**Abstract**

Polymicrobial lung infections are now known to be one of the most significant symptoms of cystic fibrosis (CF). Thickened mucus in the lungs of CF patients is colonized by a complex community of bacteria, viruses, and fungi, which can thrive in the nutrient-dense environment. In this paper, we present growth curves of four microbial species cultured from CF lung infections with population measured via an optical density in both aerobic and anaerobic conditions. We then develop a series of mathematical models to describe microbial growth inside of an optical density capsule based on nutritional availability. We use the Akaike Information Criterion to select the best fitting model for each microbial growth curve, estimate key growth parameters related to growth, and determine the sensitives to model output to changes in parameters using a complex-step approximation method to compute partial derivatives. Our results provide basic insights into the characteristics of several CF-related pathogens which can be incorporated into more complex models of the CF lung microbiome and could potentially be used to inform treatment strategies for CF lung infections.

**1) Introduction**

Improved understanding of cystic fibrosis (CF) lung microbiology has shown that it is a much more complex ecosystem than was once thought [1, 2]. It was previously thought that the CF lung was dominated by single pathogens, most commonly *Pseudomonas aeruginosa* [3, 4], however it is now understood that the CF lung is inhabited by a highly diverse community of bacteria, viruses, and fungi [1, 2]. Consequently, treatment of CF lung infections has shifted to a multi-omics approach in which specific pathogens are identified and targeted for treatment [5, 6]. Treating CF lung infections would therefore benefit from more detailed characterizations of individual pathogens that inhabit the CF lung.

While *P. aeruginosa* is one of the most common pathogens, the CF lung also regularly contains bacteria and viruses that are normally found in healthy human microbiome, and which cause common infections [3, 7, 8]. Pathogens can exhibit wide variety in their metabolisms, nutritional sources, and responses to treatment [9-11] but there is not a wide-spread method of quantifying their growth characteristics yet. Quantifying the growth behavior of individual pathogens will therefore be useful clinically for treatment of CF lung infections, but also for broader study of microbial ecology.

In this study, we quantify the behavior of four pathogens by estimating several growth-related parameters from in vitro growth measurements. The pathogens, three bacteria and one fungi, were [cultured from sputum samples taken from a CF patient at the University of California, San Diego Cystic Fibrosis Clinic and their growth measured by optical density [12]]. Optical density is frequently used to measure bacterial growth over time, but direct measurement of living and dead bacteria can take several days, and actual measurements are not fully understood with regards to cell count [12, 13]. Because of this, we also develop a mathematical model to describe microbial growth inside of an optical density capsule.

Mathematical models are becoming more commonly used to investigate the prognosis and treatment of diseases, and to identify and estimate key parameters (refs). The mathematical model we develop in this paper is a system of ordinary differential equations with several choices of nutrient-dependent growth functions. By fitting our model to experimental growth curves of several common CF pathogens, we are able to estimate parameters that characterize their growth. Our results may be useful in understanding the ecology of the CF lung microbiome, identifying possible treatment strategies for CF lung infections, and microbial ecology in general.

**2) Methods**

**Experimental data**

[Greg’s stuff in the optical density machine. C. albicans, E. faecalis, P. aeruginosa, and S. Odorifera were recovered from a CF patient and cultured in capsules. Their abundance was measured by optical density in wells. Each species was grown in both aerobic and anerobic conditions. Each growth curve is an average of a batch of wells.]

**Mathematical model**

We develop a mathematical for bacterial growth inside an optical density capsule. Bacteria are grown in a nutritional media, the capsules are agitated periodically to ensure homogenization, and there is no nutrient entering the capsule during the experiment. Some bacteria may die during the experiment and dead bacteria will contribute to OD until lysis occurs and a bacterium’s nutrients are recycled [12, 14].

Our mathematical model consists of a three-component system of ordinary differential equations (ODEs). The three components correspond to living bacteria, denoted by , dead bacteria, denoted by , and nutrient, denoted by . Living bacteria reproduce logistically up to the carrying capacity and die at rate . Growth is also limited by the total amount of space in the capsule. Since both living and dead bacteria occupy space in the capsule, we need to include both in the logistic growth term of the model. When bacteria die, they transition to the dead cell compartment at rate and lyse at rate . Nutrient is consumed by living bacteria at rate and recovered from dead bacteria at rate .

