Bayesian Hierarchical Models to Quantify and Communicate an Individual's Disease *State, Trajectory, and Likely Treatment Benefits* from Multivariate *Longitudinal* Data

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Johns Hopkins University Bloomberg School of Public Health

And

Biostatistics: *Jisoo Kim, Zhenke Wu, Yizhen Xu, Shannon Wonbgvibulsin, Gege Gui, Zitong Wang, Emily Scott, Joe Sartini, MaryGrace Bowring, Tianxu Wang, Ning Meng, Zixing Liu,…*

Clinical Sciences: *Antony Rosen, Ami Shah, Brian Garibaldi, John Robinson,…*

Johns Hopkins 1st Year Biostatistics Student Seminar
(slides from sz@jhu.edu)

September 19, 2024

What is Johns Hopkins *in*Health Precision Medicine?

https://www.hopkinsmedicine.org/inhealth/

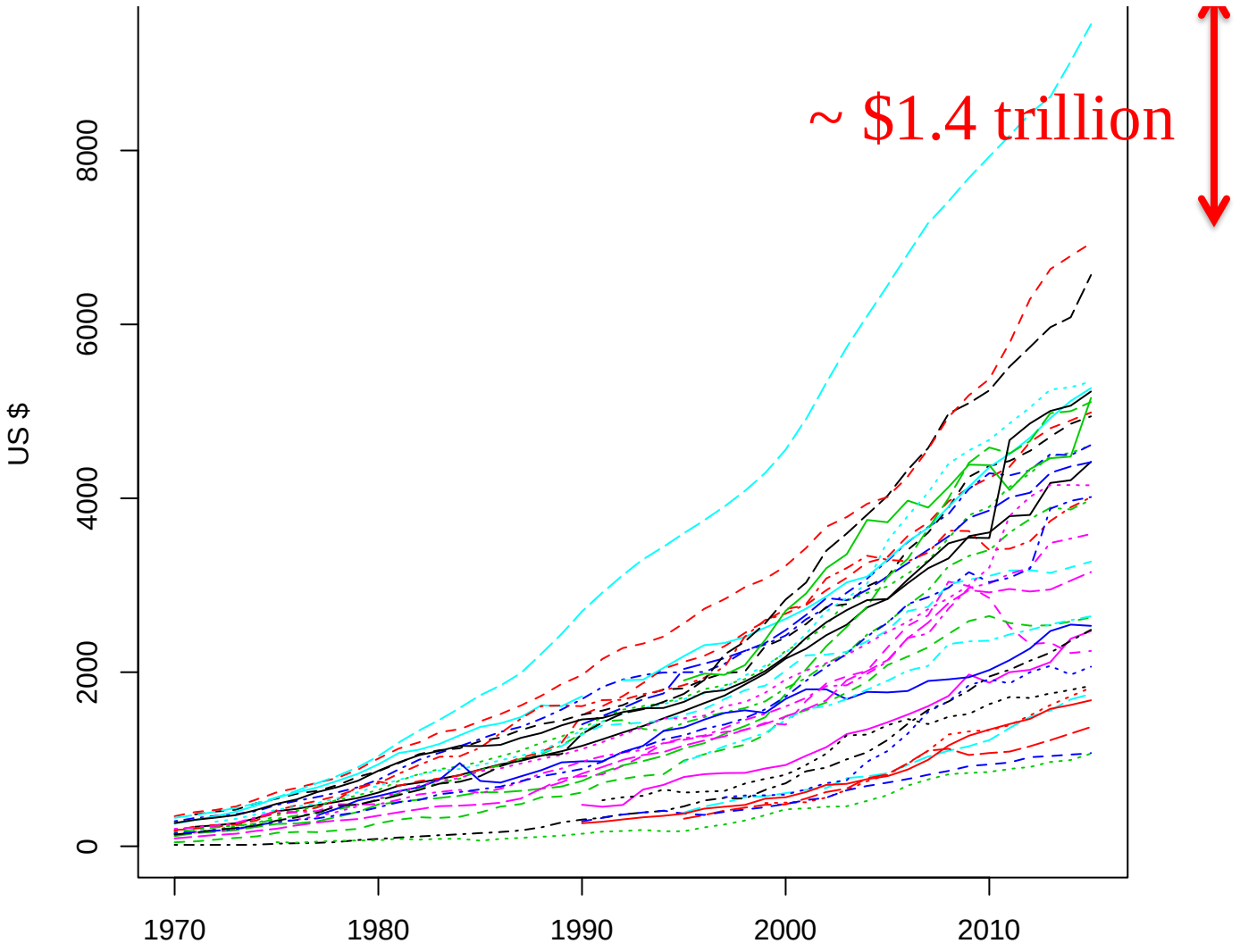
Use clinical data to answer three questions

1. What is this patient's current disease state?
2. What is their disease trajectory?
3. Do they belong to an identified subgroup?
4. Which available intervention is more likely to produce a better future state?

