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PARAMETER IDENTIFICATION AND QUANTITATIVE COMPARISON OF DIFFERENTIAL EQUATIONS THAT DESCRIBE PHYSIOLOGICAL ADAPTATION OF A BACTERIAL POPULATION UNDER IRON LIMITATION

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Abstract. The onset of a typical bacterial growth curve shows a period of very slow increase in population counts. This is a period of physiological adaptation to new environmental conditions. While in mathematical biology much progress was made in recent years to describe physiologically structured populations, these models typically have too many degrees of freedom to easily allow a model identification against experimental data. Therefore, and for all practical purposes, microbiologists have proposed simpler models of physiological adaptation in the past, usually in connection with standard growth curves. In this paper we compare the performance of four such lag-time models, each of which described by a scalar differential equation, when combined with a model of a siderophore producing bacterial population under iron limitation. In each case this yields a system of five nonlinear ordinary differential equations that we compare against experimental data, by solving the associated vector optimization problem. Our main finding is that a big step in accuracy is made already by including a simple lag-time model that only introduces one additional degree of freedom in the parameter identification problem (the initial state of health of the population), and that this can be reliably improved if a further degree of freedom, describing the dynamics of the physiological recovery process, is included. The vector optimization problem is solved by scalarizing it with a linear functional and solving the resulting scalar optimization problem. The growth parameters that are identified in this procedure are found to be robust with respect to the scalarization coefficient.

1. **Introduction.** Differential equations have been used for many decades to describe the growth of bacterial populations. The questions addressed and the mathematical tools used vary strongly with the purpose of a particular modeling study. In classical Mathematical Biology one is usually interested in the longterm behavior of the solutions, in questions of persistence and co-existence vs. extinction, and in qualitative mathematical properties, such as stability. Questions of this type are studied with techniques from Dynamic Systems theory. Engineers, on the other hand are primarily interested in quantitative predictions of complex mixed-culture populations with many different growth limiting substrates, and the design of microbial bioprocesses that are based on these systems, e.g. in wastewater treatment or waste digestion. These models easily become large, consisting of 20 or more dependent variables and an even larger number of model parameters. As these model

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are not easy to study analytically, computer simulations are the primary mathematical technique of choice. In both cases one usually is interested in the long term behavior and does not pay too much attention to the initial transient period of bacterial growth. This is different in several classical but mathematically less studied areas of microbiology, where in particular the onset of a growth curve is of interest.

A typical bacterial growth curve is composed of the following phases [13]: (i) an initial "lag-phase" in which the population does not grow notably or at most very slowly, (ii) the transient (almost exponential) growth phase in which the population develops in almost favorable conditions, (iii) the plateau phase in which population growth slows down due to substrate limitations, and, depending on the system at hand, (iv) a phase of slow decay.

The onset phase (i) is understood to be a consequence of physiological adaptations that the cells have to undergo when placed in a new environment or when the environmental conditions that they are exposed to dramatically and rapidly change. This is the case in most laboratory experiments (bacterial cultures usually are stored in refrigerators before used in the experiments), but also in many real world scenarios in medical biology (growth of a pathogenic population after inoculation or its recovery after exposure to antibiotics), or in food microbiology (food safety, spoilage due to bacterial contamination; shelf life).

Since eventually the population fully recovers and all cells contribute to the growth process, this initial phase indeed and rightfully can often be neglected by modeling studies that aim at a description of the longterm behavior. However, this phase is crucial when mathematical models are to be fitted against transient growth curves or if processes are modeled like the examples given above.

In recent decades much progress has been made in Mathematical Biology in modeling physiological structured and changing populations, most notable in the context of the McKendrick model that leads to a partial differential equation in which a continuous physiological parameter (age, size, "health", cf [10]) takes the role of an independent variable. In these models the physiological adaptation is described by a distributed parameter with too many degrees of freedom to easily be identified from sparse population counts. A less detailed but computationally much more attractive alternative is to develop lumped models that describe the physiological recovery of the population. Models of this type have been proposed in the food microbiology literature in the past [13] and are routinely used by microbiologists to analyze experimental growth curves of bacterial populations under ideal growth conditions that can be described by simple standard growth models such as the Malthusian, logistic, or Gompertz equation.