Bacteria reproduce logistically in a nutrient-dependent manner [15]. Nutrient can be recovered from dead bacteria after lysis occurs [14, 16], but no new nutrient can enter from outside the capsule. The nutrient-dependent growth rate used for the logistic growth we denote by so that the full model can be written as

We use Hill functions [17, 18] to model nutrient-dependent growth and consider three cases for the slope-factor : (constant growth), , and . The growth functions for the three cases can be written

where is the maximum possible growth rate, is the half-saturation concentration which gives a growth rate exactly half of , and the slope-factor determines how steep the growth rate curve is.

**Data fitting**

Our data is reported in optical density, a ratio of the proportion of light that passes through a material [19]. Note that both living and dead bacteria contribute to optical density until they break-up via lysis [14, 20]. Assuming that optical density is proportional to cell density, i.e., that . We also nondimensionalize our model by defining the scaled variables , , . Then the model can be rewritten in terms of the scaled variables as

where and . The growth rate functions are also rescaled to

where . The relation between the non-dimensionalized bacterial density and OD is then given by , where . For Model 1, we fit the five parameters and . For Model 2, we fit the eight parameters and . For Model 3, we fit the nine parameters and . Computations were performed in MATLAB using the functions ode15s, fminsearch, and fmincon. Parameter estimates were obtained by solving the system of ODEs and selecting values that minimize the sum of square errors (SSE) given by

where is the observed optical density at time point *i,* is the predicted bacterial density (living plus dead microbes), for Model 1, for Model 2, and for Model 3, and is the number of available data points. For each fitted parameter value, standard errors were computed using a complex-step derivative approximation [21-24].

**Model Selection**

For each microbe, we select the best model using the Akaike Information Criterion (AIC) based on the SSE, number of available data points, and number of fitted parameters [25, 26]. We calculate the AIC for each model with the formula

where is the SSE of the best fitting parameter set, is the number of data points, and is the number of parameters. We take the model with the lowest AIC to be the best choice.

**Sensitivity analysis**

To determine the sensitives of the model output to changes in parameters and compute standard errors, we construct the sensitivity matrix similar to [21-24] as

where is the partial derivate of the bacterial density at the *ith* time point with respect to the *jth* parameter, and and or for Models 1, 2 and 3, respectively. We use a complex-step approximation as described in [21-24]. The complex-step procedure is as follows: take the Taylor Series expansion of with complex step , where is the imaginary unit and is a small positive constant. The Taylor expansion is given by

After taking the imaginary part both sides and dividing by , we can rearrange to obtain

where we discard terms of order 2 and higher on the right-hand side. We construct an approximation  to by computing the partial derivatives using for each time point and estimated parameter. We then compute the standard errors for each estimated parameters using , where , is the number of timepoints where data was collected, and is the number of estimated parameters.

**3) Results**

**Explanation of data**

The three bacteria E. faecalis, P. aeruginosa, and S. Odorifera and the pathogenic yeast C. albicans were cultured in [an optical density machine] and cell densities measured in anaerobic conditions over two days and in aerobic conditions over 20 hours. The bar graphs in Figure 1 show the observed optical density for the four microbes. In anaerobic conditions (blue bars in Figure 1), P. aeruginosa and S. odorifera reached maximum densities around 0.45 OD, P. aeruginosa saw an increase at 1.2 days and was steady at 2 days. S. odorifera peaked at 0.5 days and steadily decreased from that point. E. faecalis reached peak density around 0.2 days and steadily decreased afterwards. C. albicans peaked at 0.4 days and appeared at steady state after an initial oscillation.

When grown aerobically (red bars in Figure 1), P. aeruginosa, S. odorifera, and C. albicans each have shorter initial lag phases and begin growing faster, although C. albicans has a lower density between 0.2 and 0.7 days. S. odorifera in particular reaches double the maximum density from when grown anaerobically (Figure 1c). Each of the three microbes were still growing in density when the experiment ended. E. faecalis grew similarly in both anaerobic and aerobic conditions (Figure 1a).