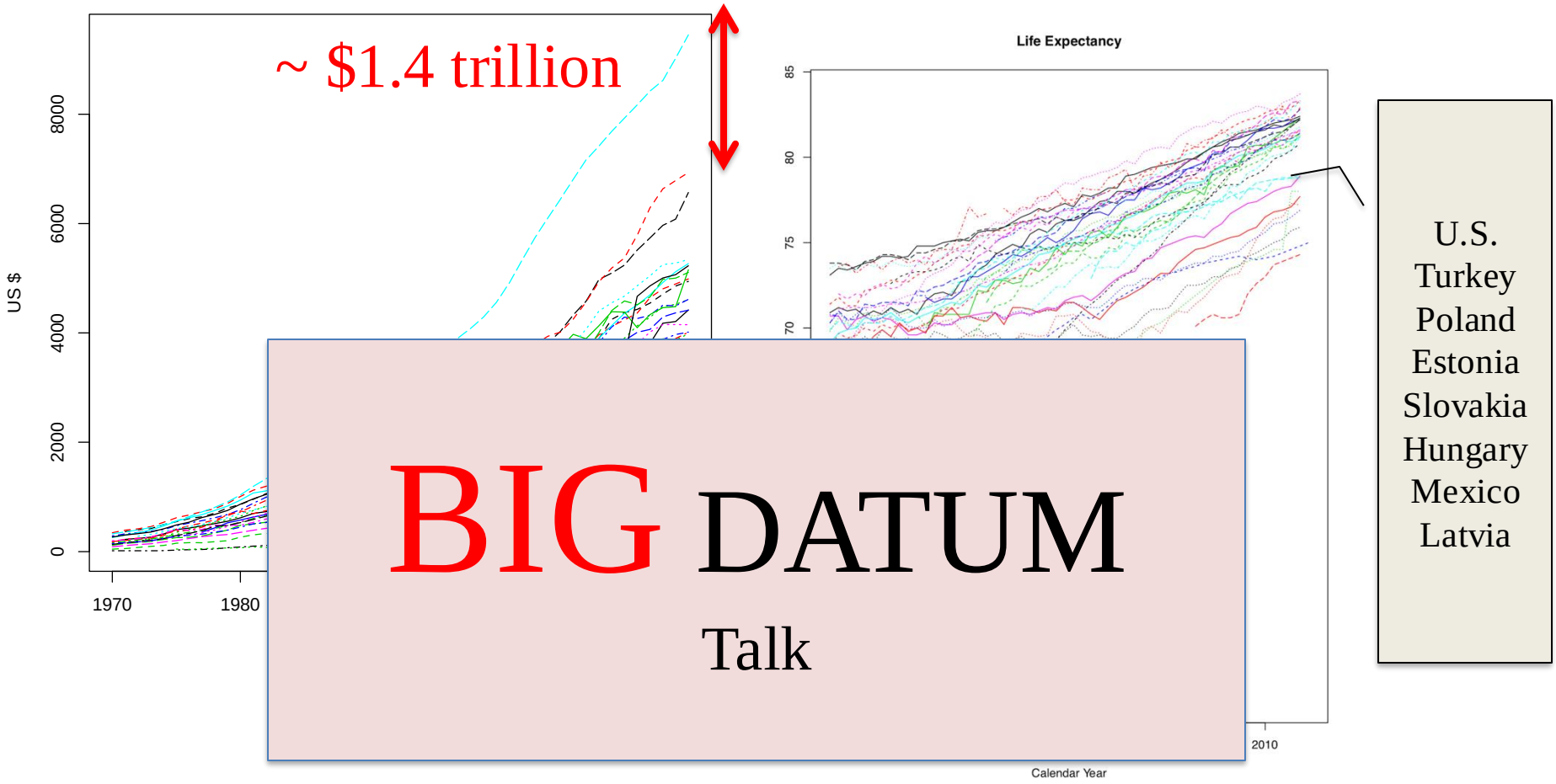
Outline

- **Context:** waste in American healthcare
- **Perspective:** individual's health
- **Statistical role:** Bayesian hierarchical models
- **Specific applications**
  - Autoimmune diseases
  - Covid-19
- Research opportunities

Per Capita Annual Medical Expenditures - OECD Countries



Per Capita Annual Medical Expenditures (left) and Life Expectancy (right) - OECD Countries



What can statisticians do about this situation (in addition to voting)?