In [4] we adapted the simplest such lumped physiological adaptation model to describe the lag phase and to fit the parameters of a model that describes the evolution of a population of *Pseudomonas fluorescens* and its production of the fluorescent pigment pyoverdine under iron limitations, using experimental measurements of population count and pyoverdine concentration. In the present study we want to investigate whether the model results can be improved and stabilized by using slightly more complex (one additional degree of freedom) models of physiological adaptation without losing robustness and reliability.

2. Governing equations.

2.1. Mathematical Model.

We assume a population of *Pseudomonas fluorescens* that lives in conditions of food abundance with iron as the only possible growth limiter. If freely dissolved iron in the growth medium becomes limited, the microorganisms start the production of the siderophore pyoverdine, which binds iron that is later internally liberated to the cells. Siderophore-mediated iron uptake plays an important role in bacterial growth. It also has tremendous therapeutic potential because of the abilities of the siderphores to carry drugs into cells [6]. Specific iron-chelating drugs, for instance, can be designed to target iron overload and toxicity, to treat cancer, and to prevent heart and other organ damage caused by iron overload [9, 14]. Another important potential application of siderophores is in the area of food safety and food preservation [7]. In particular, pseudomonads have been used as biocontrol agents against food spoilage due mainly to their ability to produce siderophores with high iron binding constants [2]. This gives a competitive advantage to pseudomonads with respect to iron uptake compared to other bacteria potentially involved in the food spoilage.

The following model for iron chelation was suggested in [4], for the dependent variables population size N, pyoverdine concentration P, dissolved iron S, and chelated iron Q:

$$\frac{dN}{dt} = \mu\alpha(t)N\frac{S}{k+S} + \sigma\alpha(t)NQ, \tag{1}$$

$$\frac{dS}{dt} = -\frac{\mu}{Y}\alpha(t)N\frac{S}{k+S} - \beta SP, \tag{2}$$

$$\frac{dP}{dt} = \delta\alpha(t)\frac{N}{S^\infty+S}\frac{dN}{dt}, \tag{3}$$

$$\frac{dQ}{dt} = \beta SP - \frac{\sigma}{Y}\alpha(t)NQ. \tag{4}$$

Monod kinetics is used for substrate dependent growth, standard inhibition kinetics for the dependency of pyoverdine production on dissolved iron, and first order kinetics for the remaining processes, in order to keep the number of model parameters small. The constants $\mu, k, \sigma, \beta, \delta, S^\infty, Y$ are positive. Hence, pyoverdine production is affected by iron availability in two ways: For large S the inhibition kinetics is rate limiting, while for small S slow biomass production is the limiting factor.

The physiological adaptation function $\alpha(t)$ describes the fraction of the population that is healthy and contributes to bacterial growth. It satisfies for $t > 0$

$$(\mathbf{A}) \qquad 0 \le \alpha(t) \le 1, \quad d\alpha/dt \ge 0. \tag{5}$$

If $\lim_{t\to\infty}\alpha(t) = \alpha^* = 1$ then eventually the entire population becomes healthy and contributes to growth. Three different models of physiological adaptation will be discussed in this paper, cf Section 2.2 below.

The qualitative behavior of the solutions to (1) to (4) is summarized as follows (cf. also [4] where this is formalised): The functions $N(t)$ and $P(t)$ are monotonously increasing, approaching a constant value. On the other hand, $S(t)$ is monotonously decreasing and approaches 0 eventually. The function $Q(t)$ eventually approaches 0 monotonously from above, but usually (depending on initial values) the decay phase is preceded by a monotonously increasing period. The positive limit value for N depends only on the initial data and Y, while the positive limit value for P also depends on reaction parameters.

2.2. **Lag time models.** In the food microbiology literature several differential equations can be found that describe the physiological adaptation phase, i.e. the function $\alpha(t)$, cf. [13]. Although these models are all biologically motivated differently, they show of course similar dynamical behavior, as described by (5). We will compare here three such models and present them in a unifying manner.

