

Supporting Information

March 9, 2022

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1 Estimated AUCs for predicting death in the TCGA dataset using both aggregation criteria from tile to whole-slide images: average and 75th percentile

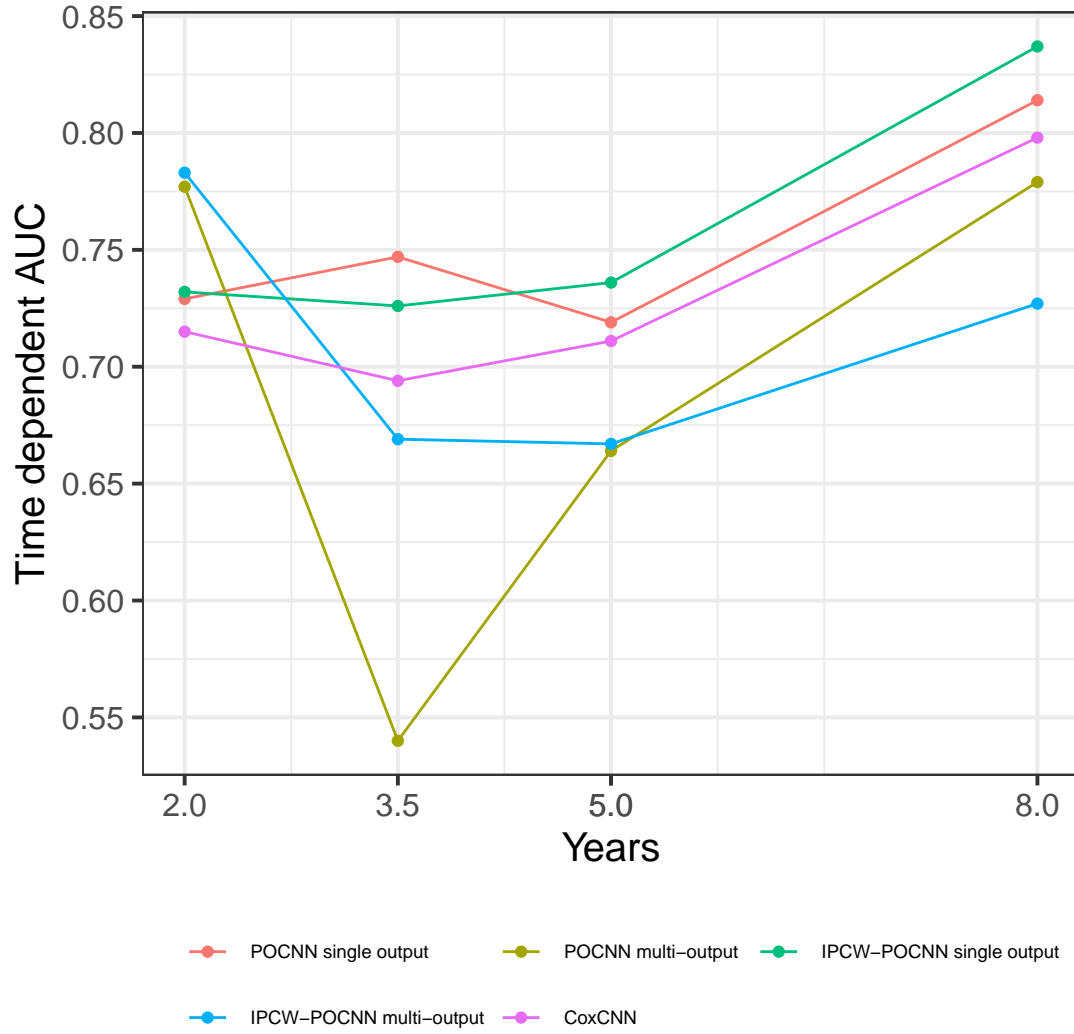


Figure 1: Estimated AUCs for predicting death at 2-year, 3.5-year, 5-year and 8-year, using the 75th percentile criteria to obtain a whole's slide prediction.

Table 1: Estimated AUCs for predicting death at 2-year, 3.5-year, 5-year and 8-year, using the average aggregation criteria.

CNN model	AUC(t=2)	AUC(t=3.5)	AUC(t=5)	AUC(t=8)
PO-CNN (one-time-point)	0.802	0.670	0.665	0.758
PO-CNN (single output)	0.750	0.772	0.730	0.822
PO-CNN (multi output)	0.781	0.532	0.671	0.776
IPCW-PO-CNN (single output)	0.736	0.731	0.720	0.832
IPCW-PO-CNN (multi output)	0.787	0.672	0.673	0.710
Cox-CNN	0.676	0.671	0.691	0.789

Table 2: Estimated AUCs for predicting death at 2-year, 3.5-year, 5-year and 8-year, using the 75th-percentile.

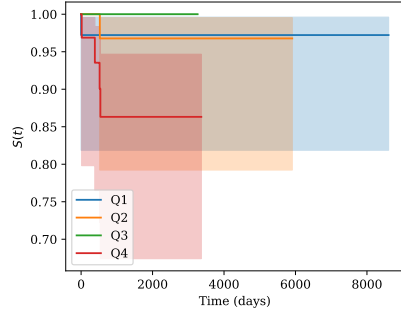
CNN model	AUC(t=2)	AUC(t=3.5)	AUC(t=5)	AUC(t=8)
PO-CNN (one-time-point)	0.805	0.684	0.660	0.735
PO-CNN (single output)	0.729	0.747	0.719	0.814
PO-CNN (multi-output)	0.778	0.540	0.664	0.779
IPCW-PO-CNN (single output)	0.732	0.726	0.736	0.837
IPCW-PO-CNN (multi output)	0.783	0.669	0.667	0.727
Cox-CNN	0.715	0.694	0.711	0.798

We included PO-CNN that uses as response variable a PO cumulative incidence computed only for one time point. We denoted this as PO-CNN one-time-point. This model is trained separately for each time point considered in the analysis and for this reason we only present the non-weighted version of it. Theoretically, multiple time points should perform as well or better than single time points, due to the fact that information across the time points is shared.

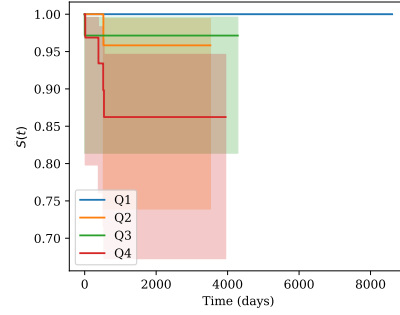
2 Kaplan-Meier survival curves stratified by quartiles of the predicted risk of death at different time points in the TCGA dataset (test set)

We show the Kaplan-Meier curves for risk groups where the risk groups are defined by quartiles of the predicted risk using the average criteria to obtain the individual risk from the tile’s risk predicted risk.

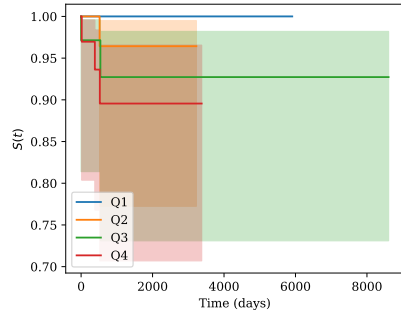
2.1 Time 2-year



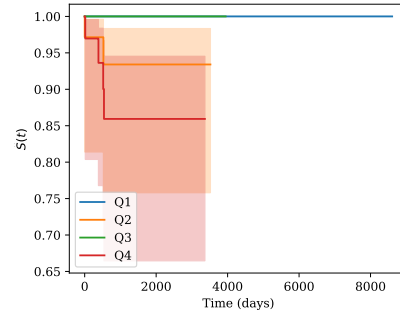
(a) CoxCNN



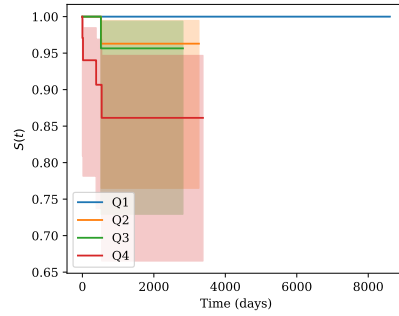
(b) POCNN single output



(c) POCNN multi-output



(d) IPCW-POCNN single output



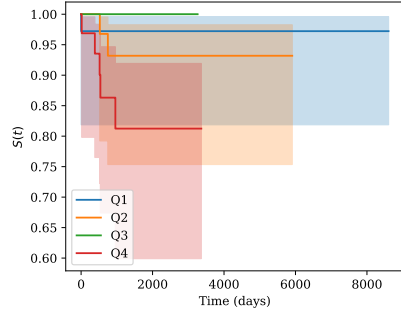
(e) IPCW-POCNN multi-output

Figure 2: Kaplan-Meier survival curves for 4 groups based on quartiles (Q1-Q4) of distribution of predicted risk of death at 2 years across models.

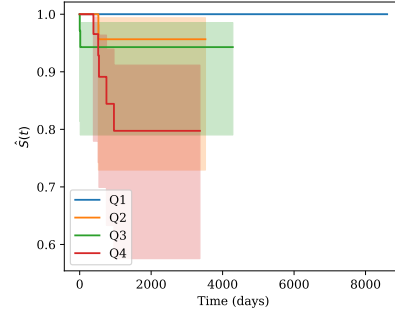
Table 3: Log-rank test comparing the survival curves for the four groups (Q1-Q4) at time 2 years across models.

		CoxCNN		POCNN single output		POCNN multi output	
		test_statistic	p value	test_statistic	p value	test_statistic	p value
Q1	Q2	0.00	0.98	1.69	0.31	1.03	0.31
	Q3	0.97	0.32	4.71	0.31	2.09	0.15
	Q4	2.00	0.16	-0.00	0.04	3.18	0.07
Q2	Q3	1.00	0.32	2.58	1.00	0.34	0.56
	Q4	1.91	0.17	2.58	0.17	1.05	0.31
Q3	Q4	4.18	0.04	1.91	0.17	0.21	0.64
		IPCW-POCNN single output		IPCW-POCNN multi-output			
		test_statistic	p value	test_statistic	p value		
Q1	Q2	2.09	0.15	1.03	0.31		
	Q3	0.00	1.00	1.03	0.31		
	Q4	4.30	0.04	4.30	0.04		
Q2	Q3	2.03	0.15	0.00	1.00		
	Q4	0.72	0.40	1.91	0.17		
Q3	Q4	4.18	0.04	1.91	0.17		

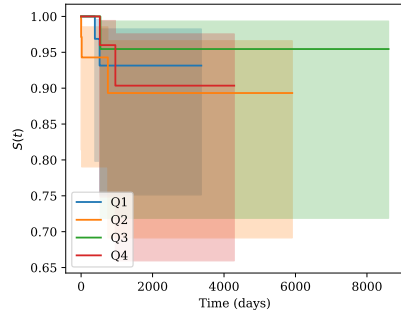
2.2 Time 3.5-year



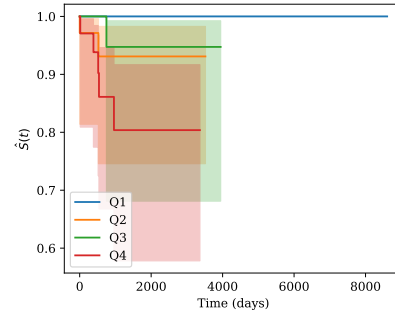
(a) CoxCNN



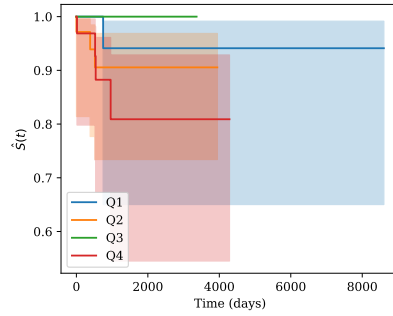
(b) POCNN single output



(c) POCNN multi-output



(d) IPCW-POCNN single output



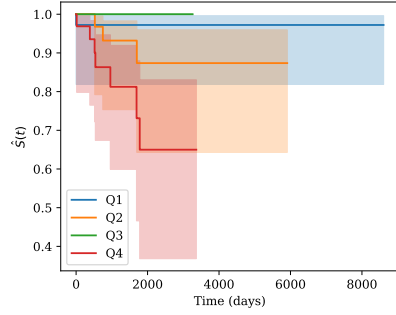
(e) IPCW-POCNN multi-output

Figure 3: Kaplan-Meier survival curves for 4 groups based on quartiles (Q1-Q4) of distribution of predicted risk of death at 3.5 years across models.

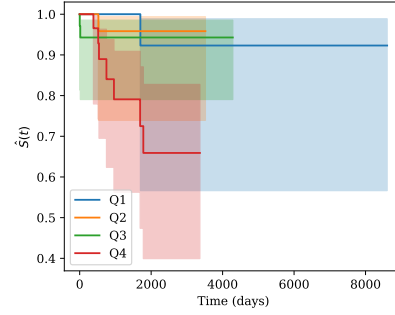
Table 4: Log-rank test comparing the survival curves for the four groups (Q1-Q4) at time 3.5 years across models.

		CoxCNN		POCNN single output		POCNN multi output	
		test_statistic	p value	test_statistic	p value	test_statistic	p value
Q1	Q2	0.37	0.54	1.03	0.31	0.24	0.62
	Q3	0.97	0.32	2.09	0.15	0.31	0.57
	Q4	3.00	0.08	5.45	0.02	0.00	0.98
Q2	Q3	2.03	0.15	0.34	0.56	1.05	0.31
	Q4	1.41	0.24	2.88	0.09	0.21	0.64
Q3	Q4	5.31	0.02	1.41	0.24	0.34	0.56
		IPCW-POCNN single output		IPCW-POCNN multi-output			
		test_statistic	p value	test_statistic	p value		
Q1	Q2	2.09	0.15	0.89	0.34		
	Q3	1.03	0.31	0.00	1.00		
	Q4	5.45	0.02	2.96	0.09		
Q2	Q3	0.34	0.56	0.89	0.34		
	Q4	1.41	0.24	0.82	0.37		
Q3	Q4	2.88	0.09	2.96	0.09		

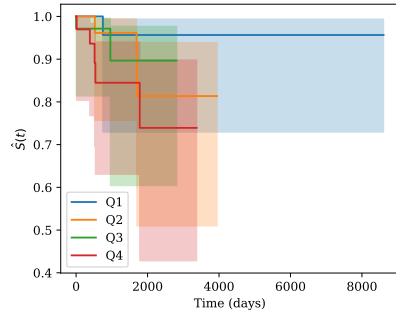
2.3 Time 5-year



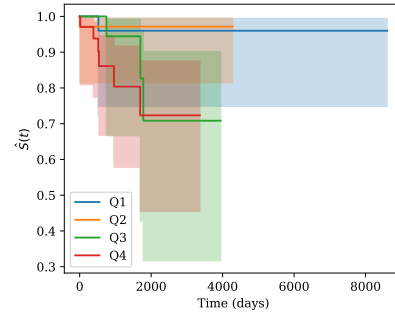
(a) CoxCNN



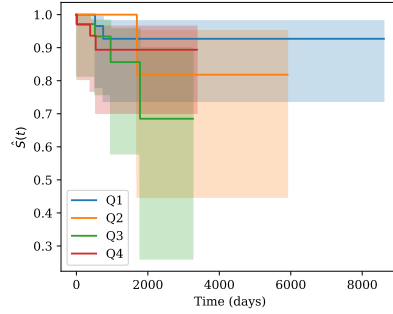
(b) POCNN single output



(c) POCNN multi-output



(d) IPCW-POCNN single output



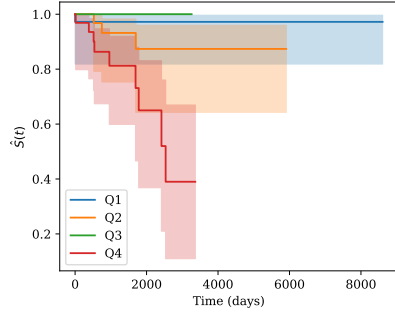
(e) IPCW-POCNN multi-output

Figure 4: Kaplan-Meier survival curves for 4 groups based on quartiles (Q1-Q4) of distribution of predicted risk of death at 5 years across models.

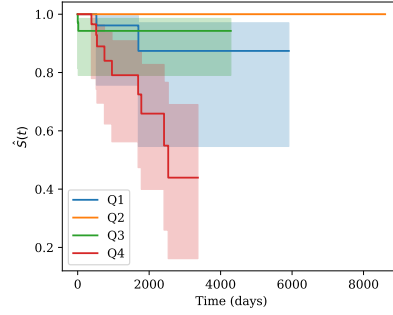
Table 5: Log-rank test comparing the survival curves for the four groups (Q1-Q4) at time 5 years across models.

		CoxCNN		POCNN single output		POCNN multi output	
		test_statistic	p	test_statistic	p	test_statistic	p
Q1	Q2	1.10	0.29	0.00	0.98	1.10	0.29
	Q3	0.97	0.32	0.37	0.54	0.37	0.54
	Q4	5.19	0.02	5.19	0.02	3.00	0.08
Q2	Q3	3.09	0.08	0.34	0.56	0.21	0.64
	Q4	1.84	0.17	5.01	0.03	0.56	0.46
Q3	Q4	7.67	0.01	3.14	0.08	1.41	0.24
		IPCW-POCNN single output		IPCW-POCNN multi-output			
		test_statistic	p	test_statistic	p		
Q1	Q2	0.00	0.98	0.00	0.98		
	Q3	1.10	0.29	0.78	0.38		
	Q4	4.06	0.04	0.24	0.62		
Q2	Q3	1.05	0.31	0.72	0.40		
	Q4	3.91	0.05	0.21	0.64		
Q3	Q4	1.13	0.29	0.16	0.69		

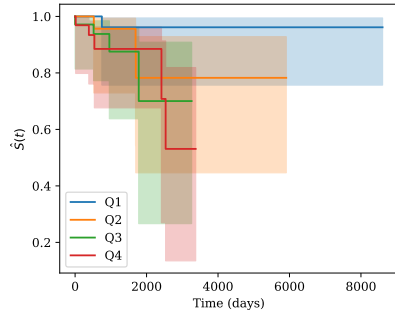
2.4 Time 8-year



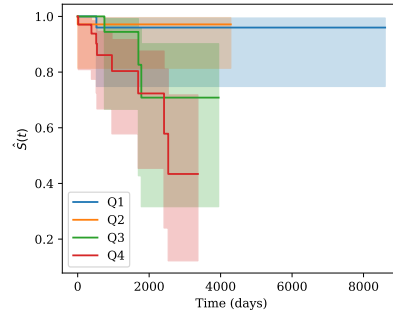
(a) CoxCNN



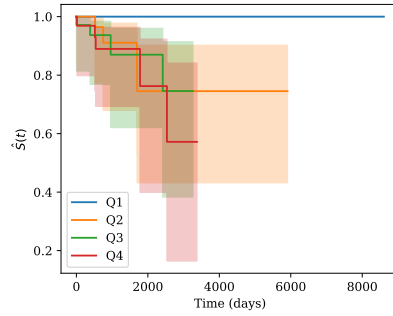
(b) POCNN single output



(c) POCNN multi-output



(d) IPCW-POCNN single output



(e) IPCW-POCNN multi-output

Figure 5: Kaplan-Meier survival curves for 4 groups based on quartiles (Q1-Q4) of distribution of predicted risk of death at 8 years across models.

Table 6: Log-rank test comparing the survival curves for the four groups (Q1-Q4) at time 8 years across models.

		CoxCNN		POCNN single output		POCNN multi output	
		test_statistic	p	test_statistic	p	test_statistic	p
Q1	Q2	1.10	0.29	1.97	0.16	1.10	0.29
	Q3	0.97	0.32	0.00	0.98	2.00	0.16
	Q4	7.61	0.01	5.43	0.02	3.00	0.08
Q2	Q3	3.09	0.08	2.03	0.15	0.16	0.69
	Q4	3.57	0.06	10.18	<0.005	0.56	0.46
Q3	Q4	10.18	<0.005	5.21	0.02	0.13	0.72
		IPCW-POCNN single output		IPCW-POCNN multi-output			
		test_statistic	p	test_statistic	p		
Q1	Q2	0.00	0.98	4.30	0.04		
	Q3	1.10	0.29	4.30	0.04		
	Q4	6.37	0.01	5.45	0.02		
Q2	Q3	1.05	0.31	0.00	1.00		
	Q4	6.16	0.01	0.13	0.72		
Q3	Q4	2.66	0.10	0.13	0.72		

3 Visualization of predictions of POCNN single output model at time 2 years; 3.5 years; 5 years and 8 years on selected patient images

Examples of predictions of POCNN single output model on selected patient images are visualized using heat-maps. In each of the following images, the panels from left to right visualize the predictions at 2 years; 3.5 years; 5 years and 8 years. We provide the clinical information associated to each image visualized.