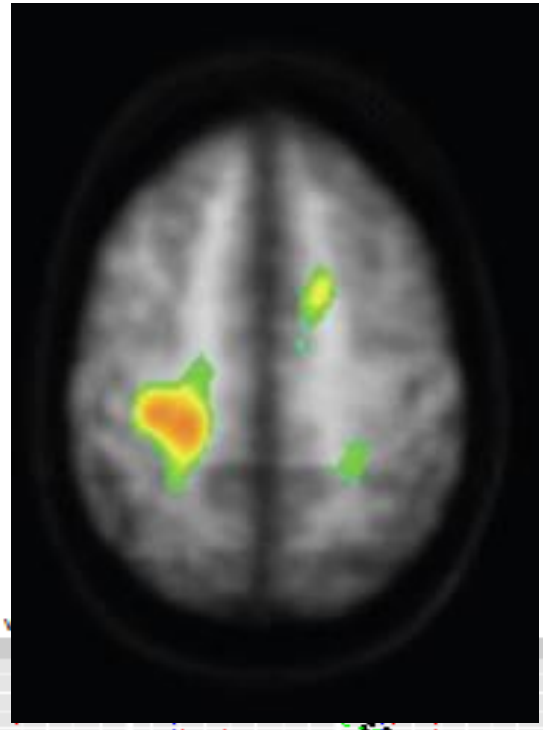
Learning in Healthcare

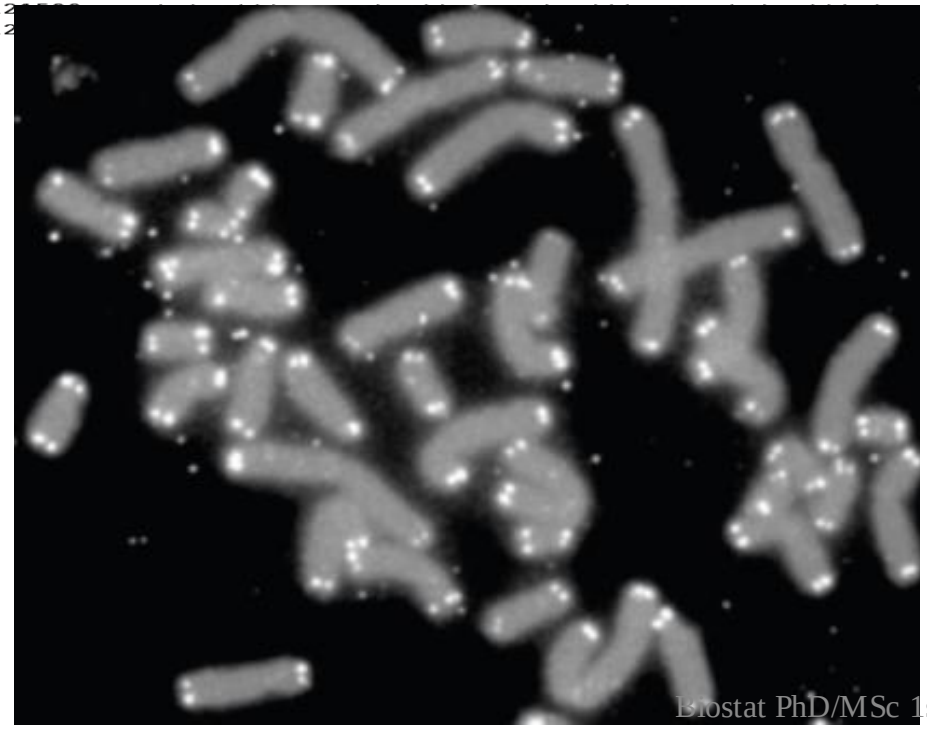
Individual's Perspective: PLAY A CLINICIAN for a moment

