.5 * ( dist - R ) * exp( -1.0 * ( x - 1.0 ) * ( x - 1.0 ) / ADHESION_S );
                }
                else {
                        mag = 0.0;
                }
        }

        for( S32 dim = 0 ; dim < DIMENSION ; dim++ ) {
                force[dim] = mag * dir[dim];
        }

        /* MODEL END */

        return;
}

void ModelRoutine::computeExtraMechIntrctSpAgent( const VIdx& vIdx0, const SpAgent& spAg                    vIdx1, const
 SpAgent& spAgent1, const VReal& dir, const REAL& dist, ExtraMechIntrctData& extraMechI                    echIntrctData
& extraMechIntrctData1, BOOL& link, JunctionEnd& end0, JunctionEnd& end1, BOOL& unlink
        /* MODEL START */

        ...

        /* MODEL END */

        return;
}
```

Evaluate direct physico-mechanical interaction between a cell pair



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BioCellion Early Adopters

William Cannon

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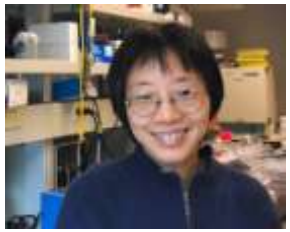

Wenying Shou

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Haluk Resat

WASHINGTON STATE UNIVERSITY

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Ilya Shmulevich

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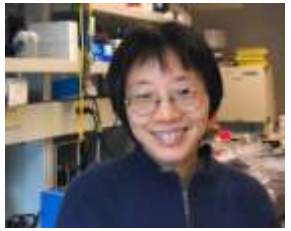
Nick Flann

Utah State University

Strong inter-population cooperation leads to partner intermixing in microbial communities

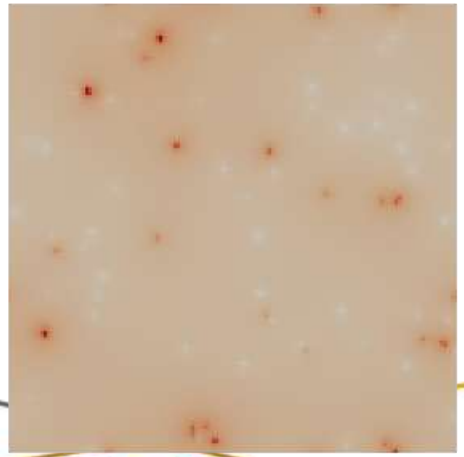


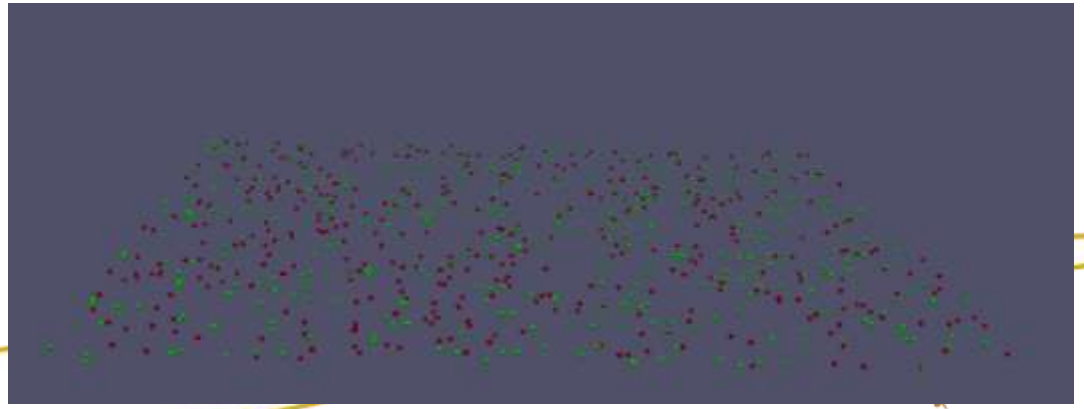
Babak Momeni[1]*, Kristen A Brileya[2], Matthew W Fields[2], Wenying Shou[1]*

- Reducing grid spacing from 50 μm → 5 μm

  - $10^3 \times 10^2$ (the original implementation uses the explicit Euler method) times increase in computing

  - BioCellion addresses the computing challenge with adaptive mesh refinement, implicit method, and high-performance computing



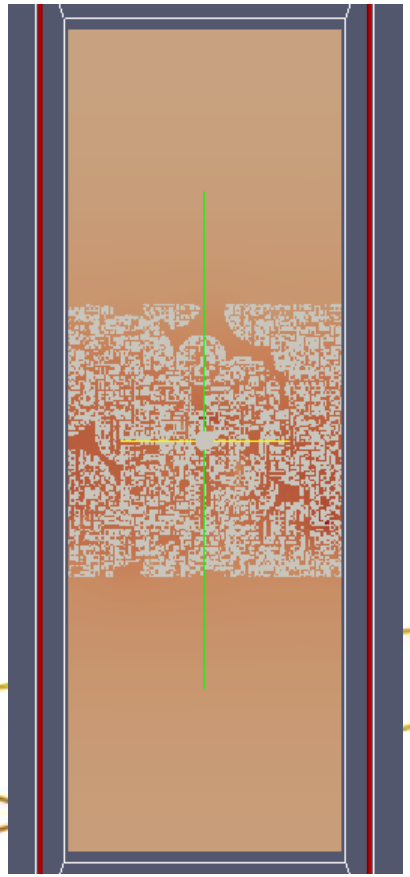


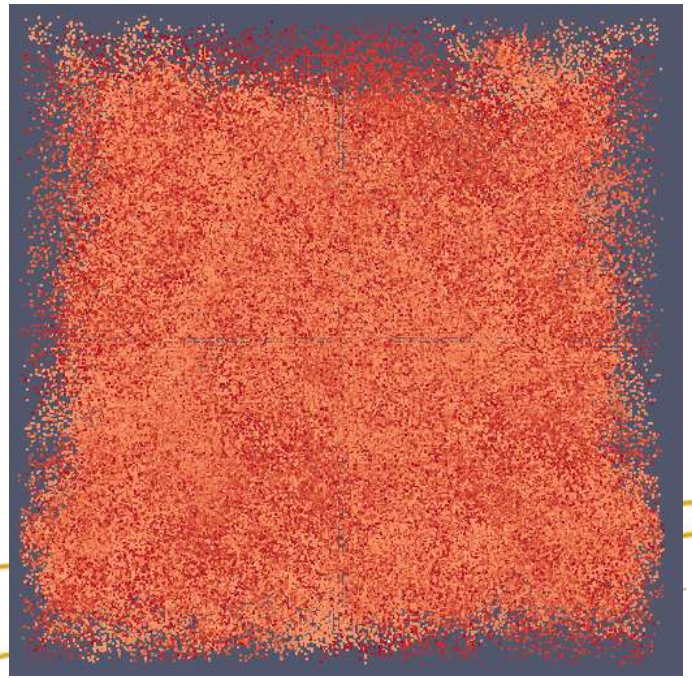
