Multimodal Alignment for Synthetic Clinical Time Series

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Abstract

Privacy concerns limit sharing of clinical data, motivating synthetic data generation. However, multimodal clinical time series are challenging due to cross-modal physiological dependencies. We investigate what mechanisms enable generative models to preserve these relationships by comparing three autoregressive conditional mean models using metrics for statistical similarity, clinical rule violations and trend consistency. Analysis on ICU sepsis data suggests that better feature ordering may improve feature-level metrics, yet does not improve cross-feature performance despite strong signals in the training data. This suggests architectural choices limit clinical plausibility, highlighting the need for joint generative architectures or explicit constraint generation for synthetic healthcare time series.

1 Introduction

Privacy concerns often limit the sharing of real clinical data, slowing research and hindering the method development [Beaulieu-Jones et al., 2019, Price and Cohen, 2019]. Synthetic data might be able to alleviate some of these limitations, particularly in exploratory research and validation, as it allows a wide range of scenarios to be tested without compromising privacy [Chen et al., 2021, Yoon et al., 2020]. However, multimodal clinical time series are challenging to synthesise as they consist of heterogeneous measurement modalities, asynchronous and different temporal resolutions and clinical assessments where each feature can have distinct dynamics and cross-modal physiological dependencies [Ghassemi et al., 2020].

The focus of many existing synthetic data methods has been on similarity with single source modalities [Choi et al., 2017, Yoon et al., 2019, Naseer et al., 2023]. However, clinical data requires not only statistical realism but also multimodal alignment to preserve the relationships between measurement types (e.g., fever in vital signs typically accompanies inflammatory markers in lab values). This gap is partly due to a lack of evaluation frameworks that assess cross-modal clinical plausibility alongside statistical similarity [Alaa et al., 2022].

In this paper, we investigate the challenge of *multimodal alignment* in synthetic clinical time series generation. We focus on understanding which model properties are required to preserve crossmodal relationships. Using an autoregressive generation framework that combines conditional mean prediction with residual modelling, we systematically compare how different conditional mean models, from a simple baseline to Ridge regression and Gradient Boosting capture cross-modal dependencies. We introduce an evaluation framework that combines statistical (conditional MMD [Gretton et al., 2012]), clinical plausibility (physiological rule violations across modalities) and trend consistency metrics. The empirical analysis on ICU sepsis data strengthens the belief that architectural limitations, and not just modal ordering, is key for cross-modal alignment. This finding raises important questions about optimal conditioning structures for multimodal clinical data and provides insights for future generative modelling research in healthcare.

2 Methods

To investigate the preservation of cross-modal alignment with different model features and ordering, we use an autoregressive generation framework that systematically varies the complexity of cross-modal dependency modelling. Here we describe our problem setup, generation approach and evaluation metrics.

2.1 Problem Setup

We consider multimodal clinical time series $X_t = [V_t, L_t]$ comprising vital signs V_t (e.g., HR, BP, temperature) and lab values L_t (e.g., lactate, WBC, pH), along with static covariates Z (e.g., gender, age). Our goal is to generate synthetic data that preserve: (1) marginal distributions, (2) temporal dynamics and (3) cross-modal physiological relationships, which is the main focus of our investigation. We ask: What model mechanisms are necessary to preserve cross-modal alignment?

2.2 Autoregressive Generation Framework

We generate features sequentially: $x_{j,t} = \mu_j(x_{< j,t}, Z, t) + \epsilon_{j,t}$, where μ_j is a conditional mean model and $\epsilon_{j,t}$ is an AR(1) residual. To isolate the effect of cross-modal dependency modelling, we compare three conditional mean models: (1) **AR-only**: constant mean $\bar{\mu}_j$ (tests if multivariate residual covariance alone suffices), (2) **Ridge**: linear model with L2 regularization, and (3) **GBM**: non-linear ensemble (100 trees, depth 3).