**Figure 1. Aerobic and anaerobic growth curves**

|  |  |
| --- | --- |
| **a)** | **b)** |
| **c)** | **d)** |

Figure 1: Observed optical densities of E. faecalis (a), P. aeruginosa (b), S. odorifera (c), and C. albicans (d) grown anaerobically (blue bars) over two days and aerobically (red bars) over 20 hours.

**Model selection**

For each microbe, we used the AIC and equation to select the best choice of model, for aerobic and anaerobic conditions. Tables 1 and 2 list the SSE and AIC for each microbe and choice of model for anaerobic and aerobic data, respectively. For each of the four microbes, Model 3 achieved the lowest AIC when fit to the anaerobic data. When fit to the aerobic data, E. faecalis and C. albicans saw the lowest AIC with Model 2, P. aeruginosa with Model 1, and S. odorifera with Model 3. Longer time series of data were available for anaerobic growth compared to the aerobic data, which may have affected the model selection for that data. However, the AIC values for Model 3 suggests that growth is related to nutrient density in a more complicated way than previously thought [15].

Table 1: Anaerobic Growth SSE and AIC

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Model 1 | | Model 2 | | Model 3 | |
|  | SSE | AIC | SSE | AIC | SSE | AIC |
| E. faecalis | 0.2627 | -895.5 | 0.0063 | -1426.1 | 0.060 | -1430.8 |
| P. aeruginosa | 0.0496 | -1135.7 | 0.0505 | -1126.1 | 0.0143 | -1305.5 |
| S. odorifera | 0.1055 | -1026.9 | 0.0527 | -1120.1 | 0.0388 | -1161.7 |
| C. albicans | 0.0322 | -1197.8 | 0.0331 | -1187.1 | 0.011 | -1342.8 |

Table 2: Aerobic Growth SSE and AIC

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Model 1 | | Model 2 | | Model 3 | |
|  | SSE | AIC | SSE | AIC | SSE | AIC |
| E. faecalis | 0.0337 | -435.5 | 0.0037 | -560.4 | 0.0070 | -518.8 |
| P. aeruginosa | 0.0165 | -478.4 | 0.0302 | -434.0 | 0.0164 | -467.8 |
| S. odorifera | 0.7187 | -251.9 | 0.6542 | -249.52 | 0.3003 | -293.3 |
| C. albicans | 0.0108 | -503.6 | 0.0092 | -505.4 | 0.0107 | -493.5 |

**Estimation of parameters**

Best fitting parameters Models 1, 2, and 3 are Tables 4, 5, and 6, respectively. Each table lists parameter values for anaerobic and aerobic growth. Figures 2 and 3 show simulations with the best fitting parameter sets for each of the three models for anaerobic and aerobic growth, respectively. Standard errors were found using a complex-step routine and calculated using equation . These values are shown in parentheses.

The best fitting models (according to AIC) tended to have smaller standard errors, whereas some models with larger AIC values showed extremely large standard errors. For parameters that did have large standard errors, this suggests that that choice of model is not able to reliably estimate a value. Note that the aerobic growth curves, which were the most complete data sets, Model 3 was the best fitting model in every case. This suggests that the microbial growth rate is dependent on nutrient density is complicated and highly non-linear ways. As a result of our scaling method and the optical density measurement, this data fitting can only uniquely identify the product and not either of the individual factors of carrying capacity and optical density scaling factor and standard errors are not shown for in Tables 3 and 4.

