

Heritability: a counterfactual perspective

Hongyuan Cao
hcao@fsu.edu

Department of Statistics, Florida State University

Joint work with Haochen Lei, Jieru Shi and Qingyuan Zhao

IMSI long-term program on digital twins
Chicago, IL

December 5, 2025

Outline

- 1 Introduction
- 2 Counterfactual heritability

Nature vs. Nurture Debate

Nature:

Our genetics determine our behavior. Our personality traits and abilities are in our "nature."



Nurture:

Our environment, upbringing, and life experiences determine our behavior. We are "nurtured" to behave in certain ways.



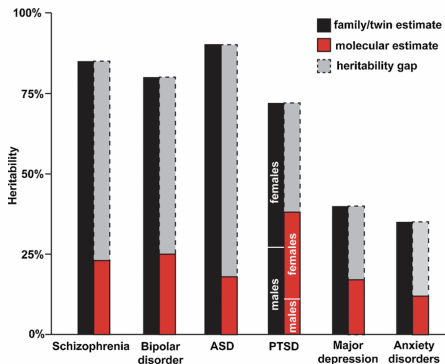
A fundamental question in behavioral, biological, and medical sciences

1.1 Heritability

- A central concept of nature vs nurture is heritability.
- Heritability measures how much genes contribute to complex human traits.
- Parallel to design-based and model-based causal inference: heritability can be derived from **twin data** and population-based **cohort studies**.
- **Identical twins** share 100% of genetics and **fraternal twins** share 50% of their genetics.
- **Twin heritability** is defined as twice the difference in the correlation coefficient of identical twins and fraternal twins.
- Population-based narrow-sense heritability accounts for **additive** genetic effects.
- Population-based broad-sense heritability encompasses both **additive and non-additive** genetic effects.

1.2 Missing heritability

The plot is adapted from Calker and Serchov (2021).



1.3 Various explanations

Finding the **missing heritability** of complex diseases

TA Manolio, FS Collins, [NJ Cox](#), [DB Goldstein](#)... - Nature, 2009 - nature.com

... many to question how the remaining, '**missing heritability**' can be explained. Here we examine potential sources of **missing heritability** and propose research strategies, including and ...

☆ Save  Cite Cited by 9806 Related articles All 33 versions Web of Science: 5614 

The mystery of **missing heritability**: Genetic interactions create phantom **heritability**

[Q Zuk](#), E Hechter, [SR Sunyaev](#)... - Proceedings of the ..., 2012 - National Acad Sciences

... The prevailing view has been that the explanation for **missing heritability** lies in the ... **missing heritability** could arise from overestimation of the denominator, creating "phantom **heritability**"...

☆ Save  Cite Cited by 1940 Related articles All 14 versions Web of Science: 980 

Missing heritability may be hiding in repeats

[M Gymrek](#), [A Goren](#) - Science, 2021 - science.org

... still fail to fully explain the **heritability** of most traits analyzed, even as sample sizes have reached hundreds of thousands of people, a problem dubbed the "**missing heritability**" (5). ...

☆ Save  Cite Cited by 11 Related articles All 4 versions Web of Science: 5 

Genetic nurturing, **missing heritability**, and causal analysis in genetic statistics

[H Shen](#), [MW Feldman](#) - ... of the national academy of sciences, 2020 - National Acad Sciences

... Both categories can contribute to **missing heritability** and ... genetic nurturing to the **missing heritability** problem (27–29). ... our understanding of the **missing heritability** problem. We also ...

☆ Save  Cite Cited by 20 Related articles All 6 versions Web of Science: 12 

2.1 Definition

- Let A denote whether certain gene is passed to the children and Y denote the phenotype.
- Denote $P(A = 1) = p$ and $q = 1 - p$.
- Suppose we use *CRISPR* to edit genes.
- $Y(0)$ is the potential outcome of the phenotype when $A = 0$ and $Y(1)$ is the potential outcome of the phenotype when $A = 1$.
- Let A' be a random variable and $A' \stackrel{d}{=} A$.
- Assume $A \perp\!\!\!\perp A' \perp\!\!\!\perp \{Y(0), Y(1)\}$
- The causal heritability is defined as

$$h^2 = \frac{\text{Var}\{Y(A) - Y(A')\}}{2\text{Var}(Y(A))}. \quad (1)$$

2.2 Interpreting h^2

Numerator

$$\begin{aligned}\text{Var}\{Y(A) - Y(A')\} &= E\{\text{Var}(Y(A) - Y(A') \mid Y(0), Y(1))\} \\ &+ \text{Var}\{E(Y(A) - Y(A') \mid Y(0), Y(1))\} \\ &= 2p(1-p)E\{(Y(1) - Y(0))^2\}.\end{aligned}$$

Denominator

$$\begin{aligned}\text{Var}(Y(A)) &= E(\text{Var}(Y(A) \mid Y(0), Y(1))) + \text{Var}(E(Y(A) \mid Y(0), Y(1))) \\ &= p(1-p)E((Y(0) - Y(1))^2) + \text{Var}(pY(1) + (1-p)Y(0)).\end{aligned}$$

- $pY(1) + (1-p)Y(0) = Y(0) + p\tau$, where $Y(1) - Y(0) = \tau$.

Thank You and Questions



1 Introduction

2 Counterfactual heritability

Digital Twin for Determining the Functional Significance of Coronary Artery Lesions

Jiguang Sun

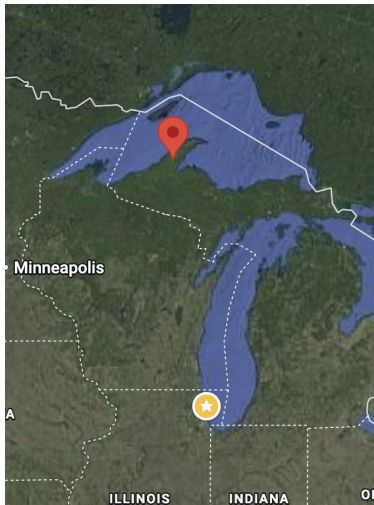
Michigan Technological University

Collaborator: Dr. Weihua Zhou

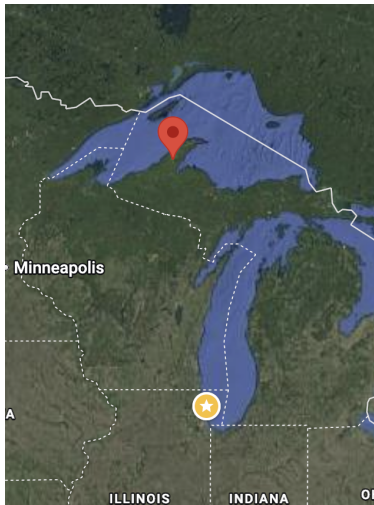
Digital Twins, IMSI, Fall 2025.



Houghton, MI



Houghton, MI



Research Interests

- Numerical Methods for PDE Eigenvalue Problems
 - Linear Eigenvalue Problems
 - Band Structures of Photonic Crystals
 - Scattering Resonances
- Inverse Problems
 - Inverse Scattering Problems
 - Inverse Spectral Problems
 - Bayesian Inversion
- Through-wall Imaging
- Diagnostic of Coronary Artery Disease (CAD)



Coronary Artery Disease (CAD)

- The gold standard for diagnosing CAD is invasive coronary angiography (ICA) - an X-ray procedure that uses a catheter to diagnose coronary artery disease by visualizing blood flow.

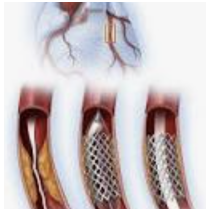


Figure: Coronary revascularization (CR) - Google.

- Fractional flow reserve (FFR) is a medical diagnostic tool used to measure the severity of a blockage in a coronary artery - comparing the blood pressure and flow in a specific part of the artery against the theoretical maximum blood flow of a normal artery. An FFR less than 0.80 is often considered abnormal.

Project Overview

multi-view ICA videos \longrightarrow FFR \longrightarrow clinical decision-making of CR

Goals:

1. understanding the mapping from "contrast dye" to images
 - blood flow
 - artery boundary - blockage/narrowing
 - dynamic motion of the heart
 - angles of the images
2. reconstructing FFR from the images.
 - boundaries
 - initial data
3. making decision based on FFR + ?
 - patient specific parameters

1. Finite element method for NS equations [Canic et al. 25]:

$$\begin{aligned}\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} &= 0, \\ \frac{\partial Q}{\partial t} + \frac{\partial}{\partial z} \left[(a + \alpha_c) \frac{Q^2}{A} \right] + \frac{A}{\rho_f} \frac{\partial p}{\partial z} &= -2(\gamma + 2)\nu \frac{Q}{A} + \frac{Q^2}{A} \frac{\partial \alpha_c}{\partial z}, \\ p &= p_{\text{ext}} + \frac{hE}{R_0^2(1 - \sigma^2)}(R - R_0) + (\gamma + 2)\rho_f \nu \frac{Q}{A} \frac{\partial \ln R}{\partial z}.\end{aligned}$$

2. Operator learning for parametrized NS equations, e.g., boundary to pressure.
3. Reduced order methods.
4. Bayesian inverse problems, e.g., image to boundary

A Data-Driven Digital Twin Framework for Non-Stationary Complex Systems

Ivan Sudakow (The Open University, UK)

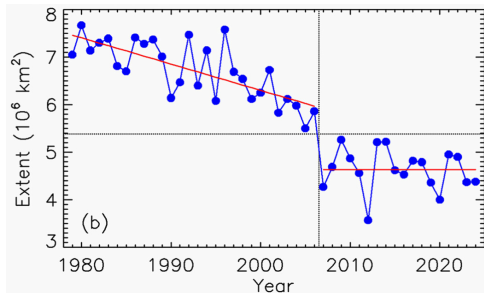
Dmitri Kondrashov (UCLA)

The Challenge: Modeling Systems Under Regime Shift

The Complex System:

- Arctic Sea Ice is characterized by high-dimensional chaos and strong atmosphere-ocean coupling.
- **The Problem:** A distinct dynamical **Regime Shift** occurred ≈ 2007 .

