FLICU: A Federated Learning Workflow for Intensive Care Unit Mortality Prediction

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Abstract—Although Machine Learning (ML) can be seen as a promising tool to improve clinical decision-making for supporting the improvement of medication plans, clinical procedures, diagnoses, or medication prescriptions, it remains limited by access to healthcare data. Healthcare data is sensitive, requiring strict privacy practices, and typically stored in data silos, making traditional machine learning challenging. Federated learning can counteract those limitations by training machine learning models over data silos while keeping the sensitive data localized. This study proposes a federated learning workflow for ICU mortality prediction. Hereby, the applicability of federated learning as an alternative to centralized machine learning and local machine learning is investigated by introducing federated learning to the binary classification problem of predicting ICU mortality. We extract multivariate time series data from the MIMIC-III database (lab values and vital signs), and benchmark the predictive performance of four deep sequential classifiers (FRNN, LSTM, GRU, and 1DCNN) varying the patient history window lengths (8h, 16h, 24h, 48h) and the number of FL clients (2, 4, 8). The experiments demonstrate that both centralized machine learning and federated learning are comparable in terms of AUPRC and F1-score. Furthermore, the federated approach shows superior performance over local machine learning. Thus, the federated approach can be seen as a valid and privacypreserving alternative to centralized machine learning for classifying ICU mortality when sharing sensitive patient data between hospitals is not possible.

Index Terms—Federated Learning, Recurrent Neural Network, ICU mortality, Prediction, Classification, MIMIC-III

I. INTRODUCTION

Healthcare generates a vast amount of data that, if adequately leveraged, has the potential to lead to improved clinical decision-making even at the single patient level. This potential is, however, yet to be fully realized. Machine Learning (ML) is a promising tool to make a step towards this goal, as it can achieve higher predictive performance against current conventional approaches for several clinical prediction tasks [1]–[3]. However, when it comes to accessing healthcare data, traditional ML faces several limitations. Due to their sensitive nature, patient data is usually stored in data silos and protected by legal and ethical practices. As a result, ML models could be trained on individual small local datasets. Nevertheless, this Local Machine Learning (LML) approach makes it challenging to obtain models that are generalizable enough, as those local datasets are generally biased and/or too limited. The standard approach to secure access to more extensive datasets is to anonymize, extract, and aggregate data from multiple healthcare institutions and train ML models centrally, outside the hospital premises. The advantage of this type of Centralized Machine Learning (CML) over LML is that the obtained models are more generalizable, as they are based on data from several healthcare institutions. However, this approach comes with heavy restrictions and several limitations in terms of scalability, security, cost-efficiency, and data privacy. For example, even anonymized data, when shared, can impose risks to patient privacy [4]. Thus, data is often required to remain inside the hospital premises.

Counteracting the previously mentioned limitations of CML and LML, Federated Learning (FL) [5], [6] trains the models over data silos while keeping the sensitive data localized (see Fig. 1). Its distributed design ensures that data is not shared between clients, for example, hospitals, but instead, only the local model parameters are shared, which are subsequently aggregated to a joint model. Thus, FL can be seen as a propitious solution for privacy-preserving ML within healthcare. An additional advantage of FL is its capability to be seamlessly integrated with existing electronic healthcare systems storing valuable data, like Electronic Health Records (EHRs) [7], [8].

One of the most researched clinical prediction tasks where ML has been applied, is predicting the probability of patient death during hospitalization [9]. The unit where this need is more prominent is arguably the Intensive care unit (ICU), since this is the unit where the patients with the most



Local Machine Learning (LML)

Centralized Machine Learning (CML)

Federated Learning (FL)

Fig. 1. Comparison of LML, CML, and FL.

severe and life-threatening medical conditions are admitted and cared for. As a result, the ICU is often the unit with the highest mortality rate. ICU mortality is defined as death during an ICU stay [10]. While the conventional way of mortality risk assessment is scoring systems, which are able to classify and stratify patients by their severity of illness [10], several traditional ML-based solutions have been recently proposed. For example, Johnson and Mark [11] focus on real-time ICU mortality prediction using logistic regression and gradient boosting, while Pattalung and Chaichulee [12] compare multiple ML algorithms for ICU mortality prediction. Additionally, Pattalung et al. [13] focus on predicting the risk of ICU mortality by combining Recurrent Neural Networks (RNNs) with interpretable explanations. Finally, Rinta-Koski et al. [14] propose Gaussian process classification for mortality prediction in a neonatal ICU.