In the *Baranyi Model* [1] the physiological state of the population is modeled by a variable Φ. For an entirely healthy population $\Phi = \infty$, while $\Phi = 0$ indicates an irrecoverable population. The state variable Φ evolves like $d\Phi/dt = \nu\Phi$. It can be mapped into the interval $[0, 1]$ by

$$\alpha(t) := \frac{\Phi}{1+\Phi} = \frac{\Phi_0 e^{\nu t}}{1+\Phi_0 e^{\nu t}}. \tag{6}$$

and thus allows for an equivalent formulation as logistic equation [4]

$$\frac{d\alpha}{dt} = \nu\alpha(1-\alpha). \tag{7}$$

Combining this model with (1)-(4) introduces two new parameters: the initial state of the bacterial population, Φ_0 or alternatively α_0, and the dynamic parameter ν that describes how fast the population adapts. Neither parameter can be measured directly in simple routine experiments, and, in general, must be estimated from measurements of population growth.

In [1] it is pointed out that the recovery rate ν often can often be be assumed to be proportional to the maximum specific growth rate of the population, i.e. $\nu \approx \mu$, which means that one of the two new degrees of freedom is fixed a priori. When we make this assumption we will refer to the model as *Baranyi 1* or the *one-parametric Baranyi model*, otherwise as *Baranyi 2* or the *two-parametric Baranyi model*. In [4], Baranyi 1 was used throughout.

In the *Hills and Wright Model* [8] the function $\alpha(t)$ is described by the differential equation

$$\frac{d\alpha}{dt} = (1-\alpha)(k_n + \mu\alpha) \tag{8}$$

where the constant k_n is related to the DNA synthesis rate and μ is the maximum specific growth rate as above. Equation (8) is a reformulation of the model, which was originally presented in terms of the excess biomass per cell s, relative to the minimum amount required for a cell to be viable. This includes amounts of DNA, RNAs, structural components and cytoplasmic mass found in rapidly growing cells, compared to cells in their minimum viable state [13]. Equation (8) is straightforwardly obtained from the original formulation

$$\frac{ds}{dt} = (\mu - k_n s)(1+s)$$

by defining $\alpha := \mu s/k_n$.

In the *McKellar Model* [11], the population at time 0 is subdivided into injured bacteria I which do not contribute to growth, and healthy bacteria $H(t)$, that do contribute to growth. The total population is then $N(t) = I + H(t)$. It is explicitly assumed that initially injured cells remain dormant throughout the duration of the experiment, $dI/dt \equiv 0$ and that all population growth is due to the initially healthy population. Defining $\alpha(t) := H(t)/N(t)$ as the growth contributing fraction of the population one obtains after some straightforward calculations, following [3], that

$$\frac{d\alpha}{dt} = \mu\alpha\left(1 - \alpha\frac{R_{max}+1}{R_{max}}\right)$$

where R_{max} depends on the carrying capacity. It is easy to verify that $\alpha(t)$ converges to $\alpha^* = R_{max}/(R_{max}+1) \leq 1$. In the case of a logistic growth model with an explicitly specified carrying capacity N_{max} one has $R_{max} := N_{max}/I(0)$. Usually, the initial population is orders of magnitudes smaller than the carrying capacity, $N_{max} \gg N(0) > I(0)$. For practical purposes it is more convenient to rewrite the above model as

$$\frac{d\alpha}{dt} = \mu\alpha\,(1-\alpha K) \tag{9}$$

where $K := (R_{max}+1)/R_{max}$.

We remark finally that, in the case of constant model parameters, which we we are interested in, the three lag-time models (7), (8), and (9) are of course mathematically equivalent in the sense that they can be linearly transformed into the logistic equation

$$\frac{da}{dt} = a(1-a), \quad a(0) = a_0.$$

The actual transformation, however, depends on the a priori unknown biological constants μ, ν, k_n, K, which need to be determined from experiments.