Figure 6: From left to right: prediction at at 2 years; 3.5 years; 5 years and 8 years. Clinical information of a patient that had an event at 749 days: age: 46; race: white; ethnicity: not hispanic or latino; pathological stage: Stage X, and molecular subtype: LumA

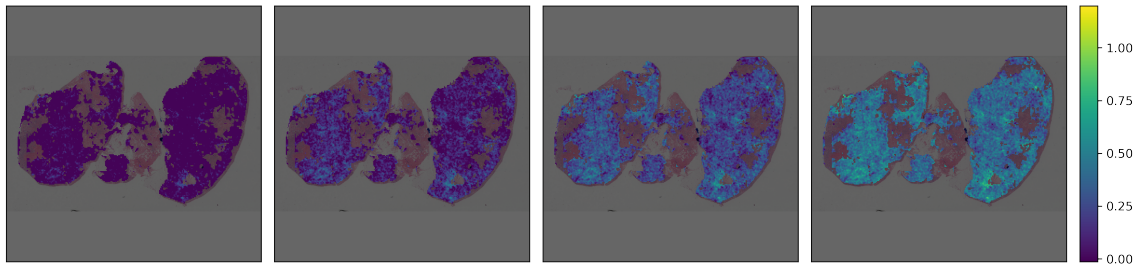


Figure 7: From left to right: prediction at at 2 years; 3.5 years; 5 years and 8 years. Clinical information of a patient that had an event at 3126 days: age: 73; race: white; ethnicity: not hispanic or latino; pathological stage: Stage X, and molecular subtype: LumA

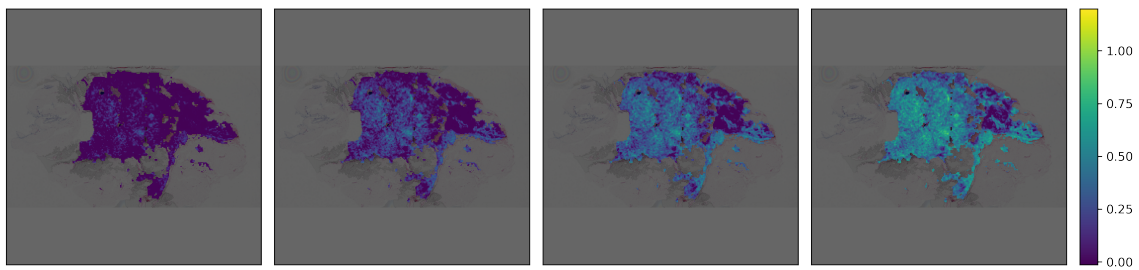
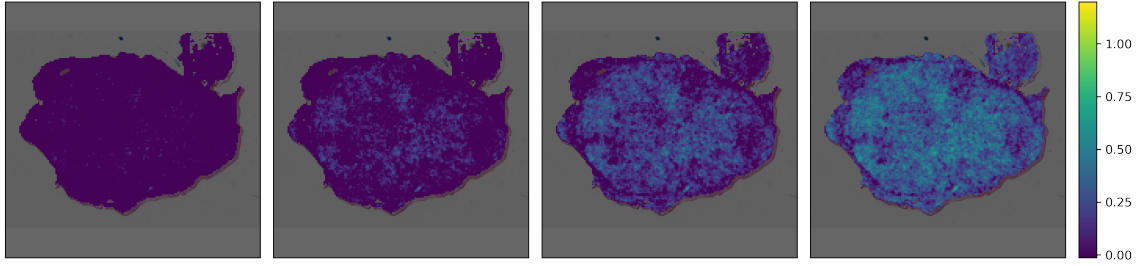


Figure 8: From left to right: prediction at 2 years; 3.5 years; 5 years and 8 years. Clinical information of a censored patient at 3204 days: age: 34; race: black; ethnicity: not hispanic or latino; pathological stage: Stage III, and molecular subtype: LumB



4 Pre-processing steps of the images in the TCGA dataset

We have obtained the pre-processed TCGA imaging data from [Wang et al., 2022, 2021]. We encourage the reader to check these papers for a detailed explanation of the pre-processing step such as the tile procedure applied to each WSI. What it follows is a brief explanation of these steps that were done in cite paper.

Pre-processing steps

Each whole-slide image (WSI) was pre-processed before inclusion into this study. As a first step, tissue masks were generated. To this end, WSIs were down-sampled by a factor of 32 and converted to the HSV color space. Tissue masks were generated by applying a pixel-wise logical “and” operation between a mask that was generated by applying the Otsu threshold Otsu [1979] to the saturation channel and by applying a cutoff of 0.75 to the hue channel. We subsequently performed morphological opening and closing to remove salt-and-pepper noise from the binary masks. WSIs were then tiled with 50% overlap at 20X magnification into image patches spanning 598x598 pixels, where 598 pixels correspond to 271 μ m of tissue section, while discarding tiles with less than 50% tissue content. Tiles were then color-normalized using the method described by Macenko et al. [2009]. We subsequently applied a cancer detection CNN to identify cancer regions and excluded all tiles that were predicted to belong to a benign tissue region. Furthermore, out-of-focus tiles with a low variance were excluded, which was computed by filtering each tile with a Laplacian.

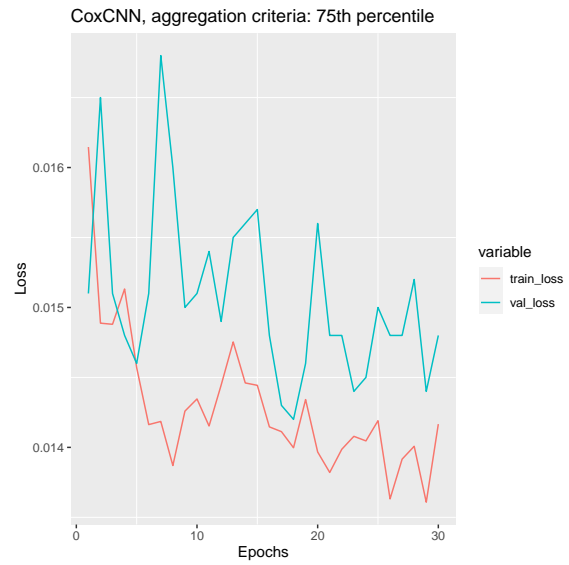
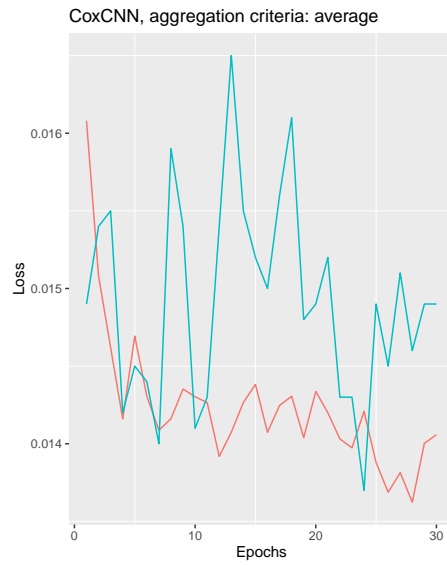
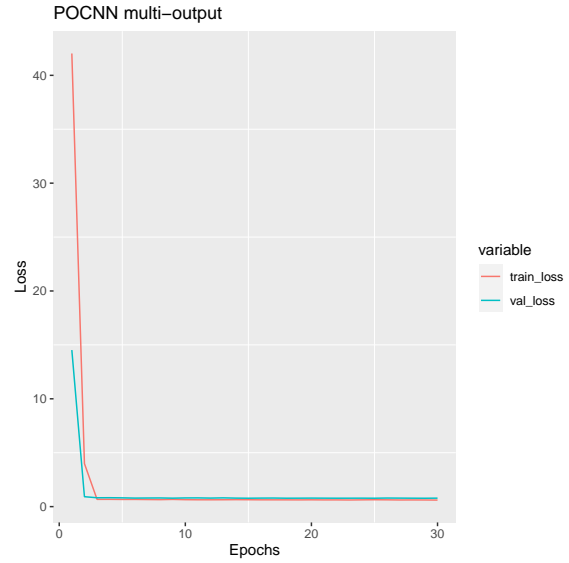
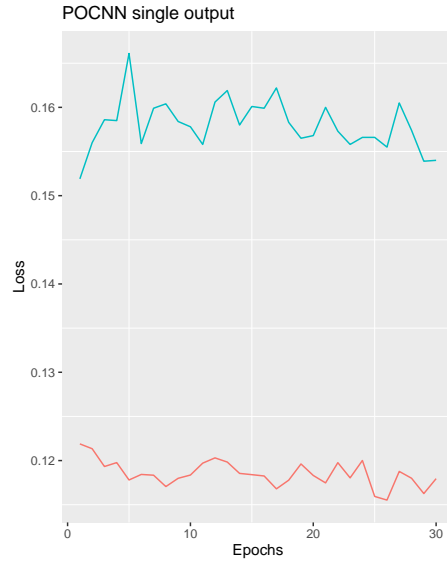
The tile’s images (.jpg) for each patient are assumed to be stored in the folder of each

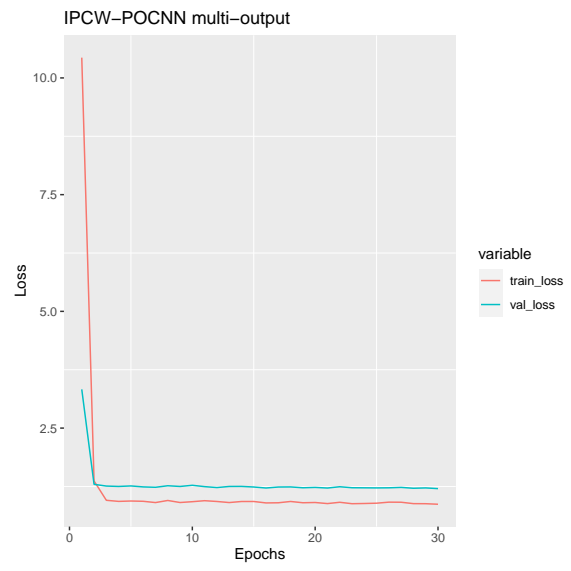
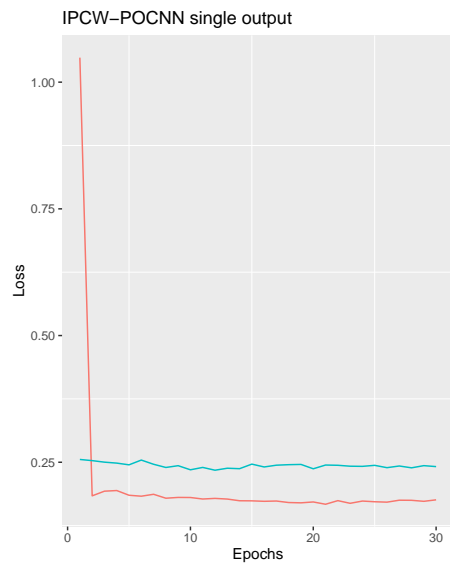
patient under the id name. Each patient is identified by the id which can be found in the column ‘Sample ID Slide’ in the clinical data. For instance: from the Sample ID Slide TCGA-D8-A1JK-01Z, the id is A1JK. In the folder A1JK should be stored all tile’s images for that patient.

References

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- N. Otsu. A threshold selection method from gray-level histograms. *IEEE Transactions on Systems, Man, and Cybernetics*, 9(1):62–66, 1979. doi: 10.1109/TSMC.1979.4310076.
- Y. Wang, K. Kartasalo, P. Weitz, B. Ács, M. Valkonen, C. Larsson, P. Ruusuvuori, J. Hartman, and M. Rantalainen. Predicting Molecular Phenotypes from Histopathology Images: A Transcriptome-Wide Expression–Morphology Analysis in Breast Cancer. *Cancer Research*, 81(19):5115–5126, 08 2021. ISSN 0008-5472. doi: 10.1158/0008-5472.CAN-21-0482. URL <https://doi.org/10.1158/0008-5472.CAN-21-0482>.
- Y. Wang, B. Acs, S. Robertson, B. Liu, L. Solorzano, C. Wählby, J. Hartman, and M. Rantalainen. Improved breast cancer histological grading using deep learning. *Annals of Oncology*, 33(1):89–98, 2022. ISSN 0923-7534. doi: <https://doi.org/10.1016/j.annonc.2021.09.007>. URL <https://www.sciencedirect.com/science/article/pii/S0923753421044860>.

5 Training and validation loss curves along epochs in the real application data.

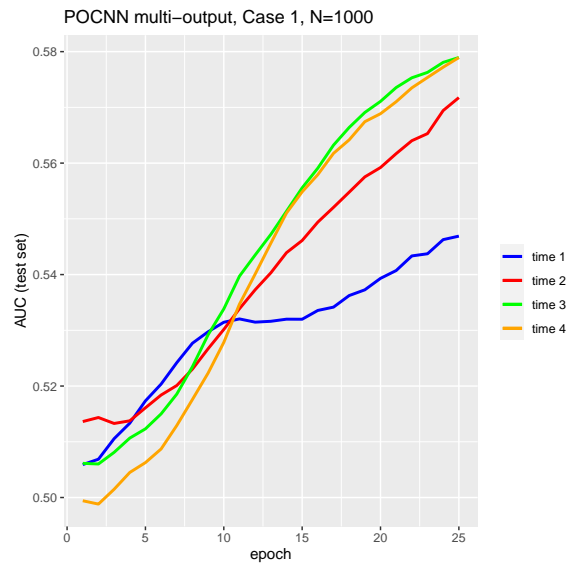
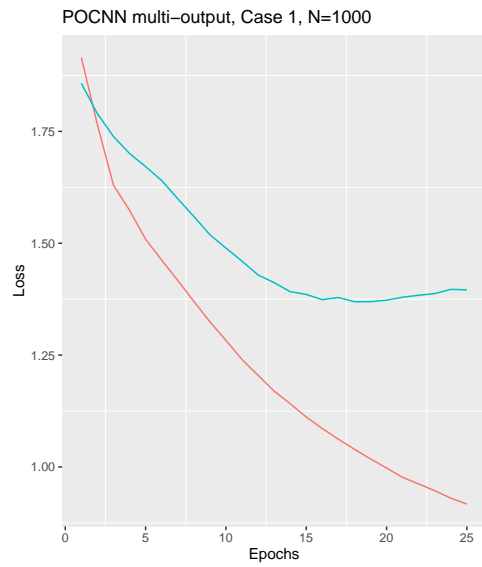
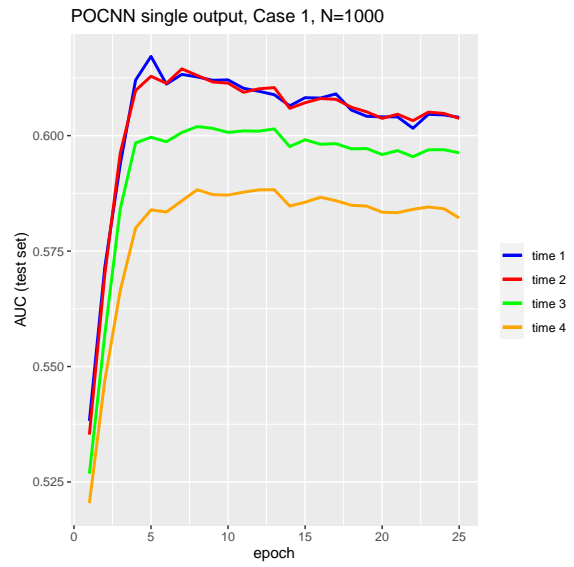
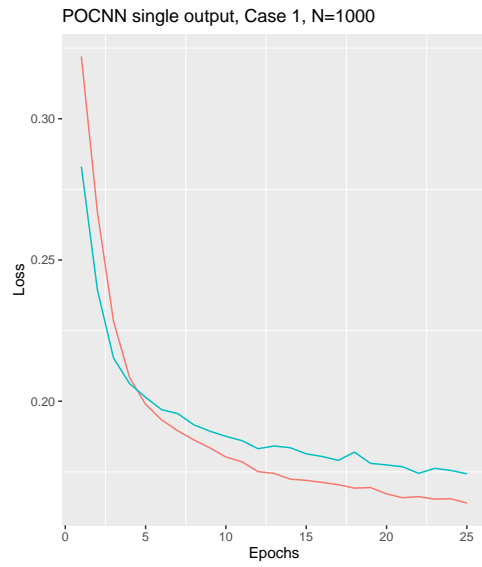


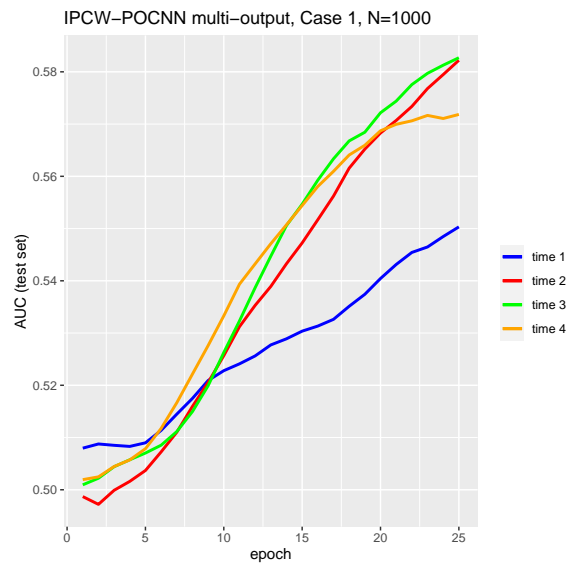
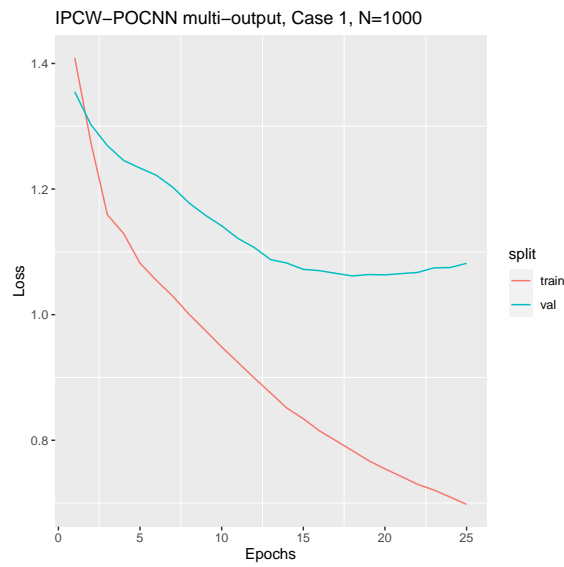
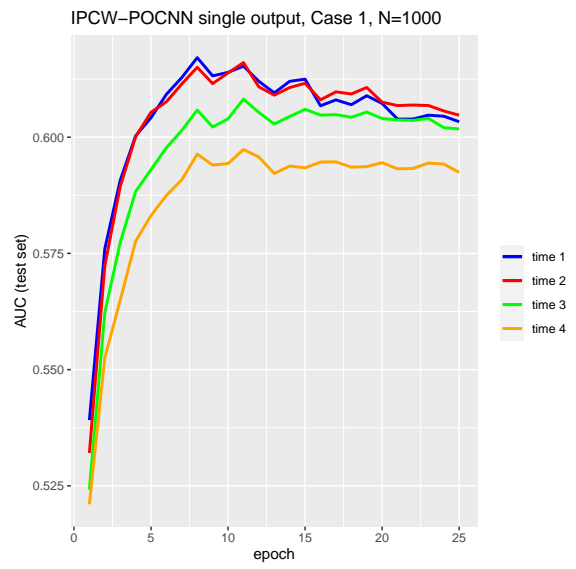
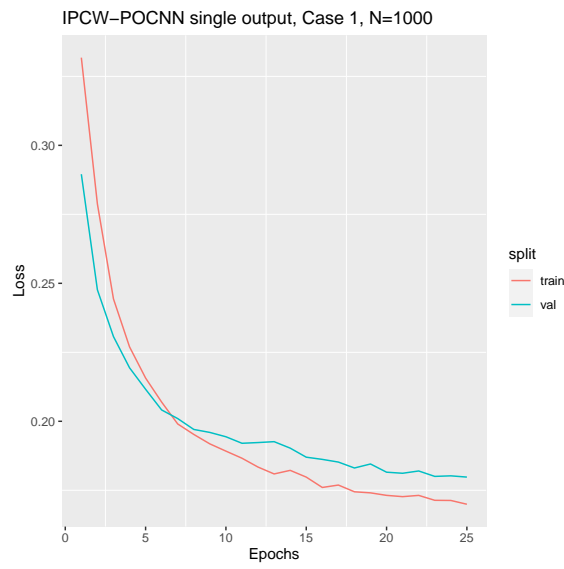