September Sea Ice Extent



Digital Twin Requirements:

- Physics-based models (GCMs) struggle with sub-grid parameterization and computational cost.

The Encoder: Data-Adaptive Harmonic Decomposition (DAHD)

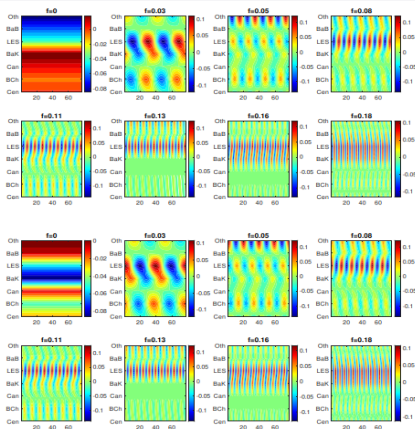
Spectral Decomposition of the State Space:

- We utilize time-embedding to compute a spectral decomposition of the system's correlation matrix.
- This provides a finite-dimensional approximation of the **Koopman Operator** for nonlinear systems.

Feature Extraction:

- The system is decomposed into d pairs of **Data-Adaptive Harmonic Modes (DAHMs)**.
- Modes appear in **phase-quadrature** (sin/cos pairs), acting as narrow-band filters isolating specific temporal scales.

The Encoder: Data-Adaptive Harmonic Decomposition (DAHD)



Space-time patterns of data-adaptive harmonic mode pair for largest λ at selected frequencies f (cycle/week), see left, x-axis – time (weeks), y-axis –

Arctic regions: units – non-dimensional.

The Generative Engine: Coupled Stochastic Oscillators

Reduced Order Modeling (ROM): We model the evolution of the mode coefficients $z(t)$ using coupled **Stuart-Landau (SL)** oscillators.

The Stochastic Generative Model

$$\dot{z} = (\mu + i\gamma)z - (1 + i\beta)|z|^2z + \eta_t$$

- **Interpretable Physics:**

- μ, γ : Linear growth rate and frequency.
- β : Nonlinear amplitude saturation (anharmonicity).

- **The "Twin" Aspect:**

- Parameters are estimated via inverse modeling (regression with linear constraints).
- η_t (Noise): Captures **unresolved sub-grid scales** and maintains variance.

Simulation: Trajectory Reconstruction & Uncertainty

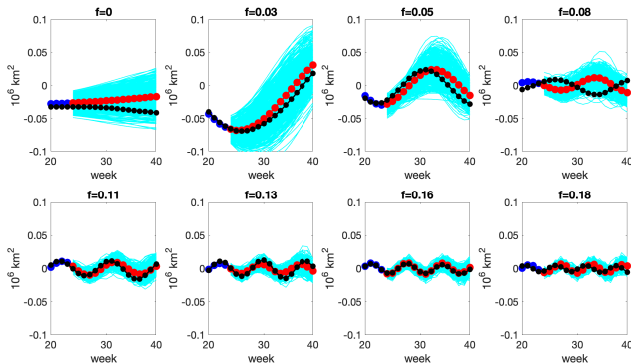
Probabilistic Digital Twin Simulation (2024 Case Study):

(blue) observed trajectory
(ground truth).

(black) observed trajectory
at the end of summer

(cyan) the digital twin's
stochastic ensemble.

(red) ensemble mean.



Key Result: The Twin accurately reproduces the **phase-space trajectory** and **amplitude modulations** of the chaotic system, providing rigorous uncertainty quantification.

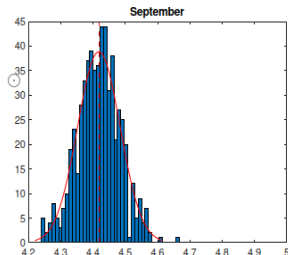
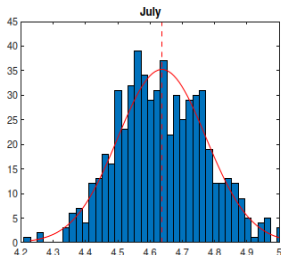
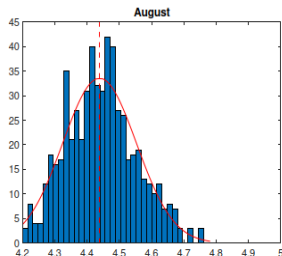
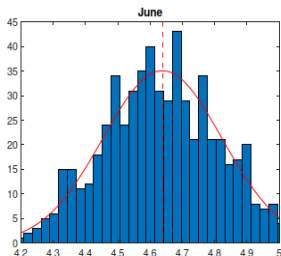
The Prediction of September Pan-Arctic SIE

Blind Prediction Performance:

- Target: September 2024 Pan-Arctic Sea Ice Extent.
- Accuracy: Ensemble mean aligns closely with observation.
- Error: $\approx 0.3 \text{ Mkm}^2$ (Competitive with physics-based GCMs).

Summary:

- DAHD-SL constitutes a rigorous, lightweight **Digital Twin**.
- Efficiently bridges Data



IMSI Long Program Report-Out: Digital Twins, Housing Analytics, and Collaborations

Nancy L. Glenn Griesinger, Ph.D.
Research Professor and Statistician
Huston–Tillotson University
Austin, Texas

December 5, 2025

Background

**N. L. Glenn
Griesinger, Ph.D.**



- **Research Expertise: Statistical Methodologist**
- **Nonparametric Statistics**
- Nuclear Physics, Brookhaven National Laboratory (2024)
- Computational Chemistry Software Development, Ames National Laboratory (2025)
- U. S. Department of Housing and Urban Development
- **Active Grant – HUD Artificial Intelligence for Housing Infrastructure** (2024 -)
- **Grant – Texas Commission on Environmental Quality** (2019 - 2024)
- **Elementary Statistics: A Guide to Data Analysis Using R** (2023)



Concept

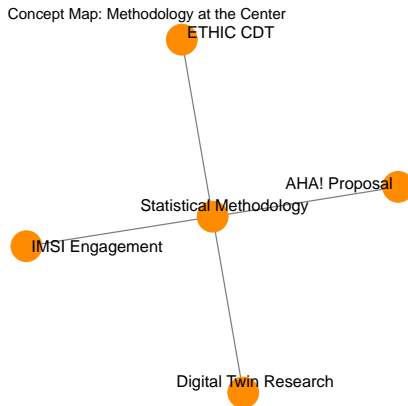


Figure: Concept Map for IMSI Projects

Overview

- ETHIC (Enabling Technologies for Housing Innovation Center) CDT architecture and collaborations
- Digital Twin theoretical research
- AHA! Affordable Housing Analytics proposal
- IMSI workshops, seminars, and standards work

KPI 1: AHA! Affordable Housing Analytics

- Proposal integrating statistical modeling, geospatial ML, digital twins
- Dynamic Opportunity Index using real-time data assimilation
- Developed during IMSI Digital Twin Workshop 1

Workshop contributions:

- Functional data analysis
- Scenario-based forecasting
- Spatial-temporal modeling

KPI 2: Digital Twin Research Supporting DOE Missions

- Real-time modeling & uncertainty quantification
- Scalable statistical DT architecture
- Integration of AI with physical systems
- Supports nomination for 2026 Enrico Fermi Presidential Award

KPI 3: IMSI Research Seminars

- Omar Ghattas: GPU Bayesian inversion for real-time prediction
- Georg Stadler: Extreme-event modeling via PDE optimization

Applications:

- Urban resilience modeling
- Sensor placement optimization
- Housing/infrastructure forecasting

KPI 4: ETHIC Digital Twin

- Student contractor supporting ML/AI for ETHIC RQ1
- Reproducible CDT architecture (R, Python, SQL, Docker)
- Dynamic systems: Lorenz96 + Kalman filtering

KPI 4: Prototype v0.1.8 System Architecture

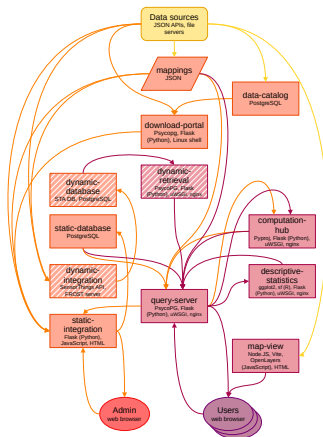
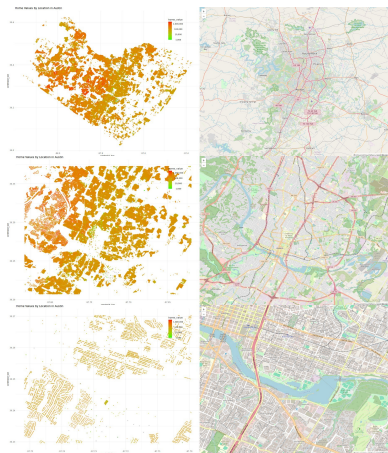


Figure: System Architecture

KPI 4: Prototype

Scatter plot



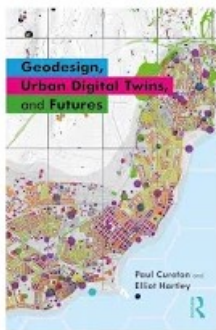
KPI 4A: ETHIC Q3 Report

- Updated H.AI (Housing Access Index)
- Added scenario-based forecasting
- Functional data analysis + data assimilation
- Started Geodesign & Ethics DT group

KPI 5: National Digital Twin Standards

- Joined Digital Twin Consortium Working Group 1
- Contributing to:
 - Data requirements
 - Interoperability standards
 - Built-environment use cases

