

000 001 002 003 004 005 CRONOS: CONTINUOUS TIME RECONSTRUCTION FOR 006 4D MEDICAL LONGITUDINAL SERIES 007 008 009

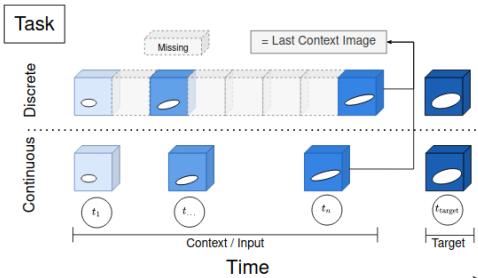
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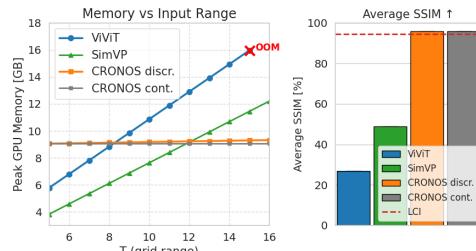
ABSTRACT

011 Forecasting how 3D medical scans evolve over time is important for disease pro-
012 gression, treatment planning, and developmental assessment. Yet existing models
013 either rely on a single prior scan, fixed grid times, or target global labels, which
014 limits voxel-level forecasting under irregular sampling. We present CRONOS, a
015 unified framework for many-to-one prediction from multiple past scans that sup-
016 ports both discrete (grid-based) and continuous (real-valued) timestamps in one
017 model, to the best of our knowledge the first to achieve continuous sequence-to-
018 image forecasting for 3D medical data. CRONOS learns a spatio-temporal ve-
019 locity field that transports context volumes toward a target volume at an arbitrary
020 time, while operating directly in 3D voxel space. Across three public datasets
021 spanning Cine-MRI, perfusion CT, and longitudinal MRI, CRONOS outperforms
022 other baselines, while remaining computationally competitive. We will release
023 code and evaluation protocols to enable reproducible, multi-dataset benchmark-
024 ing of multi-context, continuous-time forecasting.

1 INTRODUCTION



(a) Task description.



(b) Memory Efficiency vs. Performance

040 **Figure 1: Task and benchmark comparison** (a) **Task setup** Forecasting a target 3D scan from
041 multiple past volumes in two regimes. *Discrete*: acquisitions lie approximately on a regular grid, but
042 may contain missing frames (dotted boxes). *Continuous*: acquisitions occur at irregular, real-valued
043 timestamps and are used directly without grid alignment. Many-to-one task $(\{I_i\}_{i=1}^T, t_{\text{target}}) \rightarrow I_{\text{target}}$. (b) **Efficiency and performance** Left: GPU memory scaling of single forward pass with
044 sequence length T shows CRONOS to be substantially more memory-efficient than alternatives.
045 Right: Average SSIM across two datasets, where CRONOS outperforms baselines and LCI.
046

047 Longitudinal medical imaging is central to monitoring disease progression, assessing treatment
048 response, and modeling anatomical development across time (Suter et al., 2022; Rivail et al.,
049 2019; Bernard et al., 2018). Some modalities are inherently spatio-temporal, such as ultra-
050 sound (US), cine-MRI, videos, or perfusion Computer Tomography (CT). Beyond these, re-
051 peated clinical acquisitions form temporal sequences that may span over months or years and
052 are used for clinical decision making. In ophthalmology, for instance, longitudinal OCT vol-
053 umes are central to monitoring progression of age-related macular degeneration and predicting

treatment response (Rivail et al., 2019). Works such as using surgical video streams (Li et al., 2024), which are also increasingly leveraged for diverse tasks, or in (Gomes et al., 2022), where longitudinal US sequences are used, show the overall breadth of spatio-temporal imaging. Beyond individual modalities, there is also a massive and growing amount of video and longitudinal data across clinical contexts (Farhad et al., 2023), including applications such as treatment response prediction in oncology (Suter et al., 2022).

Despite its importance, spatio-temporal learning in medical imaging is centered mostly on single time-point (image-to-image) analysis. Some approaches rely on global labels e.g. Yoon et al. (2024), while many reduce to image-to-image prediction with a single context scan (Zhang et al., 2025a)). Ohters introduce task-specific prior or remain tied to one disease (e.g. Puglisi et al. (2025)). In particular, Alzheimer’s Disease (AD) has attracted a disproportionate share of longitudinal imaging research (Petersen et al., 2010; Martí-Juan et al., 2020; Chen et al., 2025), whereas other domains remain comparatively underexplored.

CRONOS addresses these challenges by introducing a unified spatio-temporal flow framework for medical sequence-to-image prediction that: ¹

- **Supports both *discrete* and *continuous* timestamps**, leveraging multiple past scans jointly on **3D** medical imaging data.
- **Avoids disease-specific assumptions**, enabling application to any medical longitudinal task.
- **Consistently outperforms prior approaches**, including standard sequence models and the Last Context Image (LCI) baseline, which is a surprisingly simple and competitive heuristic (NRMSE, PSNR, and SSIM), due to slowly changing medical images.