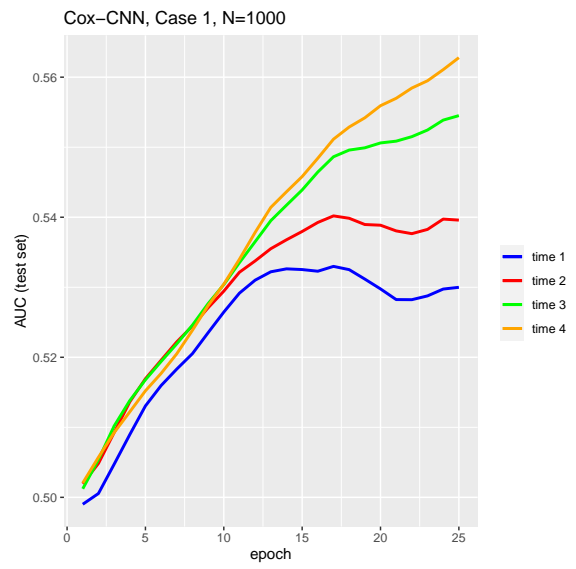
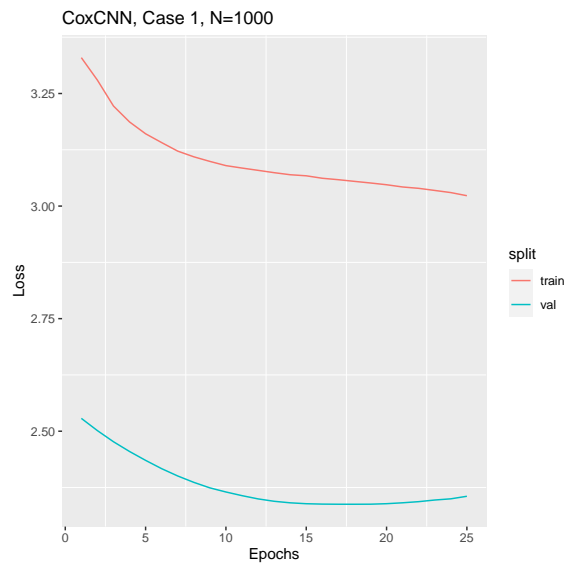
6 Training and validation loss curves along epochs in the simulations

For each Case, from 1 to 6, the training and validation loss for each epoch is the mean across the 100 simulations. Learning rate was fixed to 0.01.

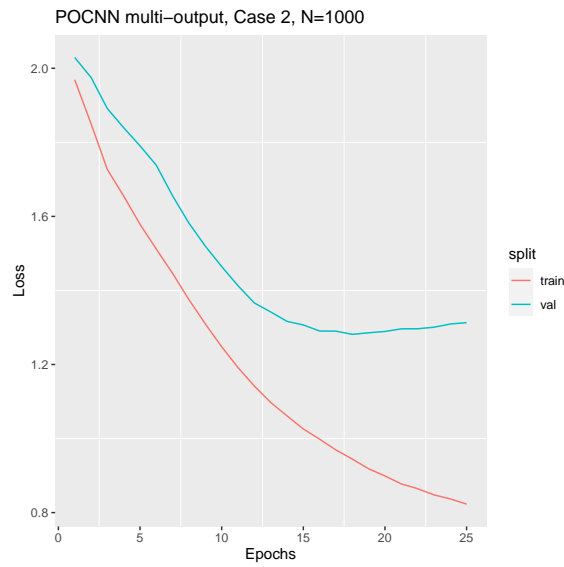
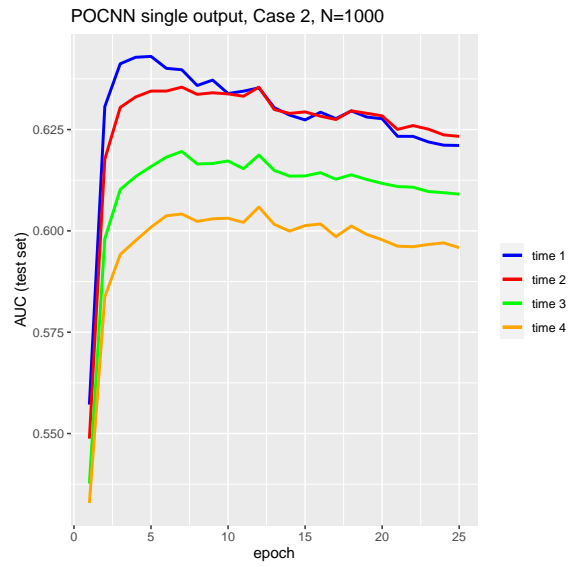
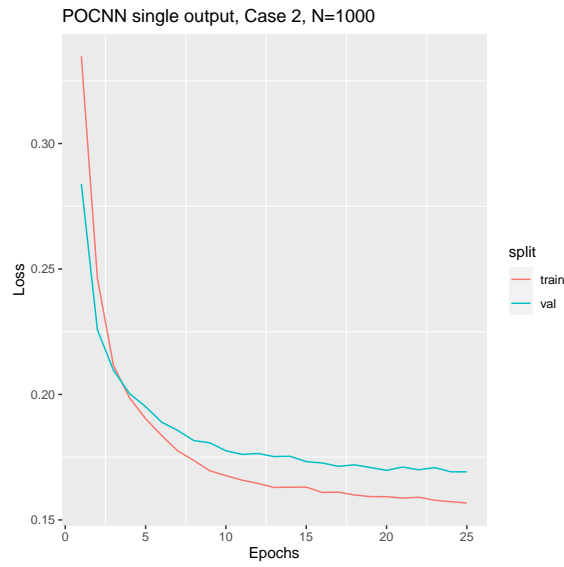
6.1 Case 1, N=1000

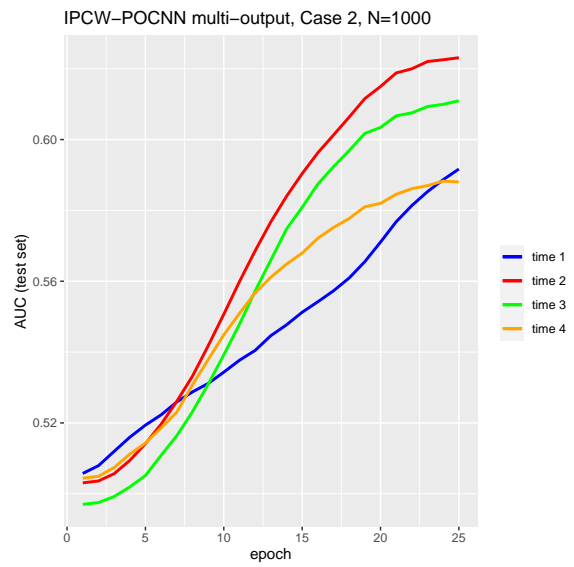
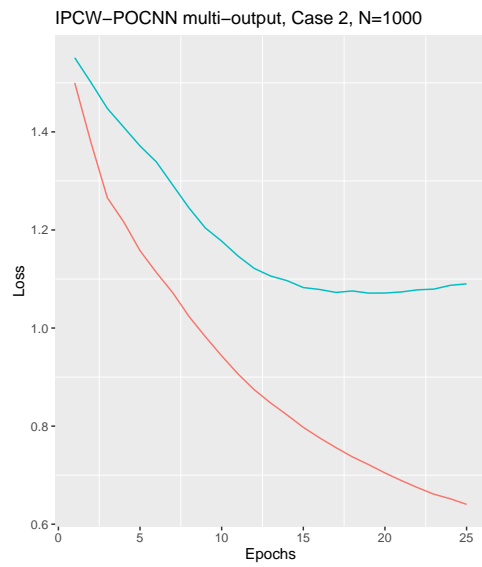
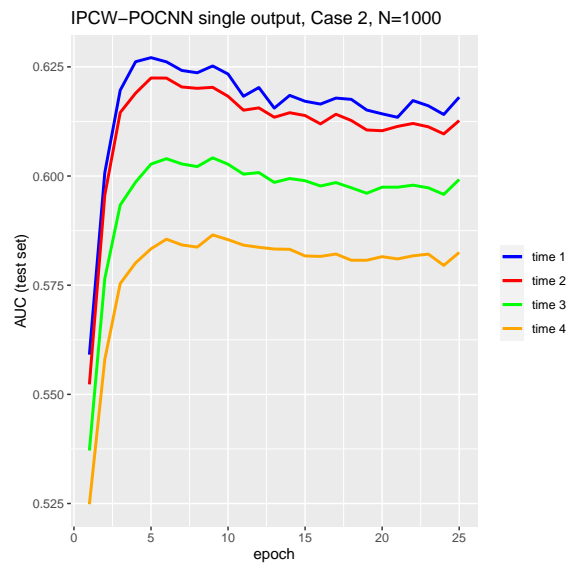
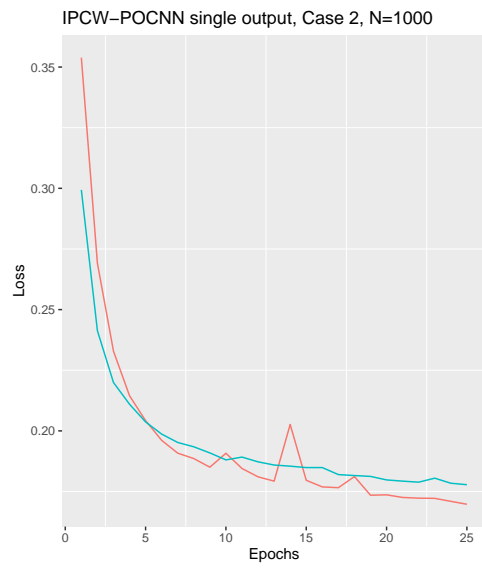


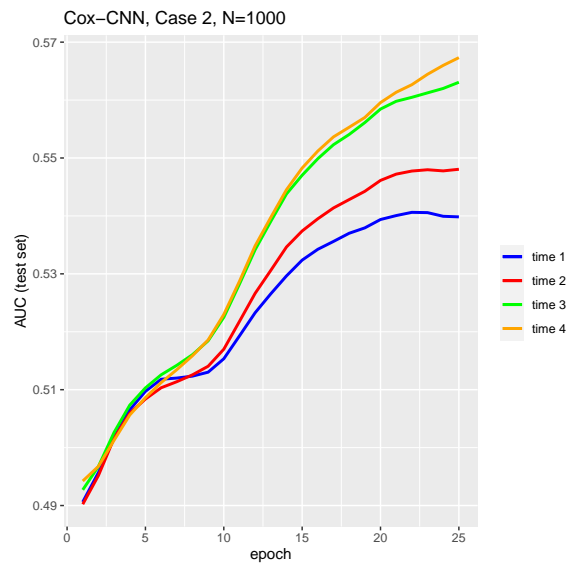
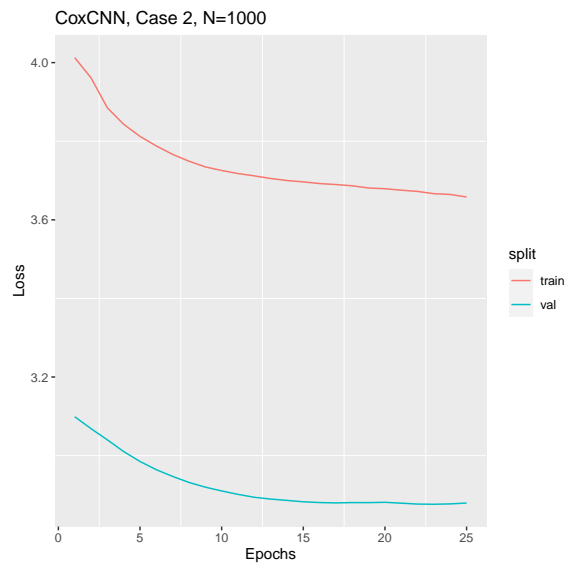




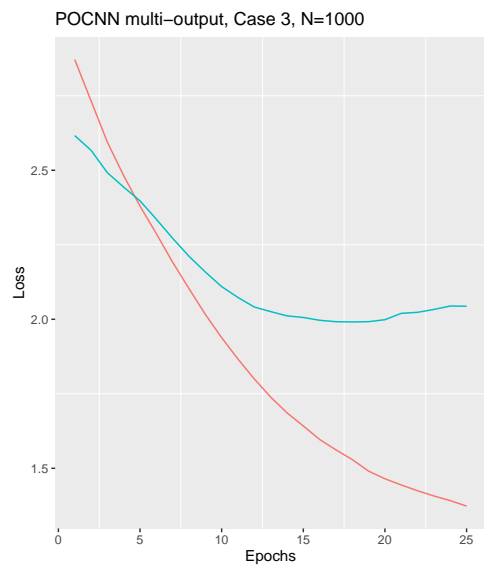
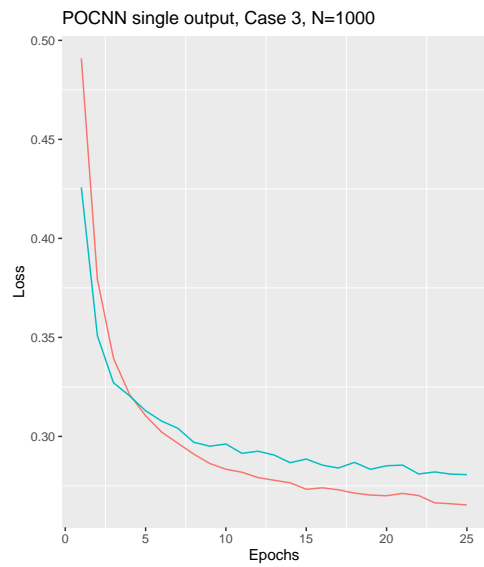
6.2 Case 2, N=1000

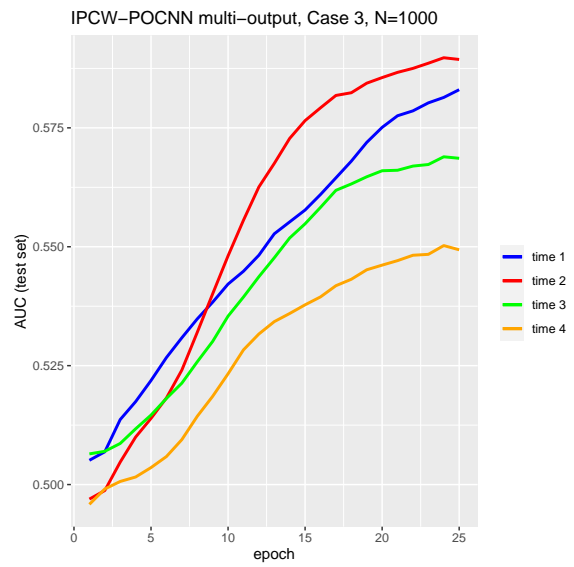
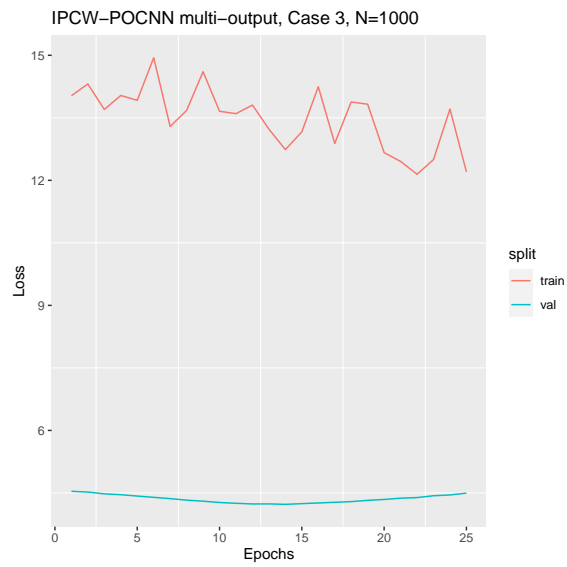
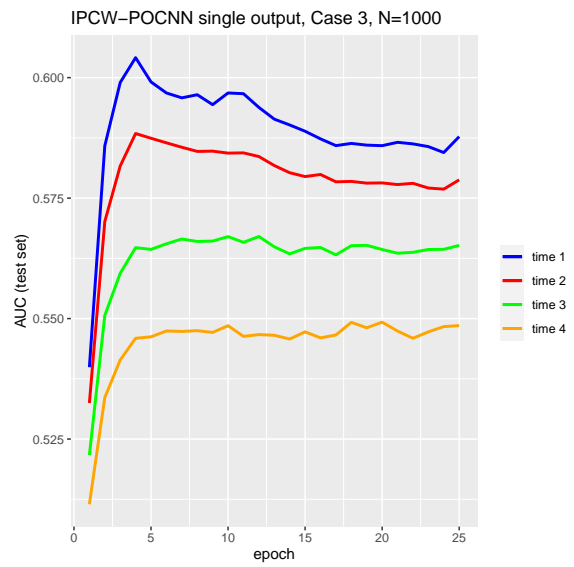
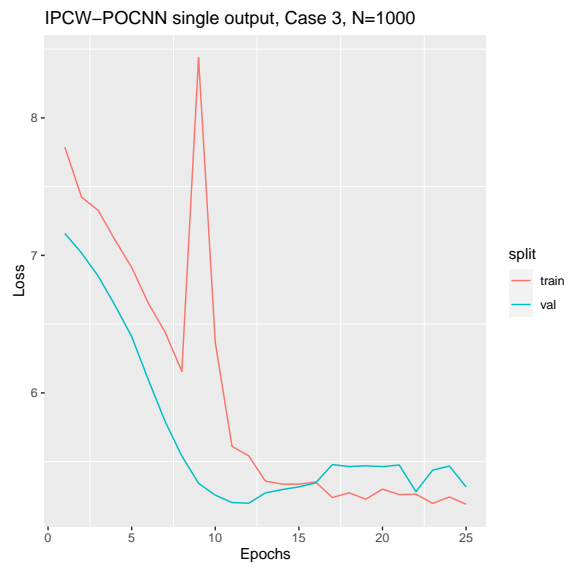


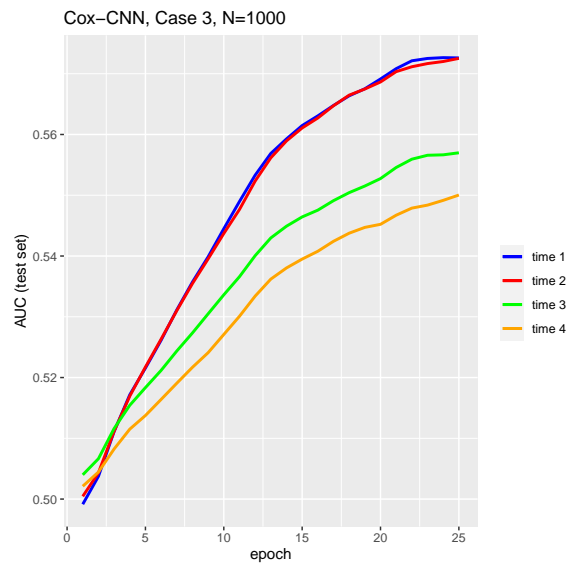
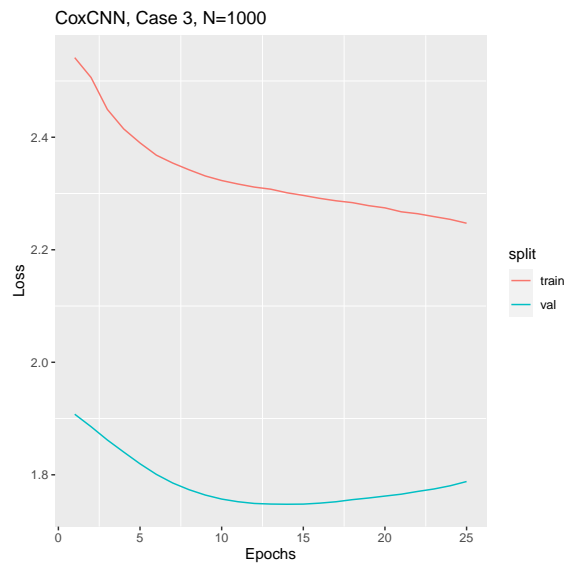




