

Learning Susceptibility of a Pathogen to Antibiotics Using Data from Similar Pathogens

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Keywords

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Summary

Objectives: Selection of empirical antibiotic therapy relies on knowledge of the *in vitro* susceptibilities of potential pathogens to antibiotics. In this paper the limitations of this knowledge are outlined and a method that can reduce some of the problems is developed.

Methods: We propose hierarchical Dirichlet learning for estimation of pathogen susceptibilities to antibiotics, using data from a group of similar pathogens in a bacteremia database.

Results: A threefold cross-validation showed that maximum likelihood (ML) estimates of susceptibilities based on individual pathogens gave a distance between estimates obtained from the training set and observed frequencies in the validation set of 16.3%.

Estimates based on the initial grouping of pathogens gave a distance of 16.7%. Dirichlet learning gave a distance of 15.6%. Inspection of the pathogen groups led to subdivision of three groups, Citrobacter, Other Gram Negatives and Acinetobacter, out of 26 groups. Estimates based on the subdivided groups gave a distance of 15.4% and Dirichlet learning further reduced this to 15.0%. The optimal size of the imaginary sample inherited from the group was 3.

Conclusion: Dirichlet learning improved estimates of susceptibilities relative to ML estimators based on individual pathogens and to classical grouped estimators. The initial pathogen grouping was well founded and improvement by subdivision of the groups was only obtained in three groups. Dirichlet learning was robust to these revisions of the grouping, giving improved estimates in both cases, while the group-based estimates only gave improved estimates after the revision of the groups.

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1. Introduction

Antibiotic treatment of bacteremia relies on knowledge of the susceptibility of the infecting pathogen to antibiotics. At the onset of infection this information is typically not available and it must be assessed from prior knowledge of the probability that a given pathogen is susceptible to a given antibiotic. In practice there are limits to how well these probabilities can be known.

Susceptibilities of bacteria to antibiotics differ between hospitals and estimation of susceptibilities from databases of *in vitro* susceptibilities must therefore be based on local data. Even for a department of microbiology serving a large hospital or several smaller hospitals, the number of positive blood cultures, i.e. the number of times bacteria can be isolated from the blood, is unlikely to be much greater than about 1000 per year. This effectively limits the size of local databases because

susceptibilities change over time. If we for the purpose of this discussion assume that data older than three years should be used with caution, then the effective upper limit on the size of the database is about 3000 bacterial isolates, distributed over about 100 pathogens. This is further aggravated because the susceptibilities for community-acquired and hospital-acquired infections are substantially different and therefore must be estimated separately. It is difficult to set a threshold for how large the sample should be to make the classical maximum likelihood (ML) estimate useful. If we consider a pathogen that has an estimated susceptibility of 70% to an antibiotic, then the standard deviation (SD), calculated based on the binomial distribution, of that estimate is 9% for a sample size $N = 25$ and 5% for $N = 100$. So it is probably safe to conclude that the lower limit for useful estimates is somewhere between $N = 25$ and $N = 100$. This obviously leaves a large fraction of the pathogens without useful ML estimates.

The simplest solution is to group the pathogens, assuming that all pathogens within a group have identical susceptibilities. This is a fairly strong assumption, and this paper will explore if it is possible to find estimates of susceptibility that represent a middle ground between the two extremes mentioned above, either using estimates based on a single pathogen or using estimates based on a whole group of pathogens. Technically, the method will be based on hierarchical Dirichlet learning [1–4], that allows a systematic approach to strengthening sparse data with educated guesses. For example, for *Proteus spp.*, which is one of seven members of the “Proteus group” of pathogens (▶ see Table 2), an educated guess, in the absence of enough data, would be to assume that it resembles other members of the Proteus group in terms of susceptibility. The Dirichlet learning then provides a mechanism which allows the susceptibility estimates for *Proteus spp.* to deviate

from the susceptibilities of other bacteria belonging to the *Proteus* group, if and when data on the actual susceptibility of *Proteus spp.* to this antibiotic becomes available.

The potential benefit of this idea will be evaluated by applying the proposed method to a bacteremia database and it will be assessed whether our method improves the estimate, relative to the ML estimate for single pathogens and the grouped estimate.