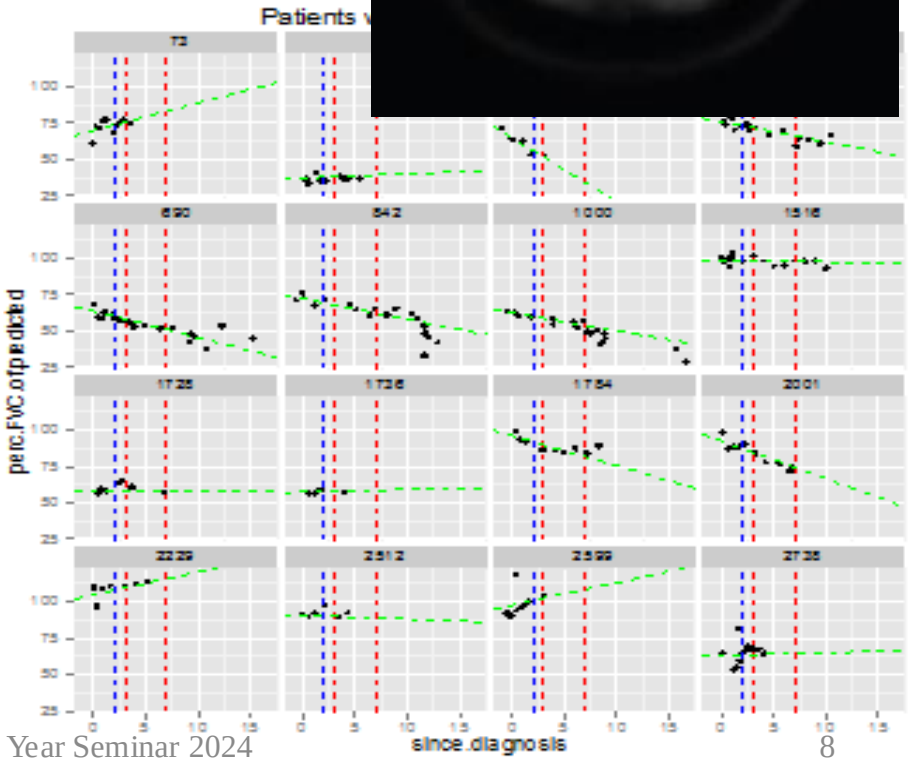
40 year old man, no family history, tests positive for a life-threatening disease in a routine screen, so comes to your office asking: what is my disease state;
what action do you recommend?

Data from prior population of similar people

	True disease status		
Exam result	Yes	No	Total
Positive	15	985	1,000
Negative	5	8,995	9000
Total	20	9,980	10,000






Patients
perc.FVC.ofpredicted
since.diagnosis

Two *in*Health Statistical Goals

- Create the inferential analogue of the 2x2 table for any measurements relevant to a major health decision

Population ⇔ Individual

- Build capacity to make tables for ever narrower sets of "otherwise similar" individuals

