Computational and Mathematical Studies of the Biomechanics of Biofilms

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May 8th, 2018

Acknowledgments

- Funding Sources:
  - Dept. of Energy's Computational Science Graduate Fellowship program
  - NSF Grants: PHY-0940991, DMS-1225878, PHY-0941227
- Advisor: Prof. David Bortz in Applied Math
- Phil Colella and Dan Martin (Lawrence Berkeley Nat'l Lab)
- CU Research Computing
- Collaborators:
  - Univ. Michigan: John Younger, Michael Solomon, Leo Pavlovsky, Elizabeth Stewart
  - Air Force Research Lab: Jason Hammond
  - CU Boulder: Vanja Dukic
- CU MathBio:
  - Sabina Altus, Lewis Baker, Harry Dudley, Eric Kightley, Taisa Kushner, Inom Mirzaev, John Nardini, Jaqueline Wentz

Bacterial Biofilms

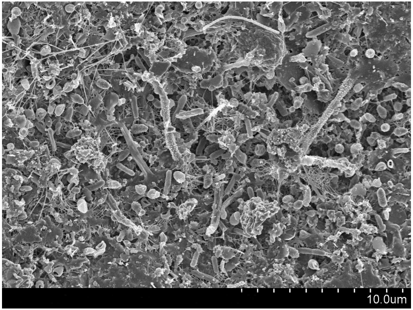


Figure: Biofilm growing on grain of sand. [1]

- Bacterial Biofilms are colonies of bacteria that have adhered to a surface
- Bacteria typically cofined within a viscous layer of extracellular polymeric substances[2]

[1] Image courtesy of the Lewis Lab at Northeastern University. Image created by A. D'Onofrio et al.

[2] Hall-Stoodley et al. 2004, *Nature Rev. Microbiol.*

Why biofilms are important

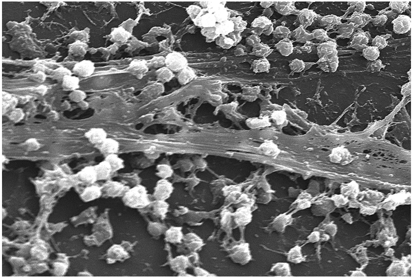
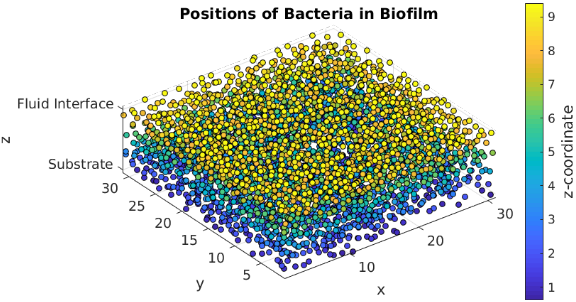


Figure: Viscoelastic fibers in biofilm. [3]

- Implicated in many bacterial infections
- Industrially, biofilm growth is a major source of corrosion
- Can also be beneficial - an important component of bioreactors.

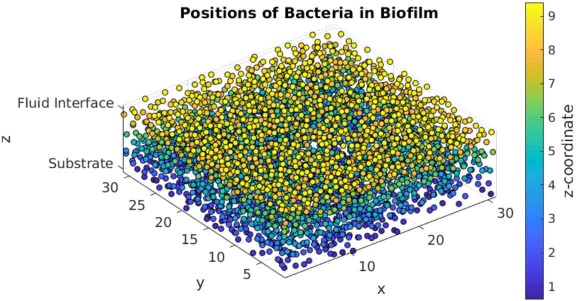
[3] 2005 R. M. Donlan, J. Carr

Spatial Statistical Analysis of Biofilm Data



- Analysis of biofilm microstructure based high-resolution microscopy data sets
- Develop a point process model based on statistical characterization of data

Spatial Statistical Analysis of Biofilm Data



- Comparison of dynamic moduli from statistical models to experimental data through computer simulation[4]
- Paper can be found in EJAM Biofilm special issue[5]

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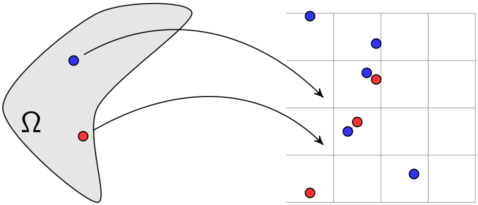
[4] Stotsky et al. 2016, *Journal of Computational Physics*.
[5] Stotsky et al. 2018, *European Journal of Applied Mathematics*.