Moreover, there are several recent FL solutions for inhospital mortality prediction [15], [16], which is defined as patient death during a hospital stay after being admitted to an ICU. Lee and Shin [15] demonstrated that FL can reach a comparable predictive performance to that of CML in predicting in-hospital mortality using a standard Long Short-Term Memory (LSTM). The authors compare the performance of CML and FL in a simple experimental FL setup with three clients and observe the influence on the performance of balanced and imbalanced distribution of data (amount not labels) amongst clients. Budrionis et al. [16] extended the work of Purushotham et al. [1], who benchmark deep learning algorithms to more traditional ML algorithms on MIMIC-III. They compare the performance of CML and FL more extensively than Lee et al. [15] with experiments in a more realistic deployment setting of FL, studying the influence of the number of clients, amount of data, and data distribution on predictive performance and inference and training duration.

Despite the FL-based solutions for in-hospital mortality prediction mentioned above, little emphasis has been given to ICU mortality prediction using FL. This paper addresses this limitation by: (1) proposing FLICU, a workflow for retrospective analysis of ICU mortality using FL alongside sequential deep neural network classifiers; (2) comparing the proposed FL solution against LML and CML in terms of predictive performance using an extract from the MIMIC-III database; (3) benchmarking four common sequential neural network architectures (1DCNN, FRNN, LSTM, and GRU) as parts of our workflow for different patient history window lengths (8h, 16h, 24h, and 48h before the discharge/death event in the ICU); (4) studying the sensitivity of the four FL models as the number of FL clients varies (2, 4, and 8).

II. PROBLEM FORMULATION

The problem studied in this paper can be formulated as a binary classification problem for ICU mortality prediction, where the label indicates whether a patient died during an ICU stay or got discharged. Given a set of p ICU patients, we define \mathcal{D} to be a collection of multivariate time series variables, with $|\mathcal{D}| = p$. Each $\mathcal{D}_i \in \mathcal{D}$ describes a set of vital signs and lab tests of the i^{th} ICU patient over time and contains qunivariate time series, with $|\mathcal{D}_i| = q$. The dimensionality (i.e., length) of the j^{th} time series $\mathcal{D}_{ij} \in \mathcal{D}_i$ may vary due to the variable sampling rates used for collecting the vital signs and lab values.

The objective of the CML approach is to learn a function $h_{CML}(\cdot)$ using \mathcal{D} , such that, given an ICU patient, it assesses whether the patient will die during an ongoing ICU admission. Moreover, consider a set of K clients, each having its own patient cohort $\mathcal{D}^k \subset \mathcal{D}$, such that $\mathcal{D}^a \cap \mathcal{D}^b = \emptyset, \forall (a, b) \in [1, K] \times [1, K]$. For LML, the goal is to build a set of classifiers $h_{LML}^k(\cdot)$, using $\mathcal{D}^k, \forall k \in [1, K]$, for solving the binary classification task of ICU mortality prediction locally at each client.

For FL, we build a local classifier $h_{FL}^k(\cdot)$ using \mathcal{D}^k for each client $k \in [1, K]$ and denote with w^k the set of the local weights learned by $h_{FL}^k(\cdot)$. Our objective is to define a global classifier $h_{FL}(\cdot)$ that is learned as a function of the local weights, i.e., $h_{FL}(\{w^1, \ldots, w^K\})$, that optimizes its weight configuration without sharing the local datasets. For example, $h_{FL}(\cdot)$ can be a weighted average of the local weights.

III. FLICU: A FEDERATED LEARNING WORKFLOW FOR INTENSIVE CARE UNIT MORTALITY PREDICTION

The proposed workflow comprises three steps: (1) feature extraction within a time window, (2) local FL model training, and (3) global FL model training.

