

# Modeling microbial growth and dynamics

Daniel S. Esser<sup>1</sup>  · Johan H. J. Leveau<sup>2</sup> · Katrin M. Meyer<sup>1</sup>

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**Abstract** Modeling has become an important tool for widening our understanding of microbial growth in the context of applied microbiology and related to such processes as safe food production, wastewater treatment, bioremediation, or microbe-mediated mining. Various modeling techniques, such as primary, secondary and tertiary mathematical models, phenomenological models, mechanistic or kinetic models, reactive transport models, Bayesian network models, artificial neural networks, as well as agent-, individual-, and particle-based models have been applied to model microbial growth and activity in many applied fields. In this mini-review, we summarize the basic concepts of these models using examples and applications from food safety and wastewater treatment systems. We further review recent developments in other applied fields focusing on models that explicitly include spatial relationships. Using these examples, we point out the conceptual similarities across fields of application and encourage the combined use of different modeling techniques in hybrid models as well as their cross-disciplinary exchange. For instance, pattern-oriented modeling has its origin in ecology but may be employed to parameterize microbial growth models when experimental data are scarce. Models could also be used as virtual laboratories to optimize experimental design analogous to the virtual ecologist approach. Future microbial growth models will likely become more complex to benefit from the rich toolbox that is now available to microbial growth modelers.

**Keywords** Model · Bacteria · Predictive microbiology · Wastewater · Food safety

## Introduction

Microbial growth is a fundamental process in microbiology. Describing, understanding, and predicting microbial growth is important for a large and widely variable number of applications. Microbial growth can be quantified at the level of the individual cell, e.g., for bacteria as the time between two consecutive doublings (Stewart et al. 2005) or with the help of bioreporters such as CUSPER (Remus-Emsermann and Leveau 2010). At the population and community level, microbial growth is measured as the change in population or community size over time, measured directly as individual cells under the microscope or in a flow cytometer, or indirectly by counting colony-forming units or rRNA gene copies, via optical densities (e.g., OD600), enzymatic activity, or the amount of a specific cell component, such as ergosterol for fungi. We will, however, focus on bacteria in this review, in line with the bacterial bias in the literature on microbial growth modeling. The typical growth curve for bacteria, at least in batch culture, consists of an initial lag phase with undetectable growth followed by a phase of exponential growth which is succeeded by a stationary phase and a mortality phase (Peleg and Corradini 2011). Different application areas have emphasized different microbial growth phases. For instance, food safety research has often focused on the factors governing the growth/no growth interface between lag phase and exponential growth phase. In contrast, and being an open system, modeling of microbial growth in wastewater systems is more focused at the stationary and mortality phase.

Modeling has become an established tool to describe microbial growth and evaluate the factors influencing it

✉ Daniel S. Esser  
desser@uni-goettingen.de

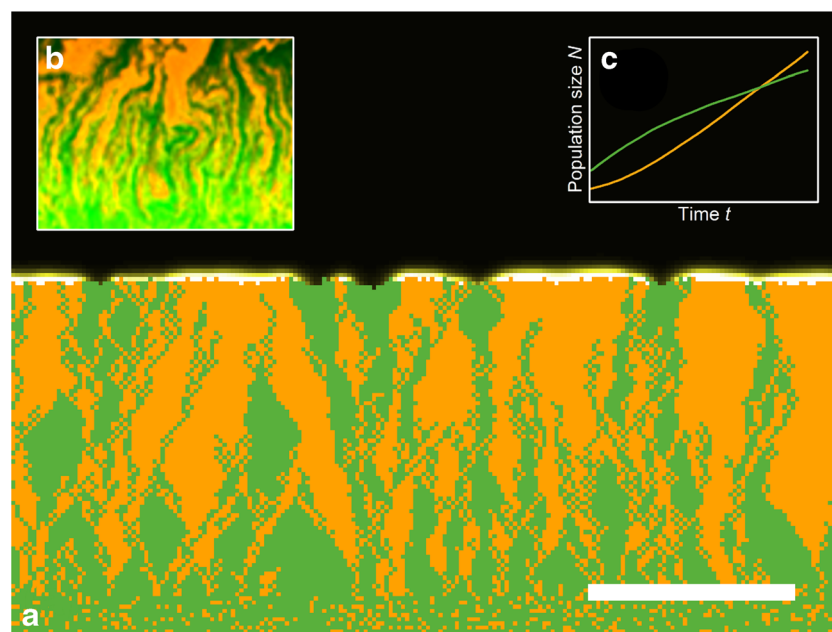
<sup>1</sup> Department of Ecosystem Modelling, University of Göttingen, Büsgenweg 4, 37077 Göttingen, Germany

<sup>2</sup> Department of Plant Pathology, University of California, Davis, CA 95616-8751, USA

(reviewed in, e.g., McMeekin et al. 2002; McKellar and Lu 2004; Li et al. 2007; Peleg and Corradini 2011). A wide variety of microbial growth models are available. In general, a scientific model is a purposeful, simplified representation of reality. Typical purposes of models in applied microbiology are to describe, explain, and predict microbial growth, spread, or activity in foods, fermentation processes, wastewater, bioremediation, bioleaching, epidemics, and other applications. Models can be conceptual (Meyer and Leveau 2012), mathematical or equation-based, rule-based, agent-based, or involve artificial neural networks (Jeyamkondan et al. 2001; Huang et al. 2007), to name only a few modeling approaches. More complex models include microbial growth as only one component among many others. Mathematical models can be purely phenomenological or more mechanistic with more informative parameters. Agent-based models encompass individual- and particle-based models and are mechanistic by definition (Grimm et al. 2005). In individual-based models (Fig. 1), agents are individual cells, whereas in particle-based models (Figs. 2 and 3), they are aggregates of individual cells. Compared to mathematical models, agent-based models usually contain more parameters, so that mathematical models are therefore often perceived to be more general (but see Evans et al. 2013). Microbial growth models can focus on one species, multiple species, or functional groups such as methanogens or phosphorous-accumulating organisms (Batstone et al. 2006). At each of these levels, models may focus on one or more different organizational scales such as

the individual cell in individual-based models (Kreft et al. 2001; Kreft et al. 2013) or particle-based models (Picioreanu et al. 2004), the population level, or greater degrees of aggregation. Model complexity can further range from including one factor such as simple substrate dependency to more bio-physicochemical processes, environmental conditions, and even biotic interactions. Most modeling approaches can be designed to include an explicit spatial component (e.g., Gatto et al. 2013; Surasani et al. 2013), but most established microbial growth models include space only implicitly if at all. The level of validation against real observations also differs depending on the available data—in the worst case, only theoretical data and qualitative expert knowledge are available, whereas sometimes regressions between modeled and observed data are possible. Ideally, the data for comparison consists of direct measurements, as it is the case in some kinetic modeling studies (e.g. Fan et al. 2012; Insel et al. 2012).