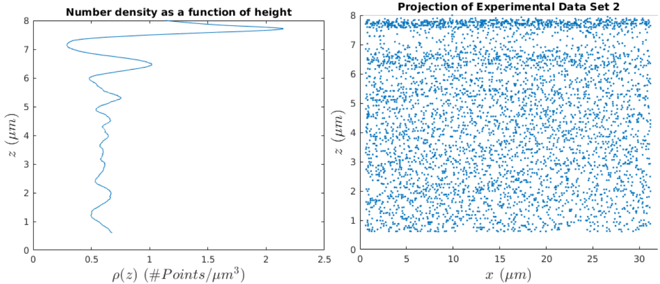
Point Processes

- Point processes are mappings from a probability space, Ω, to collections of points in Euclidean space



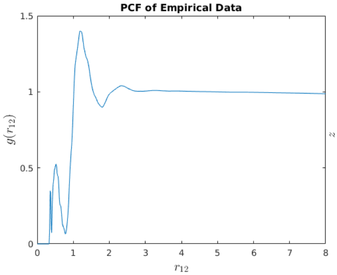
- Moments of a point process are *measures*
  - First Moment Measure: $\mu^{(1)}(B) = \mathbb{E}[\Phi(B)]$.

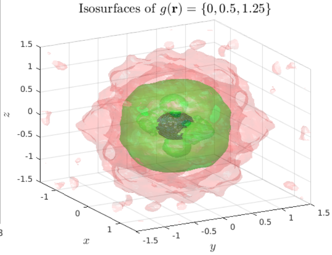
Estimation of the Number Density



- Number density defined as average number of points per volume at each point in space

Estimation of the Pair Correlation Function





- Pair Correlation Function(PCF) defined as

$$g(\boldsymbol{r}_1, \boldsymbol{r}_2) = \frac{\rho^{(2)}(\boldsymbol{r}_1, \boldsymbol{r}_2)}{\rho^{(1)}(\boldsymbol{r}_1)\rho^{(1)}(\boldsymbol{r}_2)} \tag{1}$$

- Relative likelihood of pair of points being separated by a given distance
- Quantifies interactions between pairs of points.

Pairwise Interaction Models

- Very common in the statistical study of fluids Hansen et al. 1990
- Probability density of a configuration of n particles is

$$f^{(n)}(\boldsymbol{x}^n) = \frac{1}{Z_n} \exp\left(-\sum_{i=1}^{n} \phi(\boldsymbol{x}_i) - \sum_{i=1}^{n} \sum_{j>i}^{n} v(\boldsymbol{x}_i, \boldsymbol{x}_j) \right) \quad (2)$$

- Z_n closely related to the partition function of statistical mechanics
- can often assume translation invariance and isotropicity
  - $\phi(\boldsymbol{r}) = const$
  - $v(\boldsymbol{r}_1, \boldsymbol{r}_2) = v(|\boldsymbol{r}_1 - \boldsymbol{r}_2|)$
- For biofilm case, we assume that the process is *Second order intensity reweighted stationary* (SOIRS) Baddeley et al. 2000, *Statistica Neerlandica*

The Ornstein-Zernike Equation

- Used to define a function known as the direct correlation function (DCF)