A. Feature Extraction within a Time Window

For each ICU patient *i*, we identify one of two critical time points, i.e., the time of death in the ICU (positive class) or the time of discharge from the ICU (negative class). Given a fixed time window W (8h, 16h, 24h, and 48h), for each $\mathcal{D}_{ij} \in \mathcal{D}_i$, and based on Pattalung et al. [13], we only consider the medical events that occurred within W hours before the last recorded vital sign or lab value. Knowing the time of ICU death/discharge, we assume that the most important information about the critical event is at the end of the ICU stay, and we want to explore how much of this information (window size) is really relevant based on the predictive performance achieved by the model.

For each W, we extract vital signs and lab values. As vital signs and lab values have different temporal characteristics (0.5–1.5 vital signs per hour, 1-2 lab values per 8 hours), the variables corresponding to vital signs are re-sampled in 1h time intervals, with mean as aggregation function, while lab value variables are re-sampled in 8h time intervals. Missing values are imputed using linear interpolation, as eliminating patients can bias the study. Furthermore, if certain variables are never observed for a patient, their values are set to the variable mean.

B. Local FL Model Training

In this study, we explore four neural network architectures. We first use a one-dimensional convolutional neural network (1DCNN), which creates a convolution kernel that is convolved with the input layer over one dimension. Additionally, we use three sequential deep learning architectures: a Fully-connected RNN (FRNN) architecture [17], and its two adaptations, i.e., a Long Short-Term Memory (LSTM) architecture [18], and a Gated Recurrent Unit (GRU) architecture [19].

For each client $k \in [1, K]$, the local FL models $h_{FL}^k(\cdot)$ are trained using their local cohort \mathcal{D}^k , and each set of local weights w^k is then passed to the central server. The local model consists of two parallel input channels (one for vitals and one for labs), with one Conv1D layer followed by one Flatten layer (kernel sizes 1 and 8) each, for the 1DCNN model, or with 3 RNN layers of 16 units each for the three sequential neural network classifiers (according to [13]). For all classifiers, we perform batch normalization subsequentially, followed by a concatenation of the outputs and fusion of the concatenated outputs via two fully connected layers. We calculate the final outputs ([0,1]) with a Sigmoid layer computing the risk of death in the ICU or ICU discharge. Moreover, we use Adaptive Moment Estimation (Adam) optimization [20] and binary cross-entropy loss function, which is suitable for binary classification tasks.

C. Global FL Model Training

We consider K clients, each having its own local patient cohort $\mathcal{D}^k, k \in [1, K]$. Initially, centrally (i.e., in the central server), we initialize a global model that is shared with all the clients, whereby each client represents one hospital. Subsequently, we conduct several FL rounds: all clients train their local models on their local data based on the received global model (in defined epochs and mini-batch size), then, the clients send the resulting local model to the global server, and the server aggregates the local models and updates the global model with the aggregated results. The FL rounds are repeated until a defined stopping criterion is met.

The objective for FL is to optimize the global model parameters using an aggregation of the local model parameters. This is accomplished by minimizing the following function $f_{FL}(w) = \sum_{k=1}^{K} \frac{n_k}{n} f_{FL}^k(w)$, with $f_{FL}^k(w) = \frac{1}{n_k} L(\mathcal{D}^k, w)$, $n_k = |\mathcal{D}^k|$, and w denoting the global model weights [5].

Our FL model training approach is based on the Federated Averaging (FedAvg) algorithm [5]. FedAvg is most commonly used for FL with neural networks, an algorithm based on iteratively averaging the stochastic gradient descent (SDG) weights generated locally. It has been shown that FedAvg is robust for non-IID and imbalanced data distributions [5], which is very common for medical data. In FedAvg, the local models are updated multiple times (multiple batch gradient calculations) before sending the model weights back to the server for aggregation, contrary to Federated SGD (FedSGD), where a single step of gradient descent is performed per client in each FL round.

