Multiscale computational perspective of biofilm

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Abstract

This short report reviews computation models for biofilm and bacteria cells, providing perspectives of biofilm's various properties and potentials serving as engineering living materials (ELMs). The perspective starts from the molecular regime, bottom-up to the mesoscale, to continuum, with an emphasis on the mesoscale algorithms such as dissipative particles dynamics (DPD) and individual-based modeling (IbM). The advantages and limitations of each algorithm for different scales are elaborated given the existed research works. Specifically, the potential for IbM, also known as the discrete element method (DEM) is targeted for its accurate description of both biological and mechanical properties.

1 Brief

Biofilm is bacteria communities adhered to surfaces that accommodate and clustered, exhibiting multiscale biomechanical behaviors [1]. In this section, we review the multiscale

computational modeling methods for simulating biofilms, with a concentration on mechanical properties and their applications or potentials for serving as engineering living materials (ELMs). The computational review regarding multiscale will follow Figure 1: we review all-atomic molecular dynamics (MD) techniques for molecular modeling biofilm regarding mostly on chemical and biological mechanisms, followed by a mesoscopic approach on dissipative particles dynamics (DPD) and lattice Boltzmann works; with further bottom-up to smoothed particles hydrodynamics (SPH) and discrete element method (DEM) modeling of biofilm. Note that DEM can also be called individual-based modeling (IbM) & agent-based modeling (ABM), which is one of the most adopted methods for biofilm modeling due to its accurate description and coupling of biological processes, chemical reactions, and mechanical properties, as one of the most promising techniques for bridging multiscale multiphysics properties.

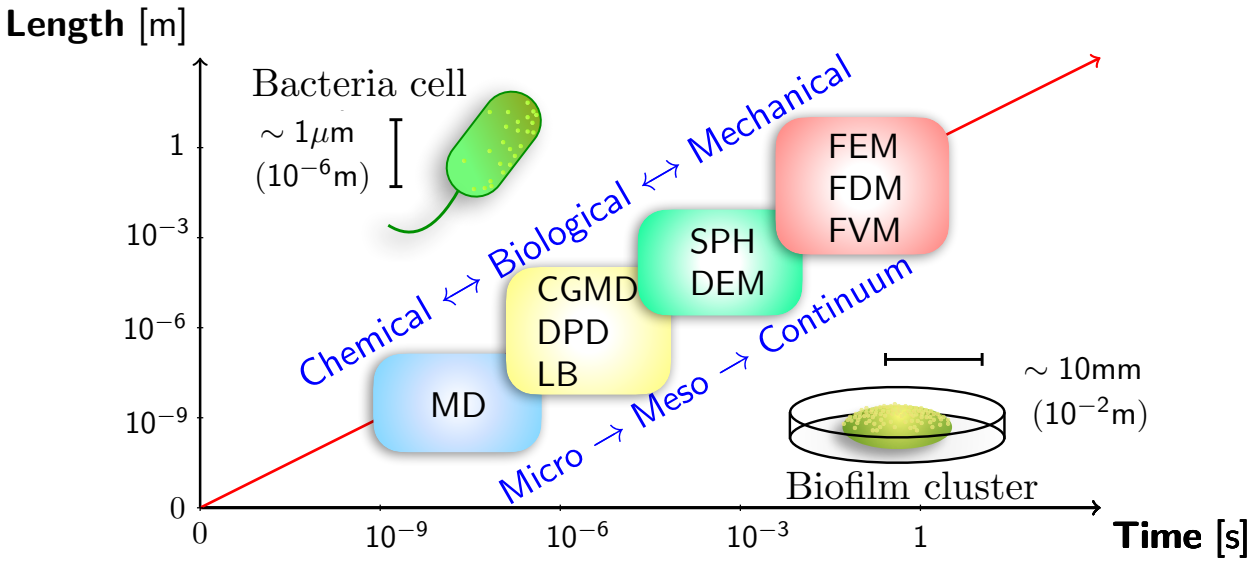

Figure 1: Schematic for multiscale computational methods for modeling biofilm, starting from the molecular scale, mesoscale, to continuum scale, where MD, DPD, etc., are abbreviations of different computation algorithms to be illustrated in the text. Note that the schematic on the left up corner indicates a single bacteria cell is approximately 1μm. The schematic on the right down corner indicates shows a matured biofilm "pancake" approximately 10mm.