2. Materials and Methods

2.1 The Bacteremia Database and ML Estimates

Prior probabilities used in the model were based on a bacteremia database collected at Rabin Medical Center, Beilinson Campus, in Israel during 2002–2004. The bacteremia database included 3350 patient- and episode-unique clinically significant isolates from blood cultures. We shall restrict our attention to the 1556 isolates from adults with hospital-acquired infections. These isolates were obtained from 76 different pathogens and each isolate was on average tested in vitro for susceptibility to 21 antibiotics (range 1–31) out of a total of 36 antibiotics. A fragment from the bacteremia database is shown in ▶ Table 1.

The bacteremia database provides the counts of susceptibilities (M_{ij}) and the number of isolates tested (N_{ij}) belonging to each pathogen for a range of antibiotics. The index i identifies the antibiotic and j identifies the pathogen. For example, ▶ Table 2 shows the counts of susceptibility (M_{ij}) and the number of isolates tested (N_{ij}) for the antibiotic tobramycin ($i = 1$) and seven pathogens belonging to the *Proteus* group ($j = 1, \dots, 7$). Using these counts, ML estimates of susceptibility (ML_{ij}) were calculated. For example, the ML estimate for the susceptibility of *Proteus spp.* ($j = 1$) to tobramycin and its SD were obtained as $ML_{11} = M_{11}/N_{11} = 2/3 = 0.67$ and $SD = \sqrt{ML_{11}(1 - ML_{11})/N_{11}} = 0.27$.

2.2 Hierarchical Dirichlet Learning over Groups of Pathogens

Dirichlet learning is a Bayesian approach for estimation of the parameters in binomial (or

Table 1 A fragment of the bacteremia database showing 4 out of the 1556 isolates from hospital-acquired infections. Amongst other information, the database contains attributes (columns) specifying the name of the pathogen and the *in vitro* susceptibility ($S =$ susceptible, $R =$ resistant) to a total of 36 antibiotics, out of which only 3 are shown here.

Pathogen	1. tobramycin	2. piperacillin	3. gentamycin
...
<i>Proteus spp.</i>	R	S	S
<i>Proteus spp.</i>	S	S	S
<i>Proteus spp.</i>	S	S	S
<i>Proteus vulgaris</i>	S	S	S
...

multinomial) distributions. In this paper it will be assumed that a priori estimates of the parameters of the binomial distribution for susceptibility can be guessed from the susceptibilities averaged over pathogens that are assumed to be similar. It is assumed, that the a priori distribution of the parameter follow the conjugated prior of the binomial distribution, which is the Beta distribution (or the Dirichlet distribution for the multinomial distribution).

In the TREAT project a decision support system for advice on antibiotic treatment has been constructed [5]. As part of this construction 40 such groups of pathogens with similar susceptibility properties have been identified by the clinicians based on the clinical knowledge. In ▶ Table 3 the 76 different pathogens from the bacteremia database have been allocated to 26 of these groups.

Assume that a group of n similar pathogens has been identified, the pathogens being indexed by $j \in \{1, \dots, n\}$. On a number of occasions the susceptibility of these pathogens to a certain antibiotic (indexed by i) has been tested, N_{i1}, \dots, N_{in} times respectively, with the counts

of susceptibility being M_{i1}, \dots, M_{in} , respectively. The average susceptibility P_i of this group is:

$$P_i = \sum_{j=1}^n M_{ij} / N_i, \text{ where } N_i = \sum_{j=1}^n N_{ij}. \quad (1)$$

The ML estimator of susceptibility of a pathogen $ML_{ij} = M_{ij}/N_{ij}$ is now replaced by the Dirichlet estimator:

$$P_{ij} = (\beta_i + M_{ij}) / (\alpha_i + N_{ij}), \quad (2)$$

where β_i and α_i are imaginary counts, $\beta_i = \alpha_i \times P_i$ representing positive outcomes in the binomial distribution and α_i representing the imaginary sample size, inherited from the pathogen group. Thus, α_i indicates how strong the confidence is in the a priori distribution of the parameters, and β_i/α_i can be used as the a priori estimate of the parameter of the binomial distribution, i.e. as an estimate of the susceptibility averaged over the pathogen group. We let all α_i assume the value A , except that we impose an upper limit on each α_i :

$$\alpha_i = \min(A, N_i), \quad (3)$$

Table 2

The counts of susceptibility, the number of isolates tested, the ML estimates and the Dirichlet estimators of susceptibility to tobramycin ($i = 1$) for seven pathogens belonging to the *Proteus* group