Modeling Microbial Dynamics in Heterogeneous Environments: Growth on Soil Carbon Sources

Haluk Resat · Vanessa Bailey · Lee Ann McCue · Allan Konopka

Before BioCellion

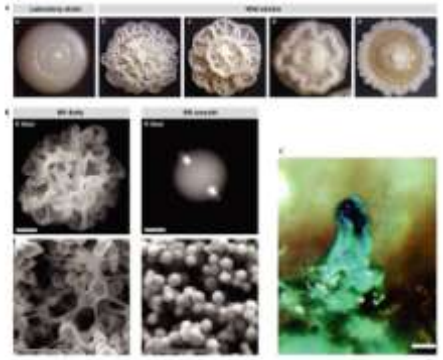
After BioCellion



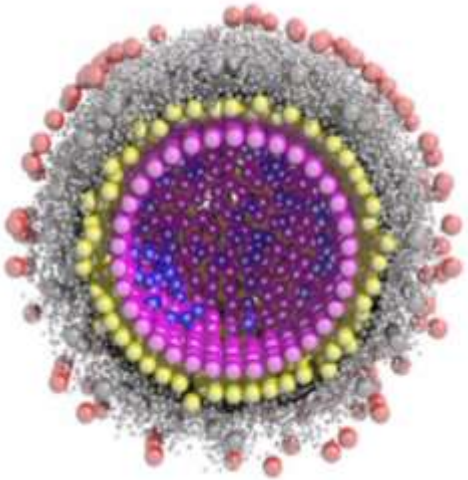


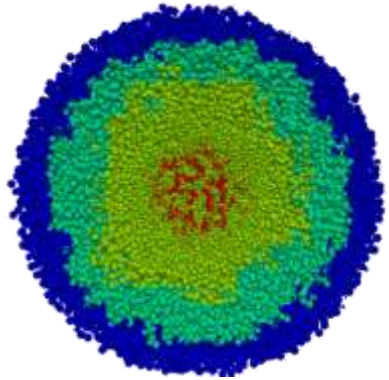
BioCellion enables scaling from micro-pore to soil aggregate of aggregate!!!

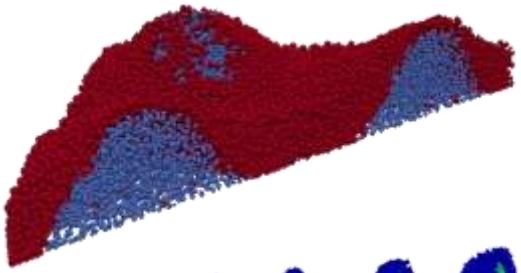
Yeast colony and micro tumor growth

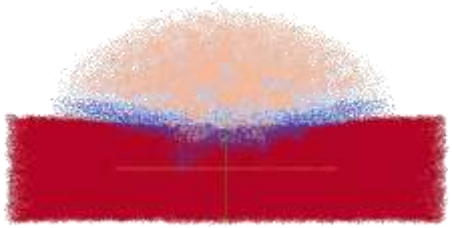


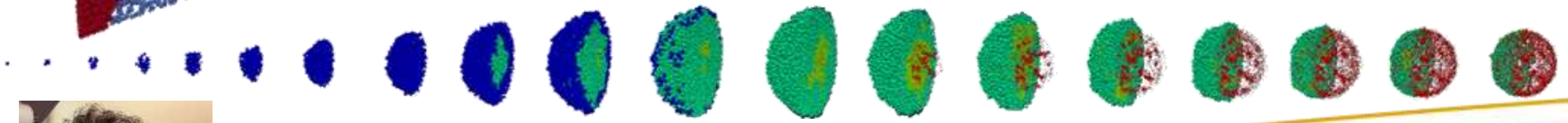
source: EMBO Rep. 2004 May; 5(5): 470–476.











Courtesy of Nick Flann , Brian Benson, and Alex Wells

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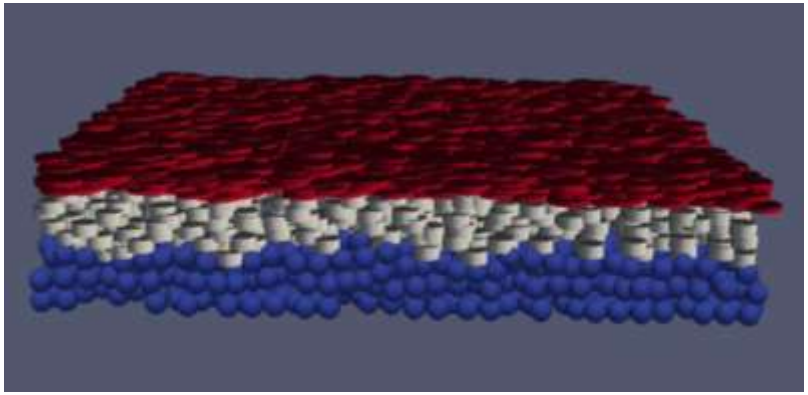
Modeling bacteria systems using thermodynamics principles

- Simulate individual cells with thermodynamics principles (Stochastic ODEs solved using Monte Carlo methods)
- Single cell simulation → Multi-cell Simulation using BioCellion