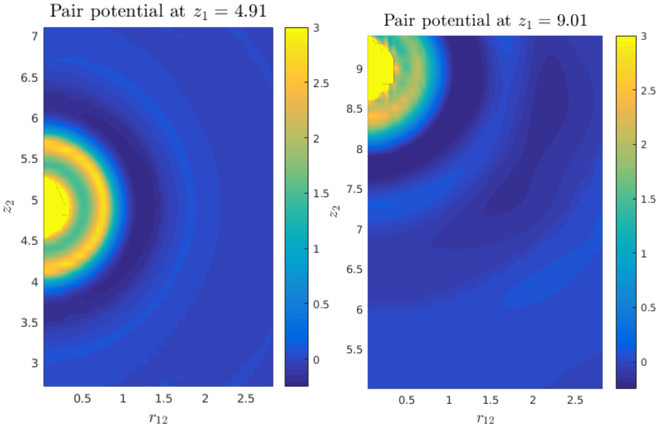
$$g(\boldsymbol{r}_1, \boldsymbol{r}_2) - 1 = c(\boldsymbol{r}_1, \boldsymbol{r}_2) + \int \rho(\boldsymbol{r}_3)(g((\boldsymbol{r}_1, \boldsymbol{r}_3) - 1)c((\boldsymbol{r}_2, \boldsymbol{r}_3)d\boldsymbol{r}_3 \tag{3}$$

- For isotropic, translation invariant case,

$$g(r) - 1 = c(r) + \rho \int (g(|\boldsymbol{r} - \boldsymbol{r}'|) - 1)c(\boldsymbol{r}')d\boldsymbol{r}' \tag{4}$$

- diagonalized by Hankel transform
  - $\mathcal{H}[f(r)](k) = \int_0^\infty f(r) r J_0(kr) dr$
  - involutive: $\mathcal{H}[\mathcal{H}[f]] = f$
- For SOIRS process, assume that $g(r)$ is isotropic, but allow for anistropy in $c(\boldsymbol{r}_1, \boldsymbol{r}_2)$ and variation in $\rho(\boldsymbol{r})$

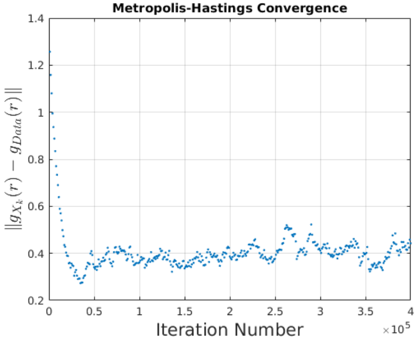
Closure Relations - The Hypernetted-Chain Equation



- Hypernetted-Chain equation

$$v(\boldsymbol{r}_1, \boldsymbol{r}_2) = g(\boldsymbol{r}_1, \boldsymbol{r}_2) - 1 - c(\boldsymbol{r}_1, \boldsymbol{r}_2) + \log g(\boldsymbol{r}_1, \boldsymbol{r}_2)$$

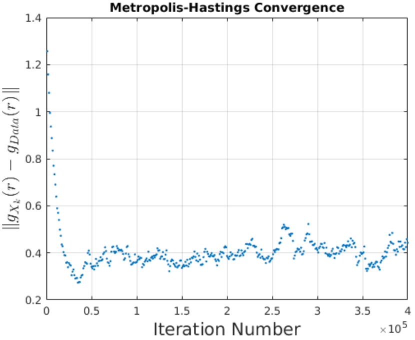
Markov-Chain Monte Carlo Methods



- Commonly used to simulate complicated point processes[6]
- Only require unnormalized probability densities

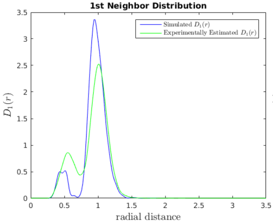
[6] Moller et al. 2003.