Table 3: Model 1 Best Fit Parameters

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| E. faecalis | Anerobic | 49.80  (3.40) | 0.51  (0.20) | 21.34  (123.29) | 0.27  (-) | 0.012  (0.0036) |
| Aerobic | 49.05  (2.04) | 4.05  (0.41) | 2.55  (0.79) | 0.34  (-) | 0.0099  (0.0019) |
| P. aeruginosa | Anerobic | 32.78  (1.31) | 15.14  (0.62) | 49.59  (12.03) | 0.76  (-) | 0.0024  (0.0005) |
| Aerobic | 27.84  (1.78) | 14.13  (0.88) | 36.48  (37.25) | 0.75  (-) | 0.0096  (0.0013) |
| S. odorifera | Anerobic | 43.02  (7.04) | 26.88  (4.40) | 30.83  (30.69) | 1.12  (-) | 0.0096  (0.0035) |
| Aerobic | 24.17  (7.29) | 6.87  (2.06) | 41.61  (329.78) | 1.08  (-) | 0.010  (0.0075) |
| C. albicans | Anerobic | 34.45  (0.90) | 10.31  (0.28) | 12.29  (1.32) | 0.48  (-) | 0.00085  (0.0001) |
| Aerobic | 15.23  (0.69) | 6.94  (0.33) | 27.00  (61.88) | 0.62  (-) | 0.016  (0.0034) |

Table 4: Model 2 Best Fit Parameters

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |
| E. faecalis | Anerobic | 49.57  (17.94) | 0.02  (0.19) | 0.60  (0.66) | 17.39  (301.90) | 13.31  (22.50) | 0.13  (2.06) | 0.33  (-) | 0.0077  (0.011) |
| Aerobic | 49.17  (2.34) | 0.065  (0.033) | 3.10  (0.27 | 28.40  (81.8256) | 49.33  (13.72) | 6.16  (14.14) | 0.45  (-) | 0.0080  (0.0007) |
| P. aeruginosa | Anerobic | 22.66  (9.62) | 0.017  (4.31) | 6.10  (102.28) | 47.46  (44.82) | 26.16  (667.97) | 43.16  (1009.3) | 0.58  (-) | 0.0056  (0.0074) |
| Aerobic | 43.04  (41463.8) | 1.14  (2061.7) | 2.89  (2.52) | 20.48  (215.54) | 0.54  (4681.1) | 1.29  (1240.4) | 0.42  (-) | 0.0093  (0.0048) |
| S. odorifera | Anerobic | 36.36  (23.07) | 0.63  (0.97) | 0.20  (0.13) | 38.65  (376.04) | 3.81  (1.15) | 0.44  (10.91) | 0.48  (-) | 0.012  (0.0021) |
| Aerobic | 47.72  (2124.0) | 0.73  (77.75) | 7.11  (47.36) | 45.94  (1306.2) | 0.025  (507.63) | 25.42  (1399.6) | 0.95  (-) | 0.10  (0.095) |
| C. albicans | Anerobic | 38.52  (13.66) | 0.10  (0.69) | 9.17  (12.56) | 37.61  (12.62) | 24.44  (30.57) | 26.98  (74.33) | 0.51  (-) | 0.00061  (0.0002) |
| Aerobic | 20.05  (94.80) | 0.17  (5.42) | 11.12  (105.96) | 27.60  (226.83) | 29.38  (383.70) | 24.74  (181.3367) | 1.63  (-) | 0.0097  (0.0119) |

Table 5: Model 3 Best Fit Parameters

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |
| E. faecalis | Anerobic | 49.51  (48.55) | 0.020  (1.20) | 1.01  (26.67 | 0.66  (2.67) | 12.04  (182.23) | 12.21  (216.83) | 0.12  (16.69) | 0.33  (-) | 0.0082  (0.013) |
| Aerobic | 48.15  (34.77) | 0.31  (3.13) | 5.64  (20.82) | 8.41  (27.92) | 11.18  (23.17) | 19.01  (134.26) | 7.35  (44.79) | 0.45  (-) | 0.0085  (0.0016) |
| P. aeruginosa | Anerobic | 27.41  (121.15) | 0.25  (2.23) | 0.67  (7.53) | 0.85  (1.22) | 40.38  (1851.1) | 48.39  (280.16) | 22.80  (1038.6) | 0.62  (-) | 0.0029  (0.0060) |
| Aerobic | 27.02  (2992.7) | 0.58  (258.46) | 4.07  (3735.2) | 9.56  (1261.7) | 26.63  (5157.1) | 8.53  (5678.3) | 23.70  (11595.3) | 0.62  (-) | 0.0096  (0.033) |
| S. odorifera | Anerobic | 30.03  (1.66) | 0.25  (51.35) | 3.88  (577.04) | 11.87  (0.66) | 41.25  (38.63) | 1.43  (202.22) | 0.10  (13.71) | 0.79  (-) | 0.012  (0.0015) |
| Aerobic | 38.70  (536.14) | 0.93  (5.76) | 8.9  (415.18) | 8.40  (122.82) | 8.56  (172.10) | 7.29  (403.03) | 8.52  387.98) | 1.42  (-) | 0.010  (0.034) |
| C. albicans | Anerobic | 27.81  (84.82) | 0.77  (1.92) | 8.92  (77.53) | 7.54  (61.53) | 5.78  (9.31) | 8.54  (80.39) | 5.36  (69.80) | 0.68  (-) | 0.0028  (0.011) |
| Aerobic | 18.95  (305.81) | 0.65  (1383.9) | 7.1  (36009.5. | 12.42  (112.03) | 16.16  (121.97) | 14.48  (48577.5) | 12.66  (23892.4) | 1.85  (-) | 0.0078  (0.011) |