2 RELATED WORK

Medical Imaging Prior work in longitudinal medical imaging focuses heavily on one-to-one, or one-to-many video prediction. While approaches like diffusion models (Litrico et al., 2024; Zhu et al.; Puglisi et al., 2025) and Neural ODEs (Lachinov et al., 2022; Liu et al., 2025) have been applied to medical imaging, these are *image-to-image*, and thus cannot canonically capture multi-input longitudinal evolution. For example, Bai & Hong (2024) propose a continuous-time model, but they predict sequences from single images. In contrast, works that jointly leverage multiple observations show improved prediction accuracy (Fang et al., 2021). The single-context nature makes these aforementioned works not sufficient for our setting. There are also **interpolation-based methods** (Zhu et al., 2024) which predict intermediate frames between two acquisitions, but this restricts their use to filling missing intervals rather than forecasting. Overall, existing medical approaches are all technically restricted; be it only single-image input, disease specific priors, limited to 2D, or not being able to forecast to arbitrary times as shown in 1.

¹Code will be released at github.com/anonymous.

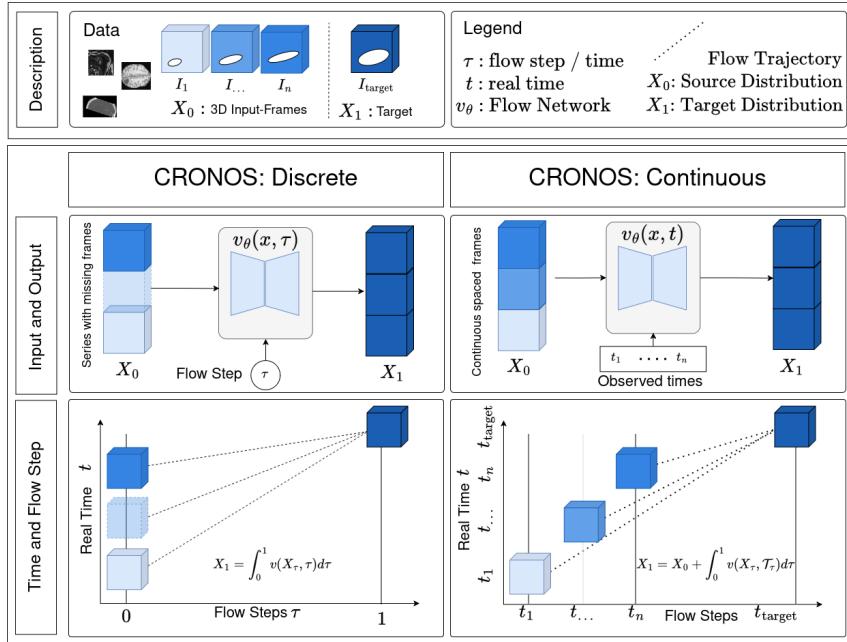


Figure 2: **CRONOS method overview:** **Left:** Discrete CRONOS treats time implicitly, interpolating between context frames and a fixed target along a normalized flow step $t \in [0, 1]$. **Right:** Continuous CRONOS explicitly conditions on real-valued timestamps t_i , allowing each context I_i to transport toward the target via its own interpolation t_i . This enables predictions at arbitrary target times while preserving the true temporal geometry.

By contrast, our work focuses on continuous-time modeling across full spatio-temporal sequences without restricting to specific modalities or diseases.

Natural Imaging and Video Prediction Spatio-temporal modeling has been extensively studied in video prediction. Early approaches such as ConvLSTM (SHI et al., 2015) introduced recurrent sequence-to-sequence architectures and remain widely used. Subsequent methods such as SimVP (Gao et al., 2022) replaced recurrence with purely convolutional designs. Transformer-based models like ViViT (Arnab et al., 2021) extended attention mechanisms to the video domain and have become a backbone in many imaging domains. More recent efforts have explored generative modeling, including video diffusion (Valeti et al., 2022; Ye & Bilodeau, 2023; Yan et al., 2021), and continuous-time formulations such as Neural ODEs (Chen et al., 2019), extended to videos in (Park et al., 2021). While these approaches are powerful, they have primarily been developed for dense 2D natural video sequences with large-scale training data. Accordingly, they transfer poorly to 3D medical images with small datasets and sparse sequences, thus motivating our work.