KPI 6: Geodesign Discussion Group



- Reading *Geodesign, Urban Digital Twins and Futures*
- Professor Gerard Awanou, University of Illinois – Chicago
- Integrating ethics + governance perspectives
- Strengthened CDT community learning

KPIs 7–15: Additional Achievements

- New collaborations (e.g., Sina Ansari, DePaul)
- DOE computational chemistry work with Siwei Luo
- AAAS S&T Policy Fellowship (HUD track)
- Connections: City of Chicago Housing, DePaul, Mansueto
- Attended all IMSI workshops + NISS Conference
- Presented DT updates to HUD ETHIC team (Oct 16)

Summary

- Digital Twin architecture advancements
- Housing analytics innovation (H.AI + AHA! proposal)
- Real-time modeling and extreme-event methods
- ML + geospatial integration
- National DT standards contributions

Acknowledgments

- Work performed while visiting IMSI, supported by NSF DMS-2425650
- Supported by HUD HSI Center of Excellence (ETHIC)

Some Thoughts on Scalable Migration Digital Twin Modeling

Li-Hsiang Lin
Georgia State University

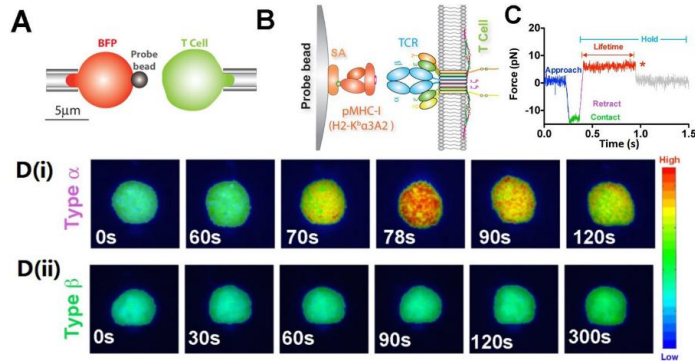
December 5 2025

Long Program on Digital Twin
Institute of Mathematical and Statistical
Innovation

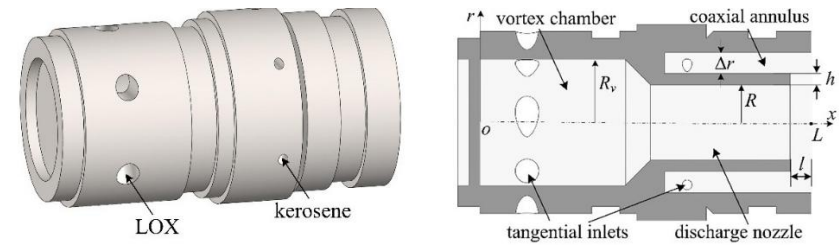




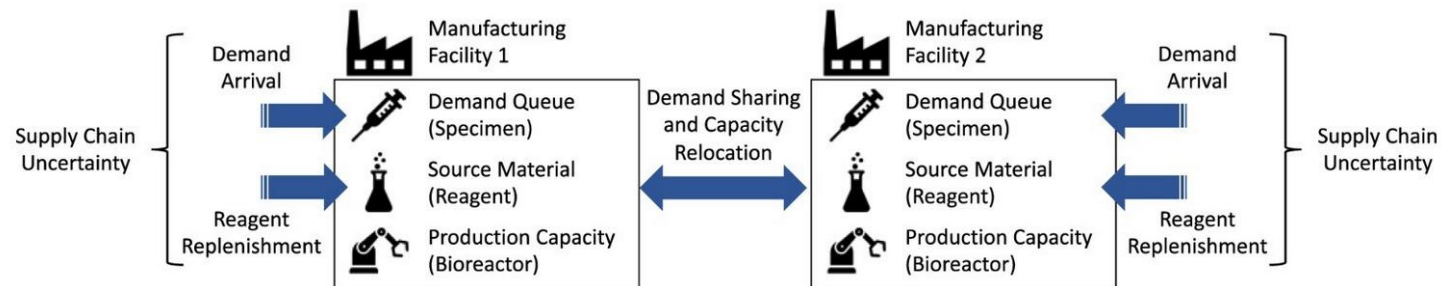
My Previous Research



Single Molecular Experiments



Rocket Engine Design Experiments



Medical Supply Chain Experiments

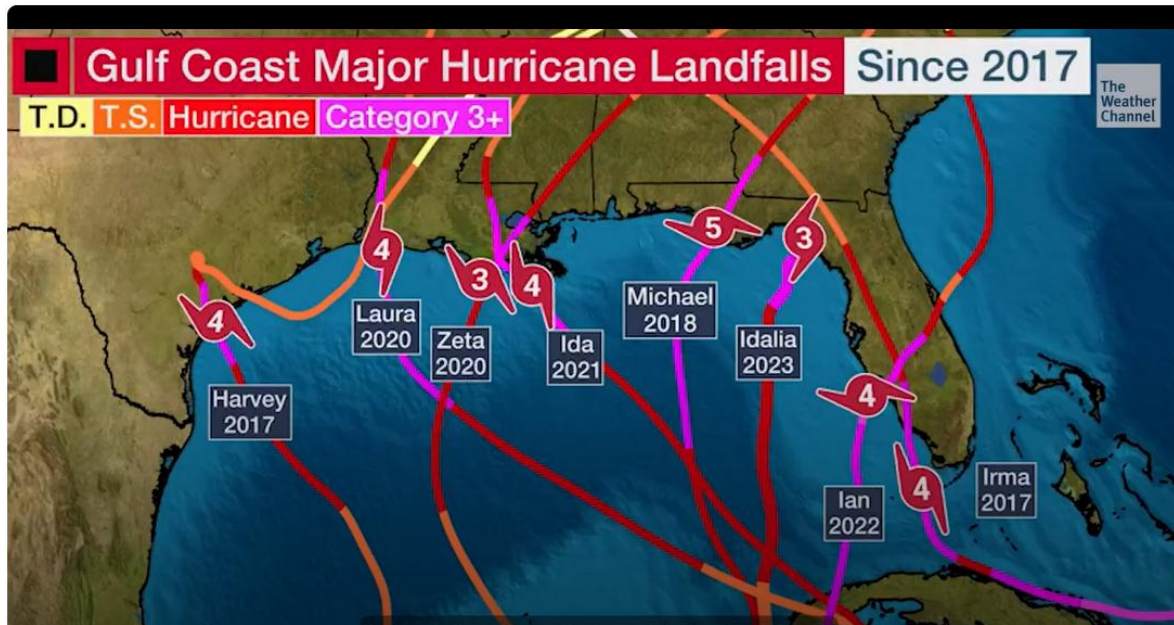


My Previous Research (Cont.)

- **Computer Experiments (CEs)** are expensive and/or requires quantify prediction uncertainty
 - Surrogate Models: For example, Transformation and Additive Gaussian Process (Lin and Joseph, Technometrics, 2020)
- **Physical Experiments** are often integrated with CEs to interact and “calibrate” computer models
 - Simulator Selection: Hung, Lin, and Wu, JASA, 2023



Motivation of Dynamic Modeling



Picture from The Weather Channel <https://weather.com>

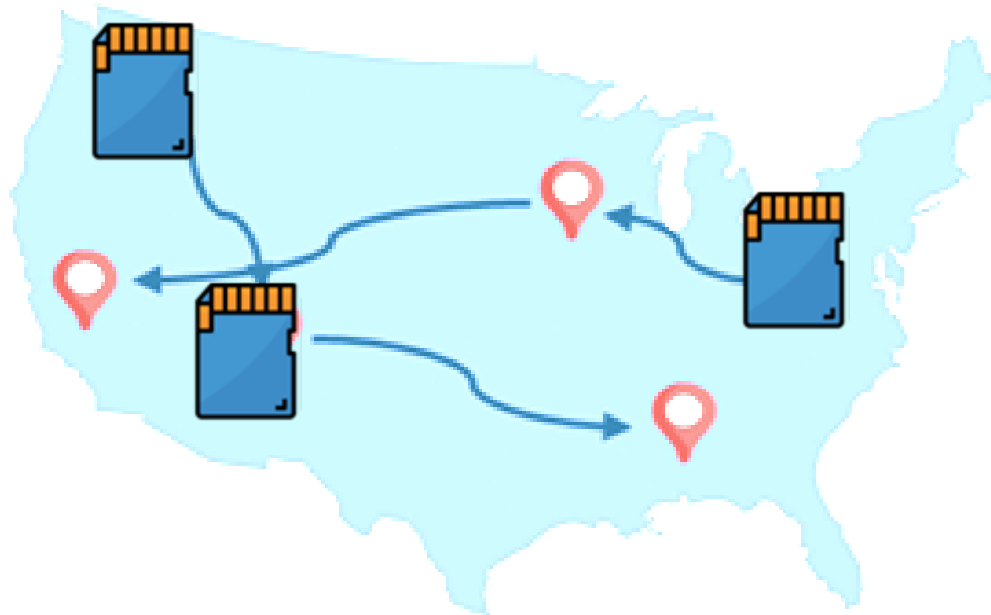
↓Picture from National Weather Services <https://www.weather.gov>





Real Migration Experiments

- Communication Constraints



Scalable and Communication-Efficient Varying Coefficient Mixed Effect Models



- Find a statistical efficient estimator under “morden data constraint”, like the communication constraint

$$\max_{\beta(\mathbf{h}), \alpha, \eta} \ell_{\text{joint}}(\beta(\mathbf{h}), \alpha, \eta) \quad \text{subject to} \quad \text{total bits communicated} \leq cdk,$$

- Show a proposed estimator

$$\theta^{(1)} = \theta_0 - \mathbf{K}_1^{-1} \mathbf{g}(\theta_0)$$

Pilot Estimator, such as
Estimator from One Node

Achieve the same first-order asymptotic efficiency as the maximum likelihood estimator with no constraint.