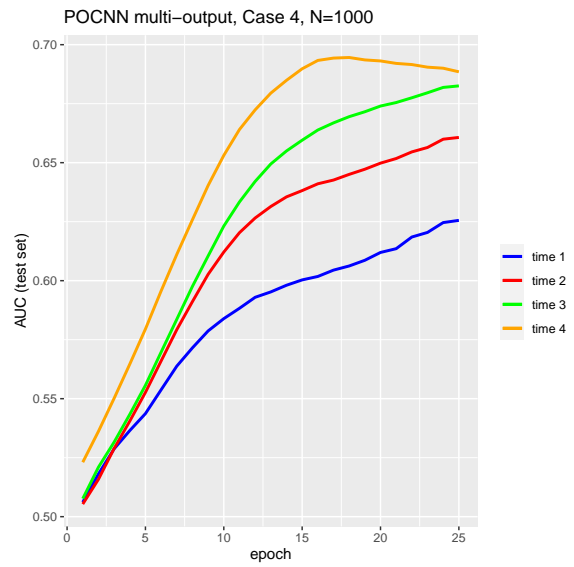
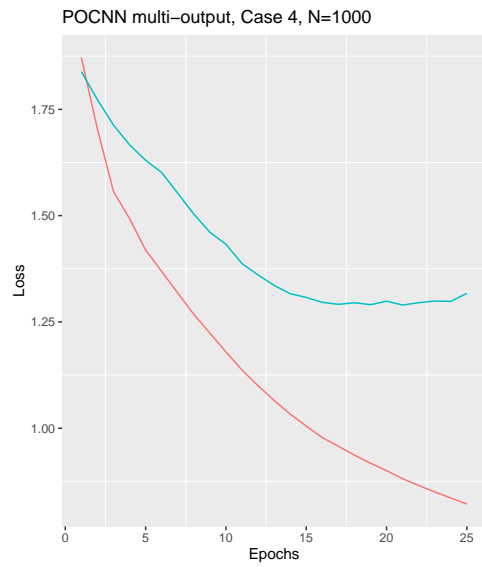
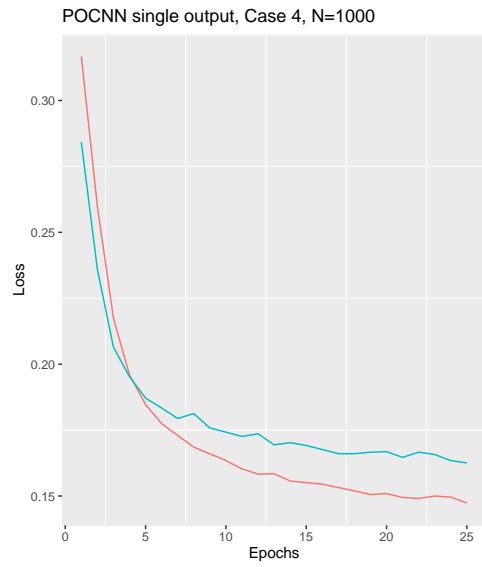
6.3 Case 3, N=1000

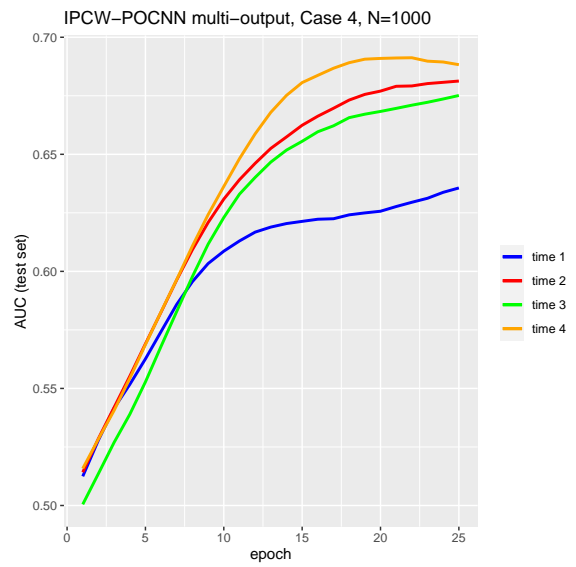
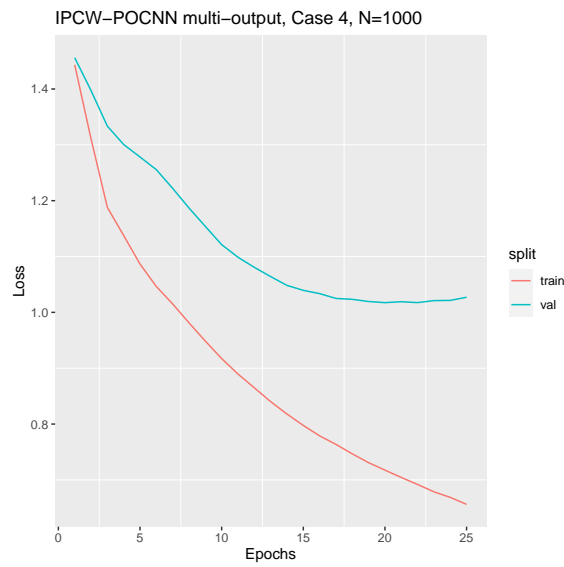
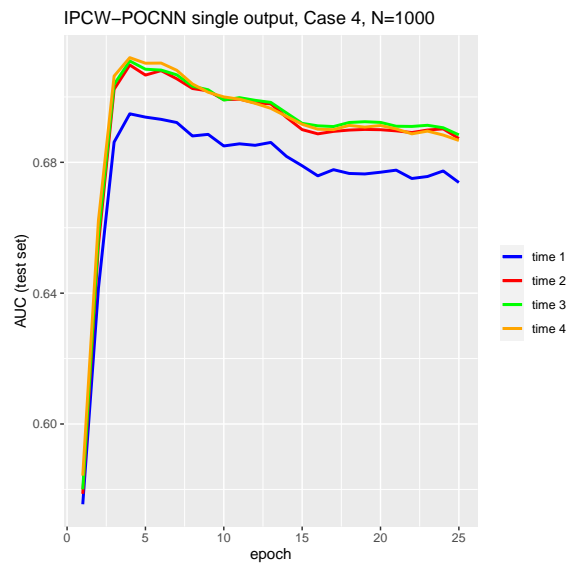
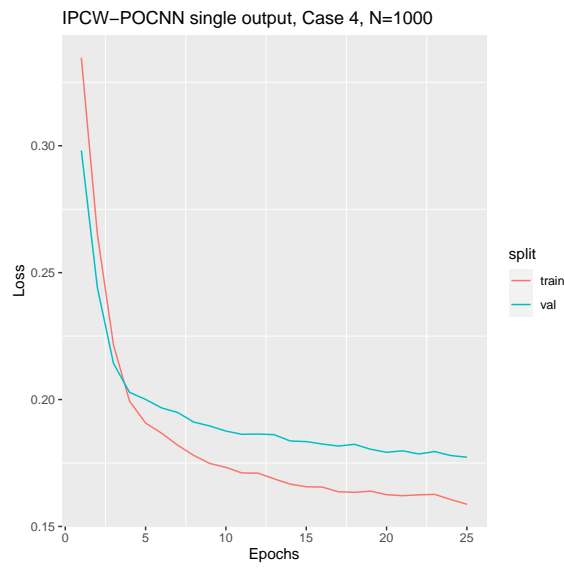


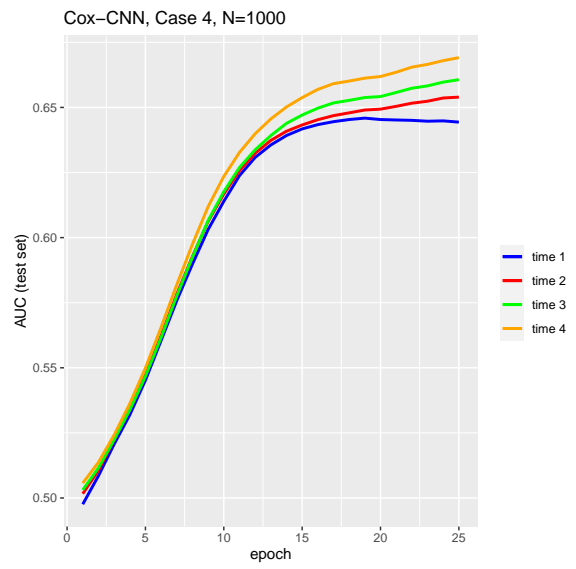
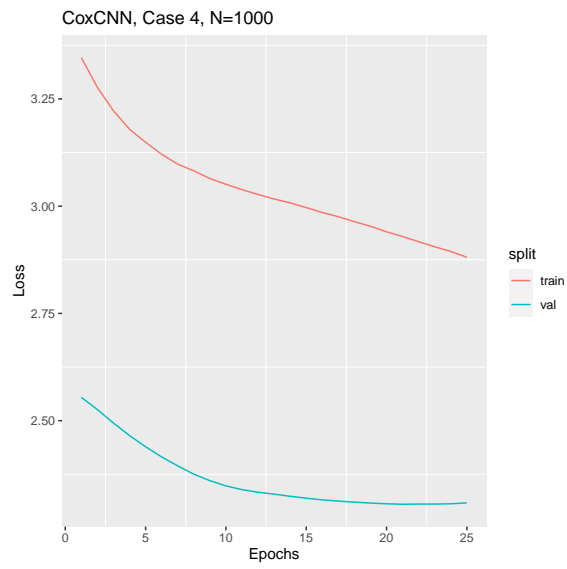




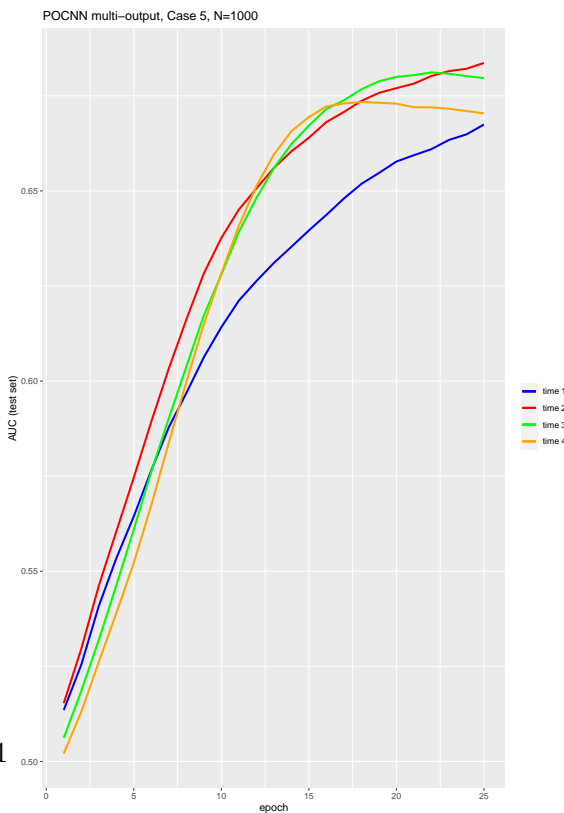
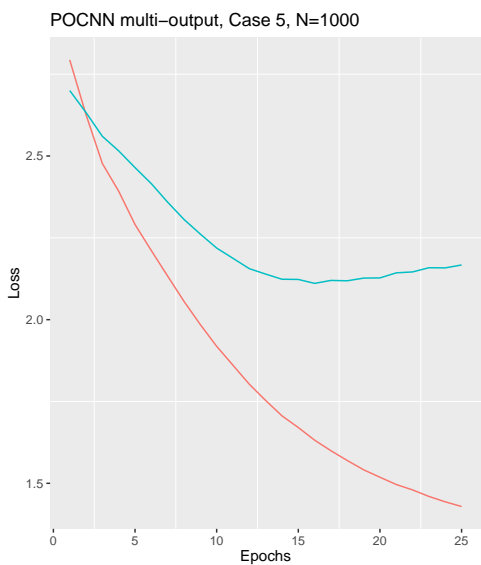
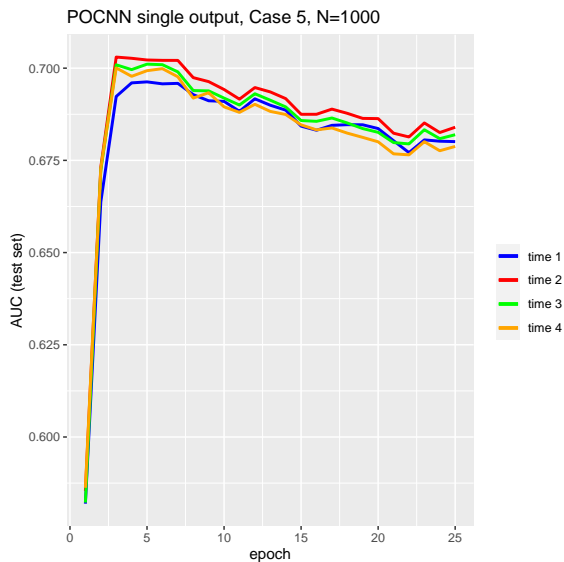
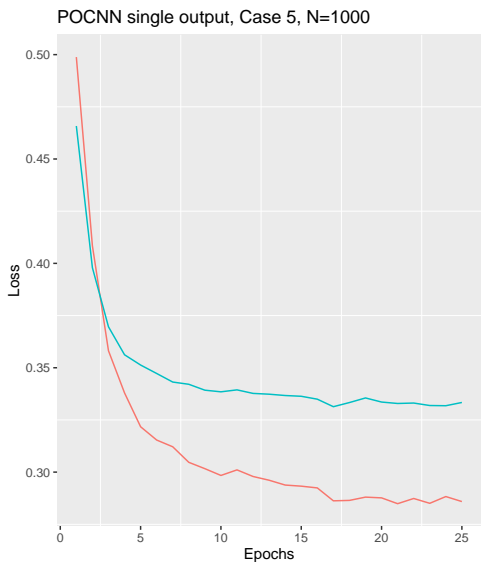
6.4 Case 4, N=1000

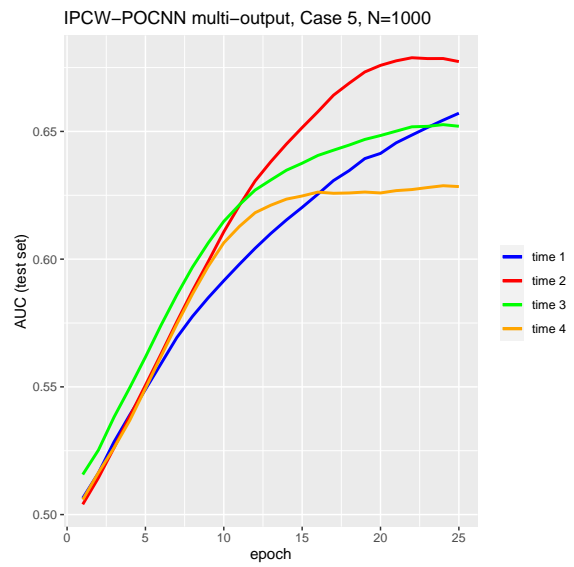
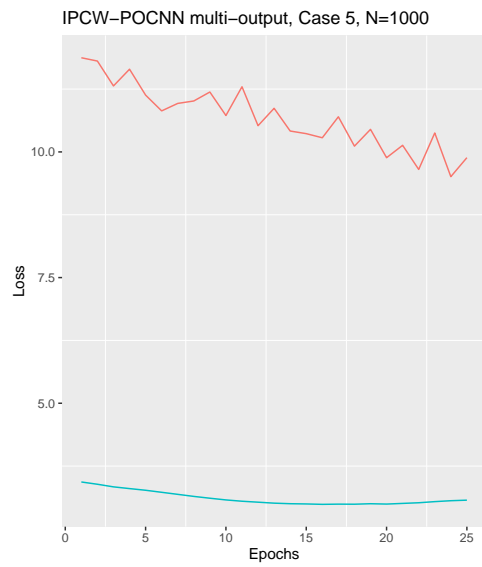
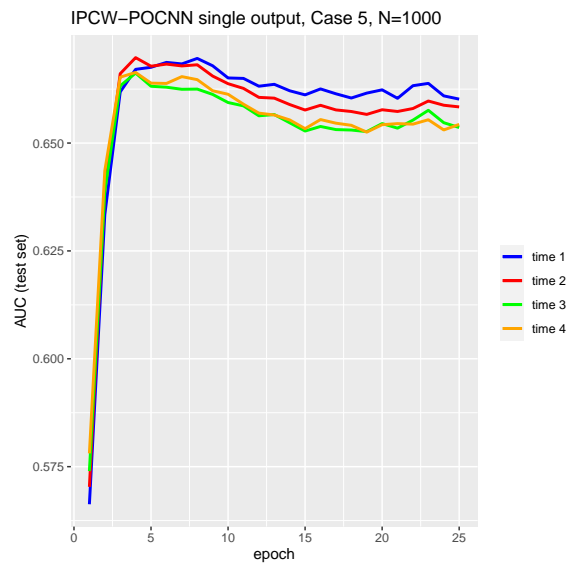
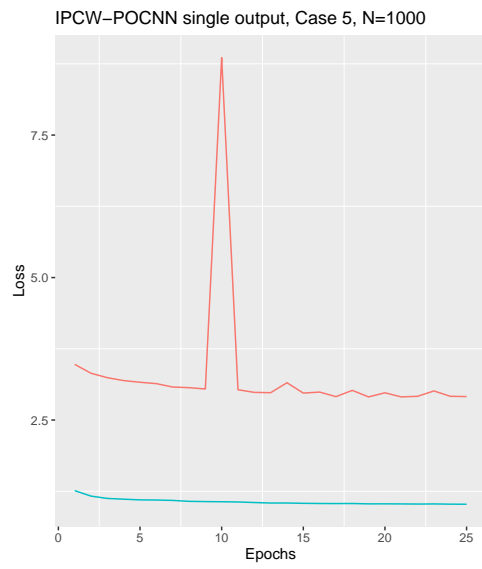


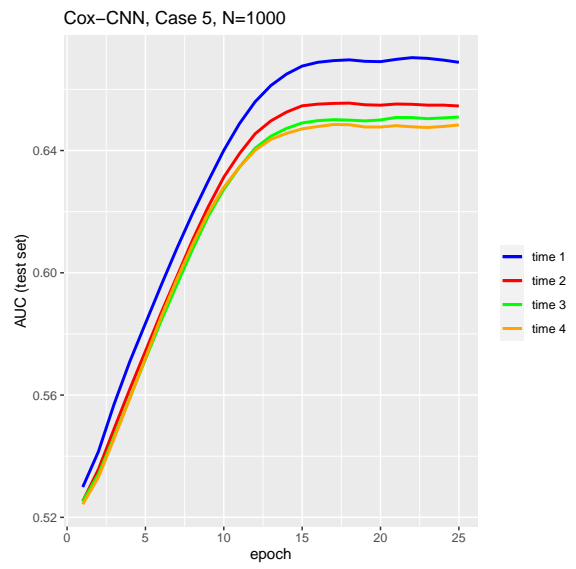
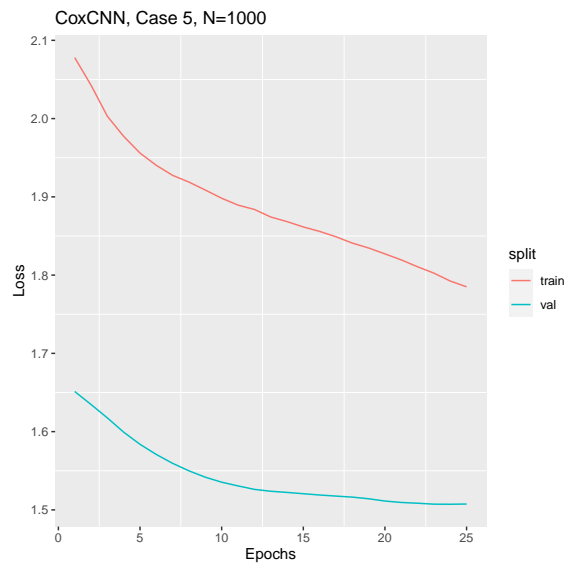