Pathogen	j	M_{1j}	N_{1j}	ML_{1j}	P_{1j}
<i>Proteus spp.</i>	1	2	3	0.67	0.7
<i>Proteus mirabilis</i>	2	39	49	0.80	0.79
<i>Proteus vulgaris</i>	3	1	1	1	0.78
<i>Proteus penneri</i>	4	2	2	1	0.82
<i>Morganella morganii</i>	5	19	20	0.95	0.91
<i>Providencia spp.</i>	6	4	10	0.4	0.49
<i>Providencia stuartii</i>	7	5	14	0.36	0.44
Sum of <i>Proteus</i> group		72	99	0.73	0.73

Table 3 Allocation of pathogens to the groups. Subgroups of Acinetobacter, Citrobacter and Other Gram-negative pathogen groups are placed in boxes.

1. Acinetobacter	10. Gram Positive Rod pathogen	18. Pseudomonas
– Acinetobacter baumannii	– Bacillus spp.	– Pseudomonas aeruginosa
– Acinetobacter spp.	– Corynebacterium aquaticum	– Pseudomonas alcaligenes
– Acinetobacter johnsonii	11. Klebsiella	– Pseudomonas cepacia
– Acinetobacter junii	– Klebsiella oxytoca	– Pseudomonas fluorescens
– Acinetobacter lwoffii	– Klebsiella pneumoniae	– Pseudomonas mendocida
2. Campylobacter	– Klebsiella spp.	– Pseudomonas putida
– Campylobacter spp.	12. Listeria	– Pseudomonas spp.
3. Candida	– Listeria monocytogenes	– Pseudomonas stutzerii
– Candida tropicalis	13. Moraxella	19. Salmonella non-typhi
4. Citrobacter	– Moraxella	– Salmonella enteritidis
– Citrobacter diversus	– Moraxella lacunata	– Salmonella Group C
– Citrobacter koserii	14. Other Gram Negative pathogen	20. Staphylococcus negative
– Citrobacter freundii	– Alcaligenes xylosoxidans	– Staphylococcus coagulase-
– Citrobacter spp.	– Methylobacterium mesophilicum	negative
5. Enterobacter	– Stenotrophomonas maltophilia	– Staphylococcus epidermidis
– Enterobacter aerogenes	– Brevundimonas vesicularis	21. Staphylococcus positive
– Enterobacter cloacae	– Chryseobacter meningosept.	– Staphylococcus coagulase-positive
– Enterobacter gergoviae	– Sphingomonas paucimobilis	22. Streptococcus Group A
– Enterobacter sakazakii	– Serratia fanticola	– Streptococcus Group A
– Enterobacter spp.	– Serratia marcescens	23. Streptococcus Group B
6. Enterococcus	– Serratia spp.	– Streptococcus Group B
– Enterococcus avium	15. Other Gram Positive	24. Streptococcus Group D
– Enterococcus durans	– Gemella spp.	– Streptococcus Bovis
– Enterococcus faecalis	– Streptococcus acidominimus	– Streptococcus Bovis I
– Enterococcus faecium	16. Pneumococcus	– Streptococcus Bovis II
– Enterococcus spp.	– Streptococcus pneumoniae	25. Streptococcus viridans
7. Eschericia coli	17. Proteus	– Streptococcus mitis
– Eschericia coli	– Proteus spp.	– Streptococcus oralis
8. Gram Negative Anaerobe pathogen	– Proteus mirabilis	– Streptococcus salivarius
– Fusobacterium	– Proteus vulgaris	– Streptococcus viridans
	– Proteus penneri	26. Streptococcus
9. Gram Positive Anaerobe pathogen	– Morganella morganii	– Streptococcus constellatus
– Peptostreptococcus	– Providencia spp.	– Streptococcus Group F
	– Providencia stuartii	– Streptococcus Group G

since it is not reasonable to let the imaginary sample size α_i exceed the number of counts N_i actually available for the group. If $A = 0$, then the Dirichlet estimate becomes equal to the ML estimate. If $A \rightarrow \infty$, then the Dirichlet estimate becomes equal to the grouped estimate P_i . In the next section it will be shown, that a “suitable” value for A can be determined empirically.