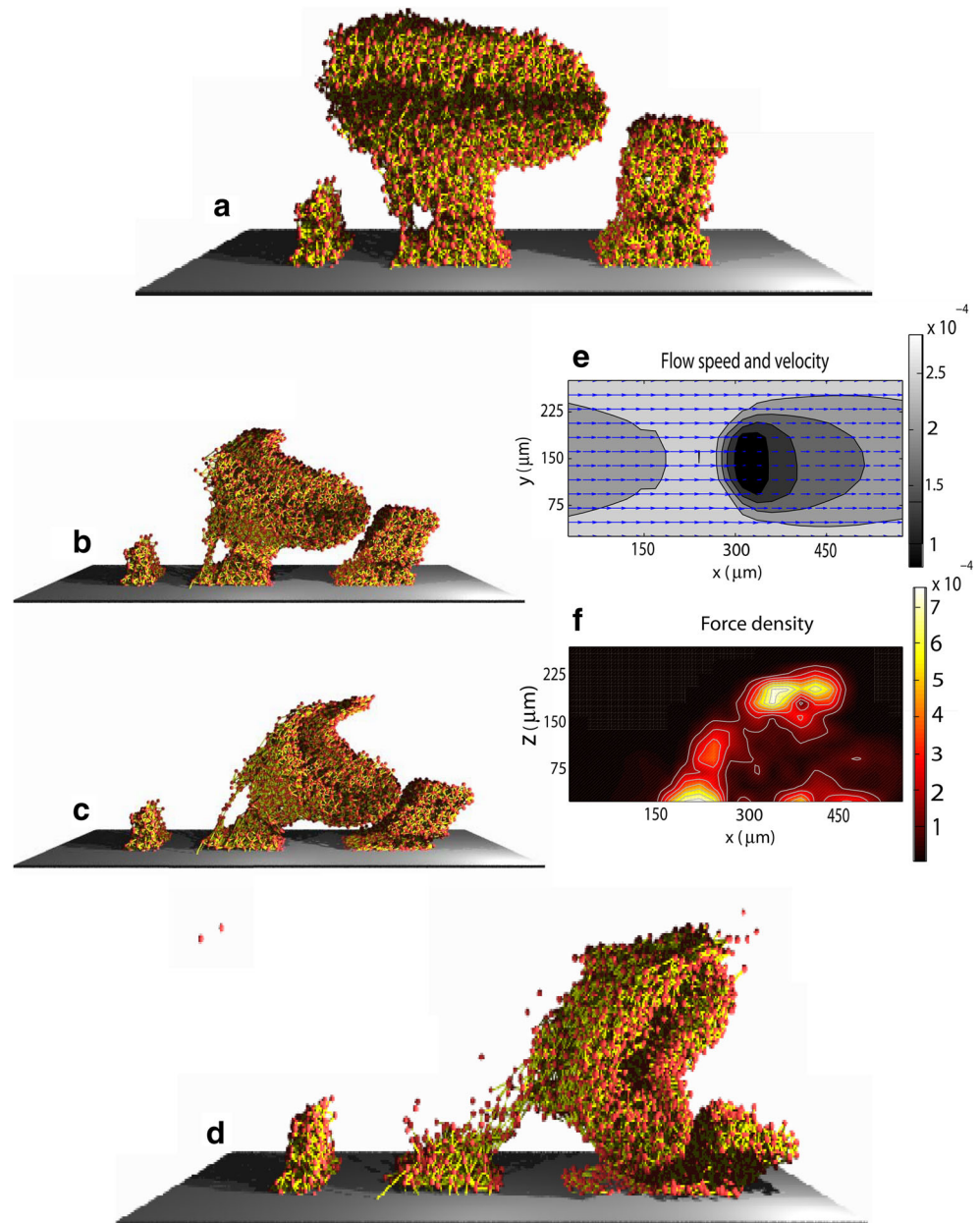
In this paper, we review models of microbial growth using examples from research in food safety and wastewater treatment which represent two major areas in applied microbiology. We point out recent advances beyond purely mathematical models and highlight the merits of spatial modeling approaches in this context and in other application areas such as bioremediation and bioclogging. Our focus is on the merits and caveats of the different approaches for applied microbiology rather than on mathematical details and formulae. Finally, we suggest to expand the toolkit of microbiological growth



**Fig. 1** Modeling the growth of bacterial cheaters (green) and cooperators (red) on an Agar surface. **a** Output of an agent-based model implemented in NetLogo showing the growth pattern of cheaters and cooperators near the margin of a circular colony. The yellow shading near the growth front represents the concentration of nutrients mobilized by the cooperators. Scale bar corresponds to approximately 250  $\mu\text{m}$ . **b** Micrograph of a

similarly sized region in an experiment with *Pseudomonas fluorescens* CHA19 (cheaters) and CHA0 (cooperators). **c** Development of population sizes of cheaters (green) and cooperators (red) over time for the model run depicted in **a**. Pictures by Anna Hille and Alexandre Jousset; simulation model by Anna Hille and Katrin Meyer

**Fig. 2** The model by Alpkvist and Klapper (2007a) illustrates the dynamic capabilities of particle-based modeling. Bulk medium flows across a biofilm which was modeled as a network of springs and bacterial particles. **a–d** The mushroom-shaped biofilm is deformed and finally sloughed by the shearing forces of the surrounding bulk fluid. Local changes in the flow speed around the biofilm **e** determine the shear forces **f** projected at the individual particles in the biofilm. Reproduced from Alpkvist and Klapper (2007a) with permission from the copyright holders, IWA Publishing



modeling by learning from other fields such as ecology and engineering by adopting new modeling approaches.