Flow Matching Flow Matching (FM) has recently emerged as a generative modeling paradigm (Lipman et al., 2023; 2024), and has been adapted to irregular time series, e.g. in (Zhang et al., 2025b), though only for low-dimensional data rather than full image sequences. Our extension therefore is: while classical FM learn a single flow from (most often) raw noise $X_0 \sim p$ to samples $X_1 \sim q$ along steps $\tau \in [0, 1]$, we re-cast

$$X_0 = [I_1, \dots, I_T], \quad X_1 = \mathcal{I}_{\text{target}} := [I_{\text{target}}, \dots, I_{\text{target}}], \quad (1)$$

interpreting p as the context sequence, and q as a broadcast stack of I_{target} (defined the stack as $\mathcal{I}_{\text{target}}$, to make dimension explicit). This temporal broadcasting turns FM into sequence-to-image transport: a shared velocity field v_θ simultaneously moves all T context volumes toward the target, effectively T per-frame transports under shared parameters. We refer to this framework as **Continuous RecOnstructioNs for medical IOn longitudinal Series (CRONOS)**.

162 3 METHODS
163
164165 **Algorithm 1** CRONOS Continuous: Training and Inference166 **Require:** Patients \mathcal{P} and initial network v_θ

```

167 1: while training do
168 2:   Sample  $\{[\mathcal{I}, I_{\text{target}}], [t_1, \dots, t_T, t_{\text{target}}]\} \sim \mathcal{P}(\mathcal{X})$             $\triangleright$  pick a random patient
169 3:   Sample  $\tau \sim \mathcal{U}(0, 1)$                                           $\triangleright$  random flow step
170 4:    $\mathcal{I}_{\text{target}} \leftarrow [I_{\text{target}}, \dots, I_{\text{target}}]$                                  $\triangleright$  repeat target  $T$  times
171 5:    $\mathcal{T}'_\tau \leftarrow (1 - \tau)[t_1, \dots, t_n] + \tau t_{\text{target}}$             $\triangleright$  interpolate timestamps
172 6:    $X_\tau \leftarrow (1 - \tau)\mathcal{I} + \tau\mathcal{I}_{\text{target}} + \sigma(\tau)\epsilon$             $\triangleright$  linear interpolation
173 7:    $\mathcal{L} \leftarrow \|v_\theta(\mathcal{T}'_\tau, X_\tau) - (\mathcal{I}_{\text{target}} - \mathcal{I})\|^2$             $\triangleright$  velocity loss
174 8:   Update  $\theta \leftarrow \text{AdamW}(\nabla_\theta \mathcal{L})$ 
175 9: return  $v_\theta$ 
176 10: if inference then
177 11:   Initialize  $X_0 \leftarrow \mathcal{I}$ 
178 12:   Define integration grid  $\{\tau_0 = 0, \dots, \tau_N = 1\}$  with  $N$  steps
179 13:    $\mathcal{T}'_\tau = (1 - \tau)[t_1, \dots, t_n] + \tau t_{\text{target}}$ 
180 14:    $\hat{X}_{0:N} \leftarrow \text{ODEInt}(v_\theta, X_0, \{\mathcal{T}'_0, \dots, \mathcal{T}'_1\})$             $\triangleright$  numerical integration
181 15: return  $\hat{X}_N$ 

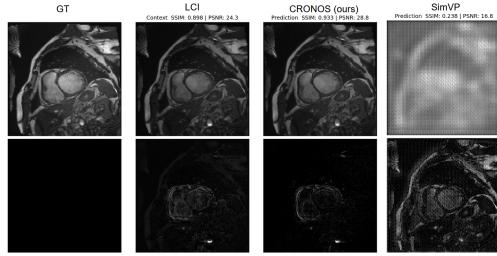
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184 3.1 PROBLEM SETUP

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186 Let $\mathcal{P} = \{(\{I_i^{(n)}, t_i^{(n)}\}_{i=1}^{T^{(n)}}, t_{\text{target}}^{(n)}, I_{\text{target}}^{(n)})\}_{n=1}^p$ denote a dataset of p patient sequences. Each
187 (patient) sequence consists of a set of T context volumes $\mathcal{I} = \{I_1, \dots, I_T\}$, with $I_i \in \mathbb{R}^{H \times D \times W}$
188 (for shorthand $S = H \times D \times W$), acquired at associated timestamps $\{t_1, \dots, t_T\} \subset \mathbb{R}_+$.

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199 **Figure 3: Qualitative comparison on the ACDC dataset.** Ground truth (GT), Last Context Image
200 (LCI), our method (CRONOS), and SimVP. Up-
201 per row: prediction, lower row: residuals.202 We consider two regimes. **Discrete:** Ac-
203 quisitions lie on a uniform time grid; some
204 frames may be missing, yielding sparse se-
205 quences (e.g., natural video, cine-MRI, perfu-
206 sion CT). **Continuous:** Acquisitions occur at
207 irregular, real-valued times that do not easily
208 align to any grid (typical in longitudinal clin-
209 ical scans). For continuous series, forcing a
210 frame grid either explodes sequence length with
211 empty slots or loses temporal precision. For in-
212 stance, daily-resolution for timepoints over sev-
213 eral years would yield T in the thousands, yet
214 in practice only a handful of scans are ever ac-