2.3 Evaluation of the Quality of the Estimates

To evaluate the quality of the estimates a threefold cross-validation procedure is applied. The three years of data are divided into three periods, each containing data from one year. In turn, one of the three periods is designated as the validation set and the other two periods are designated as the training set and used for calculation of the estimators.

We wish to evaluate how well the Dirichlet estimator P_{ij} , calculated from the training set, predicts F_{ij} , the observed frequency of susceptibility, calculated from the validation set. F_{ij} is calculated as $F_{ij} = M_{ij}/N_{ij}$. For this purpose we define the distance measure:

$$\text{Dist} = \sqrt{\sum_{ij} (P_{ij} - F_{ij})^2 N_{ij} / N}, \quad (4)$$

where $N = \sum_{ij} N_{ij}$.

This distance measure calculates the square distance between P_{ij} and F_{ij} , weighted by the relative frequency of the pathogen. It can be interpreted as the average distance between the estimate derived from the learning set and the observed frequency in the validation set. It is a modified version of the Brier score [6] and algebraically it is easy to prove that any set of estimated P_{ij} s that minimize Dist also minimize the Brier score.

The procedure followed in the threefold cross-validation described above is graphically illustrated in ► Figure 1.

Dist measures the averaged distance between the Dirichlet estimator from the training set and the observed frequency in the validation set. Since P_{ij} is a function of A (see Eqs. 2–4), Dist is also a function of A . The value of A which minimizes Dist is the optimal size of the imaginary sample to be inherited from a pathogen group to individual pathogens.

3. Results

3.1 Comparison of ML Estimates for Individual Pathogens and Grouped Estimates

Only 10 of the pathogens in the bacteremia database (13% out of 76) have been isolated more than 50 times. The counts available for estimation of susceptibility are even smaller, because susceptibility is only tested for a selection of antibiotics. This indicates, that the ML estimates of susceptibility for most combinations of pathogens and antibiotics in this database are too uncertain to be useful. When averaged over all pathogens and antibiotics the distance between the estimated susceptibilities based on individual pathogens and the observed frequency was 16.3% (Dist = 16.3%). If the estimates based on individual pathogens were replaced by estimates based on the groups of pathogens given in Table 3, then the distance between the estimators and the observed frequencies rose to 16.7%.

3.2 Hierarchical Dirichlet Learning over Groups of Pathogens

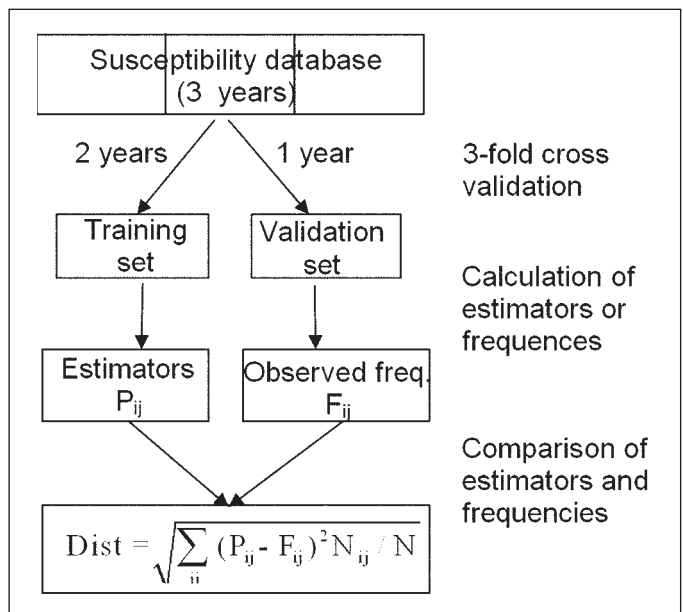
We shall now explore hierarchical Dirichlet learning over groups of pathogens, and we initially consider the *Proteus* group mentioned above, which has seven members (▶ see Table 2).