### Microbial growth models in food safety research

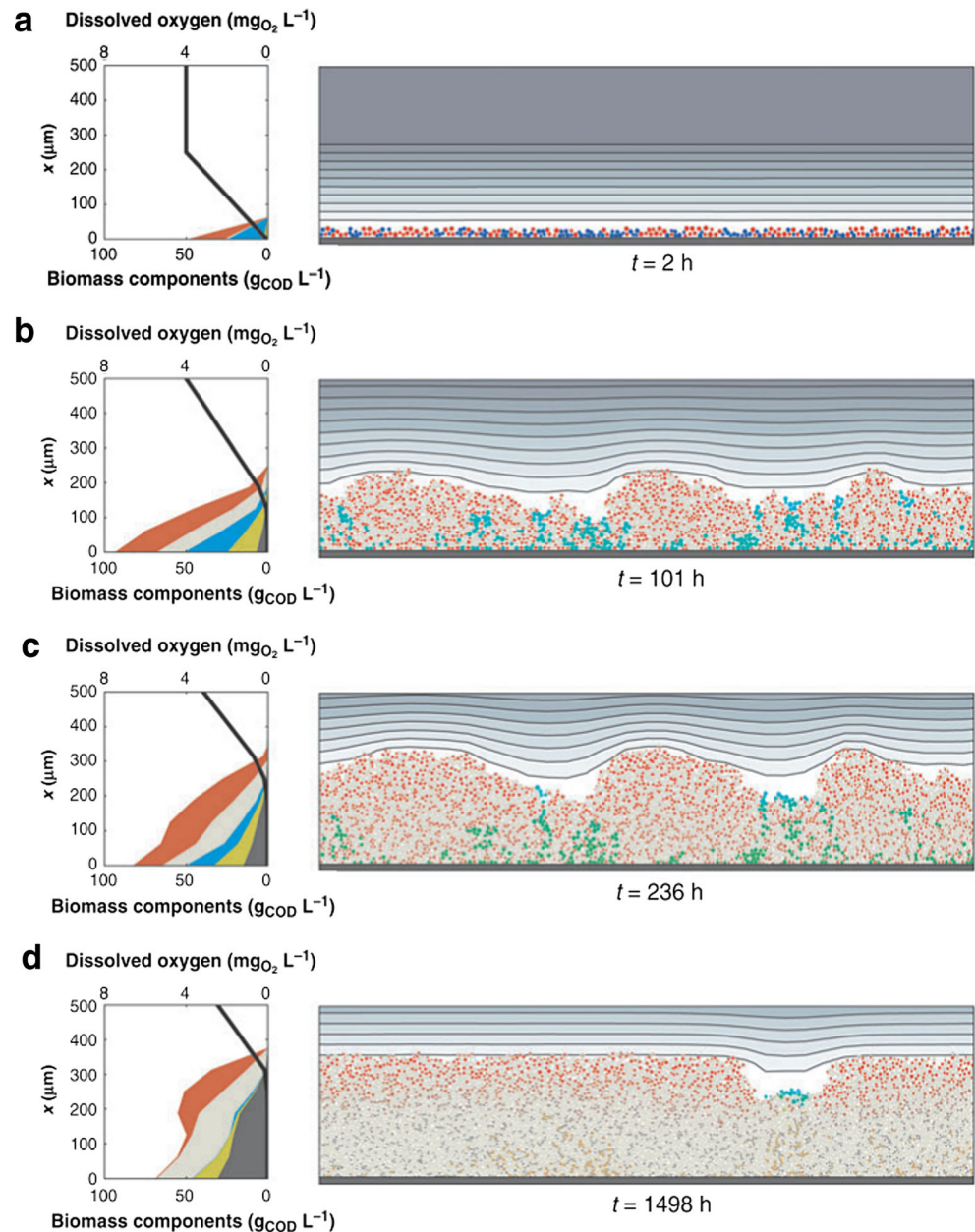
Many of the great advances in microbial model development and in the field of predictive microbiology have had their origins in food safety research (McMeekin et al. 2002; Pérez-Rodríguez and Valero 2013). Mathematical models of microbial growth are the most widely used approaches in food safety research, but alternatives such as Bayesian networks, Monte Carlo simulation modeling, agent- and individual-

based modeling, artificial neural networks, and physical process models also are becoming more popular, mainly for risk assessment studies.

Mathematical models in food safety research have been reviewed comprehensively (e.g., Li et al. 2007; Peleg and Corradini 2011; Pérez-Rodríguez and Valero 2013), so only a brief overview of the most prominent ones will suffice for this review to leave us more space to focus on more recent developments. Mathematical models can be judged with respect to different criteria: The number of parameters should be as low as possible, because this means greater parsimony and thus greater explanatory power; the more intuitive and meaningful the parameters of a model are, the more mechanistic is the model and the greater is its explanatory power; the more



**Fig. 3** The particle-based modeling approach by Xavier et al. (2005) illustrates the development of stratified surface-attached biofilms under continuous feeding conditions. Colors indicate extracellular polymeric substances (EPS, gray), EPS-producing biomass (red), and polyhydroxybutyrate-accumulating biomass in blue (depleted of PHB), yellow (PHB-enriched), and green (intermediate state). *Left column:* distribution of the components along biofilm depth. *Right column:* spatially explicit model. The spatial composition of the biofilm changes from random clusters at time  $t = 2$  h to a stratified biofilm at  $t = 1498$  h. The shading and isoclines above the biofilm represent oxygen concentrations. Reproduced from Xavier et al. (2005) with permission from the copyright holders, John Wiley and Sons



phases of microbial growth are covered, the more accurate is the model. Furthermore, mathematical models have broadly been categorized into primary, secondary, and tertiary models (Peleg and Corradini 2011).

Primary models typically try to fit isothermal growth (i.e., growth as a function of time at a constant temperature) or survival curves (i.e., the number of survivors over time, e.g., after a heat treatment). Primary models may be empirical or phenomenological, or describe inactivation or survival, or they may be rate growth models. Sometimes they are a combination of one or more of these. Commonly used empirical models are the Gompertz model (Gibson et al. 1994; McKellar and Lu 2004), the logistic model (Zwietering et al. 1990), and the three-phase linearized growth or Buchanan model

(Ingraham et al. 1983; Buchanan et al. 1997). These models and their modifications (e.g., Bhaduri et al. 1991; Peleg and Corradini 2011) have a small number of mostly intuitive parameters (three to four), but usually do not cover all phases of microbial growth or do not account for specific properties such as long lag phases. Typical parameters are the relative growth rate, the time to reach maximum growth rate, initial population size, or the asymptotic population size. Inactivation or survival models are designed to model survival over time and are often based on classical primary growth models, for example the modified Gompertz model (Bhaduri et al. 1991). In complex survival models, more than one level of heat resistance is included, e.g., in the Whiting-Buchanan Model (Whiting and Buchanan 1993) and the Xiong et al.

model (Xiong et al. 1999). The Geeraerd et al. model (Geeraerd et al. 2000) produces a better fit than previous survival models, but is limited to scenarios of mild heat treatment. The Weibull model (Li et al. 2007) considers a survival curve as a cumulative temporal distribution of lethality events and has only two parameters. This produces good fits, but the effect of environmental factors such as temperature or pH on model parameters is not always reproduced well. Rate growth models predict, as the name implies, population growth rates rather than population densities, and many of the primary growth models can be converted into rate growth models (Peleg and Corradini 2011). Well-known rate growth models are the Verhulst logistic growth model and its generalizations and modifications (Tsoularis and Wallace 2002; e.g., Peleg and Corradini 2011) and the popular Baranyi-Roberts model (Baranyi and Roberts 1994). Both models have between two and six parameters that are intuitive in the case of the Verhulst model, but less so in the other models.

Secondary mathematical models describe the dependence of microbial growth on external factors such as temperature or pH (Peleg and Corradini 2011). The classical Arrhenius model can only properly be used for microbial growth modeling in a modified form that accounts for optimal growth temperatures (McMeekin 1993). Many of the other secondary mathematical models such as the commonly used Ratkowsky model (the “square-root model,” Ratkowsky et al. 1983) or the Peleg-Corradini-Model (Peleg and Corradini 2011) provide satisfactory descriptions of the dependence of growth on temperature, pH, or other factors but are usually not amenable to mechanistic interpretation. Hence, these models should not be used for explanatory purposes but rather for description and prediction. An interesting dynamic modeling approach based on the Gompertz model includes also the temperature range at which inactivation occurs (Impe et al. 1992). Models based on the gamma hypothesis (Zwietering et al. 1992) describe the simultaneous effect of different factors such as temperature and pH by multiplying these factors, making the usually unrealistic assumption that the factors act independent of one another.