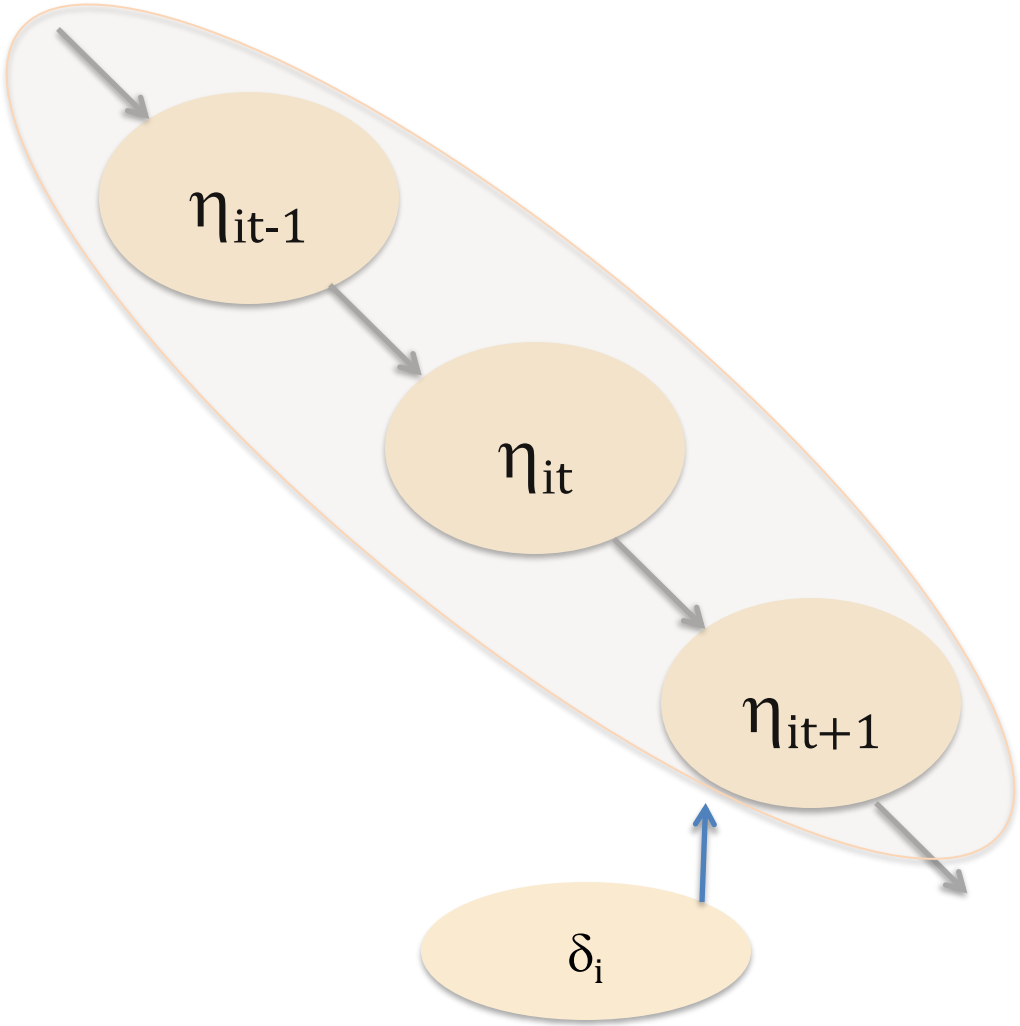
Subset, Subset, Subset

Bayesian Hierarchical Models

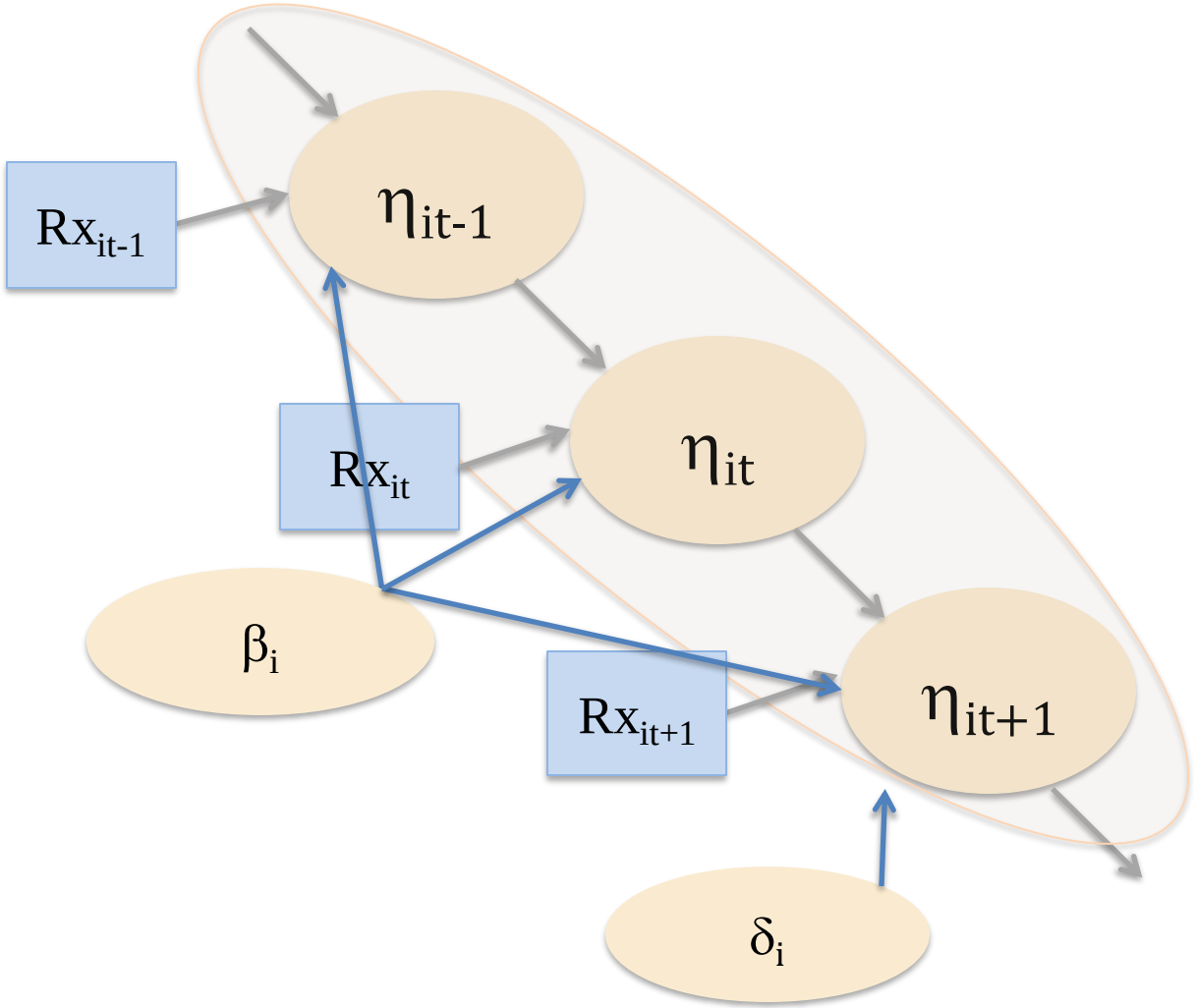
A *Really **Useful** Model for inHealth*
https://www.youtube.com/watch?v=dVmLTApnwag

What is this train's name?