2 Molecular scale

Molecular dynamics (MD) is a computer simulation technique that computes the atomic and molecular interactions pertaining time-based on Newton's law [2]. First introduced and employed for simulating water in the 1950s and 1960s [3, 4], followed by subsequent applications on biomolecular systems, such as protein or nucleic acids in the 1970s [2, 5]. Traditionally, MD are classified as ab initio (first principle) MD (AIMD) and empirical MD, which differs from atomic forces calculation accounting for the potential fields where AIMD computes potential fields from quantum-mechanical calculations yet empirical MD assumes a prescribed field. Targeting biofilm approaches MD stands for empirical methods since it allows computation of larger scales. Since in MD applications atoms are ranged in the scale of $10^{-10} \sim 10^{-9}$m, in which biofilm clusters are hardly simulated limited by computational resources, most works adopting such methods were concentrated on the chemical and biological perspective. For instance, MD simulations can explain the mechanism of hydrogen bonds in the forming of polysaccharide Granulan, a gel forming matrix component of granular microbial biofilms [6]. Also, it can assist experiments to unveil the interactions between DNA and related ions of studying mucoid *Pseudomonas aeruginosa* biofilm [7]. It can also be applied to study the membranes' interactions with Antimicrobial peptides (AMPs), for stable membrane binding [8]. In brief, the MD approach mainly tackles chemical and biological properties as unveiling the molecular insights of biofilm studies. Limited by computing powers, MD hardly unveils biofilms mechanical properties, in the scale of $10^{-9} \sim 10^{-6}$m.

3 Mesoscale

The mesoscale is defined between the molecular scale and the continuum scale, usually identified ranging from $10^{-6} \sim 10^{-3}$m, where most mechanical and biological behavior of

biofilm can be characterized in such a scale, as illustrated in Figure 1. Hence, we attach greater importance to such a regime. Following MD, coarse-grained MD (CGMD) is a method to use the simplified representation of a system for simulating its behavior, which is widely adopted in biochemical and biomolecular systems [9], specifically for studying the biochemical properties of bacteria cells [10, 11, 12]. CGMD is mostly adopted to simulate the system in the scale of micrometers, approximately the scale of a single bacteria cell, as we visualized in Figure 1. As an extension to MD, CGMD simulations was still limited in scales constrained by computational power, as it can be employed to explain the chemical and biological essence of biofilm dewetting phenomenon of *Bacillus subtilis* [13], cross-validating experiments proposed theory of biological transporation [14], and providing molecular insights for developing anti-bacteria silver drugs [15].

On top of CGMD [26], another method that bottoms from MD computation strive to accurately depict the mesoscale is Dissipative Particle Dynamics (DPD). DPD is a stochastic simulation that is widely applied for complex fluids, initially proposed by Hoogerbrugge and Koelman [16, 17], assigning statistical mechanics information beads that conserve chemical and physical properties, has mostly applied to microfluidics and complex fluid modeling. Has already been widely applied to small scales in biological systems such as cell membranes and lipid bilayers [18, 19, 20, 21], DPD was initially applied to model biofilm in 2011 by Xu et al. [22], where the fluid flow interactions and transport phenomena were keenly focused. Bacteria cells can also be modeled as a combination of hundreds of DPD beads to model biofilms [23]. What's more, DPD was adopted to investigate the biofilm constitutive model [24] and design of antibiotic drug design [25]. Lattice Boltzmann method (LBM) is a particle-based, bottom-up model that can be employed for tracing the dynamics and properties of individual bacterial cells [27], originated from classical statistical physics and lattice gas automata [28]. Applications of LBM for biofilm modeling dated back to 1999 [29, 30], which sparks a series of study on applying LBM for biofilm growth simulation in

the 2000s [31, 32, 33, 34, 35].