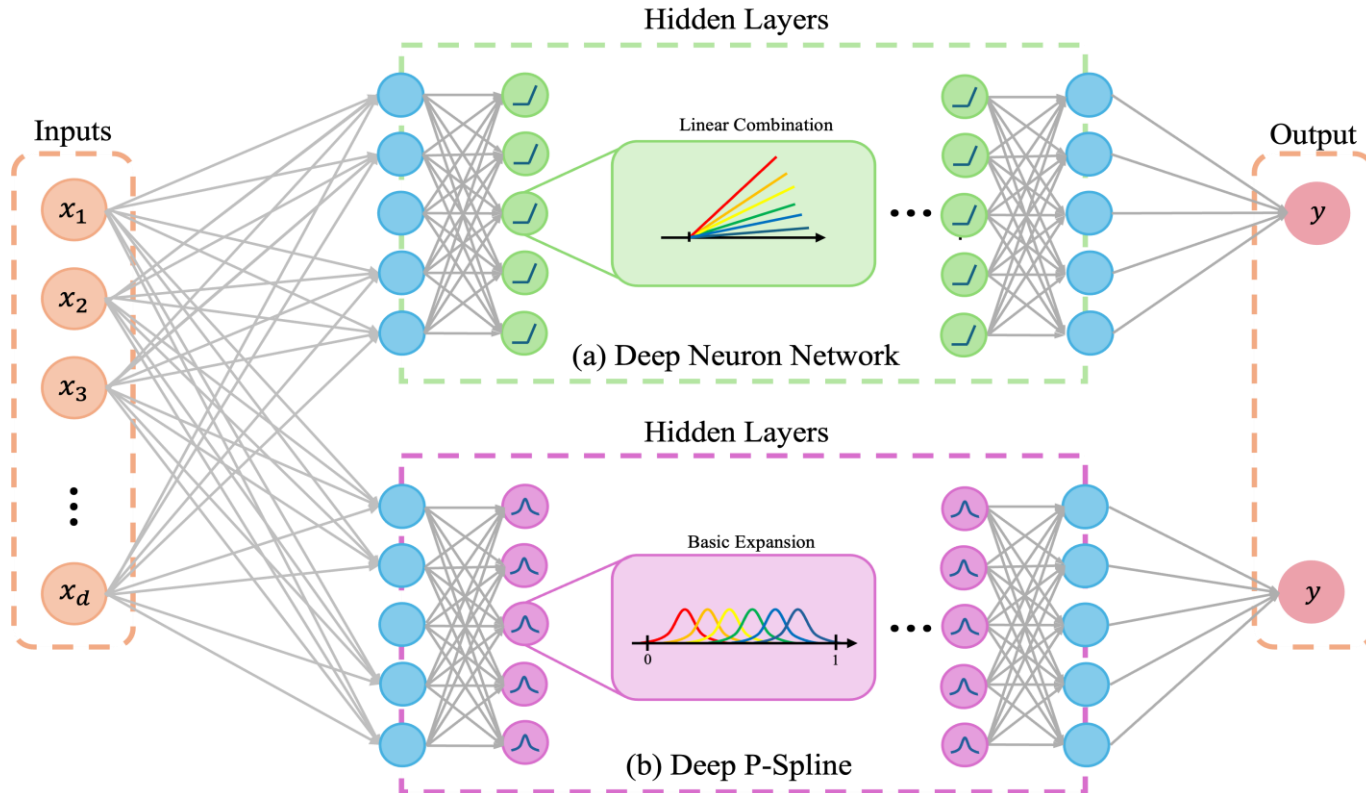
- More details can be found in Chalangar Jalili Dehkharghani, L., and Lin (2025+)

Chalangar Jalili Dehkharghani, L., & Lin, L.-H. (2025). *Scalable and Communication-Efficient Varying Coefficient Mixed Effect Models: Methodology, Theory, and Applications*. arXiv:2511.12732.

<https://doi.org/10.48550/arXiv.2511.12732>



Deep P-Spline: Surrogate Model and Fast Tuning



Objective Function:

$$\sum_{i=1}^n \left(y_i - f_{\mathbf{w}_{(1)}, \dots, \mathbf{w}_{(L-1)}, \mathbf{w}_{(L)}}(\mathbf{x}_i) \right)^2 + \sum_{\ell=2}^{L-1} \lambda_{(\ell)} \left(\sum_{j=1}^{p_{(\ell)}} \left\| \mathbf{D}_{(\ell), r} \omega_{j, (\ell)} \right\|^2 \right)$$

Difference Penalty:

$$\mathbf{D}_{(\ell), 1} = \begin{bmatrix} -1 & 1 & 0 & \dots & 0 \\ 0 & -1 & 1 & \dots & 0 \\ & & \ddots & & \\ 0 & \dots & 0 & -1 & 1 \end{bmatrix}; \quad \mathbf{D}_{(\ell), 2} = \begin{bmatrix} -1 & 2 & -1 & 0 & \dots & 0 \\ 0 & -1 & 2 & -1 & \dots & 0 \\ & & \ddots & & & \\ 0 & \dots & 0 & -1 & 2 & -1 \end{bmatrix}$$

Deep P-Spline: Surrogate Model and Fast Tuning (II)



A Fast Tuning Method:

- Find **priors** for each layer **weight** coefficients
- Connect with **Expected Maximum Likelihood** Algorithm for Structure Selection and Network Fitting

$$y_{i,(\ell)} = h_{(\ell)}(\mathbf{z}_{(\ell-1)}; \mathbf{W}_{(\ell)}) + \epsilon_{i,(\ell)}, \quad \ell = 1, 2, \dots, L-1,$$

$$\text{where } \mathbf{z}_{(\ell-1)} = h_{(\ell-1)}(\mathbf{z}_{(\ell-2)}; \mathbf{W}_{(\ell-1)}), \quad \mathbf{z}_{(0)} = \{\mathbf{x}_i\}_{i=1}^n,$$

$$y_{(L)} = h_{(L)}(\mathbf{z}_{(L-1)}; \mathbf{W}_{(L)}) + \epsilon_{(L)},$$

$$\mathbf{W}_{(\ell)} = \begin{pmatrix} \mathbf{w}_{1,(\ell)} \\ \vdots \\ \mathbf{w}_{p_{(\ell)},(\ell)} \end{pmatrix} \sim \text{Prior}, \quad \ell = 1, 2, \dots, L.$$

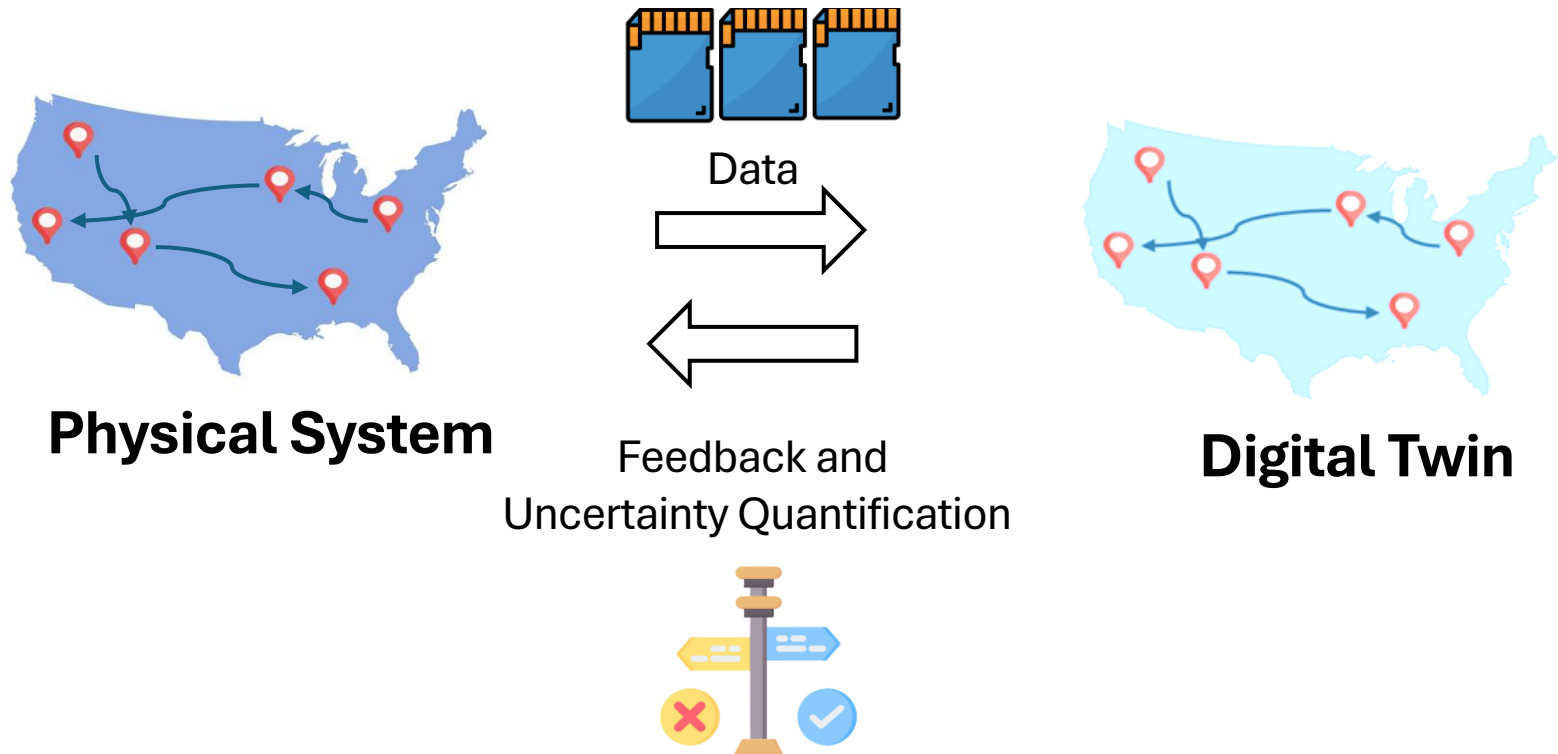
Is can be found in Hung, Lin, Calhoun (2025)

Hung, N. Y. T., Lin, L. H., & Calhoun, V. D. (2025). Deep P-Spline: Theory, Fast Tuning, and Application. *arXiv preprint arXiv:2501.01376*.