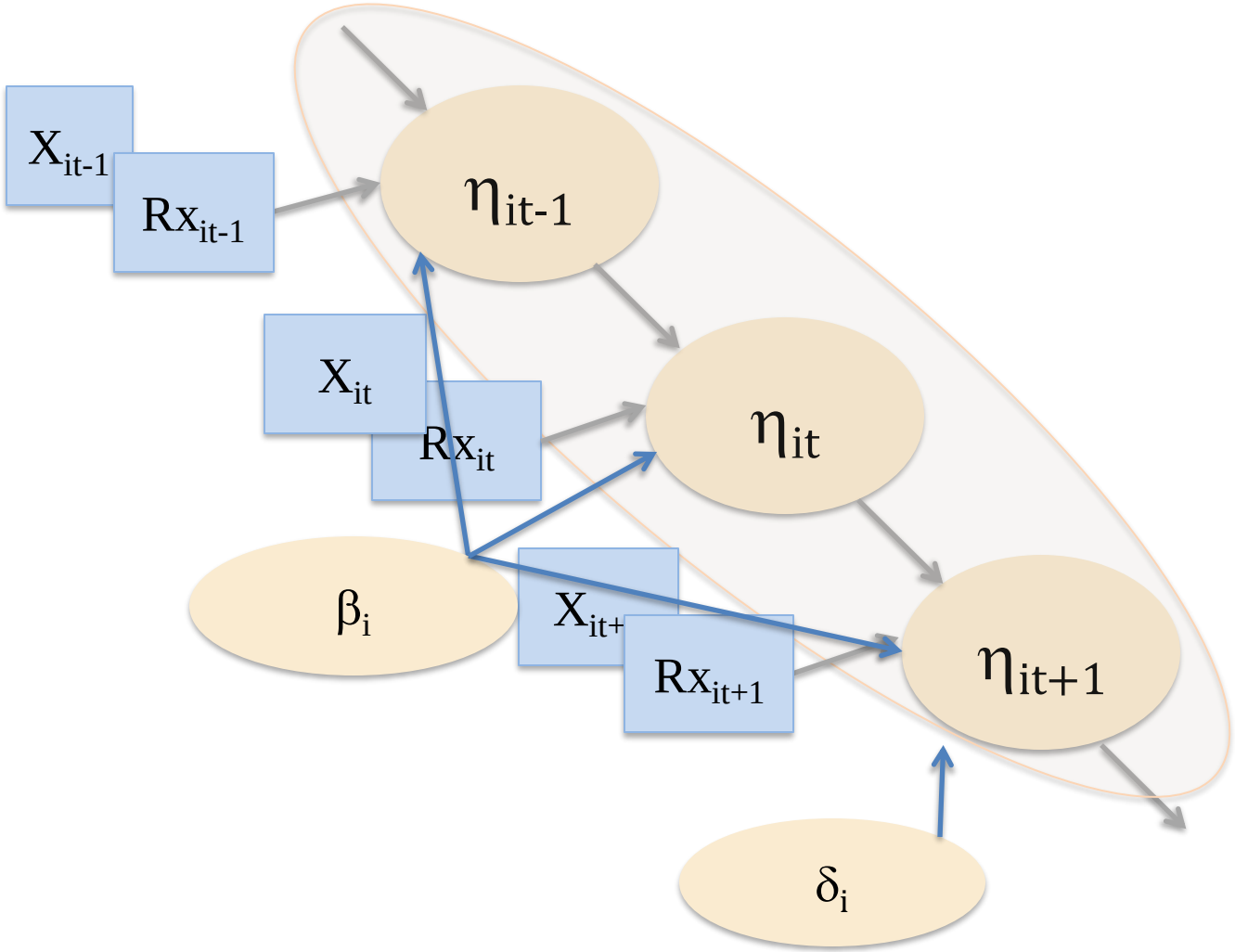
Health State/Trajectory (η_{it}) with Person-specific Indicator (δ_i)