Specifically, the most widely adopted method to model biofilms is the discrete element method (DEM), wherein biofilm modeling they are mostly referred to as individual-based modeling (IbM) or agent-based modeling (AbM). For DEM singular bacteria cells are usually identified as single elements and the duplications and interactions are based on different biological mathematical models. It is particularly suitable for biofilm modeling due to its successful coupling and accurate description of hydrodynamics, thermodynamics, biological processes, etc., and can act as a bridge between behavior at the individual and community levels [37]. In the past few years, a surge of DEM-based biofilm numerical models occurred tackle different questions in biofilms [38]. Among the numerous biofilm models, most proposed DEM biofilm models can couple physical and biological processes [39, 40, 41, 42, 43, 46, 47, 48, 49, 50, 51, 52, 53, 54], amongst some cannot include the metabolic, as to quantify the biofilm interactions with the external environment [39, 51, 53]. One of the main motivations of biofilm studies is bacteria communities generate extracellular polymeric substances (EPS) as an external engineering matrix to adhere and protect cells from drugs and environmental changes. Several proposed DEM models can successfully model EPS [44, 45, 47, 48, 49, 50, 54], which can be adopted as potential tools for studying the EPS mechanism to utilize biofilms as ELMs.

Another simulation technique widely applied in the mesoscale utilizing particle-based method yet for computing the mechanics of continuum media is smoothed particles hydrodynamics (SPH), first proposed by Gingold and Monaghan [56] and Lucy [57] in the field of aerospace. Similar to the DEM schemes, SPH methods can also successfully represent both bioreaction and nutrient diffusion with also accounting for deformation and interface erosion, according to Soleimani et al. [58], where the difference is SPH is based on a continuum approach. SPH can also be applied to study the mechanics of EPS [59] and chemotaxis [60] for biofilm under fluid flow-induced deformation.

To summary, the mesoscale computational methods provide decent characterizations of the multiphysics nature of biofilm. Coarse-grained molecular like CGMD and DPD models proffer accurate depictions of chemotaxis phenomena while DEM offers a satisfactory bridge between meso to continuum for coupling mechanical, biological and even chemoaxis biofilm signature, ranging in the scale from 10^{-6} to 10^{-3}m.

4 Continuum scale

In the continuum regime, most numerical methods aim to discretize ordinary or partial differential equations that govern the mechanical, chemical, and biological process, whereas commonly employed methods include finite element method (FEM), finite difference method (FDM), finite volume method (FVM), etc. Especially, the computational modeling provides insights on biofilms mechanical properties validating experiments since most biomechanical tests are conducted on the scale of $10^{-3} \sim 10^{-1}$m. As one of the most adopted computational mechanics methods, FEM subdivides the computational domain into smaller subdomains called finite elements, achieved through the construction of meshing, which can be traced back to the 1940s by Hrennikoff [61] and Courant [62]. The extended FEM (XFEM) method can study boundary layer behavior in elliptic equations, which can be further applied to linearized biofilm growth [64]. Followed up, XFEM can either be combined with diffusion-reaction and show the relation between colony morphology and nutrient deletion [63]; or with the level set method, algorithms widely used in multiphase flow computation, for simulate biofilms growth [67]. When investigating biofilms detachment under fluid flow with FEM, the fluid-structure interactions are of importance [65]. Notably, Feng et al. incorporate the time-discontinuous Galerkin (TDG) method as solution strategies for a multi-dimensional multi-species biofilm growth model [66]. In short, multiphysics-combined XFEM methods accurately describe biofilms' mechanical behavior as a continuum approach to computing

biofilms on the scale of $10^{-3} \sim 10^{-2}$m.

Not as widely adopted as FEM, FVM biofilm modeling begins in 1993 by combining the FVM scheme with tracking of the time evolution of the interface [68]. Followed FVM schemes by Zurek's group employs implicit Eulerian solver attempts to quantify diffusion and biomass fraction into fluid dynamics [69, 70]. Taking advantage of its simpleness, FDM were also widely employed for coupling diffusion, growth, biomass and nutrients concentrations in both 2D and 3D [71, 72, 73, 74, 75, 76]. In fine, continuum models strives to couple biological signature with growth and physics of biofilm models solved by discretizing differential equations, offers good characterizations for the overall biofilm behavior in the scale of $10^{-3} \sim 10^{-1}$m.