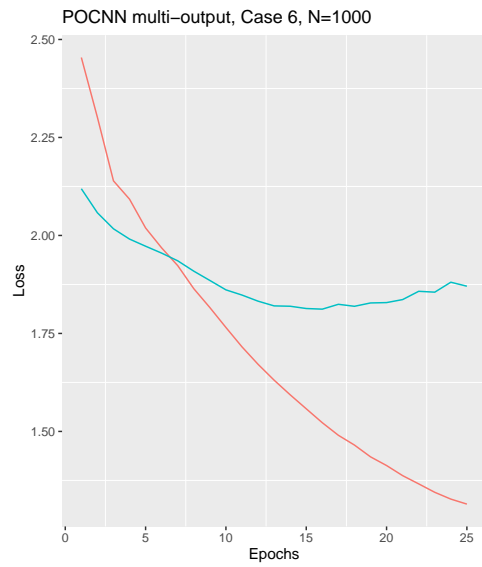
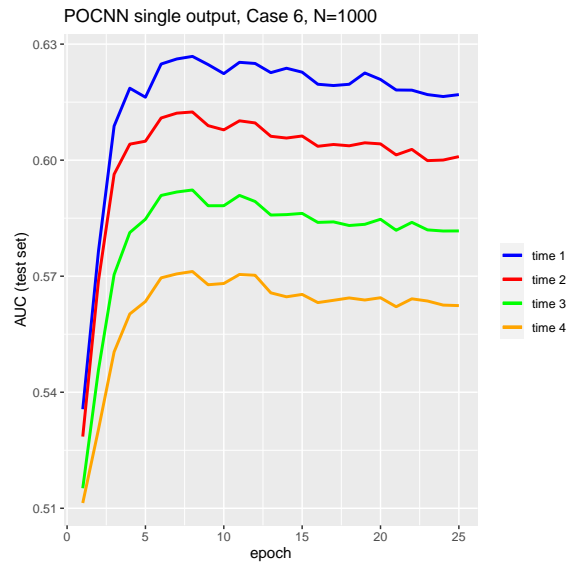
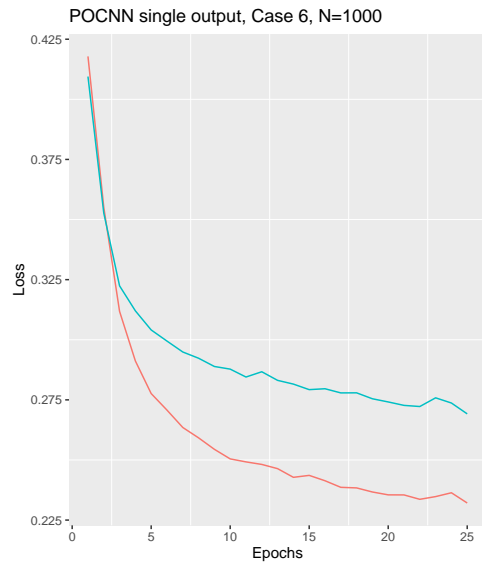
6.5 Case 5, N=1000

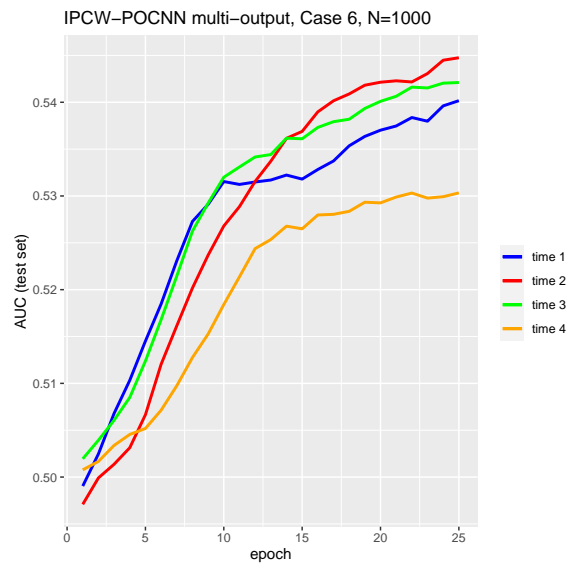
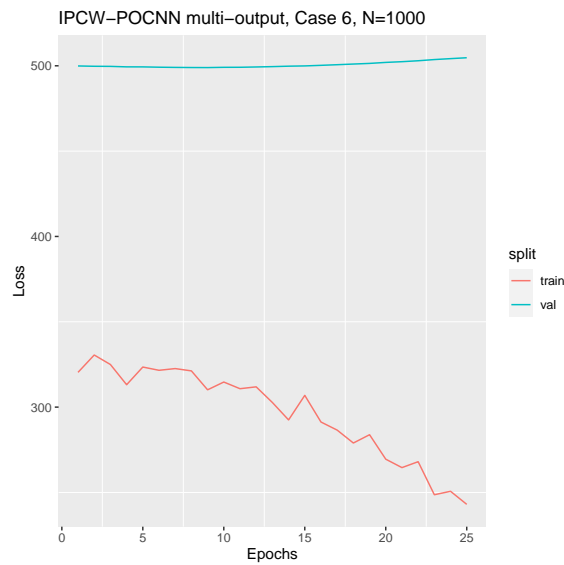
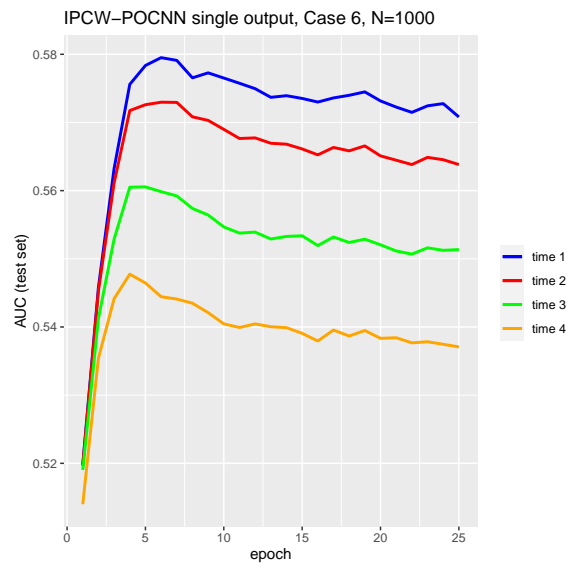
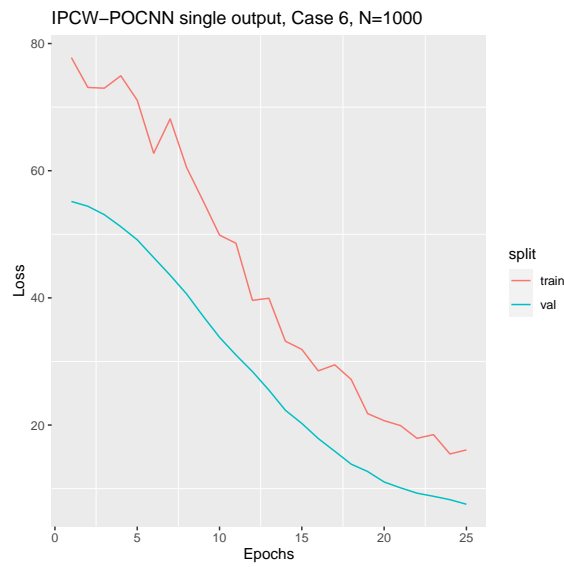


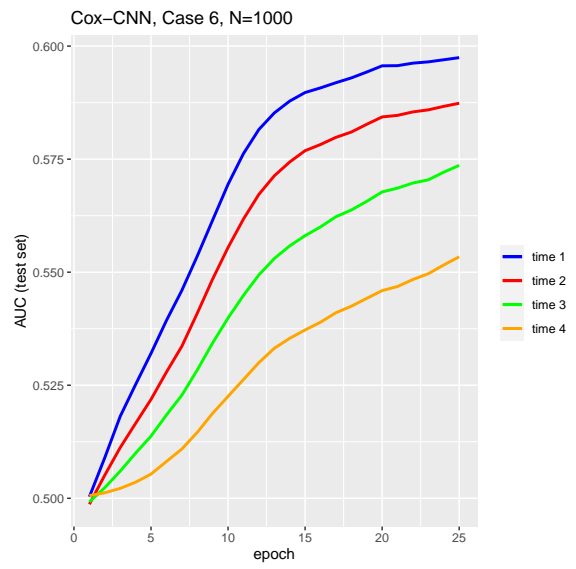
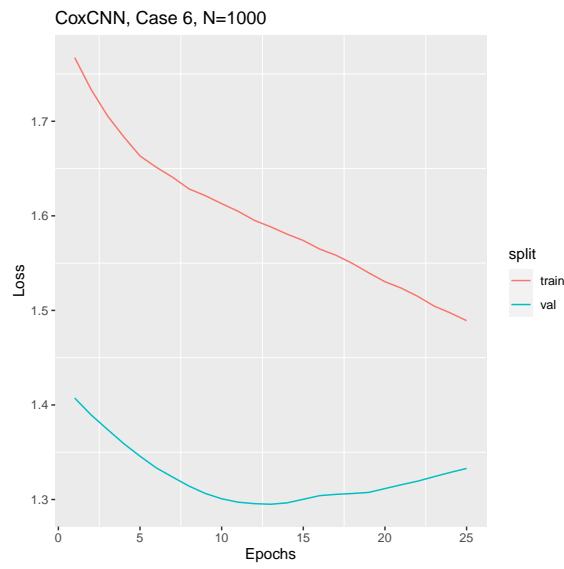




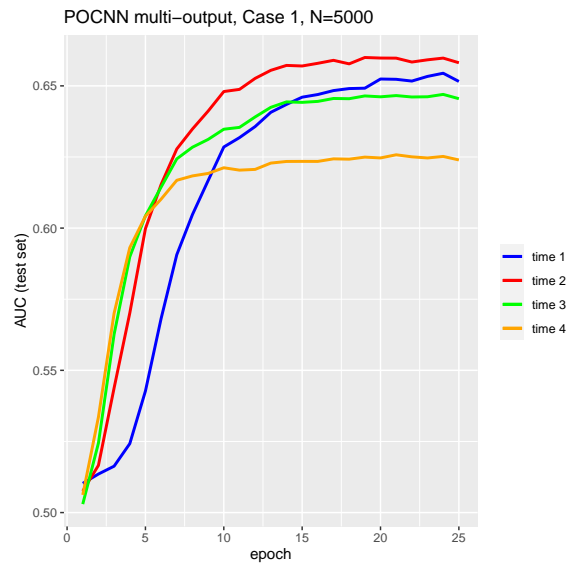
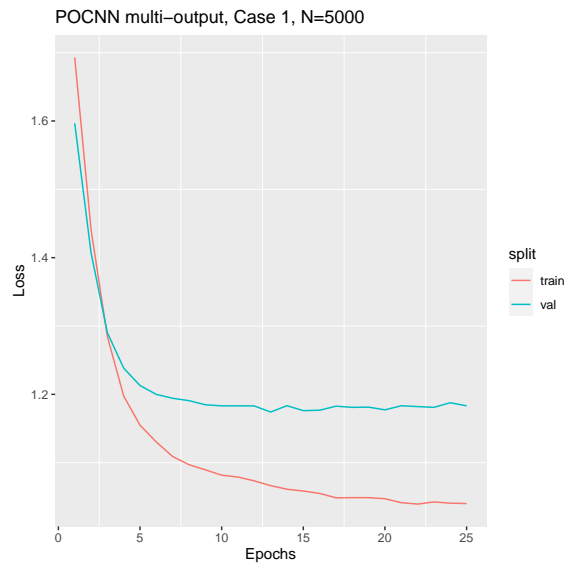
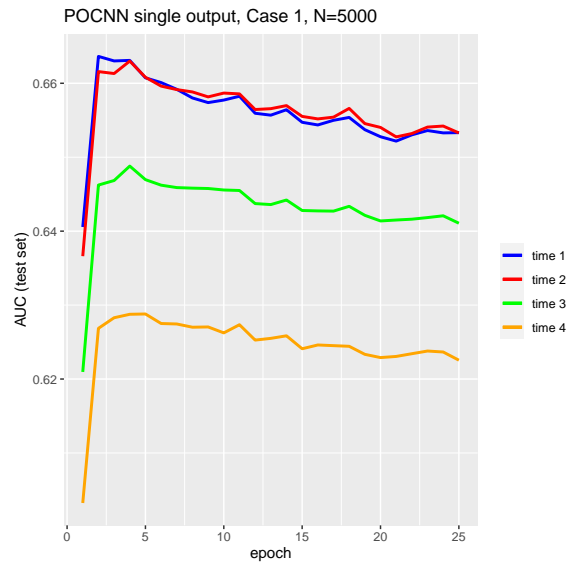
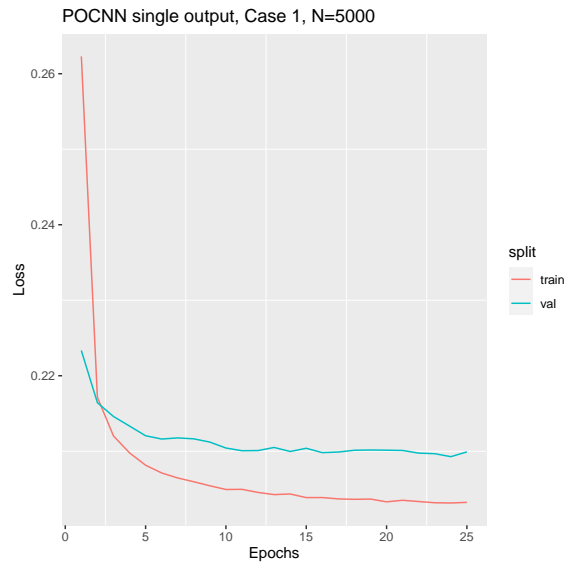
6.6 Case 6, N=1000

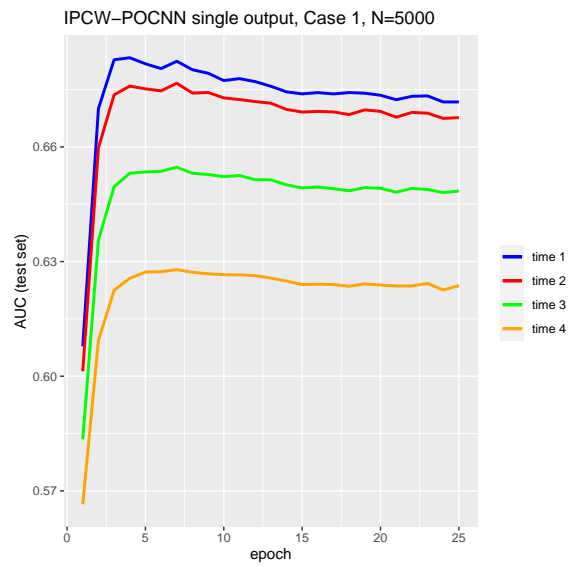
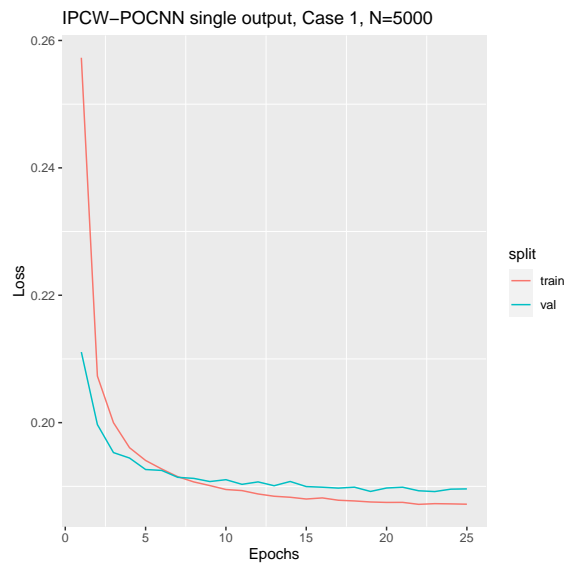
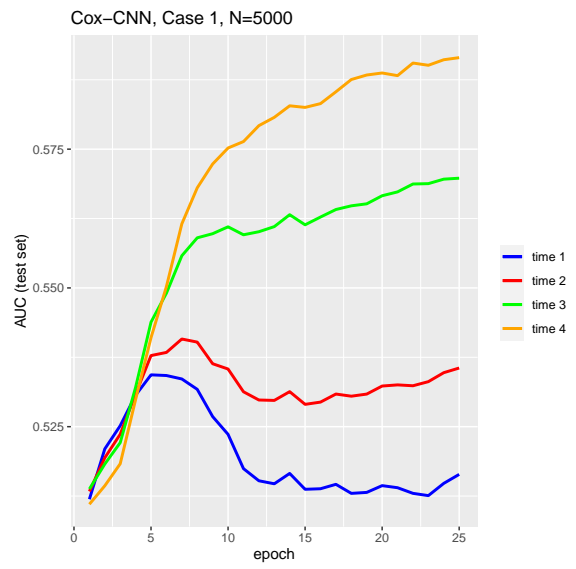
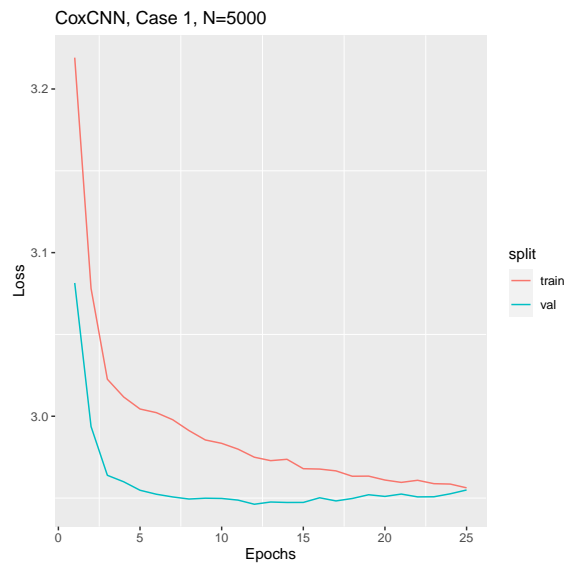


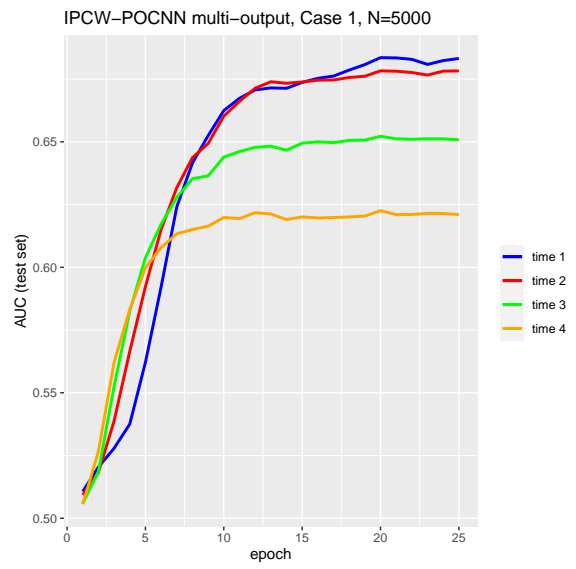
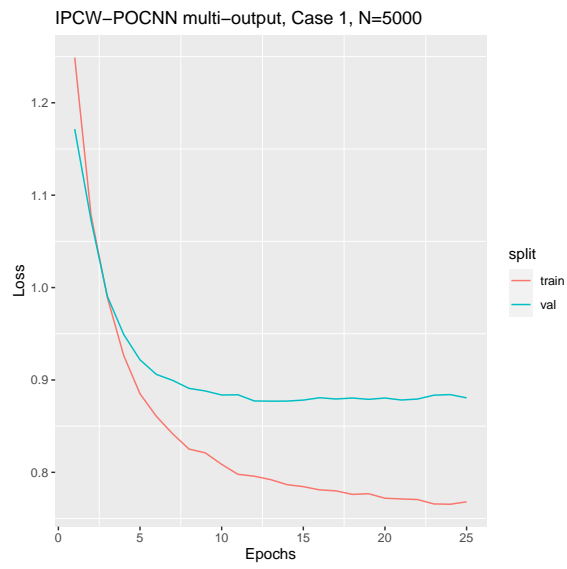