To illustrate Dirichlet learning of the susceptibility of a single pathogen to a single antibiotic, let us consider learning susceptibility of *Proteus spp.* to tobramycin using susceptibility data available for other members of the *Proteus* group. (The procedure can be applied to any of seven pathogens in the *Proteus* group.) First we assume a value for A , e.g. $A = 4$. This gives $\alpha_1 = \min(4, 99) = 4$, because for the *Proteus* group $N_1 = 99$ (see Table 2). The average susceptibility of the group is $P_1 = 72/99 = 0.728$. Next we calculate $\beta_1 = \alpha_1 \times P_1 = 4 \times 0.728 = 2.91$. Finally we can calculate the Dirichlet estimator as $P_{11} = (\beta_1 + M_{11})/(\alpha_1 + N_{11}) = (2.91 + 2)/(4 + 3) = 0.70$.

This result along with the ML estimator and the Dirichlet estimator for the remaining members of the *Proteus* group are shown in Table 2, assuming that $A = 4$.

Fig. 1

The procedure followed in the three-fold cross-validation



An optimal value for A can be determined empirically by minimizing the distance in Equation 4. We have applied the distance measure for tobramycin across the *Proteus* group (the summation in Eq. 4 was performed across one antibiotic and seven pathogens in the *Proteus* group). It was found that the distance reaches its minimum (20.2%) at $A = 4$ (▶ Fig. 2a), which is therefore the optimal imaginary sample size to be used for calculation of the Dirichlet estimator. Note, that the maximum value of Dist (25.8%) is observed at $A = 0$ and corresponds to the distance achieved by the ML estimator. The distance corresponding to the grouped estimator is observed at $A \rightarrow \infty$ and is equal to 25.2%.

Next we apply the same method to the *Proteus* group of pathogens, but averaged over all antibiotics. The result is given in ▶ Figure 2b, where it can be seen that for the

Proteus group the susceptibility estimates based on individual pathogens give Dist = 22.4% (value of Dist for $A = 0$). The estimates based on the entire *Proteus* group give Dist = 22.7% (value of Dist for $A \rightarrow \infty$). The lowest value, Dist = 20.9%, is obtained for $A = 2$.

Finally the method is applied to all pathogen groups across all antibiotics. As mentioned above, the individual and group-based estimates give Dist of 16.3% and 16.7%, respectively, and from ▶ Figure 3a (the full curve) it can be seen that the smallest value, Dist = 15.6%, is obtained for $A = 1$.

3.3 Revision of Groups of Pathogens

The value of the groups and of the group-based Dirichlet estimates depends on the quality of the groups. We therefore explored

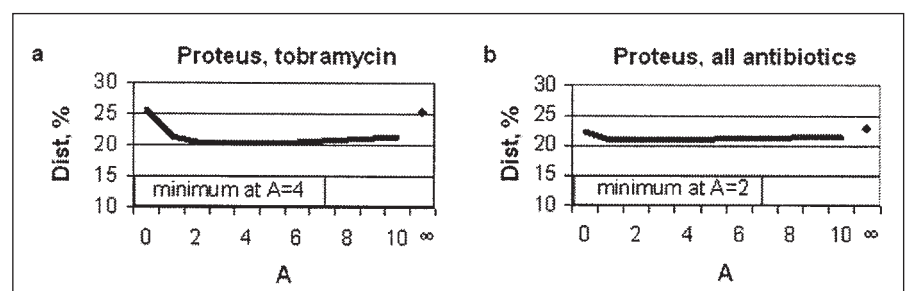


Fig. 2 The distance measure Dist as a function of A for the *Proteus* group and a) tobramycin; b) all antibiotics. The filled circles represent the distances corresponding to $A \rightarrow \infty$.