Al	Algorithm 1: Global FL Model Training					
F	Result: Optimized global model					
1 i1	1 initialize w_0 ;					
2 V	2 while stopping criterion not met do					
3	foreach client $k \in [1, K]$ do					
4	download w from central server;					
5	$w^k \leftarrow w;$					
6	foreach mini-batch do					
7	$ w^k \leftarrow w^k - \eta g^k;$					
8	end					
9	return w^k to central server;					
10						
11	update $w \leftarrow \sum_{k=1}^{K} \frac{n_k}{n} w^k$ in central server;					
12 e	12 end $\sum_{n=1}^{\infty} \frac{1}{n}$					

The pseudocode of our approach is presented in Algorithm 1, inspired by the FedAvg algorithm. In line 1, we initialize the global model weights w_0 in the central server. Then, the central server shares the current global model weights with the selected clients at the beginning of each FL round (lines 4 and 5). Subsequently, each client k computes the gradient $g^k = \nabla f_{FL}^k(w^k)$ using its local data and performs local updates with fixed learning rate η (line 7) in multiple iterations (dependent on mini-batch size), resulting in w^k . Finally, the weights are returned to the central server (line 9), and the results are aggregated and updates applied to the central server (line 11). The previously described steps are iterated for several FL rounds.

In our FedAvg setup, all clients perform computations on each FL round, as this is more suitable for the domain. Each client performs 1 training pass over the local dataset per FL

TABLE I PATIENT DEMOGRAPHICS OF FINAL STUDY COHORT.

Demographics	Total	Death	Survival	
Patients	19414	1892	17522	
Gender				
Female	8582	879	7703	
Male	10832	1013	9819	
Ethnicity				
Caucasian	13706	6021	7685	
African American	1447	801	646	
Asian	445	174	271	
Hispanic/Latino	604	249	355	
Others/Unknown	3212	1337	1875	

round, and the local mini-batch size for client updates is dependent on the number of clients K (64/K).

IV. EMPIRICAL EVALUATION

A. Dataset

We use the MIMIC-III dataset [21] for this study, which is a publicly available critical care database containing deidentified clinical data of patients admitted to an ICU at the Beth Israel Deaconess Medical Center (BIDMC) from 2001 to 2012. We follow the approach described in Pattalung et al. [13] for the pre-processing and feature extraction steps, expanding on the publicly available code of the mimic-code GitHub repository [22], [23]. We extract patient demographic information for pre-processing and labeling (icustay id, first icu stay, first careunit, length of stay icu, deathtime icu), as well as statistical purposes (gender, ethnicity, admission age), which are presented briefly in Tables I and II. Note that patients older than 89 have age values of 300 in MIMIC-III due to privacy reasons, which are set to 90 in this study to reflect reality more closely. Additionally, we extract patients' vital signs and lab values, collected during their ICU stays for modeling. We obtain 23 ICU mortality clinically relevant variables, which are in the form of time series [13], 7 vital signs (heartrate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, temperature, peripheral oxygen saturation), and 16 lab values (albumin, blood urea nitrogen, bilirubin, lactate, bicarbonate, band neutrophi, chloride, creatinine, glucose, hemoglobin, hematocrit, platelet count (platelet), potassium, partial thromboplastin time, sodium, white blood cells). Additionally, we prune data outliers and perform grouping of similar clinical variables (using the item ids, see [22]). Finally, we filter the patients, following the steps described below, resulting in a total of 19414 patients:

- 1) Filter for the first ICU stay of each patient.
- Exclude patients admitted to the Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU).
- 3) Filter for patients whose length of stay in the ICU was at least 48h to ensure sufficient data for analysis.
- 4) Filter for patients for which observations (vital signs and laboratory values) are recorded for at least 48h.

Labels are assigned to each unique patient. Patients that died during the ICU stay are included in the positive group (label = 1). Patients being alive throughout the entire ICU stay, up until ICU discharge, are included in the negative group (label

TABLE II Admission age and length of stay of final study cohort.