5 Summary

Different numerical methods satisfied for different scales are briefly explained and their applications to issues involved in biofilms modeling are reviewed. On the molecular scale, the chemical and biological properties can be decently modeled with MD. In the mesoscale, CGMD and DPD offers also good characterizations of biochemical properties with a larger scale compared with MD; while DEM provides fruitful information ranging from chemical to mechanical, as the most adopted modeling method for biofilm. SPH bottoms up as closer to the continuum regime yet not as wide applied. Continuum modleing methods such as FEM and FDM can also succesfully characterize growth, biomass diffusion, with also mechanical signature, yet hardly gives any chemical information due to the nature of the model. As specifically for the application of ELMs, since we are keenly focused on mechanical aspects with curious on biological mechanism; DEM can be adopted as one of the best tool for: (1) the abundant of existed model; (2) the multiscale nature of the model; (3) it can easily bridged to continuum regime, and offers more multiphysics information compared with continuum

models.

References

[1] J.A. Stotsky. Mathematical and Computational Studies of the Biomechanics of Biofilms. PhD Thesis. University of Colorado. https://scholar.colorado.edu/downloads/4t64gn476

[2] Meller, J. (2001). Molecular Dynamics. In eLS, (Ed.). https://doi.org/10.1038/npg.els.0003048

[3] B. J. Alder, and T. E. Wainwright. Phase Transition for a Hard Sphere System. J. Chem. Phys. 27, 1208 (1957); https://doi.org/10.1063/1.1743957

[4] A. Rahman (1964). "Correlations in the Motion of Atoms in Liquid Argon". Physical Review. 136: A405-A411.

[5] McCammon, J., Gelin, B. & Karplus, M. Dynamics of folded proteins. Nature 267, 585–590 (1977). https://doi.org/10.1038/267585a0

[6] Seviour T, Malde AK, Kjelleberg S, Yuan Z, Mark AE. Molecular dynamics unlocks atomic level self-assembly of the exopolysaccharide matrix of water-treatment granular biofilms. Biomacromolecules. 2012 Jun 11;13(6):1965-72. doi: 10.1021/bm3005808.

[7] Powell, L.C., Pritchard, M.F., Ferguson, E.L. et al. Targeted disruption of the extracellular polymeric network of Pseudomonas aeruginosa biofilms by alginate oligosaccharides. npj Biofilms Microbiomes 4, 13 (2018). https://doi.org/10.1038/s41522-018-0056-3

[8] Chakraborty, A., Kobzev, E., Chan, J., de Zoysa, G. H., Sarojini, V., Piggot, T. J., & Allison, J. R. (2020). Molecular Dynamics Simulation of the Interaction of Two Linear Battacin Analogs with Model Gram-Positive and Gram-Negative Bacterial Cell Membranes. ACS Omega, 6(1), 388–400. https://doi.org/10.1021/acsomega.0c04752.

[9] David Seiferth, Peter Sollich, Stefan Klumpp. Coarse graining of biochemical systems described by discrete stochastic dynamics. Phys. Rev. E 102, 062149. December 2020. https://doi.org/10.1103/PhysRevE.102.062149

[10] Anton Arkhipov, Peter L. Freddolino, Katsumi Imada, Keiichi Namba, Klaus Schulten, Coarse-Grained Molecular Dynamics Simulations of a Rotating Bacterial Flagellum, Biophysical Journal, Volume 91, Issue 12, 2006, Pages 4589-4597, https://doi.org/10.1529/biophysj.106.093443.

[11] Lam T. Nguyen, James C. Gumbart, Morgan Beeby, and Grant J. Jensen. Coarse-grained simulations of bacterial cell wall growth reveal that local coordination alone can be sufficient to maintain rod shape. Proceedings of the National Academy of Sciences Jul 2015, 112 (28) E3689-E3698; DOI: 10.1073/pnas.1504281112.

[12] Huilin Ma, Flaviyan Jerome Irudayanathan, Wenjuan Jiang, and Shikha Nangia. Simulating Gram-Negative Bacterial Outer Membrane: A Coarse Grain Model. J. Phys. Chem. B 2015, 119, 46, 14668–14682.