Tertiary mathematical models are software packages that combine a selection of primary and/or secondary models and often add a user interface, thus making them more user-friendly also for novice modelers. One example is the Unified Growth Prediction Model software based on a Baranyi-Roberts primary model and a temperature-dependent secondary model (Psomas et al. 2011). To further aid in the parameterization of such models, Halder et al. (2010) have compiled a database of kinetic parameters for thousands of food-pathogen combinations using first-order inactivation models, first-order growth models, and sigmoidal growth models. According to the authors, this database will enable industry, extension, and academia in food safety to design and explore the outcome of thousands of “what if” scenarios. Various other tertiary modeling packages are available (commented, e.g., in

Carrasco et al. 2012), but their compilation is outside the scope of this mini-review.

Bayesian network models basically combine a set of directed, linked transition probabilities from one stage to another stage into one overall probability. These stages can be stages along a supply chain or any other stages that are linked in one direction. For instance, Bayesian networks have been set up to study *Clostridium perfringens* in beef-in-sauce (Jaloustre et al. 2011) and *Listeria monocytogenes* in cold-smoked salmon (Delignette-Muller et al. 2006) as well as courgette puree (Rigaux Ancelet et al. 2013). Bayesian belief networks have been combined with other approaches such as Monte Carlo simulation modeling (Smid et al. 2010) and have been compared to Markov Chain Monte Carlo (MCMC) models in the context of a quantitative risk assessment study of poultry meat (Parsons et al. 2005). In this comparison, Parsons et al. (2005) found the MCMC approach to be superior to the Bayesian network approach, because the MCMC simulation did not require discretized variables and was more flexible with respect to the type of variables. However, a distinct advantage of Bayesian networks is the lower complexity of implementation—at least compared to MCMC models (Parsons et al. 2005).

Agent- and individual-based modeling can account for properties or interactions at the scale of individual microbial cells (Kreft et al. 2013) and have thus gained importance especially in combinations of foods and microbial species where very few cells are sufficient for unacceptable levels of contamination. These models usually include rules that govern the interactions of the microbial agents with each other and with their environment and thus often have to be coded in a programming language (Grimm et al. 2005). Demographic and environmental stochasticity are easily incorporated in agent-based models but requires them to be run several times to obtain average and variance outputs. Demographic stochasticity is the seemingly random variation in demographic events such as death and reproduction that is entirely due to population-inherent causes such as very small population size. Environmental stochasticity refers to the same phenomenon when it is caused by seemingly random variation around a long-term mean of some environmental parameter such as temperature. The incorporation of stochasticity is the property that agent-based models share with Monte Carlo simulation approaches. However, Monte Carlo simulation approaches do usually not operate at the level of individual cells, but at more aggregated levels. In the example of *Listeria monocytogenes* on soft cheese, an individual-based approach was chosen, because this pathogen contaminates the cheese already at very low cell numbers (Ferrier et al. 2013). This individual-based model was able to account for individual cell lag times and single-cell growth probability (Ferrier et al. 2013). Individual-based models can also be used to study the underlying mechanism of the lag phase of microbial growth (Prats et al. 2006).

In a comparison of an individual-based model and a regression analysis of the time to reach unacceptable levels of growth of *L. monocytogenes*, both approaches yielded reasonable predictions (Munoz et al. 2010).

Artificial neural networks have only recently entered food safety studies. First attempts have been summarized by Jeyamkondan et al. (2001) and by Huang et al. (2007). The great strengths of artificial neural networks are that they can model any relationship between dependent and independent variables (Jeyamkondan et al. 2001) and that a great number of independent variables can be explored simultaneously. The independent variables are called input nodes or “neurons.” An artificial neural network has an input layer with one neuron per independent variable, a hidden layer with one neuron per training pattern, and an output layer with one neuron per dependent variable. Usually, a genetic algorithm is used to minimize the error of the predicted relationship between inputs and outputs, i.e., between independent and dependent variables. More application examples to microbial growth in food safety have become available recently such as modeling the contamination of barley seeds by the fungus *Fusarium culmorum* (Mateo et al. 2011) or modeling *Escherichia coli* on beef (Gosukonda et al. 2015). Similarly, physical processes are only beginning to be in the focus of food safety models, such as in the computational fluid dynamics model of *Salmonella* on eggs (Kumar et al. 2012) and the three-dimensional-finite element model for simulating heat transfer during cooling of ready-to-eat meat (Cepeda et al. 2013).

### Microbial growth models in wastewater treatment systems

Microbial growth plays a central role in wastewater treatment (WWT) systems. Together with other prokaryotic and eukaryotic organisms, bacteria reduce the content of organic substances such as carbonaceous biological matter, ammonium, or phosphate. These substances are taken up and metabolized by the microbes and can thus be removed from the wastewater, e.g., by sedimentation of microbial flocs. Wastewater treatment systems are thus usually open systems with, heuristically speaking, an influx of fresh wastewater and an efflux of a mixture of bulk fluid and microbial biomass. The microbial community is in part a function of the composition of the available substrate, e.g., sewage (Henze et al. 2000; Makinia 2010) or industrial wastewater (Debik and Coskun 2009; Tekerlekopoulou et al. 2013; Amin et al. 2014), which in turn depends on the composition and activity of the microbial community. Consequently, the management of wastewater treatment processes, such as the activated sludge process (Ardern and Lockett 1914), membrane bioreactors (Brindle and Stephenson 1996), or membrane-aerated biofilm reactors (Casey et al. 1999), is often closely related to the management of

microbial communities and activities by providing optimal growth conditions for a target community. In order to increase efficiency (or reduce the size) of WWT plants, one goal of microbial models is to find strategies of either maximizing biological activity or reducing microbial growth while maintaining optimal microbial activity (metabolism, storage). As a consequence, scientists and water engineers developed a rich body of models including the simulation and prediction of microbial biomass, diversity, and activity, all of which are closely related to microbial growth. Important parameters are the composition and flow rate of the influent wastewater, the average microbial residence time in the reactor, and the availability of oxygen that triggers anaerobic or aerobic processes. The modeling of microbial growth is often realized using differential equations describing microbial growth in well-mixed or homogeneous systems (Andrews 1974; Henze et al. 1987; Tekerlekopoulou et al. 2013). However, microbial growth can also be modeled along a wide range, from implicit in substrate uptake (Batstone et al. 2002) to modeling changes in community structure at the level of individual species or even cells (Lu et al. 2007; Ramirez et al. 2009; Lardon et al. 2011; Storck et al. 2014).

The wastewater treatment models presented in this section are also interesting because they add a physicochemical or engineering perspective to the more classical microbiological and ecological modeling approaches. This physicochemical perspective often facilitates validation of these models by lab-scale reactor experiments. These models have usually exhibited very good agreement with the lab measurements suggesting that microbial growth in wastewater treatment systems is much better understood, not surprisingly, than in less manageable systems.