Residuals follow $\epsilon_{j,t} = \phi_j \epsilon_{j,t-1} + \eta_{j,t}$ with multivariate innovations $\eta_t \sim \mathcal{N}(0, \Sigma)$ (Ledoit-Wolf covariance [Ledoit and Wolf, 2004]). Features are ordered by measurement type (vitals, then labs) in the main experiments. We then perform order permutations which are presented in the Appendix.

2.3 Evaluation Framework

We assess multimodal alignment with three metrics:

Conditional MMD: Statistical similarity within patient subgroups (by gender) using RBF kernel two-sample test. Lower is better. **Clinical rule violations:** We define 10 expert-derived physiological rules (e.g., "hypotension \Rightarrow tachycardia", see Table 1) and measure violation rates. Real data exhibits 30-80% violations due to medications and individual variation. We aim to *match* real rates, not achieve 0%. **Trend consistency:** We compare regression slopes β_{real} vs β_{syn} for covariate-feature relationships: score $= \text{sign}(\beta_{\text{real}}\beta_{\text{syn}}) \times \min(|\beta|)/\max(|\beta|) \in [-1,1]$. Higher indicates better direction and magnitude agreement.

Implication Clinical Basis Rule Name $MAP < 65 \Rightarrow HR > 80$ Hypotension-Tachycardia Compensatory response to low blood pressure Vincent et al. [2018] $MAP < 55 \Rightarrow HR > 100$ Severe Hypotension→Tachycardia Severe shock compensation Cecconi et al. [2014] Temp > 38.3°C \Rightarrow HR > 90Metabolic demand increase O'Grady et al. [2008] Fever→Tachycardia High Fever→Tachycardia Tachypnea→Leukocytosis $Temp > 39.5^{\circ}C \Rightarrow HR > 100$ Severe febrile response O'Grady et al. [2008] $Resp > 22 \Rightarrow WBC > 11$ Inflammatory response Singer et al. [2016] Hypoxia→Tachycardia $SpO_2 < 90\% \Rightarrow HR > 90$ Hypoxic stress response Calverley [2003]

Critical hypoxia response Calverley [2003]

Lactic acidosis Kraut and Madias [2014]

Circulatory shock Hernández et al. [2019]

Respiratory compensation Berend et al. [2014]

 $\hat{SpO}_2 < 85\% \Rightarrow HR > 100 \lor Resp > 24$

 $MAP < 60 \land HR > 110 \Rightarrow Lactate > 2$

Lactate $> 4 \text{ mmol/L} \Rightarrow pH < 7.35$

 $pH < 7.30 \Rightarrow Resp > 20$

Table 1: Clinical Rule Definitions

2.4 Experiments

Severe Hypoxia -- Compensation

Acidosis→Hyperventilation

Hyperlactatemia→Acidosis

Shock→Hyperlactatemia

We use the PhysioNet Computing in Cardiology Challenge 2019 dataset [Reyna et al., 2020] for sepsis prediction. It contains approximately 40,000 ICU patients with hourly recordings of 40 clinical features including vital signs (heart rate, blood pressure, temperature, respiratory rate, oxygen saturation) and laboratory values (lactate, white blood cell count, pH, etc).

We preprocess the data by aligning all measurements to hourly intervals, applying imputation (median) for missing values and z-score normalising each feature using training set statistics. We split the data into 70% training, 15% validation, and 15% test sets. The training set is used to fit all model

parameters, the validation set for hyperparameter selection, and the test set to sample conditioning variables for synthetic generation.

For the conditional mean models, we implement Ridge regression with regularization parameter $\alpha=1.0$ and Gradient Boosting with 100 estimators, maximum depth of 3, learning rate of 0.1, and subsample ratio of 0.5. Each model is trained separately for each feature using all previously ordered features, static covariates, and time as inputs. The AR(1) coefficients are estimated per-feature from training residuals, and the innovation covariance matrix is estimated using Ledoit-Wolf regularisation to ensure positive definiteness.