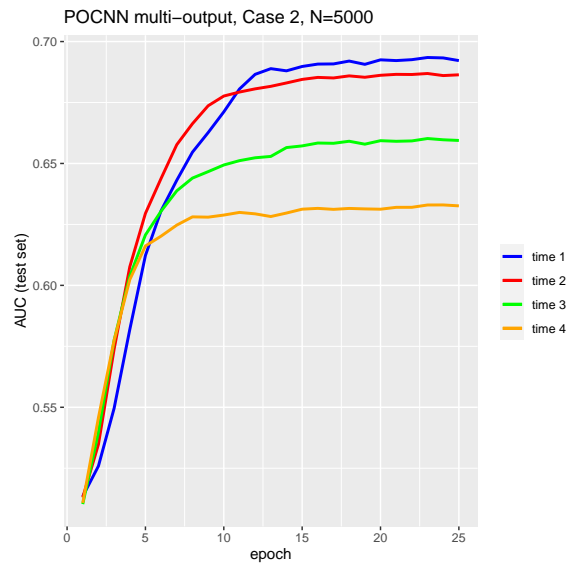
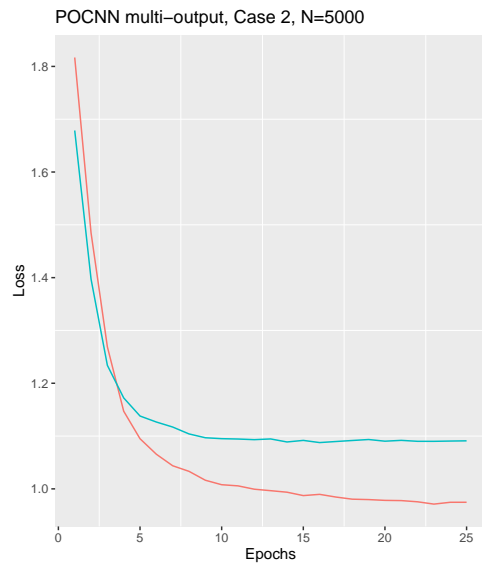
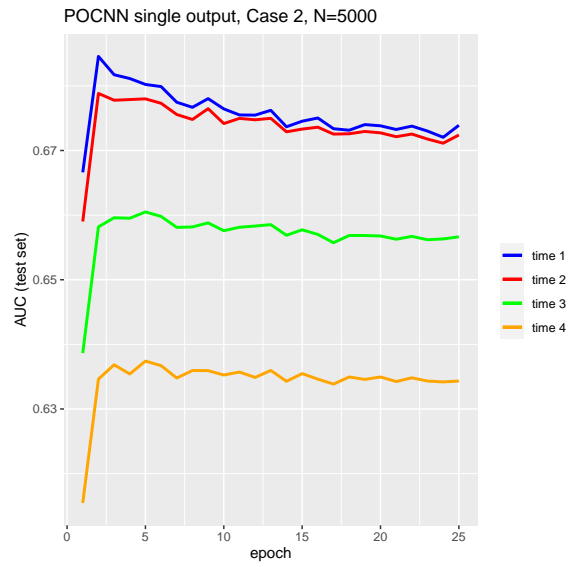
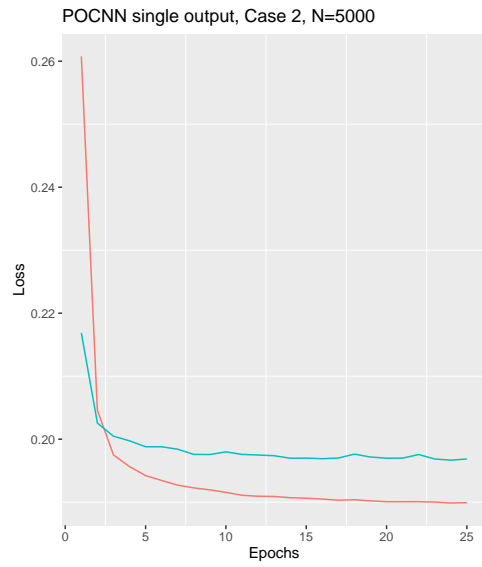
6.7 Case 1, N=5000

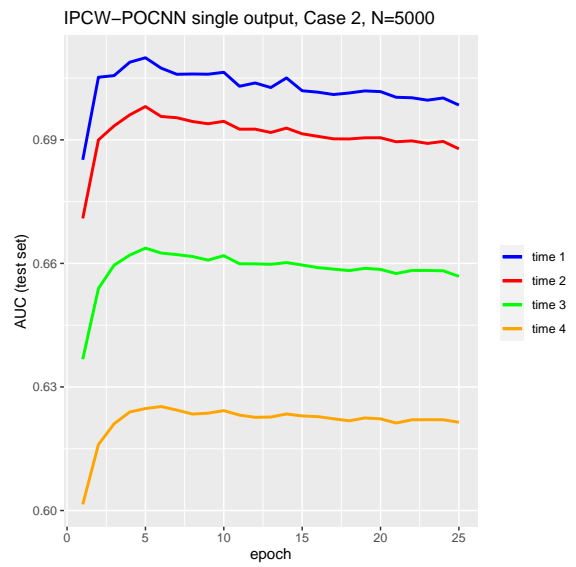
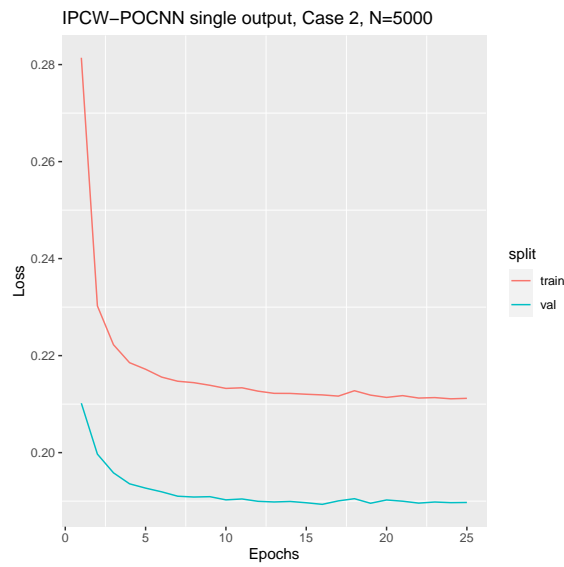
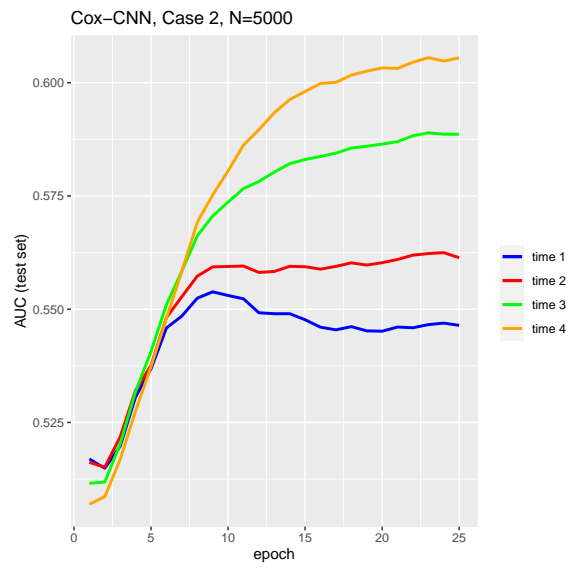
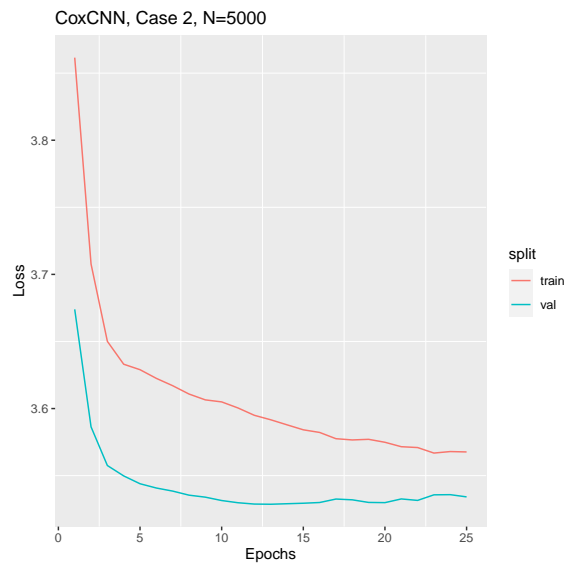


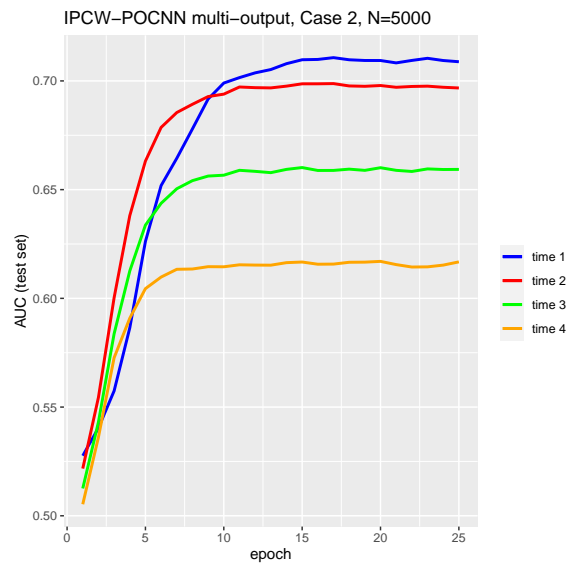
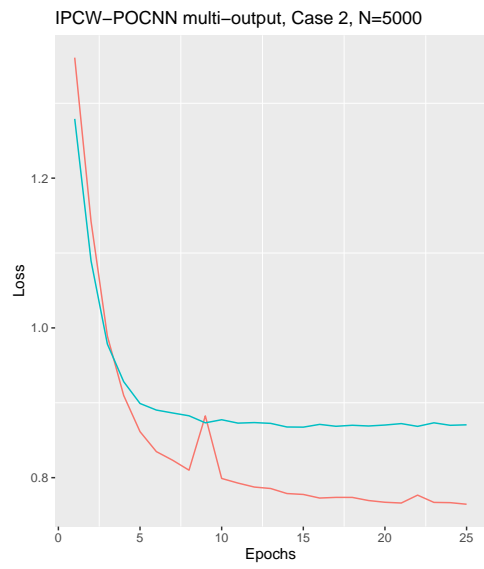




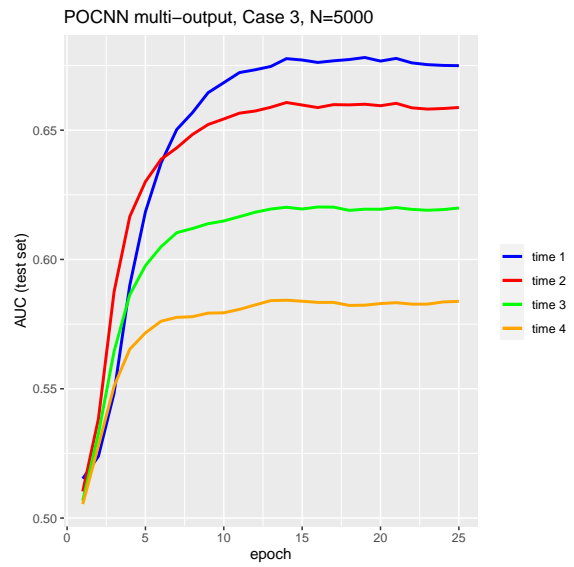
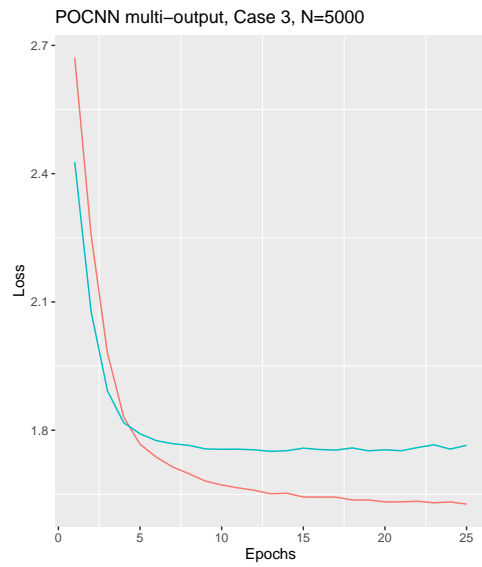
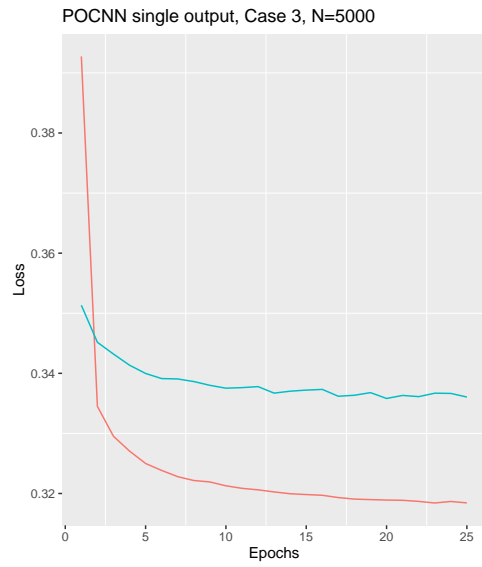
6.8 Case 2, N=5000

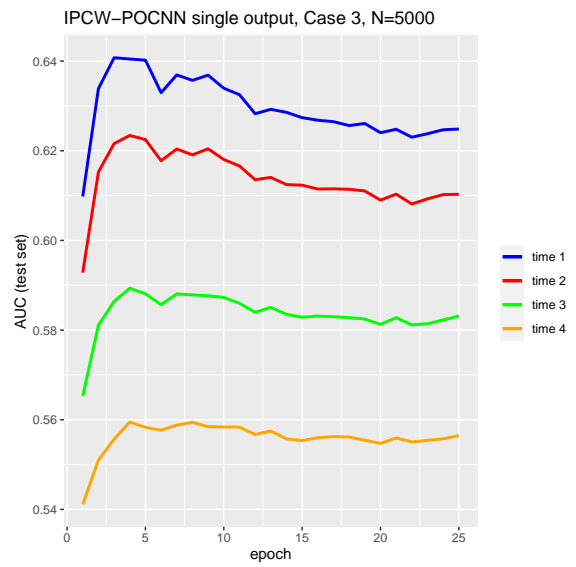
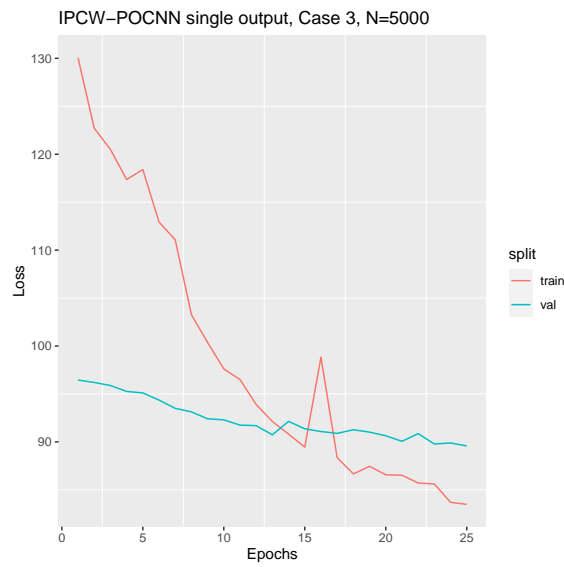
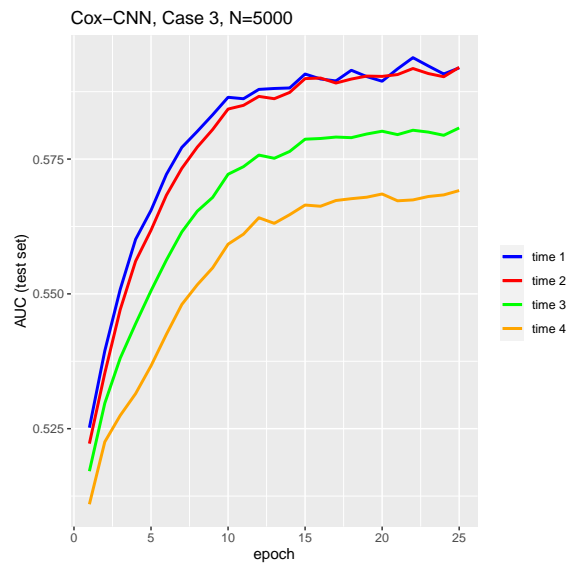
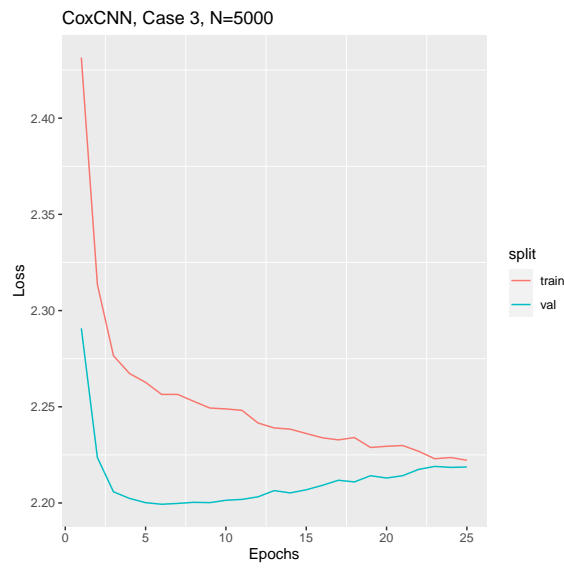


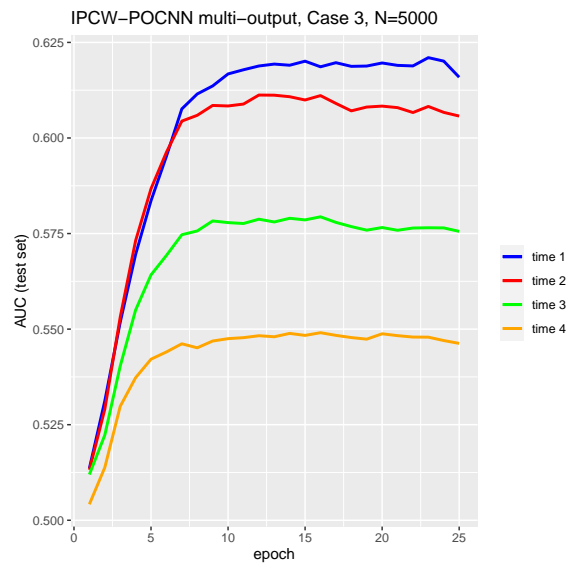
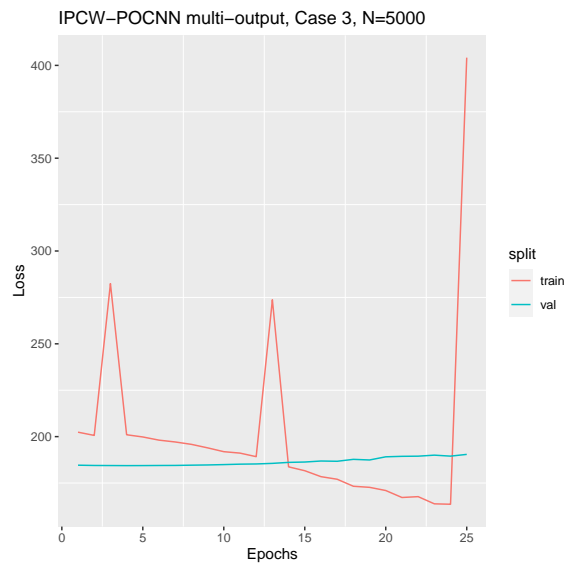