2.3. **Inverse problem.** We denote by $(\hat{N}_i, t_i^N)$ with $i = 1, \ldots, n_N$ and $t_i^N \leq t_{i+1}^N$, measurements for the population size $N(t_i^N)$ and similarly by $(\hat{P}_i, t_i^P)$, $t_i^P \leq t_{i+1}^P$, $i = 1 \ldots, n_P$ measurements for pyoverdine $P(t_i^P)$. Our aim is to use these data to quantitatively compare the physiological recovery models. To this end we need to find the model parameters that solve the vector optimization problem

$$\min_{\theta \in \mathbb{R}_+^{7+p}} \begin{pmatrix} J_1(\theta) \\ J_2(\theta) \end{pmatrix}. \tag{10}$$

Here we use θ as a short hand notation for the vector of model parameters. The first 7 coefficients $\mu, k, \sigma, \delta, S^\infty, \beta, Y$ are the same for all models in the survey, the remaining coefficients are the parameters that are newly introduced by the physiological adaptation models and vary with the particular model under investigation. By $\mathbb{R}_+^{7+p}$ we denote the $(7+p)$-dimensional positive cone, where $p \in \{0,1,2\}$ is the number of additional degrees of freedom that is introduced by the physiological adaptation model. The objective functions in (10) are the usual data-weighted least square functions

$$J_1(\theta) = \sum_{i=1}^{n_N} \left(1 - \frac{N(t_i^N;\theta)}{\hat{N}_i}\right)^2, \quad J_2(\theta) = \sum_{i=1}^{n_P} \left(1 - \frac{P(t_i^P;\theta)}{\hat{P}_i}\right)^2 \tag{11}$$

where $N(t_i^P;\theta)$ and $P(t_i^P;\theta)$ denote the solution of model (1) - (4) in dependence of the parameters θ. Thus, we are aiming at minimizing the relative deviation between experiment and model.

Since we cannot expect to find one parameter that minimizes both objective functions simultaneously, our notion of a solution to (10) is a parameter that in some sense is a best compromise for both criteria. Thus we underly the Edgeworth-Pareto optimality concept with respect to the ordering induced by the positive cone $\mathbb{R}_+^2$. We recall that a parameter is called Edgeworth-Pareto optimal if further improvement of one objective function is only possible at the expense of another one. In other words, θ^* is Edgeworth-Pareto minimal if

$$\exists\, \theta, i: \quad J_i(\theta) < J_i(\theta^*) \Longrightarrow \exists\, j, \quad J_j(\theta) > J_j(\theta^*).$$

In general, infinite many such θ^* exist, one of which can be obtained by scalarizing the vector-valued objective function of (10) with a monotonously increasing functional $F : \mathbb{R}^2 \to \mathbb{R}$ and solving the corresponding scalar optimization problem [12]

$$\min_{\theta \in \mathbb{R}_+^{7+p}} F\big(J_1(\theta) J_2(\theta)\big).$$

Most commonly used are linear functionals. Thus we solve the scalar nonlinear least-square problem

$$\min_{\theta \in \mathbb{R}_+^{7+p}} [w J_1(\theta) + (1-w) J_2(\theta)] \tag{12}$$