We generate 500 synthetic patient trajectories for each method, with static covariates sampled from the test set distribution to match the real data composition. Each experiment is repeated with 3 different random seeds. For evaluation, conditional MMD uses an RBF kernel with median heuristic bandwidth selection. Clinical rules are evaluated on all timesteps where the antecedent condition holds and trend consistency scores are computed using linear regression on gender as the primary covariate.

3 Results

Table 2 shows that conditional MMD improves with model complexity, with GBM achieving the lowest average distance (0.304 \pm 0.003) compared to Ridge (0.328 \pm 0.007) and ARonly (0.351 \pm 0.003). This suggests that modeling cross-modal dependencies through the conditional mean improves similarity within subgroups.

Table 2: Conditional MMD Comparison (mean \pm std over 3 seeds, lower is better)

Method	Gender=0	Gender=1	Average
AR(1)-only	0.342±0.006	0.358±0.009	0.351 ± 0.003
Ridge+AR(1)	0.321±0.016	0.333±0.001	0.328 ± 0.007
GBM+AR(1)	0.293±0.003	0.313±0.007	0.304 ± 0.003

However, clinical rule violations (Table 3) reveal a more complex picture. While some rules show expected patterns, the Fever \rightarrow Tachycardia relationship remained mostly unlearned across models. Further results are shown in the Appendix, where we experiment with different feature orders, which in theory should allow the model to generate more realistic Fever \rightarrow Tachycardia relationships. Even with this, the models were unable to improve their clinical realism. This was despite there being a strong signal in the training set (mean HR with fever: 99.1 bpm vs without: 84.3 bpm, Cohen's d = 0.84, p < 0.001).

This suggests that our chosen models face inherent difficulty in learning these relationships and generating realistic trajectories. The fact that the AR model performs marginally better, despite not having explicit conditionals suggesting that some parts of the signal are captured in the residuals.

Table 3: Clinical Rule Violations (closer to Real is better)

Rule	Real	AR-only	Ridge	GBM
Hypotension→Tachy	0.51	0.464 ± 0.013	0.403 ± 0.010	0.410±0.017
Severe Hypotension→Tachy	0.86	0.892 ± 0.006	0.855 ± 0.016	0.831 ± 0.038
Fever→Tachy	0.33	0.570 ± 0.029	0.689 ± 0.011	0.689 ± 0.019
High Fever→Tachy	0.37	0.601 ± 0.114	0.889 ± 0.157	0.958 ± 0.059
Tachypnea→Leukocytosis	0.53	0.437 ± 0.012	0.452 ± 0.018	0.467 ± 0.014
Hypoxia→Tachy	0.48	0.581 ± 0.020	0.595 ± 0.043	0.612 ± 0.037
Severe Hypoxia→Comp	0.54	0.167 ± 0.236	0.000	0.333 ± 0.471
Acidosis→Hypervent	0.64	0.607 ± 0.044	0.518 ± 0.038	0.618 ± 0.037
Hyperlactatemia→Acidosis	0.54	0.637 ± 0.035	0.830 ± 0.032	0.814 ± 0.059
Shock→Hyperlactatemia	0.78	0.524 ± 0.093	0.612 ± 0.155	0.671 ± 0.087

Trend consistency scores (Table 4) further illustrate the complexity. Ridge achieves strong positive consistency for blood pressure features (MAP: +0.79±0.09, DBP: +0.76±0.17) and pH (+0.80±0.09), while GBM shows comparable performance on some features but worse on others (Temp: +0.22±0.30 vs Ridge +0.45±0.48). Notably, the AR-only baseline shows near-zero or negative consistency for most features, confirming that explicit cross-modal modeling is necessary.

These results suggest that different aspects of multimodal alignment are not uniformly improved by model complexity. These patterns are further complicated by the uneven performance gains of optimising feature orders, highlighting the need for improved joint modality modelling for generative realism.