With few exceptions (e.g., Amin et al. 2014), the bulk of WWT models simulates the microbial growth process by the use of the well-established hyperbolic Monod function  $\mu = \mu_0 \cdot S/(K_S + S)$ , where the microbial growth rate  $\mu$  is modeled as a function of a maximum (biologically limited) growth rate  $\mu_0$ , the substrate concentration  $S$ , and a half-saturation constant  $K_S$  that gives the substrate concentration at which  $\mu$  takes half the value of  $\mu_0$  (Monod 1949). This growth model assumes that microbial growth is modulated and limited by only one specific substrate. This assumption may not always be realistic in a multi-substrate WWT setting. Several models therefore considered microbes processing multiple substrates by formulating Monod kinetics for each substrate. The growth rate in these models is determined by either switching between equations based on assumptions of what substance is locally limiting (Lu et al. 2007) or by summation of the relative contributions to growth from each substance (Clara et al. 2005). The availability of the substrate, and thus microbial growth, may be spatially heterogeneous and be influenced by various factors such as biofilm architecture, competition, and flow dynamics. In addition, the net microbial growth may be influenced by antibiotic interactions,

predation, and biofilm erosion or sloughing. This illustrates that the description or modeling of microbial growth cannot be reduced to the biological process of cell division but rather is the result of a complex network of dependent processes.

Microbial growth in wastewater treatment systems has been modeled by a variety of different modeling techniques such as differential equation-based models, e.g., most kinetic models such as the various activated sludge models (Henze et al. 2000), cellular automata (Picioreanu et al. 1998; Pizarro et al. 2001; Benzhai et al. 2014), or agent- or individual-based models (Batstone et al. 2006; Xavier et al. 2007; Schuler et al. 2011; Storck et al. 2014). Diffusion models and hydrodynamic models have been used to describe environmental processes which also affect microbial growth in the context of biofilm models. Often, more than one of these techniques were joined in elaborate hybrid models (Batstone et al. 2006; Lardon et al. 2011; Taherzadeh et al. 2012; Benzhai et al. 2014). In general, kinetic models, i.e., models that describe mass transport, stoichiometric balances, or energy flows, and agent-based models (including individual-based models) are currently the most widely used approaches in modeling microbial growth in WWT systems and will be reviewed in more detail in the remainder of this section.

### Kinetic models and their adaptations

Kinetic or stoichiometric models track the concentrations of multiple substances or components  $C_i$  over time. At the core of these models are differential equations that express process rates of changes in the concentration of a substance. As an example, consider the introductory model by Henze et al. (1987) where heterotrophic bacteria are growing in an aerobic environment and feed on a soluble substrate  $S$  that provides carbon  $C$  and oxygen  $O$ . The model incorporates growth and decay of microbial biomass  $B$  and, coupled to that, substrate removal and oxygen utilization. The whole model is summarized in a so-called *Peterson matrix* shown in Table 1. The kinetics of single components simply are the sum of the row-wise products

of the factors in the component's column and the process rates column. Thus, the Peterson matrix helps to break down the complex kinetic/mathematical structure of such models into the various components and processes while retaining all the information about their implementation and interactions among each other. The kinetic models reviewed below are usually much more complex by considering more components and processes but are based on the same concept. Differences between the models arise from the components and processes included and in the way that process rates and processes are implemented.

Much work on wastewater treatment modeling has been initiated and performed by the International Water Association (IWA), a non-profit association of professionals researching all aspects of the water cycle. IWA task groups published a series of activated sludge models (ASM1, Henze et al. 1987; ASM2, Gujer et al. 1995; ASM3, Gujer et al. 1999; ASM2d, Henze et al. 1999) which are among the most cited WWT models. ASM1 was the first attempt to provide a streamlined model of nitrogen removal in the activated sludge process. It already incorporated 13 components and 8 processes. ASM2 extended ASM1 by including phosphorus removal. This more complex model incorporated 19 components including various functional groups of biomass (heterotrophs, phosphate-accumulators, autotrophic nitrifiers) and several nitrogen and phosphate compounds ( $\text{NH}_4^+$ ,  $\text{NO}_3^-$ ,  $\text{N}_2$ ,  $\text{PO}_4^{3-}$ , polyphosphate, and ferric phosphate) and 19 processes including the storage and lysis of polyhydroxyalkanoate (PHA) under feast/famine conditions. The ASM2d model is an extension of ASM2 which includes denitrification related to phosphorous-accumulating organisms. At the same time, Gujer et al. (1999) published ASM3 which was based on a completely new platform. The technical differences, advantages, and drawbacks of the three ASM models, two related models (Rieger et al. 2001; Meijer et al. 2004), and two other kinetic models (Barker and Dold 1997; Hu et al. 2007) have been reviewed recently (Hauduc et al. 2013).

One other important model initiated by the IWA is the Anaerobic Digestion Model ADM1 (Batstone et al. 2002). The authors modeled 24 different components in the

**Table 1** Upper half of a Peterson matrix of a simple kinetic model of heterotrophic bacteria growing under aerobic conditions in a carbon substrate (modified after Henze et al. 2000)

		Components			Process rate
		Biomass $B$	Substrate carbon $S_C$	Substrate oxygen $S_O$	
Processes	Growth	1	$-\frac{1}{Y}$	$-\frac{1-Y}{Y}$	$\mu_0 \frac{S_C}{K_C + S_C} B$
	Decay	-1	0	-1	$bB$
Full dynamic		$\frac{dB}{dt} = \mu_0 \frac{S_C}{K_C + S_C} B - bB$	$\frac{dS_C}{dt} = -\frac{1}{Y} \cdot \mu_0 \frac{S_C}{K_C + S_C} B$	$\frac{dS_O}{dt} = -\frac{1-Y}{Y} \cdot \mu_0 \frac{S_C}{K_C + S_C} B - bB$	

The full kinetics of the three components are the sums of the products of the factors in the component's column and the respective processes rates. They are summarized in the last row. Parameters are yield coefficient  $Y$ , maximum biological growth rate  $\mu_0$ , Monod half-saturation constant  $K_C$  and microbial decay constant  $b$



anaerobic digestion process concentrating on the uptake and decay of various groups of organic compounds such as proteins, amino acids, sugars, and fatty acids. Special substances such as butyrate and valerate that are only processed by certain microbial groups and some simple molecules such as methane, carbon dioxide, or molecular hydrogen were also considered explicitly. Interestingly, microbial growth is followed only implicitly within the substrate uptake process in this model. Microbial decay remains in the system in the particulate composites component that then further degrades to simple organic molecules. The simulation of organic compounds that are processed each by a different specialist group such as acetogens or methanogens allows to indirectly track changes in microbial community composition.