215 quired. In both discrete and continuous series,
216 T is small relative to natural video.

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226 t_{target} , we aim to learn

227
$$f(\{I_i, t_i\}_{i=1}^T, t_{\text{target}}) \mapsto I_{\text{target}}. \quad (2)$$

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236 3.2 FLOW MATCHING (FM)

237 Flow Matching Lipman et al. (2023) learns a ordinary differential equation (ODE), linking the equal
238 dimensional distributions p and q via

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242
$$\frac{d}{d\tau} \psi_\tau(x) = u_\tau(\psi_\tau(x)), \quad X_1 = X_0 + \int_0^1 u_\tau(X_\tau) d\tau, \quad (3)$$

216 with $X_0 \sim p$, $X_1 \sim q$. A convenient coupling is obtained by sampling X_τ as
 217
 218

$$X_\tau = (1 - \tau)X_0 + \tau X_1 + \sigma(\tau)\epsilon, \quad (4)$$

219 where $\epsilon \sim \mathcal{N}(0, I)$ denotes random gaussian noise and $\sigma(\tau)$ its intensity, which is sampled around
 220 the straight path. The corresponding ground-truth velocity along this path is therefore constant:

$$u_\tau(X_\tau) = \frac{d}{d\tau}X_\tau = X_1 - X_0. \quad (5)$$

221 Consequently, to approximate the ground truth velocity, we train a neural network $v_\theta(X_\tau, \tau) \in$
 222 $\mathbb{R}^{T \times S}$ using:
 223

$$\mathcal{L}_{\text{CFM}} = \mathbb{E}_{X_0, X_1, \tau} \|v_\theta(X_\tau, \tau) - u_\tau(X_\tau)\|_2^2. \quad (6)$$

224 Using v_θ , we can then infer using equation 3 via an approximate ODE solver.
 225

226 3.3 CONTINUOUS AND DISCRETE RECONSTRUCTIONS FOR MEDICAL IMAGE TIME SERIES
 227 (CRONOS)

228 We introduce CRONOS, a spatio-temporal flow model that learns continuous trajectories from lon-
 229 gitudinal scans. It comes in two complementary variants: *discrete* and *continuous*.
 230

231 **Temporal broadcasting for sequence-to-image flows** To enable flow between a sequence of con-
 232 text images and a single target, we define $X_0 \sim p$ as the stack of context images (with variant-
 233 specific handling for continuous vs. discrete), and $X_1 \sim q$ as the target image broadcast to the same
 234 shape

$$X_1 = [I_{\text{target}}, \dots, I_{\text{target}}]. \quad (7)$$

235 This broadcasting ensures that X_0 and X_1 share the same dimensionality, allowing us to define a
 236 valid flow between them.
 237

238 **Discrete CRONOS.** On a regular grid with missing scans, we first *embed* each sequence onto the
 239 grid of a resolution g using a binning operator $\mathcal{E}_g^{\text{grid}}$, which assigns each I_i to the closes grid index
 240 matching t_i (proper definition in A.1.1). Missing slots are then handled by a last-observed carry-
 241 forward operator $\mathcal{F}^{\text{LOCF}}$, which fills empty positions with the most recent available scan. In short,
 242 we define

$$X_0 = (\underbrace{\mathcal{F}^{\text{LOCF}}}_{\text{fill}} \circ \underbrace{\mathcal{E}_g^{\text{grid}}}_{\text{bin to grid}})(\{(I_i, t_i)\}_{i=1}^T) = [\hat{I}_1, \dots, \hat{I}_K]. \quad (8)$$

243 This pre-processing ensures X_0 is well-defined on a uniform grid. Furthermore, LOCF handles
 244 spatial missingness: missing frames are zero-initialized and replaced by the most recent observation
 245 (Appendix A.1.2). This setup stabilizes optimization and preserves grid order while enabling many-
 246 to-one sequence transport within FM. Finally, we train on the linear interpolation $X_\tau = (1 - \tau)X_0 +$
 247 τX_1 using equation 6, where temporal order is captured *implicitly* by the flow step τ and the frame
 248 index. Additionally, we set $\sigma = 0$ during training and inference, ablations on nonzero noise levels
 249 are reported in Table 7.

250 **Continuous CRONOS** Our continuous modeling strategy extends on the discrete case by con-
 251 ditioning on *real-valued timestamps* while evolving along a scalar flow parameter $\tau \in [0, 1]$. We
 252 construct spatio-temporal tensors (using mild abuse of notation): Time enters the network only as
 253 conditioning on real timestamps. We interpolate the conditioning timestamps along the interpolated
 254 time vector \mathcal{T}_τ . X_0 is then defined as in equation 7, without embedding it to the grid, nor
 255 performing LOCF as in discrete CRONOS. We define the shifted time vector as