Future Research

- Select important spatial temporal migration events



- Many thanks to IMSI for enabling me and my students to deepen our understanding of advanced techniques for digital modeling for migration modeling.

Bayesian inverse problems: well-posedness, optimal experimental design, and computation

Duc-Lam Duong
duc-lam.duong@lut.fi

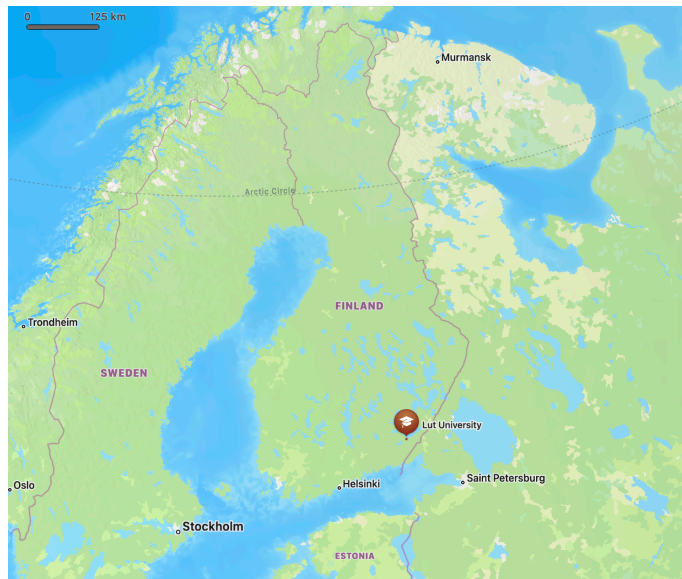
LUT University, Finland

IMSI Digital Twins Program
University of Chicago
December 5, 2025



Briefly about LUT/my background

■ Lappeenranta-Lahti University of Technology (LUT)



■ My research interests: Bayesian inverse problems, nonlinear PDEs, mathematical modelling, optimal experimental design, uncertainty quantification and machine learning

Bayesian inverse problems (BIPs)

Identify $x \in \mathcal{X}$ (Hilbert/Banach) from noisy data $y \in \mathbb{R}^n$,

$$y = \mathcal{G}(x) + \xi,$$

with a measurement map $\mathcal{G} : \mathcal{X} \rightarrow \mathbb{R}^n$ and observational noise ξ .

$$\text{prior } \mu_0 \xrightarrow{\text{measurement data } y} \text{posterior } \mu^y$$

Topics of interest include

- Well-posedness of μ^y : would μ^y be stable under perturbation in \mathcal{G} , especially when \mathcal{G} is governed by a PDE?
- Optimal experimental design: how to design data acquisition to maximize ‘information gain’ and reduce uncertainty?
- Sampling from the posterior: how to sample from μ^y efficiently in complex, large-scale problems?

Uncertainty Quantification

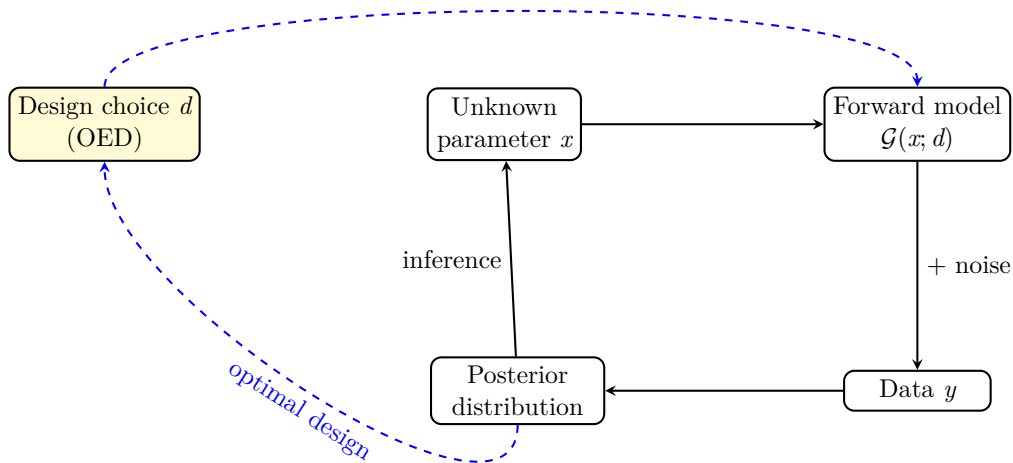
Optimal experimental design (OED)

The inverse problem can be reformulated as

$$y = \mathcal{O}_d \circ \mathcal{F}(x) + \xi,$$

i.e. $\mathcal{G} = \mathcal{O}_d \circ \mathcal{F}$, where $\mathcal{F} : \mathcal{X} \rightarrow \mathcal{X}'$ is the forward operator and \mathcal{O} is the measurement operator, which depends on a design variable d .

OED problem: how to ‘design’ d to get the ‘most informative’ y and reduce uncertainty in x at the same time?



OED criteria and their robustness

‘Informative data’? \rightarrow OED *criteria*, defined via an *expected utility* U .

◇ D-optimality:

$$U(d) = \mathbb{E}^{y|x} \mathbb{E}^{\mu_0} [D_{\text{KL}}(\mu^y \parallel \mu_0)], \quad d^* = \arg \max_d U(d).$$

◇ A-optimality:

$$U(d) = \mathbb{E}^{y|x} \mathbb{E}^{\mu_0} [-\|x - \hat{x}(y; d)\|^2], \quad d^* = \arg \max_d U(d),$$

where $\hat{x}(y; d)$ is the posterior mean/MAP estimator.

Challenges: expensive to compute, requires approximations.

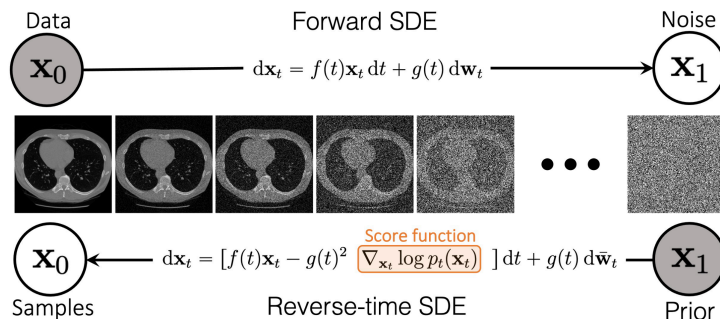
But, *how reliable are OED criteria under approximations of model or likelihood?* Our answers^{1 2}: Yes, under ‘reasonable’ assumptions.

¹D.-L. Duong, T. Helin, R. Rojo-Garcia, *Stability estimates for the expected utility in Bayesian optimal experimental design*, IPs 2023

²D.-L. Duong, T. Helin, **ongoing**

Posterior sampling: tools from ML

Diffusion models: learn/generate samples from data.



Challenges:

- (i) expensive to run, especially large-scale IPs
- (ii) may require access to a lot of data
- (iii) infinite dimension? Needs to adapt the score function

Our works^{3 4} overcome some of these with a new formulation: UCoS

³Schneider, DLD, Lassas, de Hoop, Helin, *An unconditional representation of the conditional score in infinite-dimensional linear inverse problems*, 2025

⁴Mozumder et al., *Diffusion models for diffuse optical tomography*, **ongoing**

Other activities at IMSI

- Reading groups:
 - (1) M Heinkenschloss and D P Kouri, Optimization problems governed by systems of PDEs with uncertainties, *Acta Numerica* 2025
 - (2) R Nickl, Bayesian non-linear statistical inverse problems, EMS 2023
- Research discussions with other participants: Georg Stadler, Jiguang Sun, Ruiyi Yang, Hassan Iqbal, ...
- What I take from here into future:
 - (1) Statistical aspects of inverse problems: RY
 - (2) Inverse scattering: JS
 - (3) Design and control with mobile sensors: HI ...

Special thanks to IMSI, the DT long program organizers, and IMSI staff for making all this possible!