**Figure 2. Best fitting parameter simulations for anaerobic growth**

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**Figure 2:** Anaerobic growth curves and solutions with best fitting parameters for E. faecalis (top row), P. aeruginosa (second row), S. odorifera (third row), and C. albicans (bottom row). The left column shows simulations for Model 1, the middle column for Model 2, and the left column for Model 3.

**Figure 3. Best fitting parameter simulations for aerobic growth**

|  |  |  |
| --- | --- | --- |
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|  |  |  |

**Figure 3**: Aerobic growth curves and solutions with best fitting parameters for E. faecalis (top row), P. aeruginosa (second row), S. odorifera (third row), and C. albicans (bottom row). The left column shows simulations for Model 1, the middle column for Model 2, and the left column for Model 3.

**Interpretation of estimated parameters**

Our estimate parameters can be used to infer basic characteristics of the microbes in question. For each best-fitting model and microbe, Tables 6 and 7 show the doubling time, slope factor, average death rate, and average time to cell lysis of a dead bacteria. Doubling times were recovered from maximal growth rates according to the equation , the average life span and time to lysis are the reciprocals of the death rate and lysis rate . Maximum doubling times were all between 20 and 50 minutes, consistent with what has been measured experimentally before [27].

The average lifespans were between 2 hours and 1.5 days, average times to lysis were much shorter, between 0.6 and 4.2 hours. While Model 3 was the best choice of model for E. faecalis, its estimated slope factor of 1.01 was very close to the value for Model 2. However, the other three microbes showed very non-linear dependence on nutrient, e.g., the estimated slope factor for C. albicans was 8.92. Doubling times were similar for the three bacteria, with P. aeruginosa being somewhat faster growing in anaerobic conditions. S. odorifera also had a longer average lifespan when grown aerobically, which was expected from its growth curves.

Table 6: Best-fitting parameter interpretations, anaerobic growth

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | – maximal growth rate | | – slope factor | – death rate | | – lysis rate | |
|  | Estimated value ( | Doubling time | Slope factor | Estimated value ( | Average life span ( | Estimated value ( | Average time to lysis |
| E. faecalis | 49.51 | 20 | 1.01 | 0.66 | 36.4 | 12.04 | 2.0 |
| P. aeruginosa | 27.41 | 36 | 0.67 | 0.85 | 28.2 | 40.38 | 0.6 |
| S. odorifera | 30.03 | 33 | 3.88 | 11.87 | 2.0 | 41.25 | 0.6 |
| C. albicans | 27.81 | 36 | 8.92 | 7.54 | 3.2 | 5.78 | 4.2 |

Table 7: Best-fitting parameter interpretations, aerobic growth

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | – maximal growth rate | | – slope factor | – death rate | | – lysis rate | |
|  | Estimated value ( | Doubling time | Slope factor | Estimated value ( | Average life span ( | Estimated value ( | Average time to lysis |
| E. faecalis | 49.17 | 20 | - | 3.10 | 7.7 | 28.40 | 0.8 |
| P. aeruginosa | 32.78 | 30 | - | 15.14 | 1.6 | 49.59 | 0.5 |
| S. odorifera | 38.70 | 28 | 8.9 | 8.40 | 2.9 | 8.56 | 2.8 |
| C. albicans | 20.05 | 49 | - | 11.12 | 2.2 | 27.60 | 0.9 |