[13] Brandani, G. B., Schor, M., Morris, R., Stanley-Wall, N., MacPhee, C. E., Marenduzzo, D., & Zachariae, U. (2015). The bacterial hydrophobin BslA is a switchable ellipsoidal Janus nanocolloid. Langmuir, 31(42), 11558- 11563. https://doi.org/10.1021/acs.langmuir.5b02347

[14] Tan, J., Rouse, S. L., Li, D., Pye, V. E., Vogeley, L., Brinth, A. R., El Arnaout, T., Whitney, J. C., Howell, P. L., Sansom, M. S., & Caffrey, M. (2014). A conformational landscape for alginate secretion across the outer membrane of Pseudomonas aeruginosa. Acta crystallographica. Section D, Biological crystallography, 70(Pt 8), 2054–2068. https://doi.org/10.1107/S1399004714001850

[15] Chen, Y., Ren, L., Sun, L. et al. Amphiphilic silver nanoclusters show active nano–bio interaction with compelling antibacterial activity against multidrug-resistant bacteria. NPG Asia Mater 12, 56 (2020). https://doi.org/10.1038/s41427-020-00239-y

[16] Hoogerbrugge, P. J; Koelman, J. M. V. A (1992). "Simulating Microscopic Hydrodynamic Phenomena with Dissipative Particle Dynamics". Europhysics Letters (EPL). 19 (3): 155–160.

[17] Koelman, J. M. V. A; Hoogerbrugge, P. J (1993). "Dynamic Simulations of Hard-Sphere Suspensions Under Steady Shear". Europhysics Letters (EPL). 21 (3): 363–368.

[18] R.D.Groot, K.L.Rabone. Mesoscopic Simulation of Cell Membrane Damage, Morphology Change and Rupture by Nonionic Surfactants. Biophysical Journal. Volume 81, Issue 2, August 2001, Pages 725-736.

[19] Satoru Yamamoto, Yutaka Maruyama, and Shi-aki Hyodo. Dissipative particle dynamics study of spontaneous vesicle formation of amphiphilic molecules. J. Chem. Phys. 116, 5842 (2002); https://doi.org/10.1063/1.1456031

[20] Julian C. Shillcock and Reinhard Lipowsky. Equilibrium structure and lateral stress distribution of amphiphilic bilayers from dissipative particle dynamics simulations. J. Chem. Phys. 117, 5048 (2002); https://doi.org/10.1063/1.1498463

[21] Shillcock, J., Lipowsky, R. Tension-induced fusion of bilayer membranes and vesicles. Nature Mater 4, 225–228 (2005). https://doi.org/10.1038/nmat1333

[22] Zhijie Xu, Paul Meakin, Alexandre Tartakovsky, and Timothy D. Scheibe. Dissipative-particle-dynamics model of biofilm growth. Phys. Rev. E 2011, 83, 066702. https://doi.org/10.1103/PhysRevE.83.066702

[23] Ya Liu and Anna C. Balazs. Modeling Biofilm Formation on Dynamically Reconfigurable Composite Surfaces. Langmuir 2018, 34, 1807−1816. http://dx.doi.org/10.1021/acs.langmuir.7b03765

[24] Jara J, Alarcón F, Monnappa AK, Santos JI, Bianco V, Nie P, Ciamarra MP, Canales Á, Dinis L, López-Montero I, Valeriani C and Orgaz B (2021) Self-Adaptation of Pseudomonas fluorescens Biofilms to Hydrodynamic Stress. Front. Microbiol. 11:588884. https://doi.org/10.3389/fmicb.2020.588884

[25] Da Costa, D., Exbrayat-Héritier, C., Rambaud, B. et al. Surface charge modulation of rifampicin-loaded PLA nanoparticles to improve antibiotic delivery in Staphylococcus aureus biofilms. J Nanobiotechnol 19, 12 (2021). https://doi.org/10.1186/s12951-020-00760-w

[26] Vanessa Ortiz, Steven O. Nielsen, Dennis E. Discher, Michael L. Klein, Reinhard Lipowsky, and Julian Shillcock. Dissipative Particle Dynamics Simulations of Polymersomes. J. Phys. Chem. B 2005, 109, 17708-17714.

[27] Delavar, M.A.; Wang, J. Lattice Boltzmann Method in Modeling Biofilm Formation, Growth and Detachment. Sustainability 2021, 13,7968. https://doi.org/10.3390/su13147968

[28] Frisch, U.; d'Humieres, D.; Hasslacher, B.; Lallemand, P.; Pomeau, Y.; Rivet, J.P. Lattice gas hydrodynamics in two and three dimensions. Complex Syst. 1987, 1, 649–707.

[29] Picioreanu, C.; van Loosdrecht, M.; Heijnen, J. Discrete-Differential modelling of biofilm structure. Water Sci. Technol. 1999, 59, 115–122.