Surrogate modeling for adaptive predictive control over parameter spaces

Hassan Iqbal¹

Joint work with:

Xingjian Li¹, Tyler Ingebrand¹, Adam Thorpe¹, Krishna Kumar¹, Ufuk Topcu¹, Ján Drgoňa²

¹The University of Texas at Austin

²Johns Hopkins University

Iqbal, H. et al. (2025). "Zero-Shot Function Encoder-Based Differentiable Predictive Control". In: *arXiv preprint arXiv:2511.05757*

Dec 5, 2025

IMSI, University of Chicago

Workshop on Application of Digital Twins to Large-Scale Complex Systems

Model Predictive Control (MPC)

MPC solves online the following discrete-time optimal control problem (OCP),

$$\begin{aligned} \min_{\mathbf{u}_0, \dots, \mathbf{u}_{N-1}} \quad & \sum_{k=0}^{N-1} \ell(\mathbf{x}_k, \mathbf{u}_k) + p_N(\mathbf{x}_N) \\ \text{s.t.} \quad & \mathbf{x}_{k+1} = \mathbf{f}(\mathbf{x}_k, \mathbf{u}_k), \quad k \in \mathbb{N}_0^{N-1} \\ & h(\mathbf{x}_k) \leq 0 \\ & g(\mathbf{u}_k) \leq 0 \\ & \mathbf{x}_0 = \mathbf{x}(t) \end{aligned}$$

Model Predictive Control (MPC)

MPC solves online the following discrete-time optimal control problem (OCP),

$$\begin{aligned} \min_{\mathbf{u}_0, \dots, \mathbf{u}_{N-1}} \quad & \sum_{k=0}^{N-1} \ell(\mathbf{x}_k, \mathbf{u}_k) + p_N(\mathbf{x}_N) \\ \text{s.t.} \quad & \mathbf{x}_{k+1} = \mathbf{f}(\mathbf{x}_k, \mathbf{u}_k), \quad k \in \mathbb{N}_0^{N-1} \\ & h(\mathbf{x}_k) \leq 0 \\ & g(\mathbf{u}_k) \leq 0 \\ & \mathbf{x}_0 = \mathbf{x}(t) \end{aligned}$$

A typical reference-tracking objective with a reference \mathbf{r}_k and control action penalty,

$$\ell(\mathbf{x}_k, \mathbf{u}_k, \mathbf{r}_k) = \|\mathbf{x}_k - \mathbf{r}_k\|_2^2 + \|\mathbf{u}_k\|_2^2$$

The system dynamics are assumed to be differentiable,

$$\mathbf{x}_{k+1} = \mathbf{A}\mathbf{x}_k + \mathbf{B}\mathbf{u}_k, \quad \text{or} \quad \mathbf{x}_{k+1} = \text{ODESolve}(\mathbf{f}(\mathbf{x}_k, \mathbf{u}_k)).$$

This is the discretize-then-optimize approach to OCP.

Differentiable Predictive Control (DPC)

DPC (Drgoňa et al. 2024) is sampling-based strategy with expected risk minimization loss for approximately solving the following OCP,

$$\begin{aligned} \min_{\pi \in \Pi} \quad & \mathbb{E}_{\mathbf{x}_0 \sim P_{\mathbf{x}_0}, \boldsymbol{\xi} \sim P_{\boldsymbol{\xi}}, \boldsymbol{\nu} \sim P_{\boldsymbol{\nu}}} \left(\int_0^T \ell(\mathbf{x}(t), \mathbf{u}(t); \boldsymbol{\xi}) dt + p_T(\mathbf{x}(T)) \right) \\ \text{s.t.} \quad & \frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t); \boldsymbol{\nu}), \\ & \mathbf{u}(t) = \pi(\mathbf{x}(t); \boldsymbol{\xi}, \boldsymbol{\nu}), \\ & h(\mathbf{x}(t); \boldsymbol{\xi}) \leq 0, \\ & g(\mathbf{u}(t); \boldsymbol{\xi}) \leq 0, \end{aligned}$$

Differentiable Predictive Control (DPC)

DPC (Dr̄goňa et al. 2024) is sampling-based strategy with expected risk minimization loss for approximately solving the following OCP,

















$$\begin{aligned} \min_{\pi \in \Pi} \quad & \mathbb{E}_{\mathbf{x}_0 \sim P_{\mathbf{x}_0}, \boldsymbol{\xi} \sim P_{\boldsymbol{\xi}}, \boldsymbol{\nu} \sim P_{\boldsymbol{\nu}}} \left(\int_0^T \ell(\mathbf{x}(t), \mathbf{u}(t); \boldsymbol{\xi}) dt + p_T(\mathbf{x}(T)) \right) \\ \text{s.t.} \quad & \frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t); \boldsymbol{\nu}), \\ & \mathbf{u}(t) = \pi(\mathbf{x}(t); \boldsymbol{\xi}, \boldsymbol{\nu}), \\ & h(\mathbf{x}(t); \boldsymbol{\xi}) \leq 0, \\ & g(\mathbf{u}(t); \boldsymbol{\xi}) \leq 0, \end{aligned}$$

We use penalty method to include the constraints in the loss function,

$$\begin{aligned} \min_{\mathbf{w}} \quad & \mathbb{E}_{\mathbf{x}_0 \sim P_{\mathbf{x}_0}, \boldsymbol{\xi} \sim P_{\boldsymbol{\xi}}, \boldsymbol{\nu} \sim P_{\boldsymbol{\nu}}} \left[\sum_{k=0}^{N-1} \left(\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) + p_h(h(\mathbf{x}_k, \boldsymbol{\xi})) + p_g(g(\mathbf{u}_k, \boldsymbol{\xi})) \right) + p_N(\mathbf{x}_N) \right] \\ \text{s.t.} \quad & \mathbf{x}_{k+1} = \mathbf{x}_k + \int_{t_k}^{t_{k+1}} \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t); \boldsymbol{\nu}) dt, \quad \mathbf{u}_k = \pi_{\mathbf{w}}(\mathbf{x}_k; \boldsymbol{\xi}, \boldsymbol{\nu}). \end{aligned}$$

- Assumes known differentiable dynamics and objectives for policy optimization.
- This can be considered as discretize-then-sample-and-learn approach.

Model, data-driven or learning-based control: comparison

Method	Online cost	Offline cost	Constraint-aware?	Handles unknown dynamics?
Classical MPC	 high online cost	 zero offline cost	 industry standard	 needs recursive system ID*
Approx. MPC (supervised)		 requires labelled dataset	 postprocessing & verification	 requires online correction
DPC (self-supervised)		 low cost: no labelled data needed	 constraints embedded during training	 needs known model
Goal				

Modeling the Dynamics Using Function Encoders

- FE (Ingebrand et al. 2024) learns a set of NODE basis functions $\{\mathbf{g}_1, \mathbf{g}_2, \dots, \mathbf{g}_B\}$ that span a subspace $\hat{\mathcal{F}} = \text{span}\{\mathbf{g}_1, \mathbf{g}_2, \dots, \mathbf{g}_B\}$ supported by the data.
- Given some ν , the dynamics are approximated as $\mathbf{f} \approx \hat{\mathbf{f}} \in \hat{\mathcal{F}}$, which takes the form of a linear combination of the learned basis functions under time discretization,

$$\begin{aligned}\mathbf{x}_{k+1} &= \mathbf{x}_k + \int_{t_k}^{t_{k+1}} \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t); \nu) dt \approx \mathbf{x}_k + \int_{t_k}^{t_{k+1}} \sum_{j=1}^B c_j(\nu) \mathbf{g}_j(\mathbf{x}(t), \mathbf{u}_k; \theta_j) dt \\ &\approx \mathbf{x}_k + \sum_{j=1}^B c_j(\nu) \int_{t_k}^{t_{k+1}} \mathbf{g}_j(\mathbf{x}(t), \mathbf{u}_k; \theta_j) dt \quad (1)\end{aligned}$$

where θ_j are the network parameters of the basis network \mathbf{g}_j .

- Importantly, the NODE basis functions $\{\mathbf{g}_1, \mathbf{g}_2, \dots, \mathbf{g}_B\}$ do not depend explicitly on ν ; as such, the dynamics function is uniquely determined by the coefficients $\mathbf{c} \in \mathbb{R}^B$.

Offline Learning of FE Basis Functions for System Dynamics

- The coefficients \mathbf{c} to some $\mathbf{f} \in \mathcal{F}$ can be computed in closed-form via the normal equation as $(\mathbf{G} + \lambda \mathbf{I})\mathbf{c} = \mathbf{F}$.
- Here, $\mathbf{G}_{ij} = \langle \mathbf{g}_i, \mathbf{g}_j \rangle$ and $\mathbf{F}_i = \langle \mathbf{f}, \mathbf{g}_i \rangle$ can both be easily computed using Monte Carlo integration from a small amount of input-output data collected online.

Offline Learning of FE Basis Functions for System Dynamics

- The coefficients \mathbf{c} to some $\mathbf{f} \in \mathcal{F}$ can be computed in closed-form via the normal equation as $(\mathbf{G} + \lambda \mathbf{I})\mathbf{c} = \mathbf{F}$.
- Here, $\mathbf{G}_{ij} = \langle \mathbf{g}_i, \mathbf{g}_j \rangle$ and $\mathbf{F}_i = \langle \mathbf{f}, \mathbf{g}_i \rangle$ can both be easily computed using Monte Carlo integration from a small amount of input-output data collected online.

Algorithm 2 (using $\mathbf{x}_{k+1} = \mathbf{x}_k + \Delta t \cdot \mathbf{f}(\mathbf{x}_k, \mathbf{u}_k; \nu)$ for simplicity).