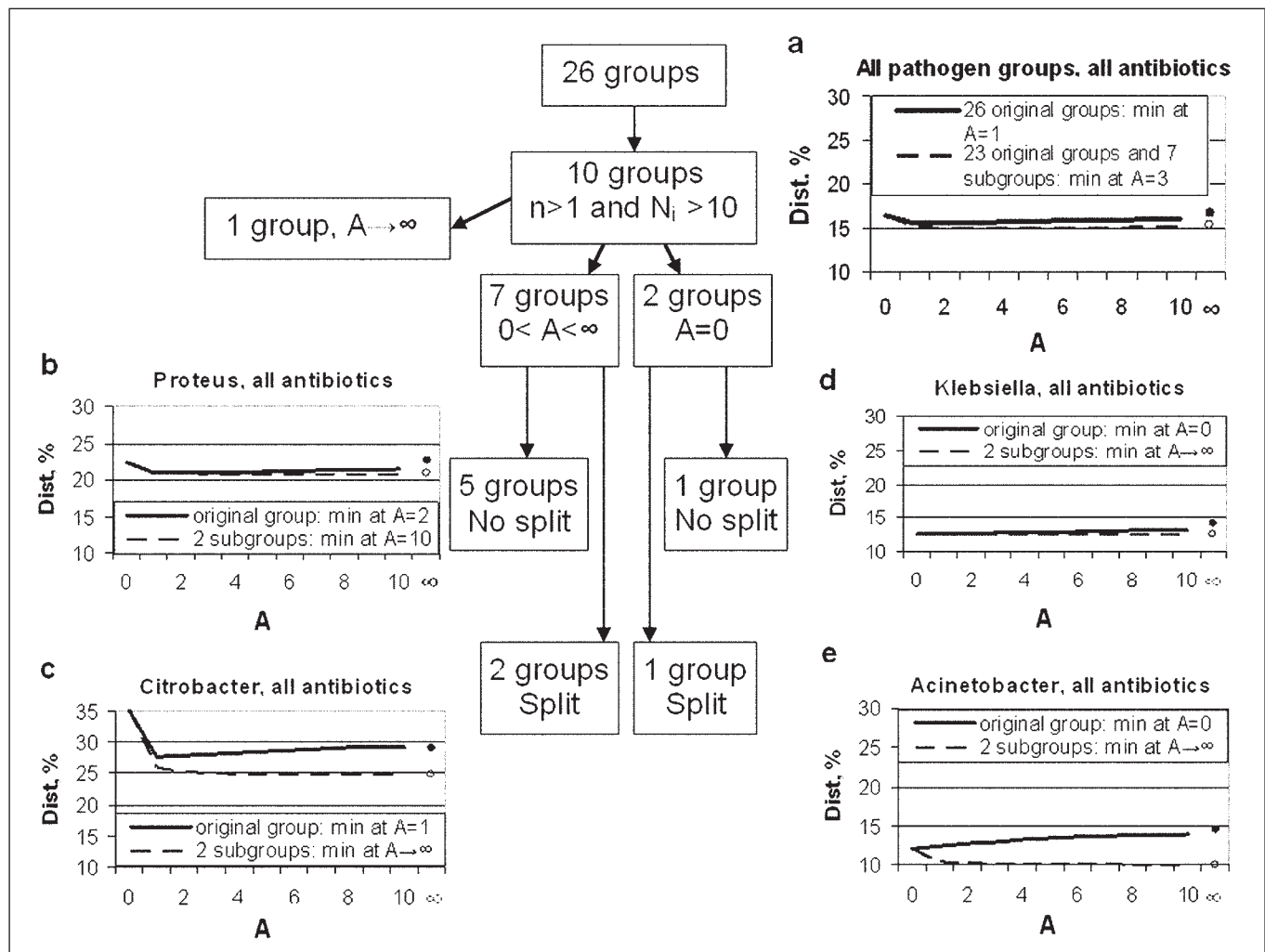


Fig. 3 The results of the Dirichlet learning applied to all pathogens in the database

whether dividing some of the pathogen groups into smaller subgroups might improve the estimates. Out of the 26 groups represented in the database 16 groups were considered not eligible for subdivision, either because the group consisted of a single pathogen ($n = 1$) or because the number of isolates in the group was very small ($N_i < 10$).