	Admi	ssion age	(years)	Length of 1st ICU stay (days)			
	Total	Death	Survival	Total	Death	Survival	
Count	19414	1892	17522	19414	1892	17522	
Mean	64.83	68.56	64.42	6.82	9.46	6.53	
Std	17.09	16.15	17.14	7.50	8.90	7.28	
Min	15.19	16.47	15.19	2.00	2.01	2.00	
Max	90.00	90.00	90.00	153.93	97.30	153.93	

= 0). The labeling process resulted in 1892 patients (9.75%) in the positive class and 17522 (90.25%) in the negative class, which demonstrates the high class imbalance of the dataset.

B. Evaluation Strategy

We evaluate LML, CML, and FL on the same testing data splits using 5-fold cross-validation to eliminate randomness induced by dataset partitioning. All folds consist of 20% of the whole data each, whereby each fold serves as a testing set once. The remaining four folds are again split into 85% training and 15% validation set (CML approach). In the FL approach, the remaining data is firstly split into K cohorts (one per client), then each client's cohort is also split into 85% training and 15% validation set. We use a stratified sampling process for each splitting procedure because the data is highly imbalanced. To further ensure comparability, each neural network type is initialized with the same random weights to ensure the same starting point for the optimization in all approaches.

In all three approaches, CML, LML, and FL, firstly, we normalize the training and validation datasets. The class imbalance is taken into consideration by using class weights during model training by giving both positive and negative classes equal importance on gradient updates. We train the CML models on a mini-batch size of 64 and the LML models (2, 4, and 8 clients) on a mini-batch size of 64/K using a maximum of 100 epochs and an initial learning rate of 0.01, which decreases by 50% every 5 epochs to avoid undesirable divergent behavior in the loss function. Furthermore, we use early stopping via monitoring the validation loss with a patience value of 30. When reaching this criterion, we restore the weights of the epoch with the best validation results and test the final model on the normalized testing dataset.

We train all FL clients' local models in 1 epoch to maintain a high training speed. This is considerably lower than the CML, and LML approaches due to the iterative averaging process, a mini-batch size of 64/K, and a maximum of 100 FL rounds (similar to max epochs in CML). As in CML, the initial learning rate is set to 0.01 for all clients. Each training round follows the aggregation of weights with FedAvg. We pass the global model with averaged weights to the clients and evaluate them locally on their validation dataset. We monitor the average validation loss as FL stopping criterion, with the patience set to the same number as in CML and LML: if the client's averaged validation loss does not improve over 30 rounds, we initiate early stopping. Eventually, we restore the FL model with the lowest loss and test it on the normalized test dataset. Finally, we repeat this process for 2, 4, and 8 clients.

C. Results and Discussion

We tackle the task of predicting ICU mortality using multiple sequential classifiers in a federated setting on the MIMIC-III dataset. We evaluate the predictive performance of 1DCNN and three types of RNNs (FRNN, LSTM, and GRU), varying the patient history window lengths (8h, 16h, 24h, and 48h) and the number of FL clients (2, 4, and 8). Additionally, we compare the results of the three approaches, FL, LML, and CML. In Table III, we comparatively present the performance of all combinations using the following evaluation metrics: AUPRC and F1-Score.

Recent research on ICU and in-hospital mortality prediction using MIMIC-III mainly focuses on AUC as an evaluation metric [13], [15]. Although AUC is widely used for evaluating classifiers built on imbalanced datasets, there is the drawback of the unreliability of the estimates when there is a low sample size of the minority class [24]. Thus, in this study, we focus our evaluation on AUPRC and F1-Score, which are common alternatives and better suited for highly imbalanced data.

We report the mean and standard deviation (std) of all approaches as follows: mean and std of all 5-fold models in CML, of $k \times 5$ -fold local models LML, and of all 5-fold global models in FL.

1DCNN vs FNN vs LSTM vs GRU Comparing the four classifiers, it is evident that all RNN classifiers, FRNN, LSTM, and GRU, are comparable. Nevertheless, on average, all three RNN classifiers are superior to 1DCNN, which underlines the fact that RNNs are designed for sequences, while CNNs are not capable of effectively learning temporal information.