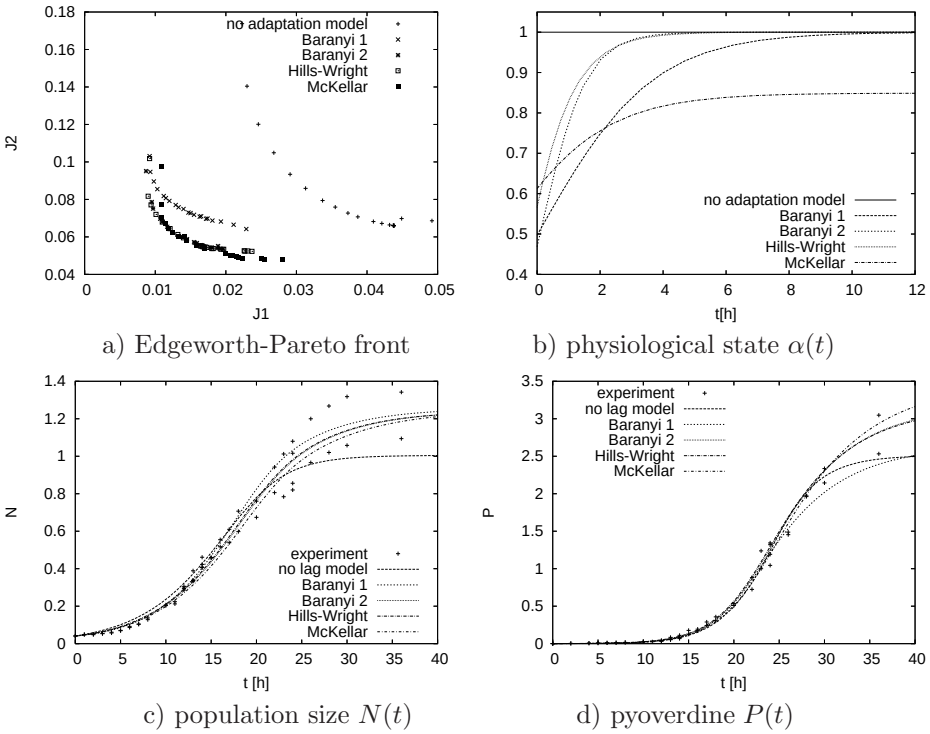
where we are free to choose $w \in (0,1)$. Of course, the optimal solution θ^* then depends on w as well. We will write θ_w^* if we want to stress this. Since we cannot distinguish between these Edgeworth-Pareto minima on an objective mathematical basis, we want to expect that a parameter that is optimal for one choice of w is still a good, albeit sub-optimal, choice for another w. This is a model validation criterion.

In our numerical realization, (12) is used with a Sequential Quadratic Programing algorithm, that treats the underlying model (1)–(4) as a constraint. Note that this model must be solved for every evaluation of the objective function. The computations were carried out in MATLAB. The data used in this study are taken from the experiments described in [4].

3. **Results and Discussion.** We compare the following five models against the experimental data: (i) model (1)-(4) without physiological adaptation model, $\alpha \equiv 1$, (ii) the one-parametric Baranyi model (7) with $\nu = \mu$, (iii), the two-parametric Baranyi model (7) with ν as a free paramemetr, (iv) the Hills-Wright model (8), and (v) the McKellar model (9).

It is obvious that the model without physiological adaptation is equivalent to the Baranyi models and the Hills-Wright model for the choice of parameter $\alpha_0 = 1$. Similarly, the McKellar model is equivalent with the model without adaptation if $\alpha_0 = 1/K$ and the parameter μ, σ, δ are multiplied with K to make up for the smaller fraction of the population that contributes to growth. Therefore, we expect that for given w the solution of the scalarized vector optimization problem (12) will be at least as good for the models with physiological adaptation than for the one without. Similarly, the one-parametric Baranyi model is a special case of three two-parametric models for the choice of parameters $\nu = \mu$ (Baranyi 2), $K = 1$ (McKellar), $k_n = 0$ (Hills-Wright). This is confirmed by the Edgeworth-Pareto fronts that are plotted in Figure 1.a. These consist of the optimal points $(J_1(\theta_w^*), J_2(\theta^*))$ of (10) for selected scalarization coefficients $w \in [0,1]$. The points (J_1, J_2) above a curve are not Edgeworth-Pareto optimal for this model, the points below this curve cannot be attained. The Edgeworth-Pareto front of the model without physiological adaptation lies clearly above the curve of the Baranyi model with a priori fixed recovery rate $\nu = \mu$. The Edgeworth-Pareto fronts of the three two-parametric adaptation models lie close together and clearly below the line of the one-parametric model, with a possible exception for the case $w = 1$. In this case only the data for N are used for parameter identification, i.e. only half of the data.