The remaining 10 groups were divided into three categories, depending on whether the optimal value of A for each group was $0 < A < \infty$, $A \rightarrow \infty$ or $A = 0$. These three categories are considered in more detail in the following.

$0 < A < \infty$

For seven groups (Coagulase-negative Staphylococcus ($n = 3$), *Proteus* ($n = 7$), *Pseudomonas* ($n = 9$), *Streptococcus viridans* ($n =$

5), *Enterococcus* ($n = 5$), *Citrobacter* ($n = 4$) and Other Gram Negative pathogens ($n = 18$)) the Dirichlet learning has minimum Dist with $0 < A < \infty$. These groups were checked for similarity between the class members by the Mantel-Haenszel method across all antibiotics tested. All groups, except Coagulase-negative *Staphylococcus*, had pathogens with susceptibility significantly different from the rest of the group ($p < 0.01$). Each of those six groups was split into two or three more homogeneous groups. For *Proteus*, *Pseudomonas*, *Streptococcus viridans* and *Enterococcus* groups the reduction of Dist resulting from such split was rather modest, prompting us to keep the original definitions of the groups as can for example be seen for the *Proteus* group in ► Figure 3b. Here the full curve, expressing the Dirichlet estimators derived using the original 7-member *Proteus* group,

is very close to the broken curve for the Dirichlet estimators derived using a 5-member *Proteus* subgroup and a 2-member *Providencia* subgroup. But for the *Citrobacter* and Other Gram Negative pathogen groups the results of the split give considerable advantage. For example, the measure Dist calculated after splitting *Citrobacter* group into two subgroups (the broken curve in ► Fig. 3c) is substantially smaller than Dist calculated for the original 4-member *Citrobacter* group (the smooth curve in Fig. 3c).

$A \rightarrow \infty$

For the *Enterobacter* ($n = 5$) group the distance Dist decays continuously for increasing A , indicating very good match between the members of this group.

A = 0

For the *Acinetobacter* ($n = 5$) and *Klebsiella* ($n = 3$) groups the minimum value of Dist was obtained for $A = 0$, indicating poor matching of the pathogens within a group. The split into new groups led to the conclusion to keep the original definition for *Klebsiella* (almost no difference between the curves in ► Fig. 3d) and to split the *Acinetobacter* group into two subgroups (► Fig. 3e).

Based on these considerations it was decided to subdivide the *Citrobacter*, Other Gram Negatives and *Acinetobacter* groups into two, three and two subgroups, respectively. These subgroups are marked in ► Table 3.

The distance for the individual ML estimators is of course not affected by the subdivision (Dist = 16.3%), but the group-based estimators have a reduced Dist = 15.4%, compared to Dist = 16.7% before the split. The effect on the Dirichlet learning of the subdivisions across all pathogen groups is shown in Figure 3a (the broken curve). The optimal value of A is $A = 3$ (compared to $A = 1$ in the case of the original 26 groups) and this gives Dist = 15.0%, marginally smaller than the value Dist = 15.6% obtained before the split.

3. Discussion

The steady decrease of bacterial susceptibility to antibiotics due to the use of antibiotics places an upper limit on the practical size of the databases from which the susceptibilities are estimated. Grouping of pathogens into groups with similar susceptibilities to antibiotics may be a useful strategy in the sense that it reduces the burden of remembering susceptibilities considerably and that it provides reasonable estimates for pathogens with very small counts. However, the results showed that under realistic assumptions about the upper limit on the number of bacterial isolates in the database these advantages came at the expense of a modest reduction of the accuracy of the estimates of susceptibility. An improvement of the estimates could be obtained by hierarchical Dirichlet learning, where the estimate is based both on data for the individual pathogen and for the group of pathogens.