Window Length All four classifiers (1DCNN, FRNN, LSTM, and GRU) have similar performance across all time windows (8h, 16h, 24h, and 48h) and approaches (CML, LML, and FL). This suggests that there is valuable information to be learned in all the windows and enough relevant information is also prevalent in the smaller time windows. This might be due to the fact that the most crucial information is observed shortly before the event of interest (ICU death/discharge). It could be argued that for dying patients, the shorter the window length, the higher the density of relevant information contained in vital signs and lab values.

Number of Clients The experiments were performed with 2, 4, and 8 FL clients, simulating a set of independent (LML) or collaborating (FL) hospitals. In LML, we notice that the performance continuously decreases with higher K as the data available at each client decreases, and it could prove to be biased and/or too limited. In FL, the results are comparable across all different number of clients, and there is no clear pattern to be observed. However, when the performance of FL with a certain number of clients is lower, the standard deviation is higher as well. This suggests that the data distribution influences the result in some rounds of the k-fold cross-validation, which could be solved by further optimization of the FL setup.

Comparison of CML, LML, and FL Our results illustrate that CML and FL have comparable performance for predicting ICU mortality. Both approaches perform well on the classification task considering the high class imbalance of only 9.75% positive samples, with a baseline AUPRC of 0.10. Additionally, it can be verified that the behavior regarding the different window sizes matches between FL and CML. Extending the study by adding attention layers to the used classifiers could further verify whether the classifiers are learning the same patterns. Furthermore, when comparing the predictive performance of LML and FL, it becomes apparent that FL performs considerably better than LML, which proves FL to be the better option over LML when data sharing amongst hospitals is not possible.

Limitations The data used (MIMIC-III) is from a single medical center, and selection bias is unavoidable. In addition, the data used is from the end of the ICU stay, knowing the time of death/discharge, and does not allow for early prediction. Thus, the retrospective nature of the analysis does not permit us to use this workflow within the scope of decision-support. Nevertheless, this study can be seen as the basis for further analysis of interpretability and feature importance.

V. CONCLUSION

We presented a federated learning workflow for predicting ICU mortality using the MIMIC-III benchmark database. We compared the predictive performance of the proposed FL approach against LML and CML, using several sequential deep neural network classifiers (1DCNN, FRNN, LSTM, GRU), expanding windows of temporal data (8h, 16h, 24h, and 48h), and different numbers of FL clients (2, 4, and 8). Our findings suggest that both CML and FL are comparable in terms of AUPRC and F1-Score. Additionally, FL is superior to LML, which is the only other alternative to guarantee data privacy.

Since the main focus of this study was on comparing the different approaches, the FL setup has not been fully optimized. Thus, future work could involve experimentation on alternative design choices, such as using fixed mini-batch size, taking into consideration communication costs, and using real client/server FL architecture. Additional improvements could include exploring the general effect of local class distribution (fraction of deaths/dismissals per local client) within FL and employing rolling windows over each patient's history. Finally, integrating an interpretability method to determine the most important features in predicting ICU mortality in an FL approach is worth studying.

Overall, the FLICU workflow that we present in this study is for predicting ICU mortality using the MIMIC-III database. Nevertheless, our approach shows great promise to be easily extended not only to predict ICU mortality using different ICU databases but also on different clinical prediction tasks.

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TABLE III
PREDICTIVE PERFORMANCE OF 1DCNN, FRNN, LSTM, AND GRU.