$$\mathcal{T}_\tau = (1 - \tau)\mathbf{t}_{\text{ctx}} + \tau \mathbf{t}_{\text{target}}. \quad (9)$$

256 The formulation in equation 9 lets flow step τ carry real temporal information, without adding extra
 257 complexity. The conditional trajectory is then
 258

$$X_1 = X_0 + \int_0^1 v_\theta(X_\tau, \mathcal{T}_\tau) d\tau, \quad (10)$$

259 where v_θ is the predicted velocity field and τ is the *flow step* (usually called time, we avoid it due
 260 to avoiding confusion). Prediction is then done via approximate solution of equation 3, solver

270 details found in C.1. This formulation lets CRONOS model continuous image evolution grounded
 271 in actual scan times, supporting interpolation or forecasting without regular sampling or artificial
 272 frame filling. It avoids zero-padding, leading to reduced computational burden compared to the
 273 discrete variant. Both variants use the same 3D U-Net backbone, further details are provided in
 274 Appendix C.3, and the training/inference procedure appears in Algorithm 1.

275 **Time Encoding.** Flow steps and continuous times are mapped to Fourier embeddings us-
 276 ing (Tancik et al., 2020), which were used e.g. in (Rombach et al., 2022): $\gamma(t) =$
 277 $[\sin(2\pi f_k t), \cos(2\pi f_k t)]_{k=1}^K$ using frequencies f_k . To preserve dimensional consistency across
 278 variable-length input sequences for the continuous setting, we compute the time embedding as
 279

$$280 \quad 281 \quad 282 \quad \text{Enc}(\mathbf{t}) = \frac{1}{T} \sum_{i=1}^T \gamma(t_i). \quad (11)$$

283 This embedding is then added to each residual layer via FiLM. The loss is then calculated via
 284 equation 6, and inference via equation 10.

286 4 DATA AND EXPERIMENTAL DESIGN

287 4.1 DATASETS

289 **ACDC** (Bernard et al., 2018) is a cardiac MRI dataset
 290 capturing different heart phases. The context tensor is
 291 reshaped to $[T, H, D, W] = [11, 32, 128, 128]$, and the
 292 target is a single image with the same spatial size. We
 293 split ACDC into 80 training, 20 validation and 50 test im-
 294 ages. This dataset served for method development; abla-
 295 tions were conducted on the validation split.

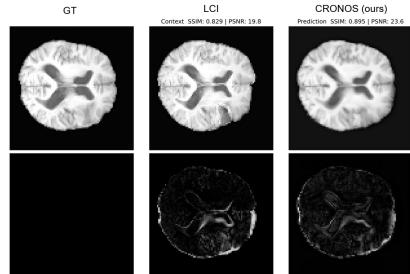
296 **ISLES** (Riedel et al., 2024) consists of perfusion CT im-
 297 age time series from stroke patients. From the normalized
 298 series, we sample 7 consecutive points, take the last as the
 299 target, and randomly mask the remaining context frames.
 300 The resulting context tensor has shape $[T, H, D, W] =$
 301 $[7, 16, 128, 128]$. We use a split of 92 training, 23 valida-
 302 tion and 34 test images. For both the ACDC and dataset,
 303 we randomly mask out time points (see Appendix C.2).
 304 **Lumiere** (Suter et al., 2022) is a longitudinal glioma
 305 MRI dataset with 3D scans. Images are reshaped to
 306 $[T, H, D, W] = [7, 96, 96, 64]$. Because some patients
 307 have few acquisitions, we prepend zeros to standardize
 308 pre-processing across cases. The split is 48 training, 12
 309 validation and 14 test images.

310 4.2 EXPERIMENTAL SETTINGS

311 Reproducibility details can be found in Section C.

312 **Discrete Setting:** As mentioned in the data section, input data has dimension T , while some frames
 313 may be missing. We apply *both* variants of CRONOS, noting that the continuous version can also
 314 operate in this regime with a smaller context window, since missing images *do not need* to be
 315 explicitly represented. The lower context window also leads to a lower computational demand.
 316 Therefore, the underlying tensors remain uniform, with some time points masked. For validation
 317 and testing we ensure that the missingness pattern is fixed across epochs, as otherwise the choice of
 318 best checkpoint would be ill-posed (further details in Appendix C.2).

319 **Continuous Setting:** As an *additional ablation and experiment*, we simulate a continuous setup on
 320 ACDC to highlight the gains from explicit timestamp conditioning. While no public dataset provides
 321 plenty of continuous acquisition protocols, this sub-sampled variant shows that CRONOS benefits
 322 from real-valued time even beyond irregular masking. Specific details of how we subsampled ACDC