In Figure 1 the model solution $\alpha(t), N(t), P(t)$ and the experimental data are plotted. The solutions of the models that account for physiological adaptation are all well within the range of the experimental data. On the other hand, the



a) Edgeworth-Pareto front b) physiological state $\alpha(t)$

c) population size $N(t)$ d) pyoverdine $P(t)$

FIGURE 1. a) Pareto fronts for all five models. b)-d) Comparison of model solutions α, N, P, where the parameter θ was chosen as the average of 1000 random simulations. Plotted are also the experimental data for N and P, presented in optical density (OD).

model without adaptation in the initial transient phase does not predict the population size well for large t. The two-parametric Baranyi model and the Hills-Wright model agree well, both in population count N and pyoverdine P. For N also the one-parametric Barnayi model and the McKellar model agree reasonably well with these two models, while the model without physiological adaptation clearly underestimates the populations growth. We do note what appears to be a very slight over estimation of population growth in the initial phase, which may be due to the fact that there are more data available for larger t, which shifts the focus of the parameter estimation there. In general, of course, the quality of a fit depends also on the quality of the data, i.e. measurements. Therefore, the high variability in our data puts an upper bound on the goodness of the fit that can be expected, cf. also the discussion in [4]. For P the three two-parametric models represent the data quite well, while the models with physiological adaptation and the one-parametric Baranyi model lead to an underestimation. In other words, introducing an additional degree of freedom in the physiological adaptation model that describes the dynamics of adaptation improves computational accuracy.

While different choices of w lead to different optimal parameter values θ_w^*, we would hope that a parameter θ that is optimal for some w is still good (albeit suboptimal) for other w. That is, we would expect for a good model that the optimal parameters θ_w^* are close together. In other words, we would hope that the identified

TABLE 1. 95% confidence intervals for model parameters estimated from 1000 simulations with randomly chosen scalarisation weight $\omega \in (0,1)$. For the Baranyi models the $\alpha(0)$ was calculated from the estimated Φ_0 as $\alpha(0) = \frac{\Phi_0}{1+\Phi_0}$.

	no lag	Baranyi 1	Baranyi 2	Hills-Wright	McKellar
μ	[.4865, .4908]	[.5495, .5509]	[.5077, .5134]	[.5102, .5170]	[.5700, .5795]
k	[3.406, 3.409]	[3.654, 3.704]	[3.756, 3.773]	[3.780, 3.789]	[3.644, 3.661]
σ	[.1476, .1504]	[.0800, .0801]	[.0800, .0803]	[.0803, .0807]	[.0832, .0845]
δ	[1.300, 1.300]	[1.997, 1.999]	[2.555, 2.586]	[2.537, 2.568]	[2.635, 2.716]
S^∞	[.0746, .0790]	[.3408, .3414]	[.3748, .3776]	[.3760, .3785]	[.3659, .3707]
β	[.2672, .2711]	[.2177, .2184]	[.2017, .2036]	[.2046, .2072]	[.2047, .2073]
Y	[.4938, .5010]	[.6070, .6082]	[.6000, .6005]	[.6001, .6007]	[.6013, .6032]
Φ_0	–	[.9693, 1.008]	[.8510, .9121]	–	–
ν	–	–	[1.282, 1.444]	–	–
$\alpha(0)$	–	*[.4922,.5019]*	*[.4598,.4770]*	[.5405, .5916]	[.5996, .6255]
k_n	–	–		[.4284, .7046]	–
K	–	–	–	–	[1.160, 1.197]

model parameters are robust with respect to the scalarization weight w. A strong dependency of θ_w^* on w would imply an over-parameterization of the model and it would make the identified best parameter a property of the optimality criterion applied rather than of model and data. Thus, the (non)dependency of θ_w^* on the scalarization weight w for us is a model validation criterion. In [4] it was found that the one-parametric model has this property, i.e. in this case θ_w^* is not overly sensitive to the choice of the degree of freedom w in the scalarized vector optimization problem. The question arises now naturally whether the improved accuracy of the two-parametric models is at the expensive of this robustness, which would be an indication of over-parameterization. To investigate this we consider w a uniformly over the interval $(0,1)$ distributed random variable. Then also θ_w^* is a random variable. We compute 1000 realizations for each of the five models. Table 1 shows the 95% confidence intervals for the model parameters that were computed from these realizations. Normal plots in each case showed that the identified parameters follow a normal distribution, as expected from the central limit theorem (data not shown due to space limitations).