Skin model

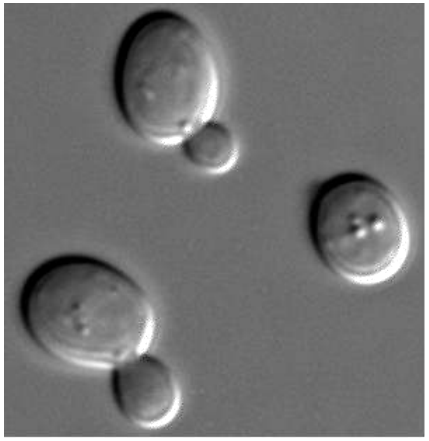


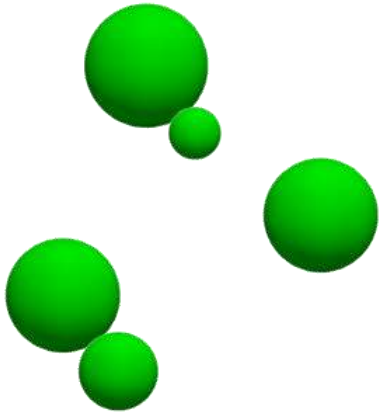
Building prototype skin models

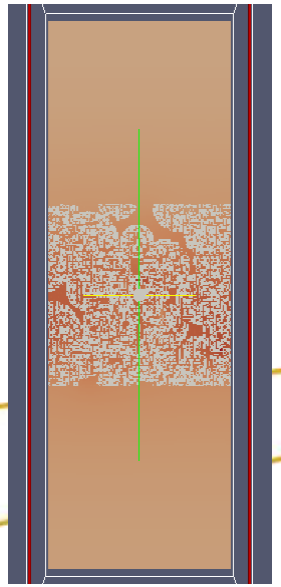
Courtesy of Ilya Shmulevich and Ryan Tasseff

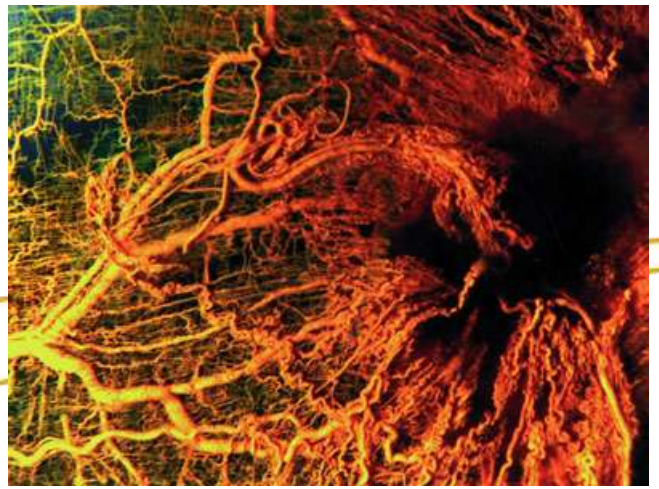
Future roadmap

- Mapping a single cell to multiple discrete agents
- Flow modeling
  - Water flow in soil aggregate
  - Blood flow modeling (in microvasculature)
- Providing various solvers for single cell modeling









Conclusions

- Computational complexity of discrete agent based modeling should NOT be a major bottleneck in understanding multicellular biological systems with help from the HPC community.
- BioCellion 1.0 release in the near future
- BioCellion promotional video in Vimeo http://vimeo.com/63245361 (search for biocellion vimeo)

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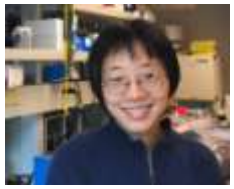
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