323 **Figure 4: Qualitative comparison on the LUMIERE dataset.** Ground truth (GT), Last Context Image (LCI), our
 324 method (CRONOS), and SimVP baseline. Lumiere is particularly chal-
 325 lenging due the very small dataset.
 326 highlighting the benefit of explicit
 327 continuous-time conditioning under ex-
 328 treme data scarcity.

324 can be found in C.1. Importantly, both the discrete and continuous formulations remain applicable
 325 to discrete grids.
 326

327 **Table 2: Discrete Time: Quantitative Evaluation on Many-to-One Sequences:** Reported values
 328 are mean (standard deviation) over three runs. Metrics include normalized root MSE , $NRMSE$,
 329 structural similarity index ($SSIM[\%]$) and peak signal-to-noise-ratio $PSNR$. *ViViT OOM on
 330 a 40 GB GPU, despite having a smaller batch size and the lowest possible feature size. Standard
 331 deviation of LCI omitted for visual clarity. Blue row: only method to beat LCI and our proposed
 332 CRONOS. Computational requirements on ACDC in A

| Dataset | Model | NRMSE [10^{-2}] \downarrow | SSIM [%] \uparrow | PSNR [dB] \uparrow |
|---------|-----------------|----------------------------------|---------------------|----------------------|
| ACDC | LCI | 4.48 | 92.79 | 28.918 |
| | ConvLSTM | 11.20 ± 0.48 | 50.44 ± 1.53 | 19.123 ± 0.312 |
| | SimVP | 9.27 ± 0.29 | 49.08 ± 4.01 | 20.715 ± 0.267 |
| | NODE + LSTM | 11.59 ± 0.18 | 36.41 ± 2.94 | 18.946 ± 0.186 |
| | ViViT | 13.90 ± 2.66 | 17.06 ± 8.60 | 17.252 ± 1.738 |
| | CRONOS discrete | 3.97 ± 1.23 | 94.51 ± 0.79 | 30.510 ± 1.560 |
| | CRONOS cont. | 3.74 ± 0.21 | 94.34 ± 0.45 | 29.750 ± 0.528 |
| ISLES | LCI | 5.25 | 96.29 | 29.002 |
| | ConvLSTM | 19.31 ± 0.18 | 39.92 ± 0.66 | 17.644 ± 0.014 |
| | SimVP | 13.06 ± 0.19 | 48.82 ± 1.60 | 20.799 ± 0.112 |
| | ViViT | 16.54 ± 0.30 | 36.76 ± 1.49 | 18.671 ± 0.134 |
| | NODE + LSTM | 15.10 ± 0.87 | 40.55 ± 7.15 | 19.481 ± 0.515 |
| | CRONOS discrete | 4.50 ± 0.76 | 97.33 ± 0.93 | 30.542 ± 1.540 |
| | CRONOS cont. | 4.38 ± 0.48 | 97.31 ± 0.38 | 30.809 ± 1.099 |
| Lumiere | LCI | 8.38 | 88.35 | 21.631 |
| | ConvLSTM | 34.79 ± 0.67 | 9.21 ± 2.81 | 9.217 ± 0.171 |
| | SimVP | 71.03 ± 0.89 | -1.92 ± 0.51 | 2.989 ± 0.109 |
| | ViViT* | OOM | OOM | OOM |
| | NODE+LSTM | 13.07 ± 1.03 | 48.66 ± 2.26 | 17.742 ± 0.659 |
| | CRONOS discrete | 7.92 ± 0.92 | 91.43 ± 1.84 | 22.427 ± 0.969 |
| | CRONOS cont. | 7.55 ± 0.86 | 89.32 ± 1.83 | 22.551 ± 0.979 |

356 **Baselines** We compare CRONOS against established spatio-temporal learning methods. As a clinically
 357 motivated heuristic, the Last Context Image baseline (LCI) simply reuses the last available
 358 image and serves as a lower bound. Among sequence models, we include ConvLSTM (SHI et al.,
 359 2015), SimVP (Gao et al., 2022), and ViViT (Arnab et al., 2021) as representative recurrent,
 360 convolutional, and transformer backbones. For continuous-time sequence modeling, we further evaluate
 361 an ODE-LSTM (Lechner & Hasani, 2020) baseline. For the flow matching library we use Tong
 362 et al. (2024b;a); Tong (2025). Together, these methods provide a spectrum of spatio-temporal
 363 architectures against which we benchmark CRONOS. Computational requirements are described in
 364 detail in the appendix.

365 **Continuous vs. Discrete.** We report results in two regimes: an *discrete* setting, which allows direct
 366 comparison to existing spatio-temporal baselines, and a *continuous* setting on ACDC, designed as
 367 an ablation to test the benefit of explicit timestamp conditioning.

369 5 RESULTS AND DISCUSSION

371 5.1 TOWARDS UNIFIED BENCHMARKING FOR MEDICAL 3D SEQUENCE-TO-IMAGE 372 FORECASTING

373 We are among the first to propose an experimental setup for the sequence-to-image task, evaluating
 374 CRONOS under two complementary regimes. The first uses *discrete* input sequences, where some
 375 context images are missing but acquisitions lie on a regular grid. This setting enables comparison
 376 against established spatio-temporal baselines. The second uses ACDC with resampled acquisitions
 377 to mimic *continuous* input, allowing us to assess the benefit of explicit timestamp conditioning.

378 For completeness, we include an image-to-image (*not sequence-to-image*) diffusion baseline on