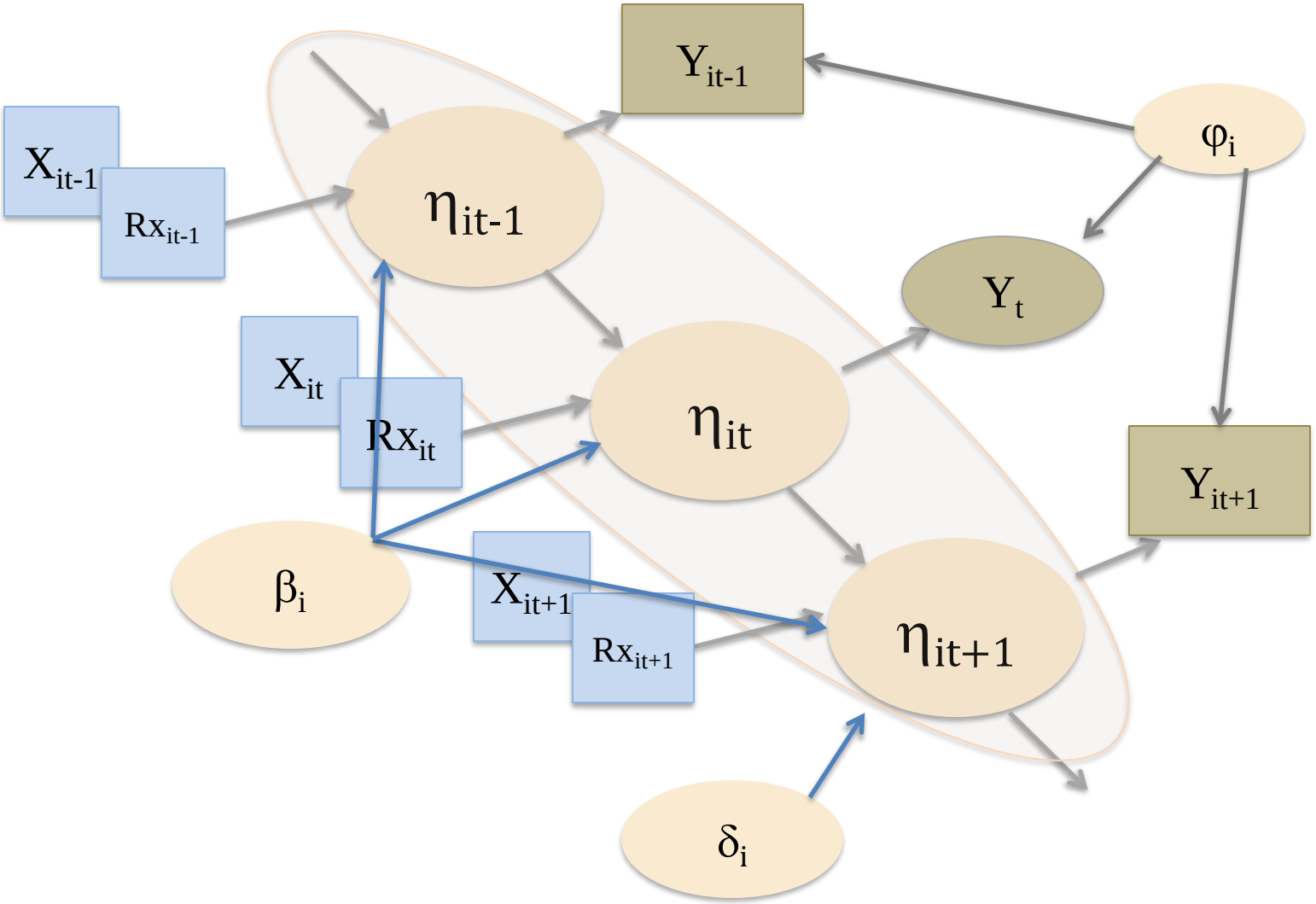
Effects of Exogenous (X) and Endogenous (Rx) Covariates on Health State/Trajectory with Person-specific Regression Coefficients (β_i)