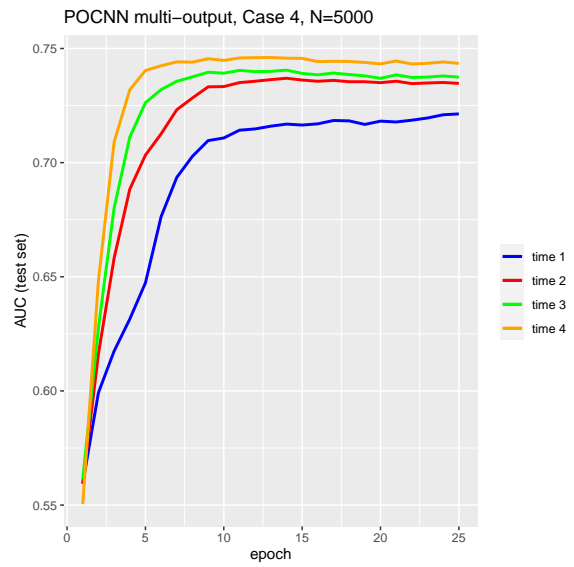
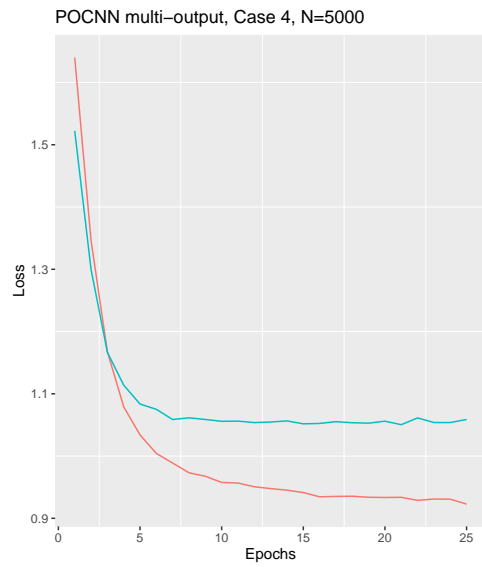
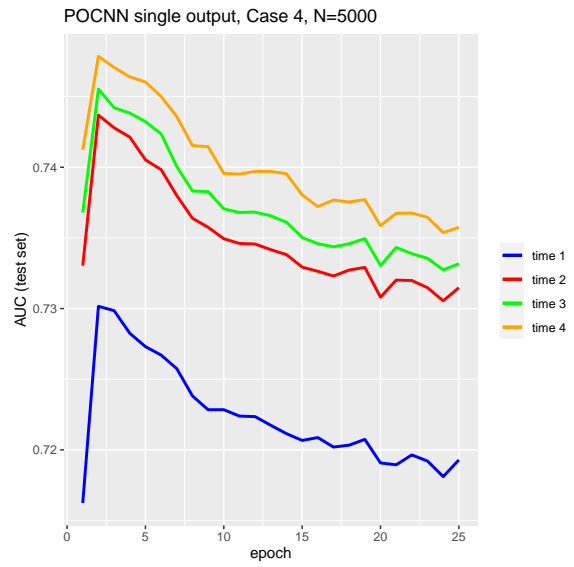
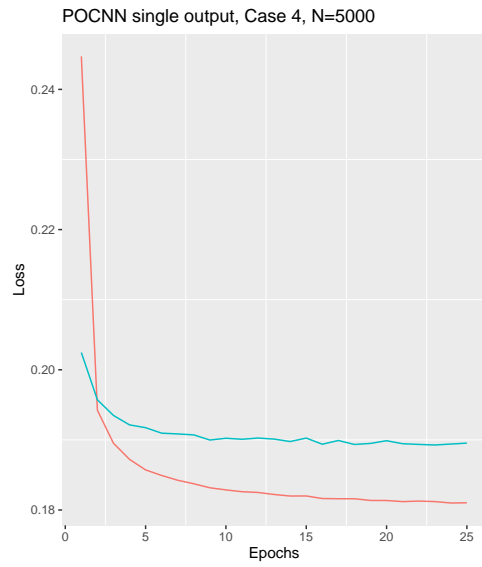
6.9 Case 3, N=5000

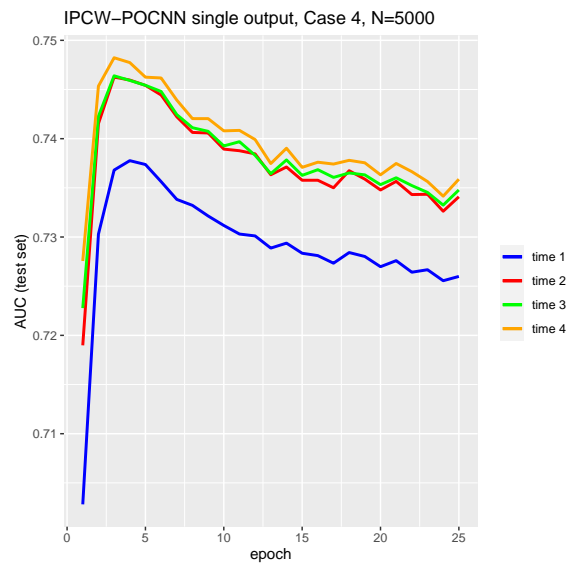
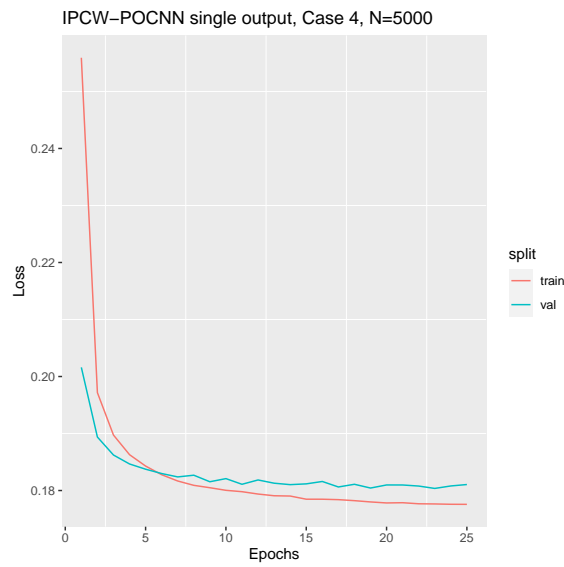
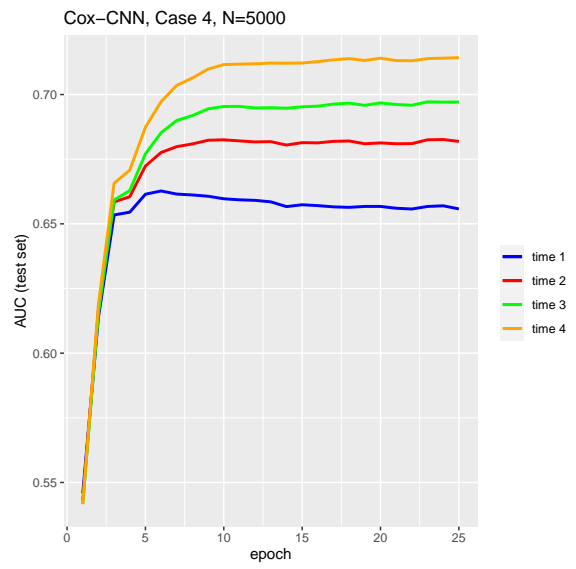
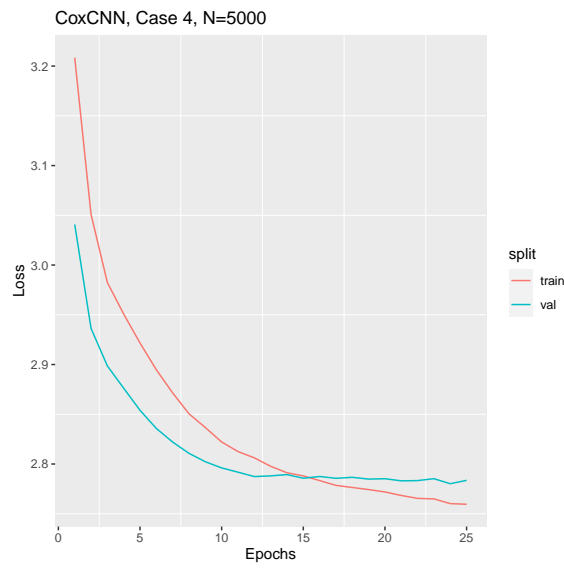


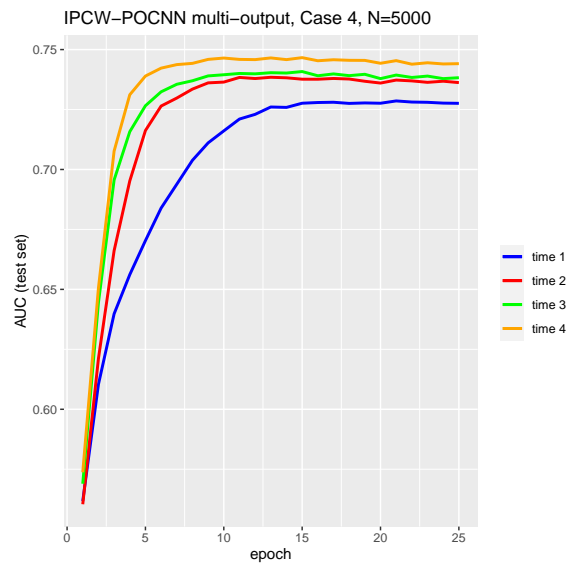
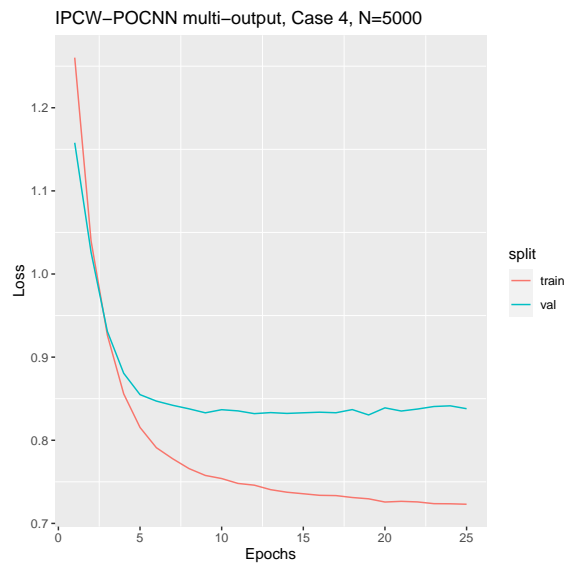




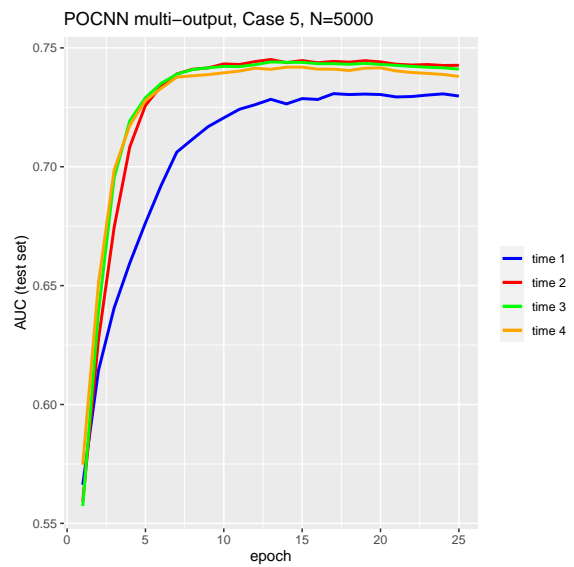
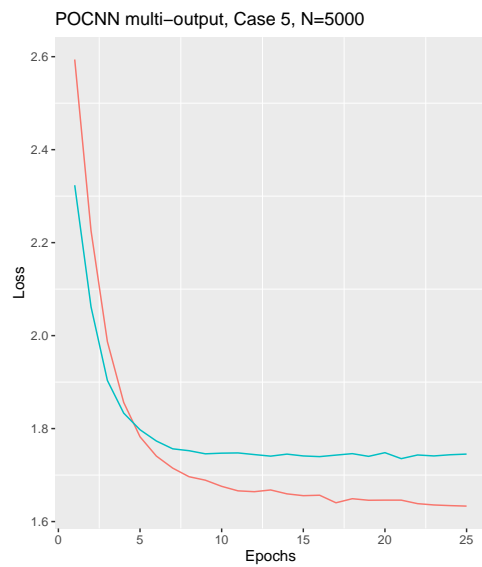
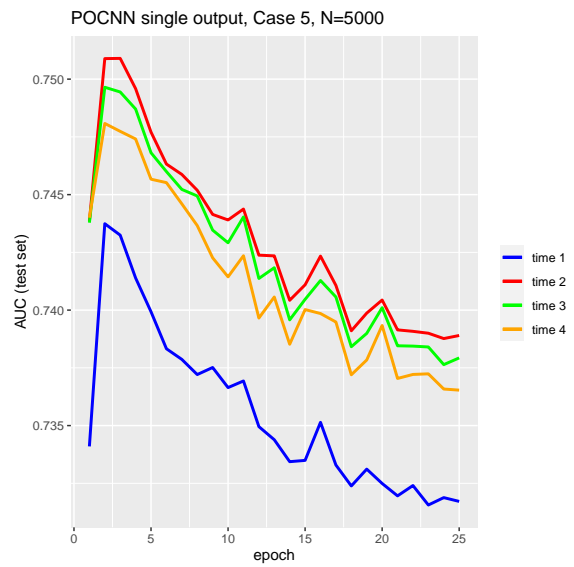
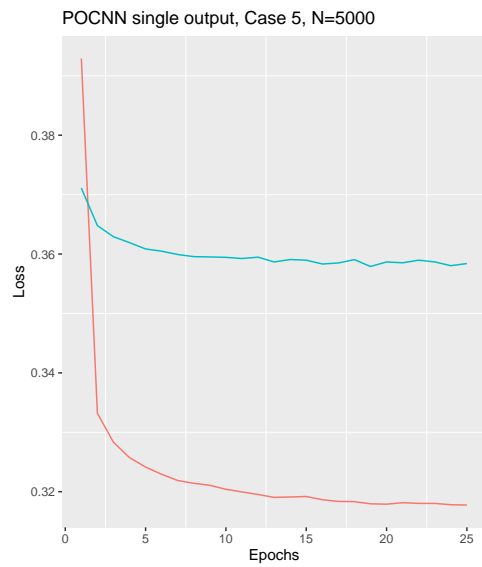
6.10 Case 4, N=5000

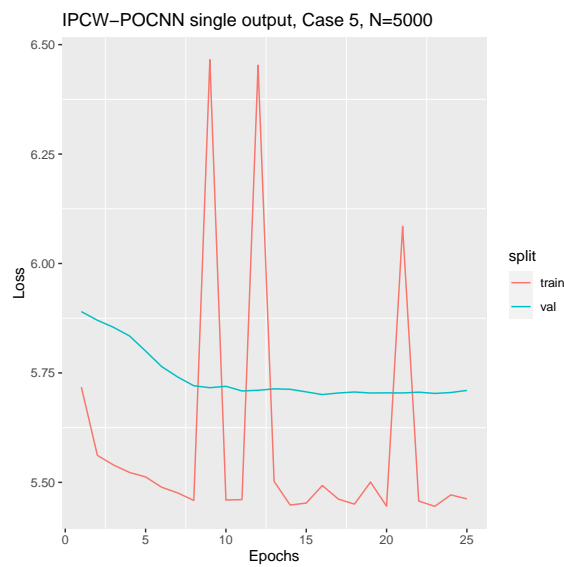
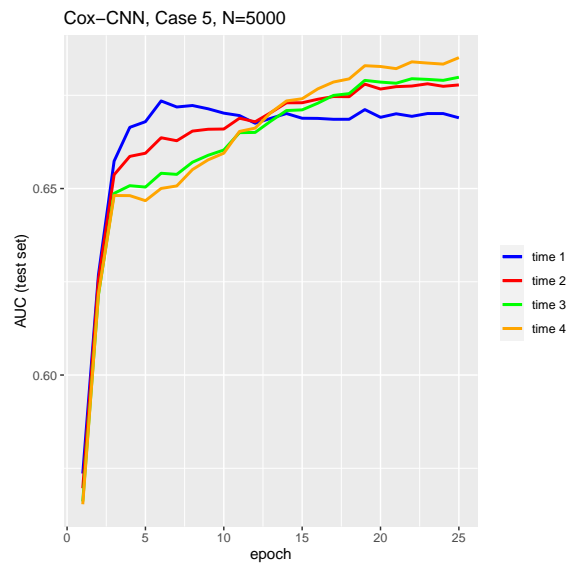
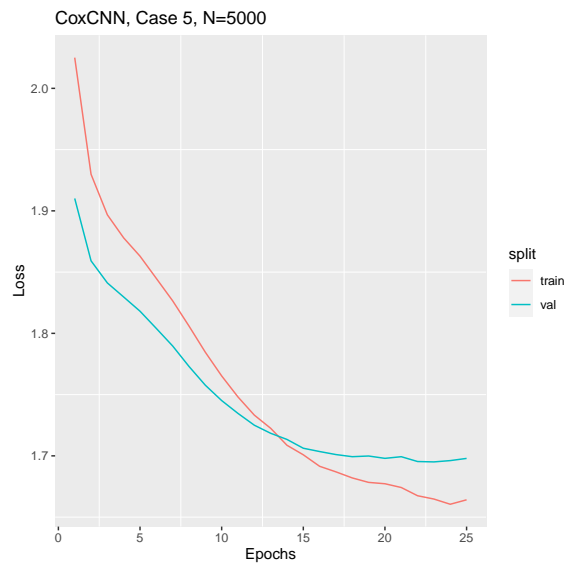


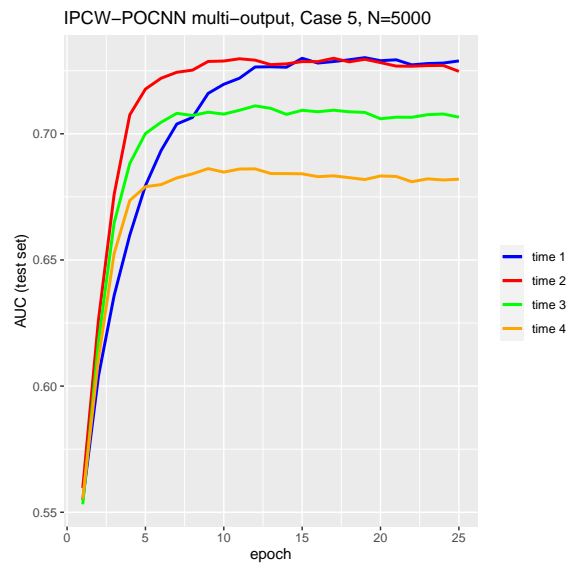
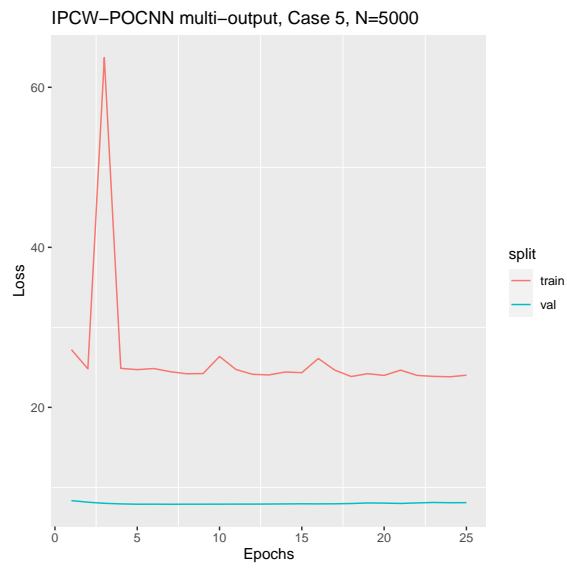