Based on the results from the database it seems that for 23 of the 26 groups of pathogens

represented in the database, the grouping inherited from the TREAT project could not be substantially improved. For three groups, *Citrobacter*, Other Gram Negatives and *Acinetobacter*, some improvement in the estimates could be achieved by splitting the groups into subgroups. After splitting these groups the estimators based on pathogen groups were actually better than the estimators based on individual pathogens, reflecting the better match of pathogens within the subgroups. A further improvement in the estimates was obtained by hierarchical Dirichlet learning, where the optimal size of the imaginary sample inherited from the group was 3. One may argue that this is a relatively low number. The reason for this is at least partially that the size of the imaginary sample is limited to the size of the group. Since many groups have small counts, this reduces the effect of increasing A , because α remains small (see Eq. 3). However, even a value of 3 or 4 would considerably stabilize estimates for small pathogens.

There is an element of regression towards the mean in the proposed method – and this applies both to the additional grouping and (to a smaller extent) to grouping with additional Dirichlet learning. It is difficult to argue that this is unconditionally a bad thing from a clinical point of view – for example it could be argued that conservative estimates of susceptibilities for “high susceptibility” antibiotics may encourage caution in the prescribing of these. However, an important consideration is that Dirichlet learning is not only about (marginally) improving the statistics. It is also about providing some kind of credible estimate for rare pathogens. As an extreme (but not very rare) situation, consider the situation where a pathogen has been identified in a sample from a patient, but no prior data exists on the susceptibility of this pathogen. It is not acceptable not to treat the patient, because we do not have estimates for the susceptibilities, and grouping with or without Dirichlet provides a way out in most of these situations.

The choice of the parameters (A and the group revisions) was performed looking at the results of the threefold cross-validation. Such design gives optimistically biased estimates of classification accuracy. A fair comparison needs an external test set, or the choice of the best value for A using only the training set in the cross-validation schema

[7]. Unfortunately, the data set does not get any bigger than what we already have, and further subdivision into training, validation and test sets is thus not attractive. We emphasize that the formation of further groups is only a hypothesis that eventually must be tested on a new dataset and that the values for the loss function Dist is optimistic, i.e. represents training, not generalization accuracy.

It can be concluded that grouping of pathogens is a useful strategy. Grouping reduces the cognitive load of remembering susceptibilities and if the groups are carefully defined it improves the accuracy of the estimates of susceptibility. Indications for further subdivision of groups was only found in three groups and it can therefore be concluded that most of the pathogen groups originally defined by clinicians were well motivated. Both with and without further subgrouping, hierarchical Dirichlet learning allowed further improvement of the estimates and the Dirichlet learning turned out to be more robust against suboptimal grouping of the pathogens, as it was able to improve estimates both for the original grouping of pathogens and for the revised grouping.

References

1. Andreassen S, Kristensen B, Zalounina A, Leibovici L, Frank U, Schönheyder H. Hierarchical Dirichlet learning – filling in the thin spots in a database. In: Proceedings of the 9th Conference on Artificial Intelligence in Medicine; 2003 Oct; Cyprus. Springer; 2003. pp 274–283.
2. Heckerman D. Tutorial on Learning with Bayesian Networks. In: Jordan M, editor. Learning in Graphical Models. Cambridge, MA: MIT Press; 1999.
3. Filho J, Wainer J. Using a hierarchical Bayesian model to handle high cardinality attributes with relevant interactions in a classification problem. In: Proceedings of the 12th International Joint Conference on Artificial Intelligence; Jan 2007; Hyderabad, India. pp 2504–2509.
4. Cestnik B. Estimating probabilities: A crucial task in machine learning. In: Proceedings of the 9th European Conference on Artificial Intelligence; 1990; Stockholm, Sweden. pp 147–149.
5. Andreassen S, Leibovici L, Paul M, Nielsen A, Zalounina A, Kristensen L, Falborg K, Kristensen B, Frank U, Schönheyder H. A probabilistic network for fusion of data and knowledge in clinical microbiology. In: Husmeier, Dybowski, Roberts, editors. Probabilistic Modeling in Bioinformatics and Medical Informatics. London: Springer; 2005. pp 451–72.
6. Brier G. Verification of forecasts expressed in terms of probability. Monthly Weather Rev 1950; 78: 1–3.
7. Hastie T, Tibshirani R, Friedman J. The elements of statistical learning. Heidelberg: Springer; 2001.