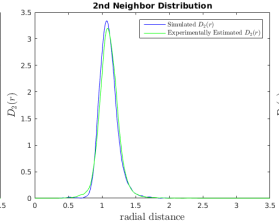
Markov-Chain Monte Carlo Methods

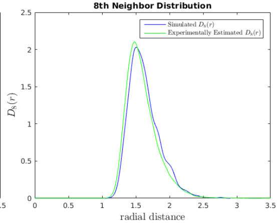


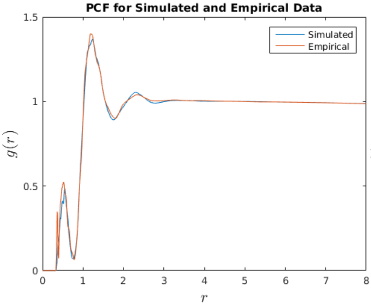
- Basic Algorithm:
  1. Choose a point $\boldsymbol{x}_i \in \boldsymbol{X} \equiv \{\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n\}$ at random
  2. Propose a new location for $\boldsymbol{x}_i$ at random, label the new dataset $\boldsymbol{Y}$
  3. Compute the ratio $\alpha = f(\boldsymbol{Y})/f(\boldsymbol{X})$
  4. if $\alpha \geq 1$, set $\boldsymbol{X} \leftarrow \boldsymbol{Y}$, otherwise $\boldsymbol{X} \leftarrow \boldsymbol{Y}$ with probability α
  5. Repeat 1-4 until convergence

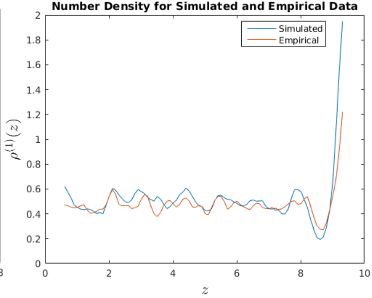
Comparison of Characteristics



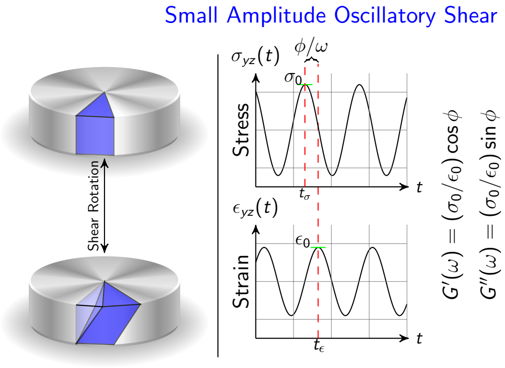






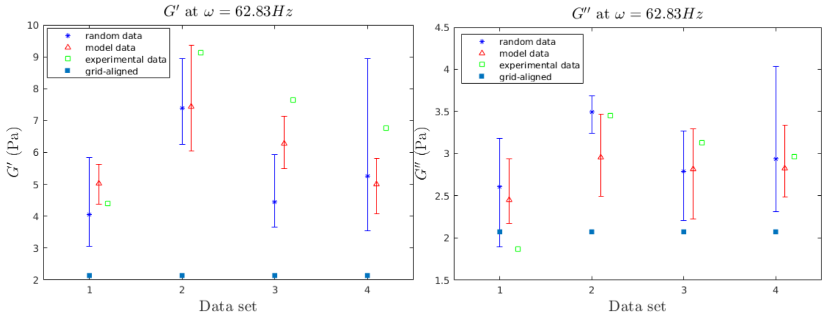


Validation: Experimental Measurement of Dynamic Moduli



- G' known as storage modulus - solid-like behavior
- G'' known as loss modulus - fluid-like behavior

Comparison of Dynamic Moduli



- Similar grid-aligned simulations done in Wrobel et al. 2014, *Physics of Fluids*
- Grid-aligned plus random perturbation in Alpkvist et al. 2006-08-05, *Biotechnol. Bioeng.*

Conclusions

- Non-uniformity increases strength of biofilm
- Pair interaction model does a good job matching characteristics of experimental data
- Correctly choosing scale parameters in the estimators is challenging
  - LSCV yields reasonable values, but fine tuning by numerical experimentation still needed
  - More information available in the paper[6], to appear in EJAM

[6]Stotsky et al. 2018, *European Journal of Applied Mathematics*.

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Thank You

- **A Point Process Model for Generating Biofilms with Realistic Microstructure and Rheology (2018) EJAM**
- Variable Viscosity and Density Biofilm Simulations using an Immersed Boundary Method, Part II: Experimental Validation and the Heterogeneous Rheology-IBM (2016) JCP
- A Posteriori Error Analysis of Fluid-Stucture Interactions: Time Dependent Error (2018) arXiv 1807.03279