 379 ACDC (details in B.5) This required a two-stage training setup, first pretraining an autoencoder and
 380 then training the diffusion module for 1000 denoising steps, which already made the approach far
 381 more computationally demanding than all other baselines. Iterative denoising leads to an order-of-
 382 magnitude longer inference time for a single image-to-image step and several orders of magnitude
 383 higher training cost, while not surpassing the simple LCI heuristic.²

384

385 5.2 CRONOS IS STATE-OF-THE-ART FOR SPATIO-TEMPORAL 3D MEDICAL IMAGE 386 FORECASTING

387 Table 2 reports the quantitative results
 388 across all three datasets. We observe
 389 that both variants of CRONOS **substan-**
 390 **tially outperform** the competing spatio-
 391 temporal baselines, as well as LCI. We
 392 also note that individually, CRONOS is
 393 better than LCI on each individual val-
 394 idation run. On LUMIERE, which is
 395 characterized by very sparse and hetero-
 396 geneous tumor trajectories, it is surpris-
 397 ing that CRONOS is even able to outper-
 398 form LCI. These results demonstrate that
 399 CRONOS is effective across different tem-
 400 poral regimes: the discrete formulation al-
 401 ready yields strong performance, while the continuous formulation provides further gains when
 402 timestampts are informative. CRONOS runs **within the same computational budget** during in-
 403 ference (see Figure 1b) and in similar orders of magnitude (VRAM and wall-clock time) during
 404 training as natural imaging baselines (see 8). Further ablations are provided in A, confirming that
 405 CRONOS is stable across variations in *feature size, training noise, and integration settings*. While
 406 small differences appear, they are not substantial, indicating that our network is *highly robust* to
 407 hyperparameter choices.

408

409 5.3 CRONOS ENABLES EFFICIENT FLOW-BASED CONTINUOUS MEDICAL MODELING

410 Table 3 demonstrates that *incorporating explicit time embeddings improves forecasting* quality when
 411 scans occur at irregular intervals. This shows that the continuous formulation of CRONOS is not
 412 only feasible but also beneficial in realistic clinical settings, where images are often irregularly
 413 sampled. In fact, if we fully remove the timestamp information entirely, performance differences
 414 increase significantly, and the continuous variant clearly outperforms the discrete one 9. Together,
 415 these results highlight that modeling real-valued timestamps can provide a measurable advantage
 416 over treating sequences as grid-aligned. However, in Table 2, we see that using the discrete variant
 417 remains highly competitive. Although any irregular series can in principle be quantized to a grid
 418 via $\mathcal{E}_g^{\text{grid}}$, doing so without loss requires increasingly fine grids. This becomes computationally
 419 inefficient, whereas the continuous variant scales with the number of context images and *not* with
 420 the grid range $K \cdot \Delta$ (see equation 12). This is reflected in Table 8 and Figure 1b, where continuous
 421 CRONOS is both more memory-efficient and faster to train than the discrete formulation. It also
 422 highlights a broader limitation of the field: the scarcity of diverse spatio-temporal datasets in which
 423 real timing information is critical.

424

425 5.4 CRONOS PRODUCES SHARPER RECONSTRUCTIONS WIT LOWER RESIDUALS

426 Figures 3, 6 and 4 highlight qualitative comparisons, as well as dataset examples. The LCI baseline
 427 often appears visually close to the target, largely because many longitudinal scans exhibit only
 428 subtle changes. However, e.g. SimVP tends to introduce artifacts and blur anatomical details. In
 429 contrast, CRONOS yields sharper reconstructions and consistently lower residuals compared to LCI,
 430 highlighting its ability to capture fine-grained temporal progression.

431 ²On our setup, a naive auto-regressive image-to-image *latent-diffusion* pipeline applied across 11 context
 432 times per subject requires \sim 5–6 hours *per validation step*; see Appendix A for details.

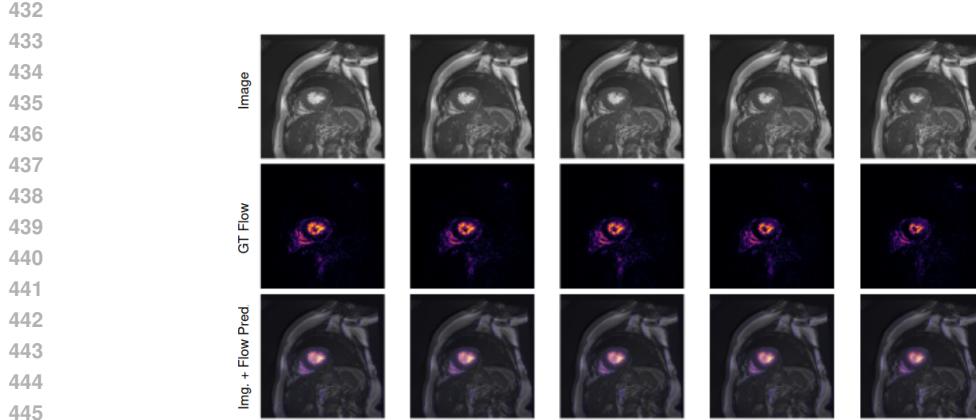