**Sensitivity**

We determined the sensitivity of the model outputs to changes in parameters using the complex-step derivative approximation given by equation . These curves are shown in Figure 4 for the anaerobic growth curves and Figure 5 for the aerobic growth curves. In all cases, the initial density of living bacteria was the most sensitive parameter by 1-2 orders of magnitude, followed by the half-saturation value .

In most cases, the growth rate and death rate were positively and negatively associated with microbial densities. Anaerobically grown P. aeruginosa as also very sensitive to changes in slope factor relative to other parameters. The nutritional consumption rate was negatively correlated with density to varying degrees.

**Figure 4. Sensitivity curves for anaerobic growth**

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**Figure 4:** Sensitivity curves for the bacterial growth curves, rows represent (from top to bottom) E. faecalis, P. aeruginosa, S. odorifera, and C. albicans. Each curve represents sensitivity indices , with more sensitive parameters having larger magnitudes. For anaerobic growth, Model 3 was the best choice model for each microbe, so . For visualization purposes, less sensitive parameters are shown in the left column and more sensitive parameters in the right.

**Figure 5. Sensitivity curves for aerobic growth**

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| --- | --- |
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**Figure 5:** Sensitivity curves for the bacterial growth curves, rows represent (from top to bottom) E. faecalis, P. aeruginosa, S. odorifera, and C. albicans. Each curve represents sensitivity indices , with more sensitive parameters having larger magnitudes. For the aerobic data, Model 2 was the best choice for E. faecalis and C. ablicans. Model 1 was the best choice for P. aeruginosa and Model 3 the best for S. odorifera.

**4) Discussion**

In this paper, we developed several mathematical models of microbial growth in an optical density capsule, fit our models to in vitro growth curves of four cultured cystic fibrosis pathogens, and estimated key parameters related to their growth. The models we developed were three variations of nutrient dependent logistic growth models, with added components for nutrient density and deceased microbes which also contribute to optical density measurements, and increasingly complex growth functions. For each set of microbe data, we selected the best choice of model using the Akaike Information Criterion (AIC) and performed sensitivity analysis for the estimated parameters. We found that models with more complex growth functions were able to fit the data better, particularly when more data was available as was the case with the anaerobic growth curves. Nutrient dependent growth has been used previously in modeling bacterial growth [15], but our use of an Emax model for a growth function suggests that the relation between growth and nutrient availability has many possible mechanisms which may be vary depending on the microbial species.

Biofilm formation is strongly associated with CF lung infections, and its microbial makeup is significant for prognosis and treatment [5]. Our results in this paper provide quantitative information fundamental characteristics of microbes found in CF lungs, such as doubling time, lifespan, and time to recycle nutrients from deceased cells. Lifespan and growth rate are both important factors in biofilm formation since a longer lifespans can contribute to antibiotic resistance [28, 29]. Our results may therefore be useful clinically in determining what microbes respond well to antibiotic treatments [30]. Our sensitivity analysis showed that the initial bacterial population and half-saturation nutrient concentration were the most sensitive parameters.

Our modeling in this study was highly parameterized and due to non-dimensionalization some parameters could not be uniquely identified. However, it may be possible to identify parameters such as the rate of lysis and carrying capacity by taking direct counts of cells at certain time points along with recording the optical density. Estimating such parameters experimentally would reduce uncertainty of the remaining parameters estimated via data fitting.

In summary, the mathematical models presented here quantified some basic characteristics of four pathogens found in CF lung infections. The parameters estimated from experimental growth curves can now be incorporated into more complicated models of the CF lung ecosystem, as well as to catalog basic characteristics of the microbes we investigated in a quantitative manner. Since much of the treatment for CF lung infections involves the use of antibiotics, our results could also potentially be used to investigate treatment options to be used clinically.

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