Both the ASM models and ADM1 have been further developed, also outside IWA task groups, to include additional functionality. Batstone et al. (2006) hybridized ADM1 with the particle-based biofilm model of Picioreanu et al. (2004) and their results exhibited a complex layered structure of spherical biofilm granules: around an inactive center of decayed cells, intermingled colonies of methanogens, butyrate/valerate oxidizers, and propionate utilizers form finger-like structures that pierce through a surrounding layer of decayed acidogens. The whole structure is finally encapsulated by a thick layer of active acidogens. The ADM1 model was also extended having an arbitrarily chosen number (10) of microbial species per functional group performing the same reactions but with stochastically varying parameters (Ramirez et al. 2009). Insel et al. (2012) used the ASM1/ASM3 architecture for a model of simultaneous growth and storage of polyhydroxybutyrate (PHB) to study the short-term fluctuations in growth and storage kinetics under disturbed feeding conditions in the activated sludge process. Their results suggest that external substrate availability moderates a tradeoff between growth rate and storage capacity. ASM2 has recently been adapted to specifically model enhanced biological phosphorus removal (EBPR, Zhang and Chen 2013). Based on the ASM2d model, Kagawa et al. (2015) developed a multi-scale kinetic model that connects the microbial community modeling within granules with a reactor-scale model. The model displayed the important role of dissolved oxygen for the stability of nutrient removal in aerobic granular sludge systems.

Finally, an IWA task group formulated three benchmark problems (BM1, BM2, BM3) to evaluate the suitability of different approaches of biofilm models (Noguera and Morgenroth 2004) which can also be applied to WWT systems. They evaluated the predictive power of analytical and pseudo-analytical approaches (Sáez and Rittmann 1992) that avoid computationally expensive numerical approaches versus one-dimensional (Wanner and Reichert 1996) and multi-dimensional numerical solutions (Eberl et al. 2000; Pizarro et al. 2001). BM1 (Morgenroth et al. 2004) considered a

biofilm of a single heterotrophic species on a flat surface in a completely mixed bioreactor. It was shown that spatial numeric models could play out their advantages over simpler kinetic models only if a heterogeneous biofilm structure was assumed. BM2 (Eberl et al. 2004) studied the effect of bulk fluid flow over the surface of a biofilm and its effect on mass transfer and substrate utilization in the biofilm. Using an elaborate three-dimensional model as a benchmark and nine levels of simplifications, the authors showed that even one-dimensional models with a pseudo-analytical description were able to predict substrate concentration at the biofilm surface and total mass flux with high precision. They stated that “the best effort/accuracy/reliability trade-off depends largely on the hydrodynamic regime” (Eberl et al. 2004). BM3 took the BM1 into a multi-species/multi-substrate setting (Noguera and Picioreanu 2004; Rittmann et al. 2004). Here, it was shown that computationally inexpensive one-dimensional solutions are a reasonable choice if a differentiation of fast- and slow-growing bacteria is of minor importance. Two- and three-dimensional models are important where more complex biofilm architectures have to be expected. In such biofilms, mass transport and biomass spread within the biofilm may not be sufficiently homogeneous to be modeled in only one spatial dimension.

Outside the spheres of ASM- and ADM1-based models, there remains an extensive body of kinetic models that consider various aspects influencing microbial growth in WWT systems. Brockmann et al. (2013) presented a multi-species kinetic model incorporating biofilm detachment that was used to study the effect of hydraulic retention times (HRT) and bulk fluid species composition on the selection of dominant species in a biofilm. Multi-substrate kinetic models have been developed by (Lu et al. 2007) by switching between different growth rates depending on the locally limiting resource but one may assume that multiple, complementary resources influence the growth rate at the same time (Makinia 2010, p. 134). In their model, Clara et al. (2005) calculated a growth rate as the summation of contributions from different resources. However, even if only one resource is considered, it remains often unclear how it is divided between microbial growth and investment into storage molecules for growth during famine conditions. This trade-off has recently been considered in several models (Fan et al. 2012; Insel et al. 2012; Tamis et al. 2014). The model by Fan et al. (2012) also incorporated specifically the production of soluble microbial products (SMP) which play an important role in wastewater treatment effluent (Barker and Stuckey 1999). Several models considered the effect of protozoan and metazoan predation on microbial biomass in activated sludge (Moussa et al. 2005; Ni et al. 2010; Ni et al. 2011). Heavy metals in the bulk fluid may as well influence the growth rates at least for certain microbial groups. The model by Rial et al. (2011) used a Weibull function to describe the dose-dependent variations



in growth parameters for copper, nickel, and cadmium. The model by Tekerlekopoulou et al. (2013) incorporated an optimum Cr(VI) concentration at which the growth rate of chrome-reducing bacteria is maximized. Similarly, substrate inhibition has been modeled in multilayered biofilms in bioreactors (Soda et al. 1999).

Clearly, kinetic models have greatly contributed to our understanding of WWT systems and have been successfully implemented as tools in WWT control processes. The success of these models is partly due to the fact that they can be parameterized using kinetic rates obtained from lab experiments. With the advent of membrane/filter technology in WWT plants, the assumption of a well-mixed system, however, might be no longer valid because active biofilms colonize the filter systems. Thus, kinetic models of such WWT systems may require a coupling to other modeling techniques, such as spatially explicit agent-based models, to account for spatial heterogeneity and intraspecific individuality.

### Agent-based models (ABMs) and adaptations

Agent-based models are quickly gaining popularity among WWT models of microbial growth. We already discussed briefly the hybrid model by Batstone et al. (2006) who implemented the IWA Anaerobic Digestion Model no. 1 (ADM1) into the spatial, particle-based biofilm model by Picioreanu et al. (2004). The hybrid model highlights three important points about the use of agent-based models in WWT systems: (1) biofilms are the typical target level of agent-based models, (2) it is challenging to scale up agent-based modeling results to full-scale WWT systems, and (3) spatial models make important contributions to our understanding of WWT processes.

Two advantages of agent-based models are that spatial heterogeneity in communities of individuals can be taken into account as can inter-individual plasticity down to individual life histories. Within WWT systems, these individual characteristics may be as different as individual growth rates, taxonomic or functional affiliation, or residence times in a bioreactor. Spatial heterogeneity of environmental factors drives intra- and interspecific variability. In their model, Batstone et al. (2006) demonstrated how the co-location of syntrophic bacteria shape microbial community structures on a functional group level. Agent-based models, especially when combined with hydrodynamic models of the surrounding bulk liquid, also can help to better understand physical properties of biofilms and their effect on substrate availability in biofilms and consequently on microbial growth. Alpkvist and colleagues presented particle-based biofilm models that implemented the extracellular matrix either as a continuous incompressible viscous fluid (Alpkvist et al. 2006) or as microbial particles being connected by a network of springs (Alpkvist and Klapper 2007a, Fig. 2) that respond to the shear forces

imposed by the bulk fluid flowing across the biofilm (the so-called immersed boundary (IB) method; Peskin 2002). Especially this last issue of biofilm sloughing by fluid shear stress has recently been studied intensively in several simulation models (Duddu et al. 2009; So et al. 2015; Sudarsan et al. 2015). Most of the above models (Picioreanu et al. 2004; Alpkvist et al. 2006; Batstone et al. 2006; Alpkvist and Klapper 2007a; So et al. 2015; Sudarsan et al. 2015) share the approach that the agents are particles of microbial biomass and appropriate size such that it can be assumed that groups of particles follow, in average, the same rules. Some models have already been adapted to incorporate additional functionality such as tracking oxygen profiles within biofilms in membrane-aerated biofilm (MAB) reactors (Matsumoto et al. 2007) or predicting the spatial community structure in nitrifying granules (Matsumoto et al. 2010). Several models suggested that spherical flocs that are ubiquitous in the activated sludge process, exhibit a complex layered structured with microbial communities near the floc surface differing from the communities near the core (Picioreanu et al. 2005; Batstone et al. 2006; Xavier et al. 2007; Matsumoto et al. 2010). Similar layering is also characteristic for surface-attached biofilms as has also been modeled using agent-based models, e.g., by Xavier et al. (Xavier et al. 2005, Fig. 3).