Figure 5: **Network Flows**: Top: input images at the first five timestamps. Middle: ground-truth voxel-wise differences ($|I_i - I_{\text{target}}|$). Bottom: predicted velocity fields $v_{\theta}(\hat{X}_0, 0)$, overlaid on the corresponding inputs. The highlighted regions coincide with the areas of the largest temporal changes (primarily the ventricular cavities and myocardial boundaries).

5.5 FUTURE WORK: UNLOCKING GENERAL SPATIO-TEMPORAL MEDICAL FORECASTING

While voxel-wise fidelity metrics such as NRMSE, PSNR, and SSIM remain the community standard, they do not fully capture clinically relevant trajectory modeling. As highlighted in recent efforts on image analysis validation Maier-Hein et al. (2024), such metrics may not always align with actual domain interest. Developing metrics for spatio-temporal forecasting is therefore an important future direction. In parallel, the scarcity of longitudinal and spatio-temporal datasets (beyond the ones we used in this study), poses a broader challenge for robust evaluation. Encouragingly, our results on LUMIERE suggest that progress is possible even under severe data limitations, and we hope to motivate further work on curating larger and more diverse publicly available cohorts. Finally, the absence of large-scale foundation models for medical imaging, particularly in the spatio-temporal domain, remains a major bottleneck. We view our work as a keystone contribution: establishing a unified flow-based framework for continuous spatio-temporal medical volumetric forecasting that can *both benefit from, and motivate*, future developments in medical imaging.

6 CONCLUSION

In this work, we presented CRONOS (Continuous RecOnstructioNs for medical 10ngitudinal Series), a unified spatio-temporal framework that forecasts 3D medical volumes at arbitrary target times by combining multiple context scans with explicit real-valued time conditioning. Unlike single-image or time-agnostic methods, CRONOS handles both grid-aligned and continuous timestamps within one architecture, and makes no disease-specific assumptions, it is among the first methods to demonstrate continuous sequence-to-image forecasting for 4D medical data. Across three publicly available datasets (Cine-MRI, perfusion CT, longitudinal MRI), it outperforms baselines—including the strong Last Context Image

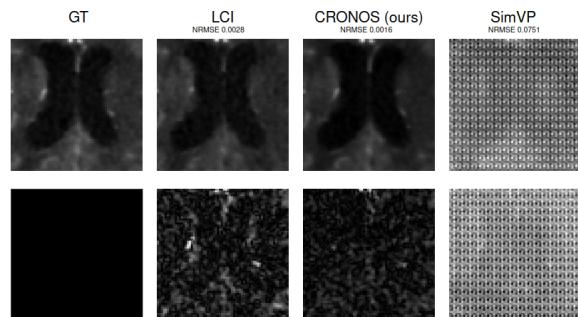


Figure 6: **Zoomed-in qualitative comparison on the ISLES dataset**. Ground truth (GT), Last Context Image (LCI), our method (CRONOS), and SimVP baseline. Shown here for visibility is a zoomed in patch of the qualitative results of the ISLES dataset.

486 (LCI)-and remains robust under hyper-
487 parameter changes while remaining computationally competitive. By resolving the aforementioned
488 limitations, our method enables clinically specific studies and advances patient-level forecasting for
489 personalized precision medicine.
490

491 BROADER IMPACT 492

493 Longitudinal modeling of medical images has the potential to improve patient care by enabling ear-
494 lier detection of disease progression, monitoring of treatment response, and improved personaliza-
495 tion of therapy. By explicitly modeling continuous temporal evolution, our approach could support
496 clinicians in making more informed decisions. However, there are also risks: mispredictions may
497 lead to incorrect clinical conclusions if models are deployed without careful validation and without a
498 human in the loop. Biases in training data (e.g., underrepresentation of certain populations or imag-
499 ing modalities) may propagate to predictions, raising concerns about fairness and generalizability,
500 which is a common problem in medical imaging. We emphasize that our method is a research con-
501 tribution intended to advance especially technical methodology. Clinical deployment would require
502 extensive validation, regulatory approval, and integration into existing workflows. We believe that
503 by releasing code and benchmarks, this work will support the community in building transparent,
504 reproducible, and safe spatio-temporal models for healthcare. But by proposing this method, we
505 hope to support a general-purpose foundation for medical spatio-temporal and longitudinal model-
506 ing, which could massively propel this area forward.
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