Input: set of datasets \mathcal{D} collected from dynamics \mathcal{F} , learning rate α
Initialize basis functions $\mathbf{g}_1, \dots, \mathbf{g}_B$ with trainable parameters $\theta_1, \dots, \theta_B$
while not converged **do**
 for all $\mathcal{D}_l \in \mathcal{D}$ **do**
 reset loss $L = 0$
 for all $(\mathbf{x}_k, \mathbf{u}_k, \mathbf{x}_{k+1}) \in \mathcal{D}_l$ **do**
 $\mathbf{c} \leftarrow (\mathbf{G} + \lambda \mathbf{I})^{-1} \mathbf{F}$
 $\hat{\mathbf{x}}_{k+1} \leftarrow \hat{\mathbf{x}}_{k+1}$ from (1)
 $L \leftarrow L + \|\mathbf{x}_{k+1} - \hat{\mathbf{x}}_{k+1}\|_2^2$
 end for
 $\theta \leftarrow \theta - \alpha \nabla_{\theta} L$
 end for
end while
Output: trained basis functions $\mathbf{g}_1, \dots, \mathbf{g}_B$

$$\min_{\mathbf{W}} \mathbb{E}_{\mathbf{x}_0 \sim P_{\mathbf{x}_0}, \boldsymbol{\xi} \sim P_{\boldsymbol{\xi}}, \mathbf{c} \sim P_{\mathbf{c}}} \left[\sum_{k=0}^{N-1} \left(\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) + p_h(h(\mathbf{x}_k, \boldsymbol{\xi})) + p_g(g(\mathbf{u}_k, \boldsymbol{\xi})) \right) + p_N(\mathbf{x}_N) \right] \quad (2)$$

$$\text{s.t. } \mathbf{x}_{k+1} = \mathbf{x}_k + \int_{t_k}^{t_{k+1}} \sum_{j=1}^B c_j \mathbf{g}_j(\mathbf{x}(t), \mathbf{u}_k; \boldsymbol{\theta}_j) dt, \quad (3)$$

$$\mathbf{u}_k = \pi_{\mathbf{W}}(\mathbf{x}_k; \boldsymbol{\xi}, \mathbf{c}). \quad (4)$$

Algorithm 3

Offline learning of parametric neural policies via DPC

Input: pre-trained NODE basis functions $\mathbf{g}_1, \dots, \mathbf{g}_B$, learning rate β

Initialize policy network $\pi_{\mathbf{W}}$ with parameters \mathbf{W}

while not converged **do**

for all $\mathbf{x}_0 \sim P_{\mathbf{x}_0}, \boldsymbol{\xi} \sim P_{\boldsymbol{\xi}}, \mathbf{c} \sim P_{\mathbf{c}}$ **do**

 loss $L \leftarrow 0$

for $k = 0, 1, N - 1$ **do**

$\mathbf{u}_k \leftarrow \pi_{\mathbf{W}}(\mathbf{x}_k; \boldsymbol{\xi}, \mathbf{c})$

$\mathbf{x}_{k+1} \leftarrow \mathbf{x}_{k+1}$ from (3)

end for

$L \leftarrow L$ from (2)

$\mathbf{W} \leftarrow \mathbf{W} - \beta \nabla_{\mathbf{W}} L$

end for

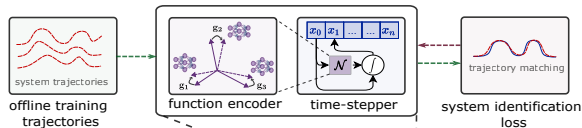
end while

Output: trained policy network $\pi_{\mathbf{W}}$

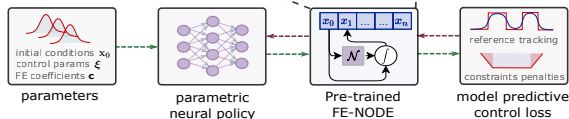
DPC with FE-NODE Dynamics and Neural Policies

Offline Learning of Function Encoder (FE) Dynamics and Control Policies

1. Offline Learning of FE-NODE Basis Functions

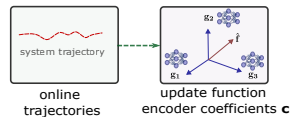


2. DPC Policy Learning

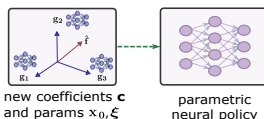


3. Online Adaptation

Step 1: Update FE Coefficients



Step 2: Zero-shot Adaptive Control Policy



Example 1: Stabilizing a Van der Pol Oscillator

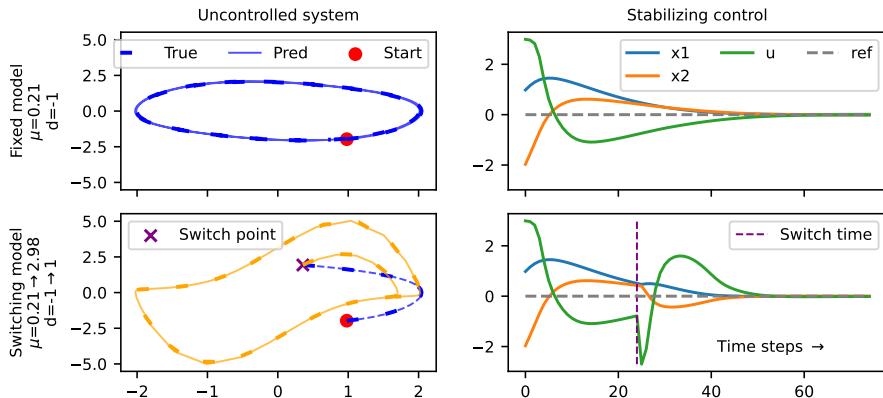
$$\begin{cases} \dot{x}_1 &= d \cdot x_2, \\ \dot{x}_2 &= \mu(1 - x_1^2)x_2 - x_1 + u, \end{cases}$$

where $[x_1, x_2]^\top \in [-2, 2] \times [-5, 5]$, $u \in [-3.0, 3.0]$, and parameters $\mu \sim \mathcal{U}[0.1, 3.0]$ and $d \in \{-1, 1\}$ determine the dynamics. The objective is, $p_N(\mathbf{x}_N) = \|\mathbf{x}_N\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) = \|\mathbf{u}_k\|^2$.

Example 1: Stabilizing a Van der Pol Oscillator

$$\begin{cases} \dot{x}_1 = d \cdot x_2, \\ \dot{x}_2 = \mu(1 - x_1^2)x_2 - x_1 + u, \end{cases}$$

where $[x_1, x_2]^\top \in [-2, 2] \times [-5, 5]$, $u \in [-3.0, 3.0]$, and parameters $\mu \sim \mathcal{U}[0.1, 3.0]$ and $d \in \{-1, 1\}$ determine the dynamics. The objective is, $p_N(\mathbf{x}_N) = \|\mathbf{x}_N\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \xi) = \|\mathbf{u}_k\|^2$.



Example 2: Reference Tracking of a Two-tank System

$$\begin{cases} \dot{x}_1 &= d_1(1 - v)p - d_2\sqrt{x_1}, \\ \dot{x}_2 &= d_1vp + d_2\sqrt{x_1} - d_2\sqrt{x_2}. \end{cases}$$

where $[x_1, x_2]^\top \in [0, 1]^2$, control inputs $[p, v]^\top \in [0, 1]^2$, $d_1 \sim \mathcal{U}[0.06, 0.1]$ and $d_2 \sim \mathcal{U}[0.01, 0.06]$. The objective is $p_N(\mathbf{x}_N) = \|\mathbf{x}_N - \mathbf{x}_{\text{ref}}(\boldsymbol{\xi})\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) = \|\mathbf{x}_k - \mathbf{x}_{\text{ref}}(\boldsymbol{\xi})\|^2 + \|\mathbf{u}_k\|^2$.

Example 2: Reference Tracking of a Two-tank System

$$\begin{cases} \dot{x}_1 &= d_1(1-v)p - d_2\sqrt{x_1}, \\ \dot{x}_2 &= d_1vp + d_2\sqrt{x_1} - d_2\sqrt{x_2}. \end{cases}$$

where $[x_1, x_2]^\top \in [0, 1]^2$, control inputs $[p, v]^\top \in [0, 1]^2$, $d_1 \sim \mathcal{U}[0.06, 0.1]$ and $d_2 \sim \mathcal{U}[0.01, 0.06]$. The objective is $p_N(\mathbf{x}_N) = \|\mathbf{x}_N - \mathbf{x}_{\text{ref}}(\boldsymbol{\xi})\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) = \|\mathbf{x}_k - \mathbf{x}_{\text{ref}}(\boldsymbol{\xi})\|^2 + \|\mathbf{u}_k\|^2$.

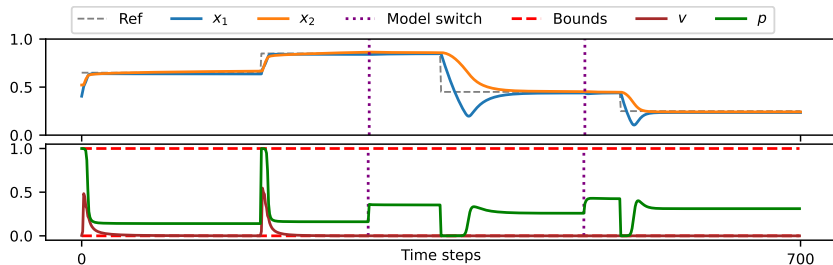


Figure: Two-tank system reference tracking under multiple system switches using FE-DPC.

Example 3: Reference Tracking of a Glycolytic Oscillator (GO)

$$\begin{cases} \dot{x}_1 &= J_0 - \frac{k_1 x_1 x_6}{1+(x_6/K_1)^4} + u, \text{ (no control in below figure)} \\ \dot{x}_2 &= 2 \frac{k_1 x_1 x_6}{1+(x_6/K_1)^4} - k_2 x_2 (N - x_5) - k_6 x_2 x_5, \\ \dot{x}_3 &= k_2 x_2 (N - x_5) - k_3 x_3 (A - x_6), \\ \dot{x}_4 &= k_3 x_3 (A - x_6) - k_4 x_4 x_5 - \kappa (x_4 - x_7), \\ \dot{x}_5 &= k_2 x_2 (N - x_5) - k_4 x_4 x_5 - k_6 x_2 x_5, \\ \dot{x}_6 &= -2 \frac{k_1 x_1 x_6}{1+(x_6/K_1)^4} + 2k_3 x_3 (A - x_6) - k_5 x_6, \\ \dot{x}_7 &= \psi \kappa (x_4 - x_7) - k x_7. \end{cases}$$

where $k_1 \in \{80, 90, 100\}$ and $K_1 \in \{0.5, 0.75\}$.