[30] Picioreanu, C.; van Loosdrecht, M.; Heijnen, J. Multidimensional Modeling of Biofilm Structure. In Microbial Biosystems: New Frontiers; Bell, C.R., Brylinsky, M., Johnson-Green, P., Eds.; Atlantic Canada Society for Microbial Ecology: Halifax, NS, Canada, 1999.

[31] Eberl, H.; Picioreanu, C.; van Loosdrecht, M. Modeling geometrical heterogeneity in biofilms. In High Performance Computing Systems and Applications; Pollard, A., Mewhort, D.J.K., Weaver, D.F., Eds.; Springer: Boston, MA, USA, 2002; pp. 497–512.

[32] Knutson, C.; Werth, C.J.; Valocchi, A.J.; Travis, B.J. Modeling biofilm morphology along a transverse mixing zone in porous media at the pore scale. In Developments in Water Science; Miller, C.T., Farthing, M.W., Gray, W.G., Pinder, G.F., Eds.; Elsevier: Amsterdam, The Netherlands, 2004; Volume 55, pp. 61–69.

[33] Knutson, C.E.; Werth, C.J.; Valocchi, A.J. Pore-scale simulation of biomass growth along the transverse mixing zone of a model two-dimensional porous medium. Water Resour. Res. 2005, 41, W07007.

[34] Singh, R.; Paul, D.; Jain, R.K. Biofilms: Implications in bioremediation. Trends Microbiol. 2006, 14, 389–397.

[35] Seo, Y.; Lee, W.H.; Sorial, G.; Bishop, P.L. The application of a mulch biofilm barrier for surfactant enhanced polycyclic aromatic hydrocarbon bioremediation. Environ. Pollut. 2009, 157, 95–101.

[36] Tian, Z, Wang, J. Lattice Boltzmann simulation of biofilm clogging and chemical oxygen demand removal in porous media. AIChE J. 2019; 65:e16661. https://doi.org/10.1002/aic.16661

[37] Hellweger, F., Clegg, R., Clark, J. et al. Advancing microbial sciences by individual-based modelling. Nat Rev Microbiol 14, 461–471 (2016). https://doi.org/10.1038/nrmicro.2016.62

[38] Koshy-Chenthittayil,S.; Archambault, L.; Senthilkumar, D.; Laubenbacher, R.; Mendes, P.; Dongari-Bagtzoglou, A. Agent Based Models of Polymicrobial Biofilms and the Microbiome—A Review. Microorganisms 2021, 9, 417. https://doi.org/10.3390/microorganisms9020417

[39] Acemel, R.D.; Govantes, F.; Cuetos, A. Computer simulation study of early bacterial biofilm development. Sci. Rep. 2018, 8, 1–9.

[40] Bauer, E.; Zimmermann, J.; Baldini, F.; Thiele, I.; Kaleta, C. BacArena: Individual-Based metabolic modeling of heterogeneous microbes in complex communities. PLoS Comput. Biol. 2017, 13, e1005544.

[41] Beroz, F.; Yan, J.; Meir, Y.; Sabass, B.; Stone, H.A.; Bassler, B.L.; Wingreen, N.S. Verticalization of bacterial biofilms. Nat. Phys. 2018, 14, 954–960.

[42] Carvalho, G.; Balestrino, D.; Forestier, C.; Mathias, J.-D. How do environment-dependent switching rates between susceptible and persister cells affect the dynamics of biofilms faced with antibiotics? npj Biofilms Microbiomes 2018, 4, 6.

[43] Das, J.; Mokrzan, E.; Lakhani, V.; Rosas, L.; Jurcisek, J.A.; Ray, W.C.; Bakaletz, L.O. Extracellular DNA and type IV pilus expression regulate the structure and kinetics of biofilm formation by nontypeable haemophilus influenzae. mBio 2017, 8, 1–19.

[44] Gogulancea, V.; González-Cabaleiro, R.; Li, B.; Taniguchi, D.; Jayathilake, P.G.; Chen, J.; Wilkinson, D.; Swailes, D.; McGough, A.S.; Zuliani, P.; et al. Individual based model links thermodynamics, chemical speciation and environmental conditions to microbial growth. Front. Microbiol. 2019, 10, 1–17.