Another common approach is the simulation of bacterial cells in individual-based models to study the individual properties and location in surface-attached and free floating biofilms in WWT systems. Individual cell shape, cell division, and motility have been used in several models to study cluster formation (Chen et al. 2014), complex filamentous floc formation (Storck et al. 2014) and fractal patterning of cell layers (Rudge et al. 2013), or the formation of mushroom-like biofilm colonies (Picioreanu et al. 2007). The first individual-based model of a biofilm, BacSim, was developed by Kreft et al. (1998, 2001). The model produced finger-like structures in flat surface-attached biofilms similar to the ones simulated by Dockery and Klapper (2001) using a continuous pressure field model to simulate microbial growth. The BacSim model quickly evolved towards including production of extracellular polymeric substances (EPS) that are an important component of the biofilm matrix (Kreft and Wimpenny 2001). This latter model showed the substantial impact of EPS production on biofilm structure and ever since there has been a series of increasingly elaborate biofilm/EPS models, mostly targeted at the role of detachment of single cells (erosion) and larger particles (sloughing) from the biofilm (Picioreanu et al. 2001; Xavier et al. 2005; Alpkvist et al. 2006; Alpkvist and Klapper 2007a; Horn and Lackner 2014). Horn and Lackner (2014) argue that although the development of more complex multi-dimensional or multi-physics models improve our understanding of biofilm processes, the entirety of a full-scale biofilm reactor will remain difficult to capture in one model. Consequently, agent-based modeling offers insights into local

processes in WWT systems but can only be one component in full-scale activated sludge or batch reactor models. Xavier et al. (2007) presented a promising modeling framework that combined kinetic, individual-based, and particle-based models for multi-scale modeling of a lab-scale aerobic granular sludge reactor that simulates individual growth and granular flock development as well as reactor dynamics. The authors acknowledge the still limited applicability in process control due to computational costs, but even today, such models have great potential as a research tool for studying microbial growth and activity in wastewater treatment.

### Spatial models of microbial growth in other fields of basic and applied microbiology

Spatial patterns and processes are implicitly considered in many of the modeling approaches presented in the previous sections on food safety and wastewater treatment. In this section, we review spatially explicit modeling approaches, irrespective of the field of application, to emphasize the similarities in modeling methodology and to encourage cross-disciplinary exchange.

Multiple fields of applied microbiology have become very active areas of microbial growth modeling. A major challenge in modeling (or generally studying) microbial processes is the complexity of their spatial structure. In soils, for example, the network of heterogeneously sized pore spaces constructs a complex structure of habitat surfaces and volumes that is difficult to measure and sample and, at the scale of the individual microbe, is outside our typically Cartesian conception of space. Distances in this complex environments are not necessarily linear but, depending on the process at focus, need to be measured along the convex and concave surfaces of the soil/pore space interface or the shortest path through the three-dimensional pore space network. As a consequence, parameters such as porosity, permeability, and the surface-to-volume ratio are important to predict transport and microbial activity in these environments. The importance of considering geophysical and geochemical dynamics when modeling substrate-limited microbial growth at pore scale has been recently shown in a numerical study by Gharasoo et al. (2015). Centler et al. (2011) and Gharasoo et al. (2014) both presented models of chemotactic bacteria in homogeneous porous media. They showed that chemotaxis can lead to local aggregation of cells which may cause a decrease in degradation efficiency, e.g., of soil contaminants in bioremediation. Interesting about the model by Centler et al. (2011) is that the bacterial growth is not modeled using substrate-dependent Monod kinetics but combining a linearly substrate-dependent growth rate with a logistic restriction term that represents the space limitations set by the pore space. Similarly, but in a very different context, Cogan et al. (2013) utilized spatial constraints

in a multiphase xylem model to limit the growth in different fluid phases (free bacteria, bacteria in biofilm, extracellular polymeric substances (EPS), and sap) in a system where bacterial EPS production disrupts water transport from the plant root and causes symptoms of leaf wilting. This system again shares conceptual similarities with bioclogging, a process of enhancing growth of EPS-producing bacteria in soil targeted at reducing soil permeability in order to redirect water flow around contaminated sites or for enhanced oil recovery (Bozorg et al. 2011; Surasani et al. 2013; Rosenzweig et al. 2014). Bacteria are also used to enhance recovery of other natural resources such as in copper bioleaching, where specialized copper-oxidizing species such as *Acidithiobacillus ferrooxidans* mobilize copper ions into a recoverable solute. This process is usually inhibited by the formation of an impervious layer on the mineral surface. A spatially explicit agent-based model by Olivera-Nappa et al. (2010) illustrated how the growth of *A. ferrooxidans* leads to the formation of microbial *mining pits* that penetrate this passivation layer and thus increase copper mobilization.

Other spatial soil or pore space models were directed at studying basic processes in microbial ecology (Dechesne et al. 2010; Gharasoo et al. 2012; Resat et al. 2012; Wang and Or 2013; Wang and Or 2014). These models gave important insights into the microbial life in soils, for example showing how multiple strategies of resource utilization may reduce stochasticity in biofilm dynamics (Resat et al. 2012), or how spatial segregation of cells is achieved either by temporal habitat fragmentation by varying hydration conditions (Wang and Or 2013) or simply by limits in chemotaxis that define a trophic interaction distance (Wang and Or 2014). Models from spatial statistics have been used to reveal such interaction distances between bacteria on the leaf surface and between bacteria and leaf surface structures (Esser et al. 2015). Reactive transport models in ground water have been coupled with constraint-based genome-scale models which makes microbial reaction rates and growth more flexible and reduces the need for their empirical calibration (Scheibe et al. 2009; Fang et al. 2011). Even more, constraint-based models coupled to individual-based models can be used to perform in silico gene deletion screenings including their effect on microbial growth (Biggs and Papin 2013).