Example 3: Reference Tracking of a Glycolytic Oscillator (GO)

$$\begin{cases} \dot{x}_1 = J_0 - \frac{k_1 x_1 x_6}{1 + (x_6/K_1)^4} + u, \text{ (no control in below figure)} \\ \dot{x}_2 = 2 \frac{k_1 x_1 x_6}{1 + (x_6/K_1)^4} - k_2 x_2 (N - x_5) - k_6 x_2 x_5, \\ \dot{x}_3 = k_2 x_2 (N - x_5) - k_3 x_3 (A - x_6), \\ \dot{x}_4 = k_3 x_3 (A - x_6) - k_4 x_4 x_5 - \kappa (x_4 - x_7), \\ \dot{x}_5 = k_2 x_2 (N - x_5) - k_4 x_4 x_5 - k_6 x_2 x_5, \\ \dot{x}_6 = -2 \frac{k_1 x_1 x_6}{1 + (x_6/K_1)^4} + 2 k_3 x_3 (A - x_6) - k_5 x_6, \\ \dot{x}_7 = \psi \kappa (x_4 - x_7) - k x_7. \end{cases}$$

where $k_1 \in \{80, 90, 100\}$ and $K_1 \in \{0.5, 0.75\}$.

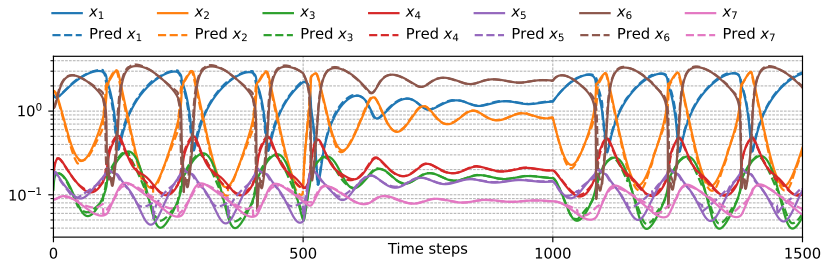


Figure: Parameters switch every 500 step, predictions calibrated against true states every 50 step.

Example 3: Reference Tracking of a Glycolytic Oscillator (G0)

Control objective is defined by $p_N(\mathbf{x}_N) = \|\mathbf{x}_{1,N} - \mathbf{x}_{1,\text{ref}}(\boldsymbol{\xi})\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) = \|\mathbf{x}_{1,k} - \mathbf{x}_{1,\text{ref}}(\boldsymbol{\xi})\|^2 + \|\mathbf{u}_k\|^2$.

Example 3: Reference Tracking of a Glycolytic Oscillator (G0)

Control objective is defined by $p_N(\mathbf{x}_N) = \|\mathbf{x}_{1,N} - \mathbf{x}_{1,\text{ref}}(\boldsymbol{\xi})\|^2$ and $\ell(\mathbf{x}_k, \mathbf{u}_k, \boldsymbol{\xi}) = \|\mathbf{x}_{1,k} - \mathbf{x}_{1,\text{ref}}(\boldsymbol{\xi})\|^2 + \|\mathbf{u}_k\|^2$.

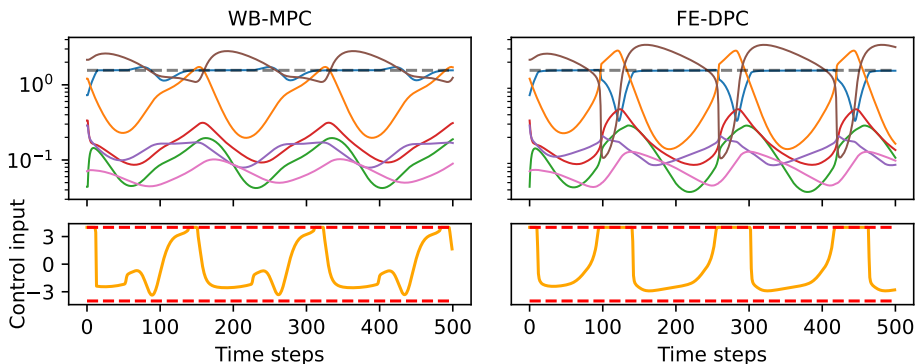


Figure: WB-MPC (left) and FE-DPC (right) based reference tracking of x_1 (blue) state.

Example 4: Controlling a Quadrotor

$$\begin{cases} \dot{p}_n = \cos \theta \cos \psi u \\ \quad + (\sin \phi \sin \theta \cos \psi - \cos \phi \sin \psi) v \\ \quad + (\cos \phi \sin \theta \cos \psi + \sin \phi \sin \psi) w, \\ \dot{p}_e = \cos \theta \sin \psi u \\ \quad + (\sin \phi \sin \theta \sin \psi + \cos \phi \cos \psi) v \\ \quad + (\cos \phi \sin \theta \sin \psi - \sin \phi \cos \psi) w, \\ \dot{h} = \sin \theta u - \sin \phi \cos \theta v - \cos \phi \cos \theta w, \\ \dot{u} = rv - qw - g \sin \theta, \\ \dot{v} = pw - ru + g \cos \theta \sin \phi, \\ \dot{w} = qu - pv + g \cos \theta \cos \phi - (F/m), \\ \tau_\psi = 0., \end{cases}$$

$$\begin{aligned} F &= mg - 10(h - \alpha_1) + 3w, \\ \tau_\phi &= -(\phi - \alpha_2) - p, \\ \tau_\theta &= -(\theta - \alpha_3) - q, \end{aligned}$$

$$\begin{aligned} \dot{\phi} &= p + \sin \phi \tan \theta q + \cos \phi \tan \theta r, \\ \dot{\theta} &= \cos \phi q - \sin \phi r, \\ \dot{\psi} &= (\sin \phi / \cos \theta) q + (\cos \phi / \cos \theta) r, \\ \dot{p} &= ((J_y - J_z)/J_x) qr + (1/J_x) \tau_\phi, \\ \dot{q} &= ((J_z - J_x)/J_y) pr + (1/J_y) \tau_\theta, \\ \dot{r} &= ((J_x - J_y)/J_z) pq + (1/J_z) \tau_\psi, \end{aligned}$$

$$[\alpha_1, \alpha_2, \alpha_3]^\top \in [\alpha_{\min}, \alpha_{\max}] = \begin{bmatrix} 0, -0.524, -0.524 \\ 1.5, 0.524, 0.524 \end{bmatrix}^\top \subset \mathbb{R}^3,$$

$$m \sim \mathcal{U}[1.2, 1.6], \quad J_x = J_y \sim \mathcal{U}[0.050, 0.058], \quad J_z \sim \mathcal{U}[0.090, 0.110].$$

Objective: maintain an altitude of 0.4m with zero linear and angular velocities.

Example 4: Controlling a Quadrotor

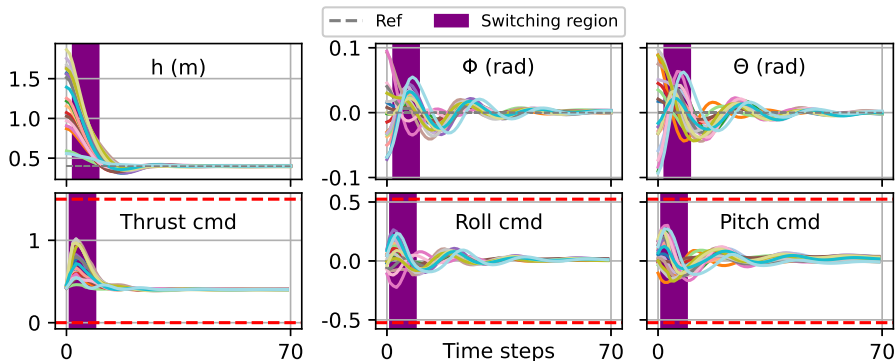


Figure: 20 quadrotor models with distinct dynamics parameterization are randomly initialized within state bounds. Each experiences a random dynamics switch between 2–20 s.

Inference Times

The main trade-off

Algorithm	Metric	Van der Pol	Two Tank	GO (7D)	Quad (12D)
FE-DPC	Error (MSE)	0.0027	0.0085	0.1803	0.0220
	Time (s)	0.53	1.13	5.89	1.93
WB-MPC*	Error (MSE)	0.0027	0.0042	0.0323	0.0242
	Time (s)	1.21	6.75	136.07	155.85

Table: Comparison of error (MSE) and computation time (s) for each benchmark.

* Assumed no plant-model mismatch.

We introduced FE-DPC, a framework for zero-shot adaptive predictive control:





- FE-NODE to identify unknown dynamics online from a few data points.
- DPC to learn a parametric policy offline conditioned on identified dynamics.
- Instantly adapts to unknown dynamics without retraining.
- Examples shown for high-dimensional (12D) and stiff (7D) systems.
- Achieves accuracy competitive with MPC at fraction of computational cost.

We introduced FE-DPC, a framework for zero-shot adaptive predictive control:

- FE-NODE to identify unknown dynamics online from a few data points.
- DPC to learn a parametric policy offline conditioned on identified dynamics.
- Instantly adapts to unknown dynamics without retraining.
- Examples shown for high-dimensional (12D) and stiff (7D) systems.
- Achieves accuracy competitive with MPC at fraction of computational cost.

Some remarks and future work:

- Complimentary to model-based approaches, potential benefits by combining e.g. parameter estimation, warm starting, stochastic processes etc.
- Closed-loop guarantees.
- Surrogate modeling for complex engineering systems (PGD etc.).

-  Drgoňa, J. et al. (2024). “Learning constrained parametric differentiable predictive control policies with guarantees”. In: *IEEE Transactions on Systems, Man, and Cybernetics: Systems* 54.6, pp. 3596–3607.
-  Ingebrand, T. et al. (2024). “Zero-shot transfer of neural ODEs”. In: *Advances in Neural Information Processing Systems* 37, pp. 67604–67626.
-  Iqbal, H. et al. (2025). “Zero-Shot Function Encoder-Based Differentiable Predictive Control”. In: *arXiv preprint arXiv:2511.05757*.
-  Low, S. A. et al. (2025). “Function Spaces Without Kernels: Learning Compact Hilbert Space Representations”. In: *arXiv preprint arXiv:2509.20605*.