$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		AUPRC				F1-Score			
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		1DCNN	FRNN	LSTM	GRU	1DCNN	FRNN	LSTM	GRU
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	8h								
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	CML	0.68 ± 0.02	0.71 ± 0.02	0.71 ± 0.02	0.72 ± 0.02	0.86 ± 0.02	0.83 ± 0.02	0.83 ± 0.02	0.84 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML2	0.64 ± 0.04	0.69 ± 0.02	0.67 ± 0.04	0.67 ± 0.02	0.77 ± 0.04	0.81 ± 0.02	0.80 ± 0.03	0.80 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML4	0.63 ± 0.04	0.66 ± 0.05	0.68 ± 0.04	0.67 ± 0.03	0.76 ± 0.04	0.79 ± 0.03	0.80 ± 0.03	0.80 ± 0.03
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	LML8	0.58 ± 0.09	0.61 ± 0.07	0.61 ± 0.10	0.63 ± 0.06	0.71 ± 0.10	0.74 ± 0.07	0.75 ± 0.09	0.76 ± 0.06
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL2	0.70 ± 0.01	0.69 ± 0.03	0.70 ± 0.02	0.70 ± 0.02	0.81 ± 0.01	0.81 ± 0.02	0.82 ± 0.02	0.82 ± 0.01
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL4	0.66 ± 0.03	0.67 ± 0.04	0.70 ± 0.03	0.64 ± 0.04	0.79 ± 0.03	0.80 ± 0.03	0.82 ± 0.02	0.78 ± 0.03
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL8	0.68 ± 0.01	0.67 ± 0.04	0.67 ± 0.05	0.69 ± 0.04	0.80 ± 0.01	0.80 ± 0.03	0.81 ± 0.03	0.81 ± 0.03
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	16h								
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	CML	0.66 ± 0.04	0.72 ± 0.02	0.72 ± 0.02	0.71 ± 0.04	0.79 ± 0.03	0.83 ± 0.02	0.84 ± 0.02	0.83 ± 0.03
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML2	0.65 ± 0.04	0.68 ± 0.03	0.69 ± 0.03	0.69 ± 0.03	0.78 ± 0.03	0.80 ± 0.03	0.82 ± 0.02	0.81 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML4	0.63 ± 0.05	0.65 ± 0.05	0.67 ± 0.04	0.65 ± 0.06	0.76 ± 0.04	0.78 ± 0.04	0.80 ± 0.03	0.78 ± 0.05
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML8	0.56 ± 0.07	0.59 ± 0.09	0.63 ± 0.09	0.64 ± 0.07	0.70 ± 0.07	0.73 ± 0.08	0.76 ± 0.08	0.77 ± 0.06
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL2	0.67 ± 0.02	0.67 ± 0.03	0.71 ± 0.02	0.69 ± 0.03	0.80 ± 0.02	0.79 ± 0.03	0.83 ± 0.02	0.81 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL4	0.67 ± 0.04	0.70 ± 0.02	0.66 ± 0.07	0.68 ± 0.05	0.80 ± 0.03	0.82 ± 0.01	0.79 ± 0.05	0.81 ± 0.03
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL8	0.64 ± 0.04	0.70 ± 0.03	0.69 ± 0.02	0.65 ± 0.05	0.78 ± 0.04	0.82 ± 0.02	0.82 ± 0.01	0.79 ± 0.04
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	24h								
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	CML	0.67 ± 0.02	0.71 ± 0.03	0.72 ± 0.03	0.72 ± 0.02	0.79 ± 0.02	0.82 ± 0.03	0.83 ± 0.02	0.84 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML2	0.68 ± 0.02	0.68 ± 0.04	0.68 ± 0.04	0.69 ± 0.03	0.80 ± 0.02	0.81 ± 0.03	0.80 ± 0.03	0.81 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML4	0.63 ± 0.04	0.67 ± 0.03	0.66 ± 0.07	0.68 ± 0.03	0.77 ± 0.04	0.80 ± 0.03	0.79 ± 0.05	0.80 ± 0.02