[45] Hartmann, R.; Singh, P.K.; Pearce, P.; Mok, R.; Song, B.; Díaz-Pascual, F.; Dunkel, J.; Drescher, K. Emergence of three-dimensional order and structure in growing biofilms. Nat. Phys. 2019, 15, 251–256.

[46] Head, D.; Devine, D.A.; Marsh, P.D. In silico modelling to differentiate the contribution of sugar frequency versus total amount in driving biofilm dysbiosis in dental caries. Sci. Rep. 2017, 7, 1–10.

[47] Jayathilake, P.G.; Gupta, P.; Li, B.; Madsen, C.; Oyebamiji, O.; González-Cabaleiro, R.; Rushton, S.; Bridgens, B.; Swailes, D.; Allen, B.; et al. A mechanistic Individual-based Model of microbial communities. PLoS ONE 2017, 12, e0181965.

[48] Kragh, K.N.; Hutchison, J.B.; Melaugh, G.; Rodesney, C.; Roberts, A.E.L.; Irie, Y.; Jensen, P.; Diggle, S.P.; Allen, R.J.; Gordon, V.; et al. Role of multicellular aggregates in biofilm formation. mBio 2016, 7, 1–11.

[49] Li, C.; Zhang, Y.; Yehuda, C. Individual based modeling of Pseudomonas aeruginosa biofilm with three detachment mechanisms. RSC Adv. 2015, 5, 79001–79010.

[50] Li, B.; Taniguchi, D.; Gedara, J.P.; Gogulancea, V.; Gonzalez-Cabaleiro, R.; Chen, J.; McGough, A.S.; Ofiteru, I.D.; Curtis, T.P.; Zuliani, P. NuFeb: A massively parallel simulator for individual-based modelling of microbial communities. PLoS Comput. Biol. 2019, 15, e1007125.

[51] Naylor, J.; Fellermann, H.; Ding, Y.; Mohammed, W.K.; Jakubovics, N.S.; Mukherjee, J.; Biggs, C.A.; Wright, P.C.; Krasnogor, N. Simbiotics: A multiscale integrative platform for 3D modeling of bacterial populations. ACS Synth. Biol. 2017, 6, 1194–1210.

[52] Pérez-Rodríguez, G.; Dias, S.; Pérez-Pérez, M.; Fdez-Riverola, F.; Azevedo, N.F.; Lourenço, A. Agent-Based model of diffusion of N-acyl homoserine lactones in a multicellular environment of Pseudomonas aeruginosa and Candida albicans. Biofouling 2018, 34, 335–345.

[53] Rudge, T.J.; Steiner, P.J.; Phillips, A.; Haseloff, J. Computational modeling of synthetic microbial biofilms. ACS Synth. Biol. 2012, 1, 345–352.

[54] Schluter, J.; Nadell, C.D.; Bassler, B.L.; Foster, K.R. Adhesion as a weapon in microbial competition. ISME J. 2015, 9, 139–149.

[55] Sudarsan, R., Ghosh, S., Stockie, J., & Eberl, H. (2016). Simulating Biofilm Deformation and Detachment with the Immersed Boundary Method. Communications in Computational Physics, 19(3), 682-732. https://doi.org/10.4208/cicp.161214.021015a

[56] R.A. Gingold; J.J. Monaghan (1977). "Smoothed particle hydrodynamics: theory and application to non-spherical stars". Mon. Not. R. Astron. Soc. 181 (3): 375–89.

[57] L.B. Lucy (1977). "A numerical approach to the testing of the fission hypothesis". Astron. J. 82: 1013–1024.

[58] Soleimani, M., Wriggers, P., Rath, H. et al. Numerical simulation and experimental validation of biofilm in a multi-physics framework using an SPH based method. Comput Mech 58, 619–633 (2016). https://doi.org/10.1007/s00466-016-1308-9

[59] Avesani, D., Dumbser, M., Chiogna, G. et al. An alternative smooth particle hydrodynamics formulation to simulate chemotaxis in porous media. J. Math. Biol. 74, 1037–1058 (2017). https://doi.org/10.1007/s00285-016-1049-6

[60] Dianlei Feng, Insa Neuweiler, Moubin Liu, Udo Nackenhorst. Numerical modeling of the mechanical response of bacterial biofilm to flow by using an SPH poroviscoelastic model. PAMM·Proc. Appl. Math. Mech.2020; 20:1 e202000214. https://doi.org/10.1002/pamm.202000214

[61] Hrennikoff, Alexander (1941). "Solution of problems of elasticity by the framework method". Journal of Applied Mechanics. 8 (4): 169–175.