Spatial modeling of microbial growth and proliferation has also become an important tool in understanding host-pathogen systems. Wave-like chlamydial infections have been modeled with an ordinary differential equation model where the infection waves move along a vaginal genital tract where microbial growth is mediated by the lysis of infected host cells (Mallet et al. 2013). Merkey et al. (2011) applied the individual-based model iDynoMiCS (Lardon et al. 2011) to study growth-dependent horizontal gene transfer and showed how the spread of plasmids within biofilms is limited if the exchange of genetic information depends on the growth of individual

cells. These findings have important implications for example for the spread of resistance to antibiotics within hosts or within the environment. On this topic, Zhang et al. (2013) recently proposed a differential equation-based framework for the prediction of spatial and temporal patterns of gene expression in biofilms. The model incorporated many processes other than gene transfer, including microbial growth and biomass advection, substrate diffusion, mRNA and protein synthesis, and protein turnover.

On larger spatial scales, e.g., on a landscape scale, microbial growth is tightly correlated to microbial dispersal. With respect to pathogens, growth then depends on the probability to reach a host at which population growth can continue. This has been modeled, for example, by Hancock and Godfray (Hancock and Godfray 2012) in a one-dimensional cellular automaton model that observed the spread of the bacterial endosymbionts of genus *Wolbachia* within insect populations. Some insects require a *Wolbachia* infection for reproduction. Understanding these complex mutualistic interactions may facilitate establishing *Wolbachia* as a control agent against insect vectors of human diseases. A spatially more complex model has been presented to simulate infection rates of water-borne pathogens dependent on (human) host mobility (Gatto et al. 2013). In this model, pathogen transport by water flow is considered and infections are modeled by ordinary differential equations along a river network.

Clearly, spatially explicit models of microbial growth have proven their potential in advancing knowledge about microbes in technical processes such as safe food production, wastewater treatment, or the management of sub-surface microbial systems, as well as in health management. Many other models are directed at general ecological processes in basic microbiology without being tailored to specific technological applications. A transfer of their insights to applied technologies, however, can be anticipated. For example, various recent studies have targeted the question if and how the spatial structure of microbial communities facilitates the evolution of cooperative traits and the exclusion of cheaters, i.e., individuals that can grow faster for being relieved from the costs of the cooperation trait (Nadell et al. 2010; Boyle et al. 2012; Van Dyken et al. 2013; Hol et al. 2013; van Gestel et al. 2014). Using different modeling techniques (equation-based (Hol et al. 2013), lattice-based (Van Dyken et al. 2013) or agent-based (Nadell et al. 2010; Boyle et al. 2012; van Gestel et al. 2014, also cf. Fig. 1), these studies showed that even in homogeneous environments, the evolution of cooperative traits is possible as long as some level of segregation of cooperators and cheaters can be maintained. These results have promising implications for the development of synthetic microbial communities. They point towards conditions under which single strains can provide services to the whole synthetic community, e.g., mobilization of nutrients, without being excluded. Finally, Klapper and Szomolay (2011) described

the “exclusion principle” where many one-dimensional biofilm models predict that only bacteria that are able to persist at the base of a biofilm can persist anywhere else in the biofilm. They show that this is true for all models that do not allow a constant back-flow of cells from the biofilm top to the base. Even then, this flow needs to exceed the growth velocity of the biofilm. The authors state that this is an obligate process in these models, but it remained unclear if it is a required process in real biofilms. Their paper can be seen as an example that microbial models can be used to attest the validity of ecological principles, but they do not necessarily prove their existence in nature.

## Conclusions

Clearly, scientists and engineers concerned with microbial growth can already rely on a rich body of published literature and models that help to understand and control microbial growth in many applications. The diversity of models originates both from the multitude of applicable modeling techniques as well as the various fields of application and research questions. Although a specific research question usually will require a specialized model or set of models that account for all its relevant processes and conditions, there exist overarching themes in modeling methodology. Kinetic models target process rates in well-mixed, or genuinely homogeneous environments, whereas individual-based and spatially explicit models reveal the effect of individual or spatial heterogeneity. Bayesian network models can incorporate and link any data that are in the form of discrete probability distributions. Artificial neural network models can capture any relationship between sets of dependent and independent variables. Particle-based models can be used to transfer individual-based modeling results to larger spatial scales, if a local-scale homogeneity has been found, or at least can be assumed. Constraint-based models emerge as a standard tool for including genetic diversity, whereas reactive transport models or multiphase models have been used to model substrate availability and environmental factors such as shearing forces of surrounding viscous media. These different techniques have been used in applied microbiological fields to varying extent, and thus we see great potential for cross-disciplinary exchange that may facilitate modeling of complex systems at a production scale.

Key to such efforts would be the synthesis of different modeling techniques to produce robust multi-scale hybrid models. In our mini-review, we have presented various examples where different model types have been combined to form such elaborate hybrid models (e.g., Picioreanu et al. 2005; Xavier et al. 2007; Rudge et al. 2012; Clark et al. 2013). Especially the combination of agent-based models with kinetic models (e.g., Lardon et al. 2011) or genome-scale constraint-based models (e.g., Biggs and Papin 2013) promise

great advances in modeling microbial growth for various applications not only at the scale of the individual cell but also at larger scales (Picioreanu et al. 2004; Xavier et al. 2007). Differential equation-based continuum biofilm models that represent microbial biomass as viscous fluids (Dockery and Klapper 2001; Cogan and Keener 2004; Alpkvist and Klapper 2007b) are well suited for simulating biofilms at larger scales at which agent-based methods are computationally constrained. Such continuum-based models however have limited ability to capture individual multi-species interactions and individual life histories (but see Ayati and Klapper (2007) for a physiologically structured population) and so they would probably benefit from including an agent-based model component. The modeling approach of Xavier et al. (2007), despite its high computational demands, also promises great potential for multi-scale models even outside the field of wastewater treatment. As a consequence of such multi-scale hybrid models, the modeling of microbial growth might evermore convert into the modeling of microbial activity and diversity. Nevertheless, we expect the modeling of microbial growth to develop further as new modeling techniques developed in other fields of general ecology and biology are implemented in the microbiological context. For instance, pattern-oriented modeling has been used in ecological case studies where parameterization became challenging due to lack of concrete experimental data (Grimm et al. 2005). Here, pattern-oriented modeling draws on broad patterns for inverse parameterization. This approach is beneficial when data on broad patterns such as spatial growth patterns are more readily available than direct parameter values. Another example is the implementation of virtual laboratories analogous to the virtual ecologist approach (Zurell et al. 2010). Agent-based models are highly suitable for this purpose. In a virtual laboratory, complex experiments can be simulated that would not or only partly be possible in reality (Meyer et al. 2009), similar to the in silico gene deletion screenings by Biggs and Papin (2013). Simulations in a virtual laboratory can also guide the design of real laboratory experiments, e.g., with respect to sampling schemes and sample sizes. Moreover, qualitative expert knowledge could more often complement “hard” quantitative data during the construction and parameterization of microbial growth models. Mathematical models accommodate qualitative data only with difficulty (if at all), but the more recent agent- and rule-based approaches as well as Bayesian network techniques are well equipped to capture qualitative expert knowledge. We are confident that these new model types and the exploitation of cross-disciplinary synergies will help to advance our understanding of microbial life and function in all fields of applied microbiology in the near future.

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