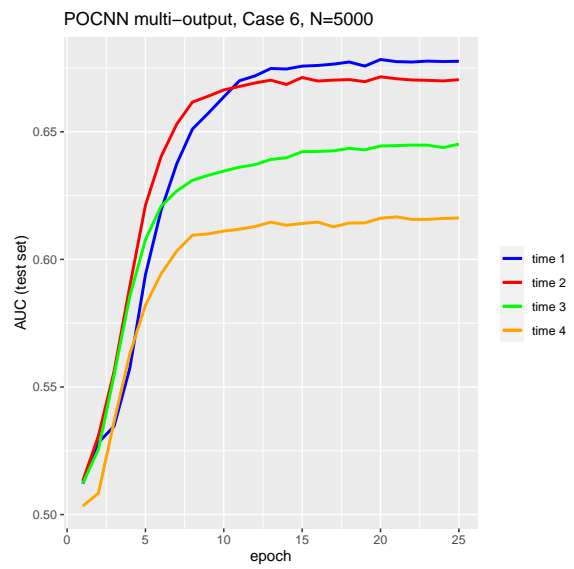
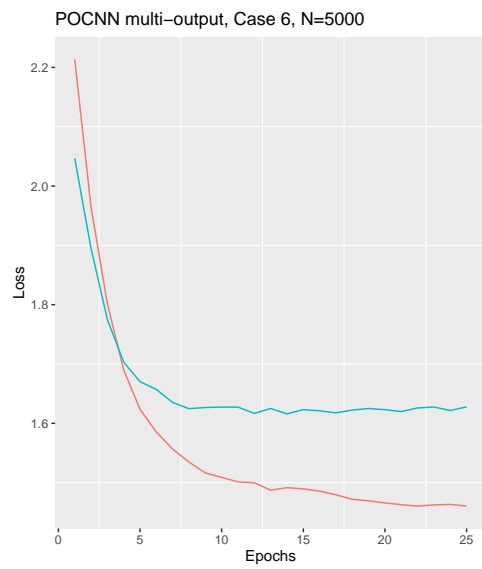
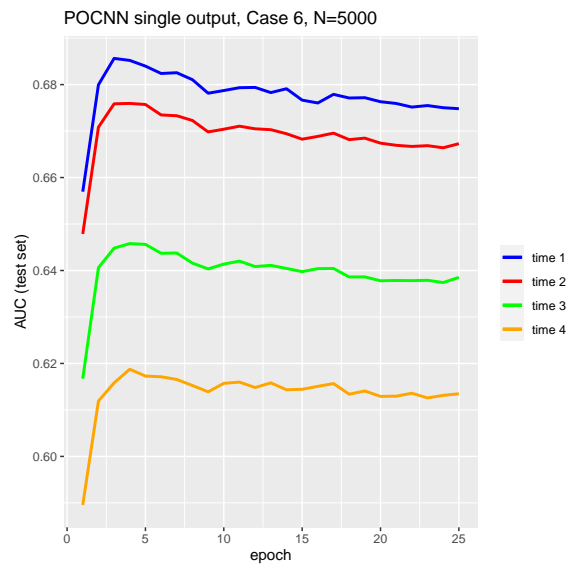
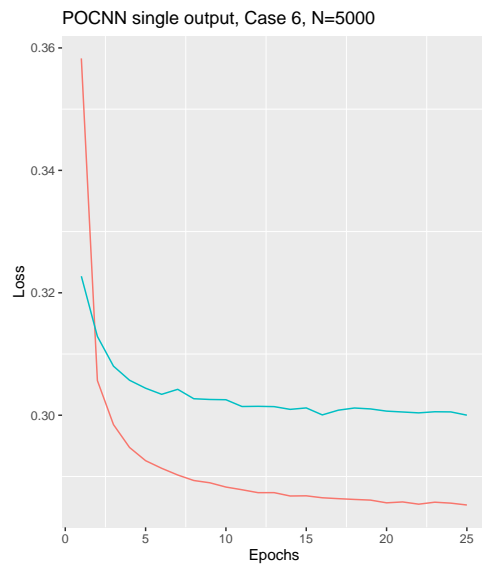
6.11 Case 5, N=5000

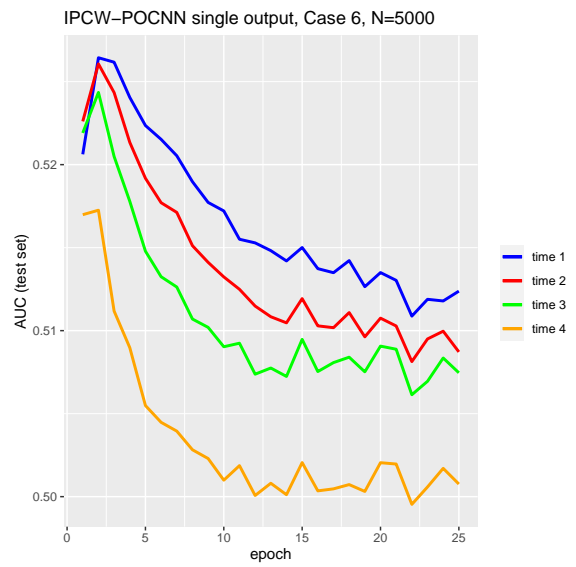
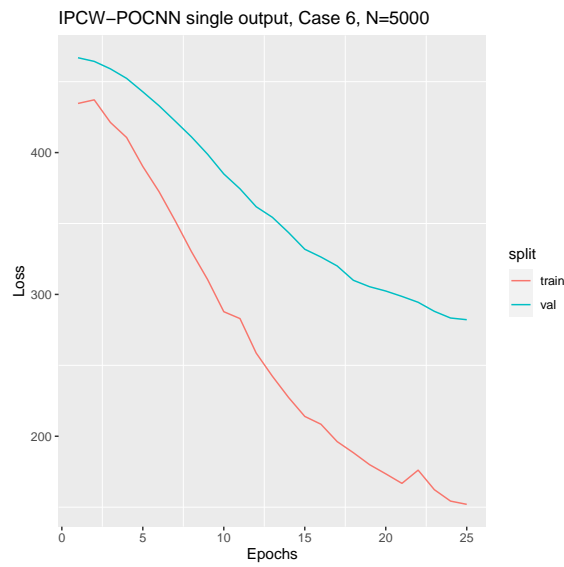
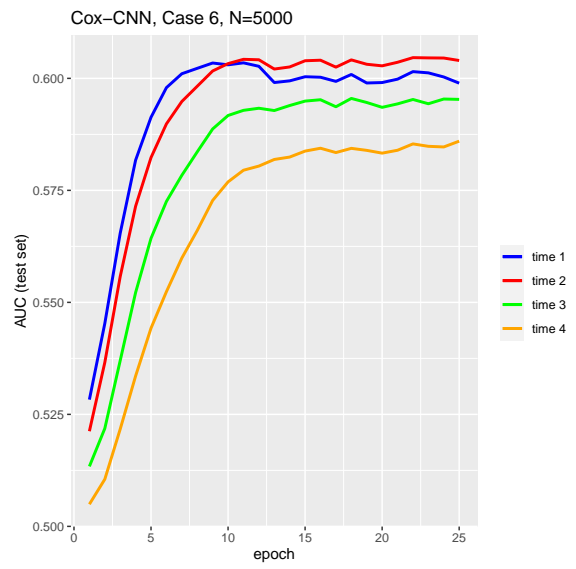
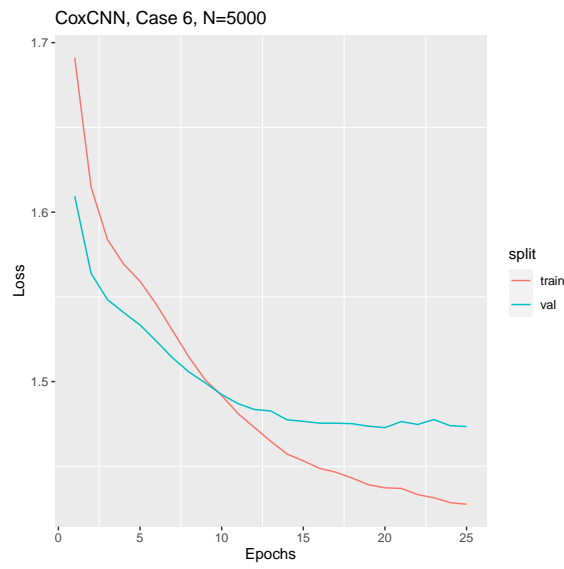


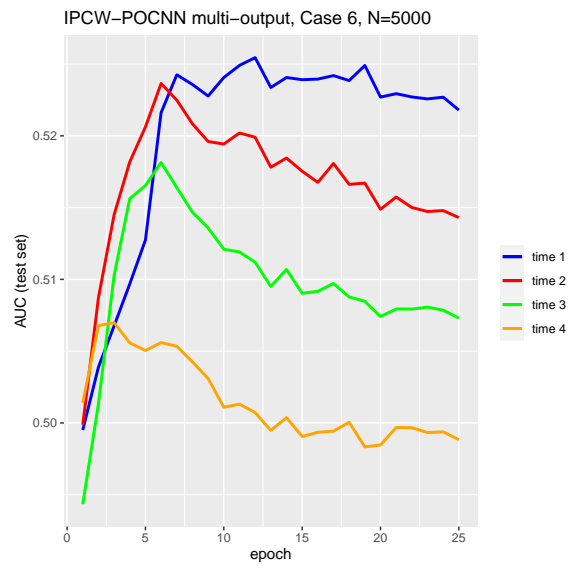
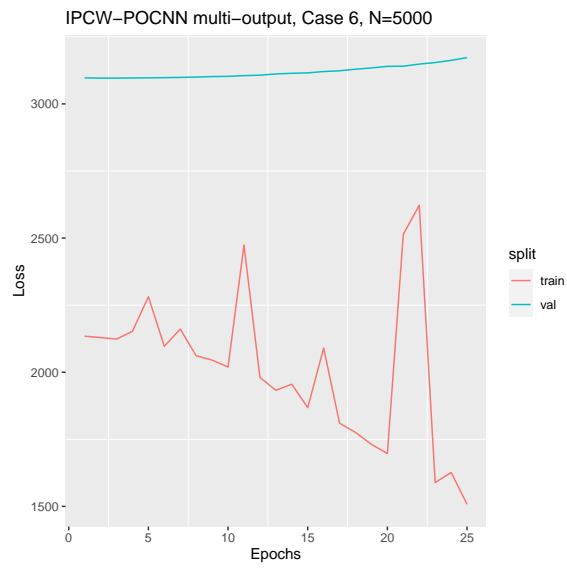




6.12 Case 6, N=5000







7 Kaplan-Meier curves stratified by CIFAR-10's classes for each case considered in the simulations

Figure 9: Case 1

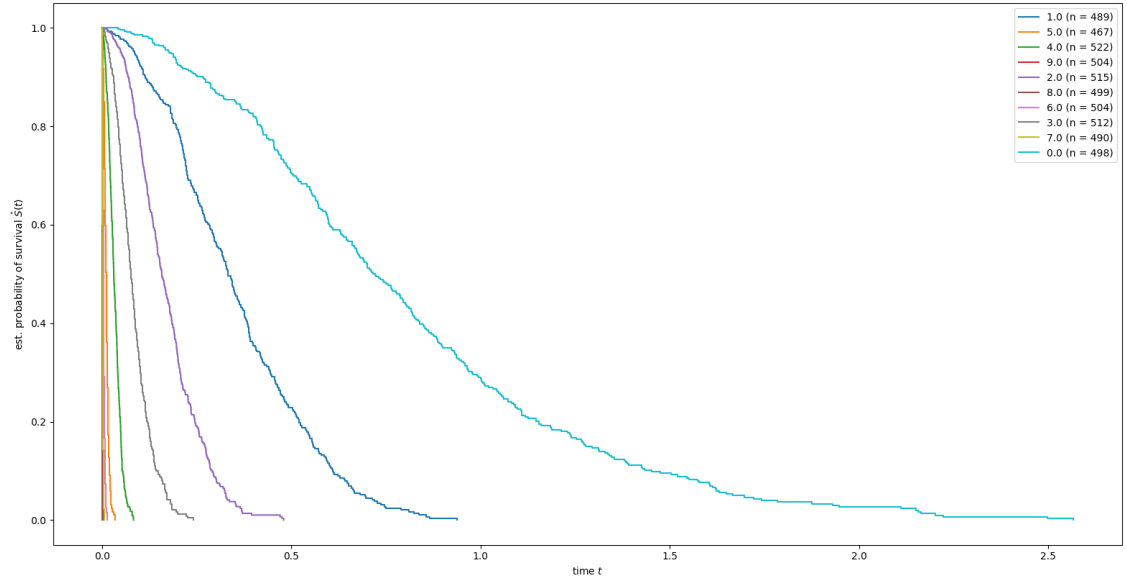


Figure 10: Case 2

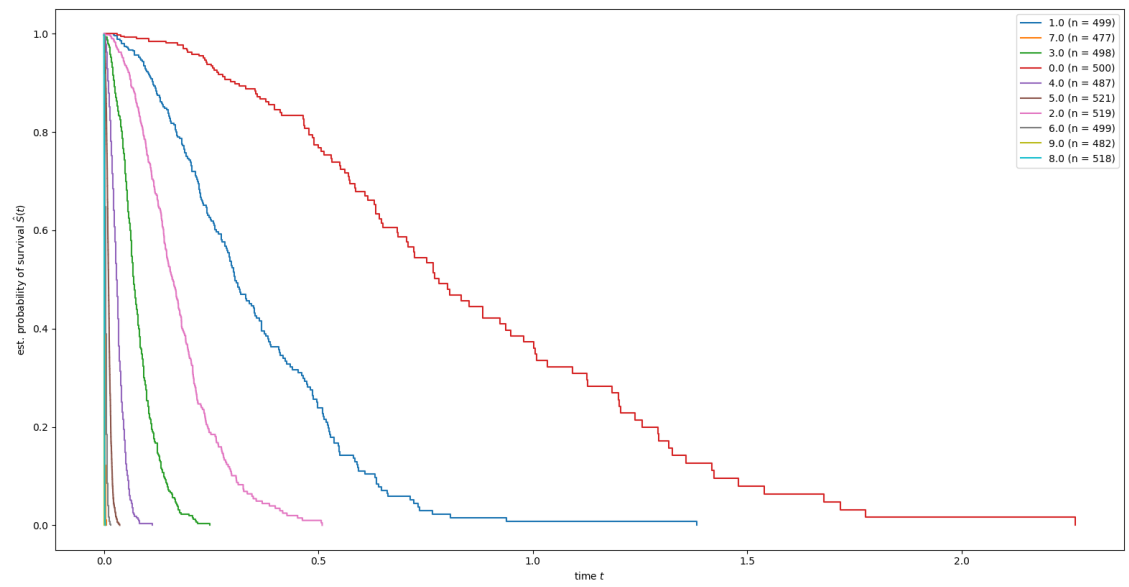


Figure 11: Case 3

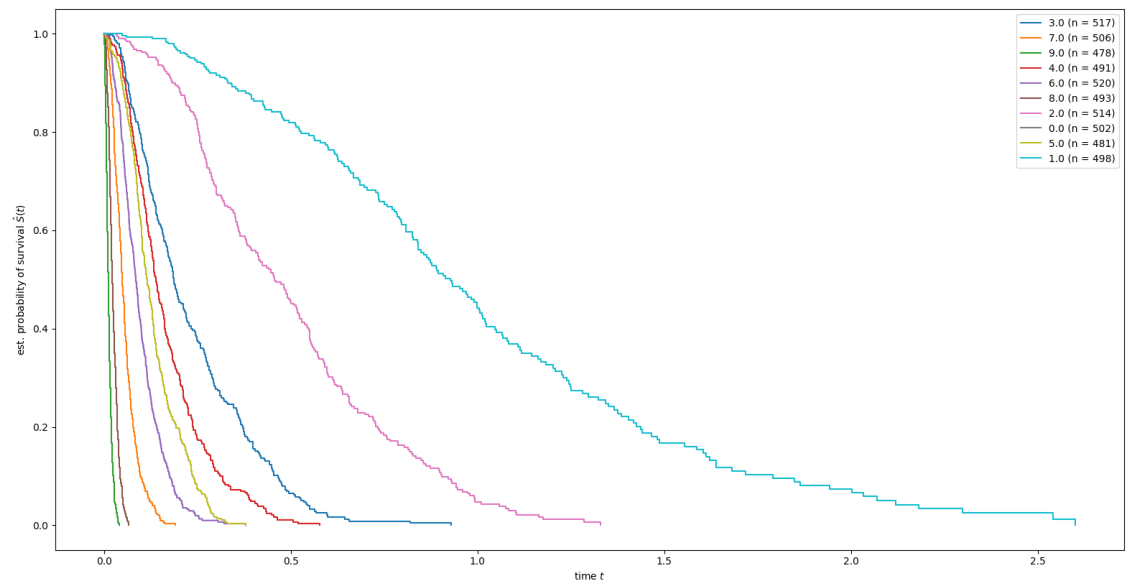


Figure 12: Case 4

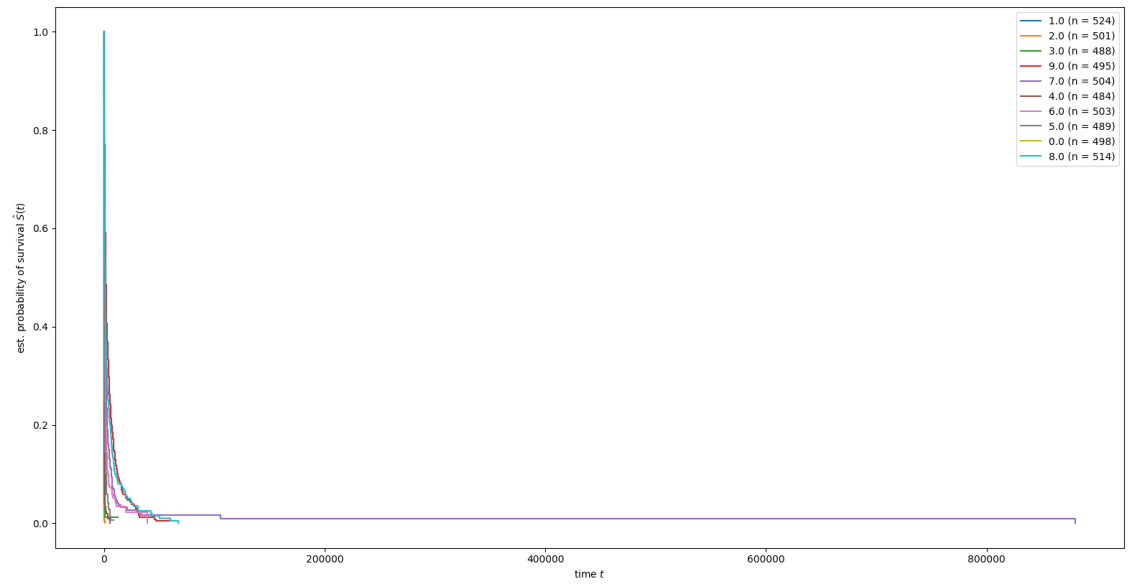


Figure 13: Case 5

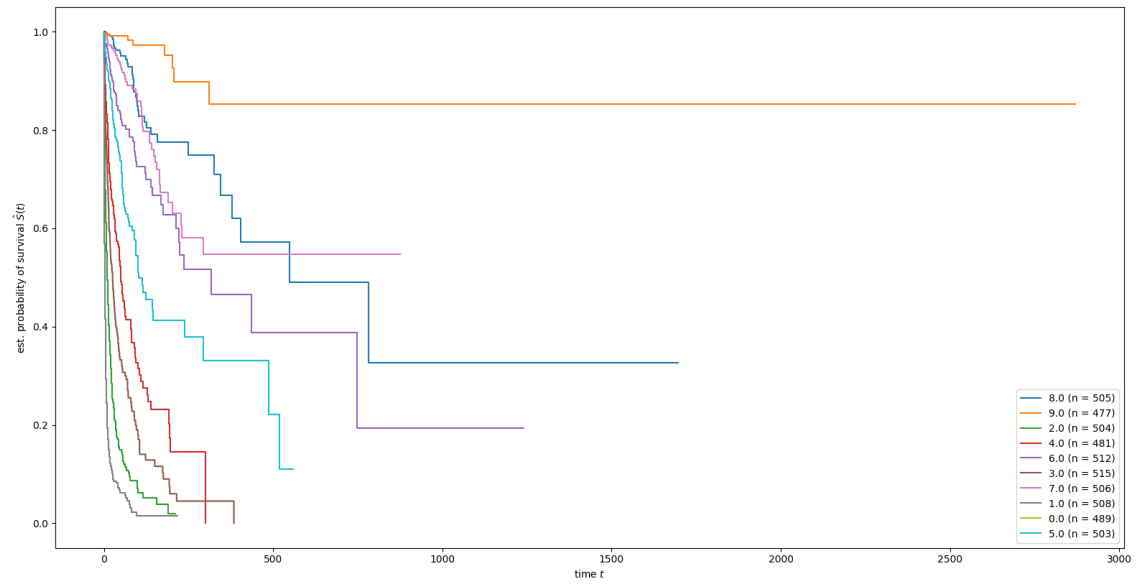


Figure 14: Case 6