[62] Courant, R. (1943). "Variational methods for the solution of problems of equilibrium and vibrations". Bulletin of the American Mathematical Society. 49: 1–23.

[63] Xianlong Zhang, Xiaoling Wang, Qingping Sun. Modeling of Biofilm Growth on Ager Substrate Using the Extended Finite Element Method. Procedia IUTAM. Volume 23, 2017, Pages 33-41. https://doi.org/10.1016/j.piutam.2017.06.003

[64] Bryan Smith, Benjamin Vaughan, David Chopp. The extended finite element method for boundary layer problems in biofilm growth. Commun. Appl. Math. Comput. Sci. 2(1): 35-56 (2007). DOI: 10.2140/camcos.2007.2.35

[65] Böl M, Möhle RB, Haesner M, Neu TR, Horn H, Krull R. 3D finite element model of biofilm detachment using real biofilm structures from CLSM data. Biotechnol Bioeng. 2009 May 1;103(1):177-86. doi: 10.1002/bit.22235.

[66] Feng, D., Neuweiler, I. & Nackenhorst, U. A spatially stabilized TDG based finite element framework for modeling biofilm growth with a multi-dimensional multi-species continuum biofilm model. Comput Mech 59, 1049–1070 (2017). https://doi.org/10.1007/s00466-017-1388-1

[67] Ravindra Duddu, Stéphane Bordas, David Chopp, Brian Moran. A combined extended finite element and level set method for biofilm growth. Int. J. Numer. Meth. Engng 2008; 74:848–870. https://doi.org/10.1002/nme.2200

[68] Sandor Szego, Pasquale Cinnella, and A1 B. Cunningham. On Finite-Volume Techniques for Unsteady, Multi-Phase, Reactive Flows: Biofilms in Closed Conduits. 11th Computational Fluid Dynamics Conference. 1993. https://doi.org/10.2514/6.1993-3326

[69] Esther S Daus, Ansgar Jüngel, Antoine Zurek, Convergence of a finite-volume scheme for a degenerate-singular cross-diffusion system for biofilms, IMA Journal of Numerical Analysis, Volume 41, Issue 2, April 2021, Pages 935–973, https://doi.org/10.1093/imanum/draa040

[70] Christoph Helmer, Ansgar Jüngel, Antoine Zurek. Analysis of a finite-volume scheme for a single-species biofilm model. arXiv preprint. arXiv:2110.14933

[71] Eberl, Hermann & Laurent, Demaret. (2007). A finite difference scheme for a degenerated diffusion equation arising in microbial ecology. Electronic Journal of Differential Equations. CS15.

[72] J.E. Macías-Díaz. A positive finite-difference model in the computational simulation of complex biological film models. Journal of Difference Equations and Applications. Volume 20, 2014 - Issue 4. https://doi.org/10.1080/10236198.2013.863284

[73] G. F. Sun, G. R. Liu, and M. Li. An Efficient Explicit Finite-Difference Scheme for Simulating Coupled Biomass Growth on Nutritive Substrates. Mathematical Problems in EngineeringVolume 2015, Article ID 708497, 17 pages. http://dx.doi.org/10.1155/2015/708497

[74] Eva Balsa-Canto, Alejandro López-Núñez, Carlos Vázquez. Numerical methods for a nonlinear reaction–diffusion system modelling a batch culture of biofilm. Applied Mathematical Modelling. Volume 41, January 2017, Pages 164-179.

[75] Eva Balsa-Canto, Alejandro López-Núñez, Carlos Vázquez. A two-dimensional multi-species model for different Listeria monocytogenes biofilm structures and its numerical simulation. Applied Mathematics and Computation. Volume 384, 1 November 2020, 125383.

[76] Tijani, Y.O.; Appadu, A.R.; Aderogba, A.A. Some Finite Difference Methods to Model Biofilm Growth and Decay: Classical and Non-Standard. Computation 2021, 9, 123. https://doi.org/10.3390/computation9110123