Table 4: Trend Consistency (higher is better)

Feature	AR-only	Ridge	GBM
HR	+0.08±0.04	+0.45±0.15	+0.28±0.22
O2Sat	-0.22 ± 0.31	$+0.41\pm0.11$	$+0.52\pm0.15$
Temp	-0.61 ± 0.40	$+0.45\pm0.48$	$+0.22\pm0.30$
SBP	$+0.01\pm0.25$	$+0.07\pm0.28$	-0.12 ± 0.60
MAP	$+0.10\pm0.64$	$+0.79\pm0.09$	$+0.68\pm0.18$
DBP	-0.40 ± 0.21	$+0.76\pm0.17$	$+0.79\pm0.12$
Resp	-0.54 ± 0.48	-0.06 ± 0.64	-0.13 ± 0.67
Lactate	$+0.06\pm0.36$	-0.18 ± 0.05	-0.29 ± 0.17
WBC	$+0.27\pm0.38$	$+0.46\pm0.09$	$+0.53\pm0.27$
pН	$+0.18\pm0.42$	$+0.80\pm0.09$	$+0.21\pm0.29$

4 Discussion

Our investigation uncovers patterns suggesting an underexplored factor in multimodal clinical time series generation: feature ordering in autoregressive models may act as an inductive bias affecting which cross-modal relationships can be learned. Consider the Fever—Tachycardia rule. In our original experiments, heart rate appears before temperature, meaning the conditional mean model predicts HR without access to temperature information. This architectural constraint could have explained why models fail to capture fever—tachycardia. However, in our additional systematic experiments (see Appendix) where we vary feature order we did not observe improvement for cross-feature or cross-modal clinical rules, suggesting the root cause is deeper than feature ordering. Improvements were, however, observed in feature-level metrics.

This finding connects to broader work in autoregressive generation and modeling. Autoregressive models in vision and language implicitly encode ordering assumptions through raster scan or left-to-right generation [van den Oord et al., 2016, Vaswani et al., 2017], though some work has explored learned orderings and parallel generation to mitigate this [Uria et al., 2016, Niu et al., 2020]. In causal inference, variable ordering in structural equation models similarly determines which relationships can be represented [Pearl, 2009, Spirtes et al., 2000]. Our contribution is demonstrating that these architectural choices have measurable consequences for domain-specific plausibility in healthcare data, where the "correct" ordering may correspond to physiological causality rather than data structure.

The practical implications are significant. For practitioners generating synthetic clinical data, our results suggest that distributional metrics alone are insufficient and that domain-specific evaluation is necessary to verify clinical plausibility. Moreover, our findings indicate that simpler models may sometimes be preferable if they preserve critical cross-modal relationships better than complex models that overfit spurious patterns in the chosen feature ordering. For researchers, our work highlights underexplored factors that warrant systematic investigation, possibly through causal discovery methods that optimise for domain-specific constraints.

Our study has the following limitations. We evaluate on a single dataset (ICU sepsis), use one conditioning variable for MMD (gender), and manually define 10 clinical rules. The feature ordering is varied in only three different permutations, and we do not compare to deep generative models like GANs or VAEs. Future work should explore joint generation of all features per timestep, and more comprehensive rule sets possibly discovered through automated mining of clinical literature.

5 Conclusion

We investigate what mechanisms enable generative models to preserve cross-modal physiological relationships in synthetic clinical time series. Through systematic comparison of three conditional mean models evaluated with statistical, clinical plausibility and trend consistency metrics, our results suggest that feature ordering may constrain which cross-modal relationships can be learned. When heart rate is predicted before temperature, the model could struggle to learn that fever causes tachycardia. This suggests that architectures implicitly encode causal assumptions with measurable consequences for domain-specific plausibility. Our results show that distributional metrics alone are insufficient and that specific evaluation is essential for synthetic healthcare data. Future work should explore principled feature orderings through causal discovery or joint generation architectures.