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML8	0.60 ± 0.06	0.61 ± 0.10	0.63 ± 0.07	0.62 ± 0.09	0.74 ± 0.06	0.74 ± 0.09	0.76 ± 0.07	0.75 ± 0.08
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL2	0.66 ± 0.03	0.69 ± 0.02	0.71 ± 0.02	0.71 ± 0.02	0.78 ± 0.03	0.81 ± 0.02	0.83 ± 0.02	0.83 ± 0.01
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL4	0.67 ± 0.03	0.67 ± 0.06	0.70 ± 0.01	0.65 ± 0.08	0.80 ± 0.03	0.80 ± 0.04	0.83 ± 0.01	0.78 ± 0.06
$ \begin{bmatrix} \text{CML} & 0.68 \pm 0.02 & 0.72 \pm 0.03 & 0.71 \pm 0.03 & 0.72 \pm 0.03 & 0.81 \pm 0.02 & 0.83 \pm 0.02 & 0.82 \pm 0.02 & 0.83 \pm 0.02 \\ \text{LML2} & 0.64 \pm 0.04 & 0.68 \pm 0.04 & 0.70 \pm 0.01 & 0.70 \pm 0.02 & 0.77 \pm 0.04 & 0.81 \pm 0.03 & 0.82 \pm 0.01 & 0.82 \pm 0.01 \\ \text{LML4} & 0.61 \pm 0.06 & 0.64 \pm 0.04 & 0.68 \pm 0.04 & 0.66 \pm 0.04 & 0.66 \pm 0.04 & 0.74 \pm 0.06 & 0.77 \pm 0.04 & 0.80 \pm 0.03 & 0.79 \pm 0.04 \\ \text{LML8} & 0.58 \pm 0.05 & 0.62 \pm 0.05 & 0.63 \pm 0.08 & 0.63 \pm 0.08 & 0.71 \pm 0.03 & 0.75 \pm 0.05 & 0.75 \pm 0.07 & 0.76 \pm 0.07 \\ \text{FL2} & 0.68 \pm 0.03 & 0.70 \pm 0.03 & 0.68 \pm 0.06 & 0.71 \pm 0.03 & 0.80 \pm 0.02 & 0.81 \pm 0.02 & 0.80 \pm 0.04 & 0.82 \pm 0.02 \\ \end{bmatrix} $	FL8	0.67 ± 0.03	0.68 ± 0.04	0.66 ± 0.05	0.65 ± 0.05	0.80 ± 0.02	0.81 ± 0.03	0.80 ± 0.03	0.79 ± 0.04
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	48h								
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	CML	0.68 ± 0.02		0.71 ± 0.03	0.72 ± 0.03	0.81 ± 0.02	0.83 ± 0.02	0.82 ± 0.02	0.83 ± 0.02
$ \begin{bmatrix} LML8 \\ FL2 \end{bmatrix} 0.58 \pm 0.05 & 0.62 \pm 0.05 & 0.63 \pm 0.08 & 0.63 \pm 0.08 & 0.72 \pm 0.05 & 0.75 \pm 0.07 & 0.76 \pm 0.07 \\ FL2 \end{bmatrix} 0.68 \pm 0.03 & 0.70 \pm 0.03 & 0.68 \pm 0.06 & 0.71 \pm 0.03 & 0.80 \pm 0.02 & 0.81 \pm 0.02 & 0.80 \pm 0.04 & 0.82 \pm 0.02 \\ \end{bmatrix} $	LML2	0.64 ± 0.04		0.70 ± 0.01	0.70 ± 0.02	0.77 ± 0.04	0.81 ± 0.03	0.82 ± 0.01	0.82 ± 0.01
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LML4	0.61 ± 0.06	0.64 ± 0.04	0.68 ± 0.04	0.66 ± 0.04	0.74 ± 0.06	0.77 ± 0.04	0.80 ± 0.03	0.79 ± 0.04
	LML8	0.58 ± 0.05	0.62 ± 0.05	0.63 ± 0.08	0.63 ± 0.08	0.72 ± 0.05	0.75 ± 0.05	0.75 ± 0.07	0.76 ± 0.07
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	FL2	0.68 ± 0.03	0.70 ± 0.03	0.68 ± 0.06	0.71 ± 0.03	0.80 ± 0.02	0.81 ± 0.02	0.80 ± 0.04	0.82 ± 0.02
	FL4	0.66 ± 0.03	0.69 ± 0.04	0.70 ± 0.03	0.67 ± 0.06	0.79 ± 0.03	0.81 ± 0.02	0.82 ± 0.02	0.80 ± 0.04
$ \left \begin{array}{c c c c c c c c c c c c c c c c c c c $	FL8	0.67 ± 0.03	0.68 ± 0.03	0.72 ± 0.02	0.67 ± 0.05	0.80 ± 0.01	0.81 ± 0.02	0.83 ± 0.01	0.81 ± 0.03

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