The variations in the reaction parameters $\mu, k, \sigma, \delta, S^\infty, \beta, Y$ with respect to w are small, in the third or fourth digit. This lets us to conclude that the reaction parameters can safely be carried over from one choice of w to another, i.e. the identification of the reaction parameters is robust with respect to the scalarization weight. The situation is different for the parameters that describe the physiological adaptation, where much larger uncertainties are found. However, $\lim_{t\to\infty} \alpha(t) = \alpha^*$ in all cases, and for all practical purposes $\alpha(t)$ reaches its stationary plateau within $t \approx 4$ and $t \approx 8$, depending on the underlying physiological adaptation model, cf Figure 1.b. Thus only the experimental data for small t contribute usable information for the parameter identification problem, while the values for large t do not help in this process. That said, the data base to estimate the lag-time parameters is much smaller than for the reaction parameters, which naturally must lead to increased uncertainty.

It remains to compare the values of the model parameters across the models. The difference in reaction parameters between the model without physiological adaptation and the models that account for recovery of the population are across the board substantial (with the possible exception of the Monod half saturation constant k). In fact, they are more pronounced than the differences between the individual models with adaptation. This implies that including a lag phase model in the process description indeed stabilizes the reaction parameters. On the other hand, in the model without physiological adaptation the lag phase is to be described by the growth kinetics. This leads naturally to a much smaller maximum growth rate μ, which not only leads to an underestimation of population size, cf. Fig. 1.c, but also affects the other model parameters.

Much smaller are the differences between the parameters for the one-parametric Baranyi model and the 2-parametric Baranyi model. They are most emphasized in the maximum growth rate μ and the iron chelation parameters β and δ. In the Baranyi 1 model the physiological adaptation rate ν is considerably smaller than in the case of the Baranyi 2 model. Thus, the fraction of the population contributing to growth recovers slower. Hence, in order to obtain comparable population counts, the maximum growth rate μ must be higher for the Baranyi 1 model. The same argument, indirectly via the iron concentration S, may be applied to explain the increased value of β in the Baranyi 1 model compared to the Baranyi 2 model. Pyoverdine production becomes notable for larger t, after the population is completely recovered, cf also Fig. 1.b,d. The decreased value δ for the Baranyi 1 model is, therefore, a consequence of the larger value of μ in an attempt to avoid over-prediction of pyoverdine production.

The reaction parameters found for the Baranyi 2 and the Hills-Wright model are in very good agreement. This should be expected because both models are equivalent up to a linear transformation. The parameters found for the third two-parametric model deviate from them a little, most notably the maximum growth rate μ. This, however, can be put into perspective by the following observation: While for both other models the adaptation function is scaled between 0 and 1, it is scaled between 0 and $1/K < 1$ for the McKellar model. Thus in order to obtain the same effective growth rate $\alpha(t)\mu$ for the population, the maximum growth rate must be larger for the McKellar model than for the other two models. In deed, the difference in μ between the Baranyi 2 and Hills-Wright models on the one side and the McKellar model on the other side is approximately the K. That is, the effective growth rate $\alpha^*\mu$ in the longterm is indeed about the same for all three two-parametric models.

4. **Conclusion.**

The above computations show that a big step in the accuracy of describing the bacterial lag-phase at the onset of a laboratory experiment can be made already by including a simple lag-time model that only introduces one additional degree of freedom in the parameter identification problem (the initial state of health of the population), and that this can be reliably improved if a further degree of freedom is included that describes the longterm dynamics of the physiological recovery process. That said, the two-parametric models that were studied here keep the good properties (robustness with respect to scalarization weight) of the one-parametric model that was used in [4], while improving accuracy of the description of the initial phase of physiological adaptation.

Since the physiological adaptation of the bacterial population is described by few (one or two) lumped parameters, the associated inverse parameter identification problem is much easier to handle than in the case of the mathematically much more challenging distributed McKendrick model that leads to a partial differential equation for the physiological structure of the population instead. An interesting question for future investigation is whether these simple lumped models of physiological adaptation that have been derived by microbiologists in recent years can be formally derived from the more detailed distributed models.

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