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A Appendix

We perform further experiments to investigate the impact of ordering on our metrics. In addition to the default order (vitals—labs), we try reverse order (labs—vitals) and temperature first (temperature and HR before other features) to target the fever+tachycardia relationship directly. We test this across all models with three random seeds, taking the mean and standard deviation between runs.

The real data signal is strong between fever \rightarrow tachycardia, mean HR with fever: 99.1 bpm vs without: 84.3 bpm, Cohen's d = 0.84, p < 0.001.

Temperature first improves the learned temperature trend across models (Table 7), indicating that improved ordering can improve feature-level metrics in some cases. This is possibly due to relaxed constraints or inductive bias.

However, placing the temperature generation step before HR did not lead to meaningful and consistent improvement on the clinical rule violation metric. This suggests that simple reordering that theoretically allows more realistic generation is insufficient for improving cross-feature relationships. Other rules show minimal sensitivity to changed ordering (Table 6. This pattern is consistent across all models tested (Table 8), further supporting the hypothesis that simple reordering is insufficient.

Distributional similarity showed minimal variance across the orders we tested (Table 5).

Table 5: Distributional Similarity (Conditional MMD) by feature ordering for the Ridge Model (lower is better). We see that Conditional MMD with mean±std across three random seeds. Ordering has minimal impact on distribution properties.

Metric	Default	Temp first	Reversed	Δ (Def $ ightarrow$ Temp)
Average MMD	0.336±0.003	0.325±0.004	0.329±0.002	-0.011

Table 6: Clinical Rule Violations by feature ordering for the Ridge model. Results show violation rates with mean±std across three random seeds. The Fever—Tachycardia rule shows minimal sensitivity to ordering despite temp first placing Temperature before HR during learning and generation steps.

Rule	Real	Default	Temp first	Reversed	Δ
Hypotension→Tachy	0.51	0.403±0.010	0.400±0.013	0.401±0.008	-0.003
Fever → Tachy	0.33	0.689±0.011	0.697±0.042	0.713±0.029	+0.008
Tachypnea→Leukocytosis	0.53	0.452±0.018	0.456±0.018	0.446 ± 0.008	+0.004
Acidosis→Hypervent	0.64	0.518±0.038	0.531±0.018	0.542±0.020	+0.013
Hyperlactatemia→Acidosis	0.54	0.830 ± 0.032	0.853 ± 0.041	0.842±0.015	+0.023

Table 7: Trend Consistency by feature ordering for the Ridge model. Results show trend consistency scores with mean±std across three random seeds. Temp first ordering substantially improves Temperature trend consistency, demonstrating ordering affects feature-covariate alignment.

Feature	Default	Temp first	Reversed	Δ (Def $ ightarrow$ Temp)
HR	+0.45±0.15	+0.43±0.23	+0.44±0.14	-0.02
Temp	+0.45±0.48	$+0.75\pm0.16$	-0.56±0.43	+0.30
MAP	+0.79±0.09	+0.48±0.30	+0.69±0.14	-0.31
pН	+0.80±0.09	+0.51±0.24	+0.73±0.10	-0.29
Resp	-0.06±0.64	+0.49±0.18	-0.06±0.29	+0.55

Table 8: Ordering Effects on Key Metrics Across All Conditional Mean Models. Summary of Temperature trend consistency improvements and Fever—Tachycardia rule insensitivity across ARonly, Ridge and GBM models. Values show mean±std across three random seeds. All models show consistent patterns: Temp trend improves with temp first ordering, while Fever—Tachy rule violations remain largely unchanged.

Model	Metric	Default	Temp first	Δ
AR-only	Temp Trend	-0.61±0.40	+0.33±0.40	+0.94
	Fever→Tachy	0.570±0.029	0.548±0.023	-0.022
Ridge	Temp Trend	+0.45±0.48	+0.75±0.16	+0.30
	Fever→Tachy	0.689±0.011	0.697±0.042	+0.008
GBM	Temp Trend	+0.22±0.30	+0.64±0.28	+0.42
	Fever→Tachy	0.689±0.019	0.693±0.044	+0.003