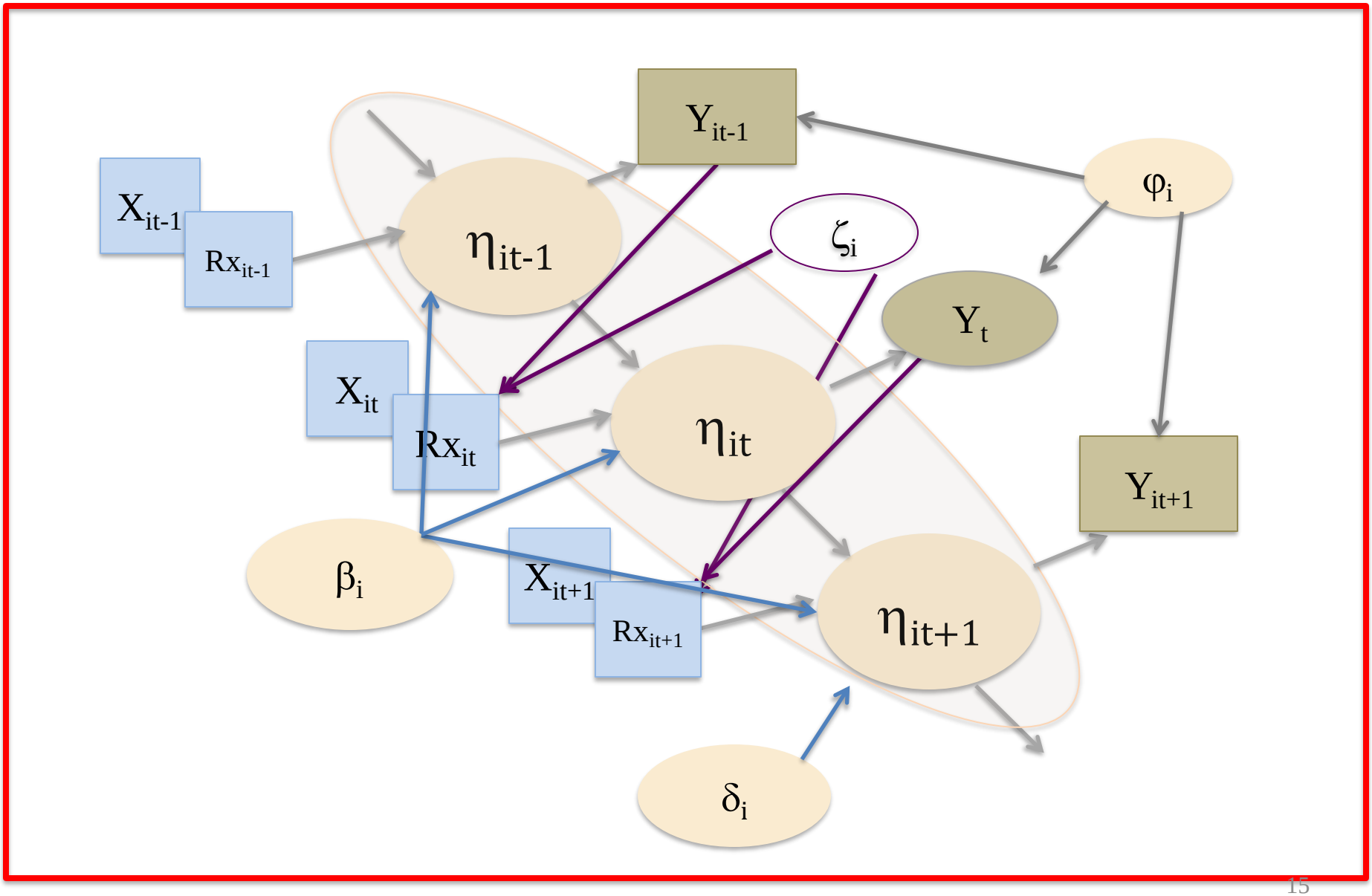
Effects of Exogenous (X) and Endogenous (Rx) Covariates on Health State/Trajectory with Person-specific Regression Coefficients (β_i)

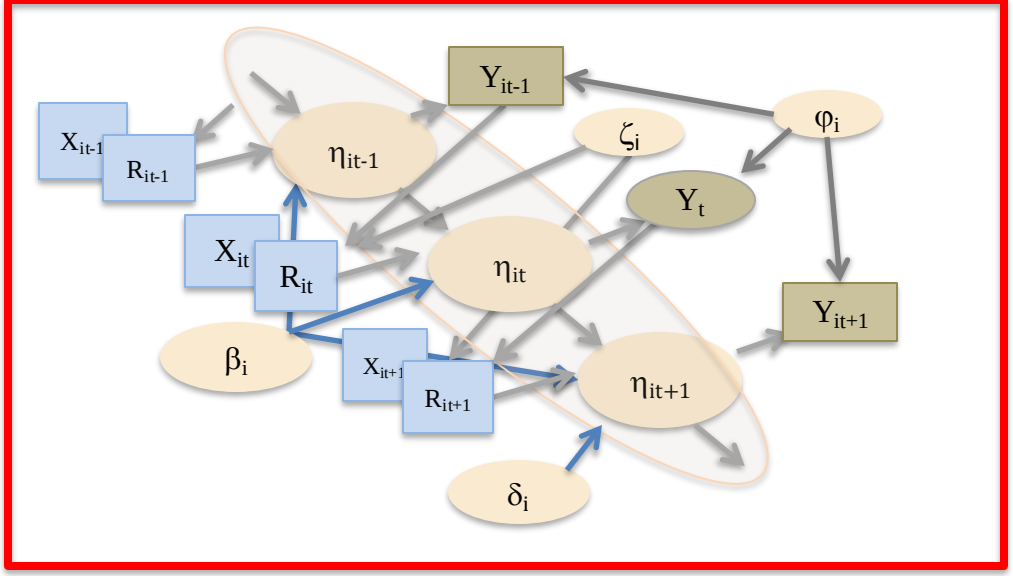


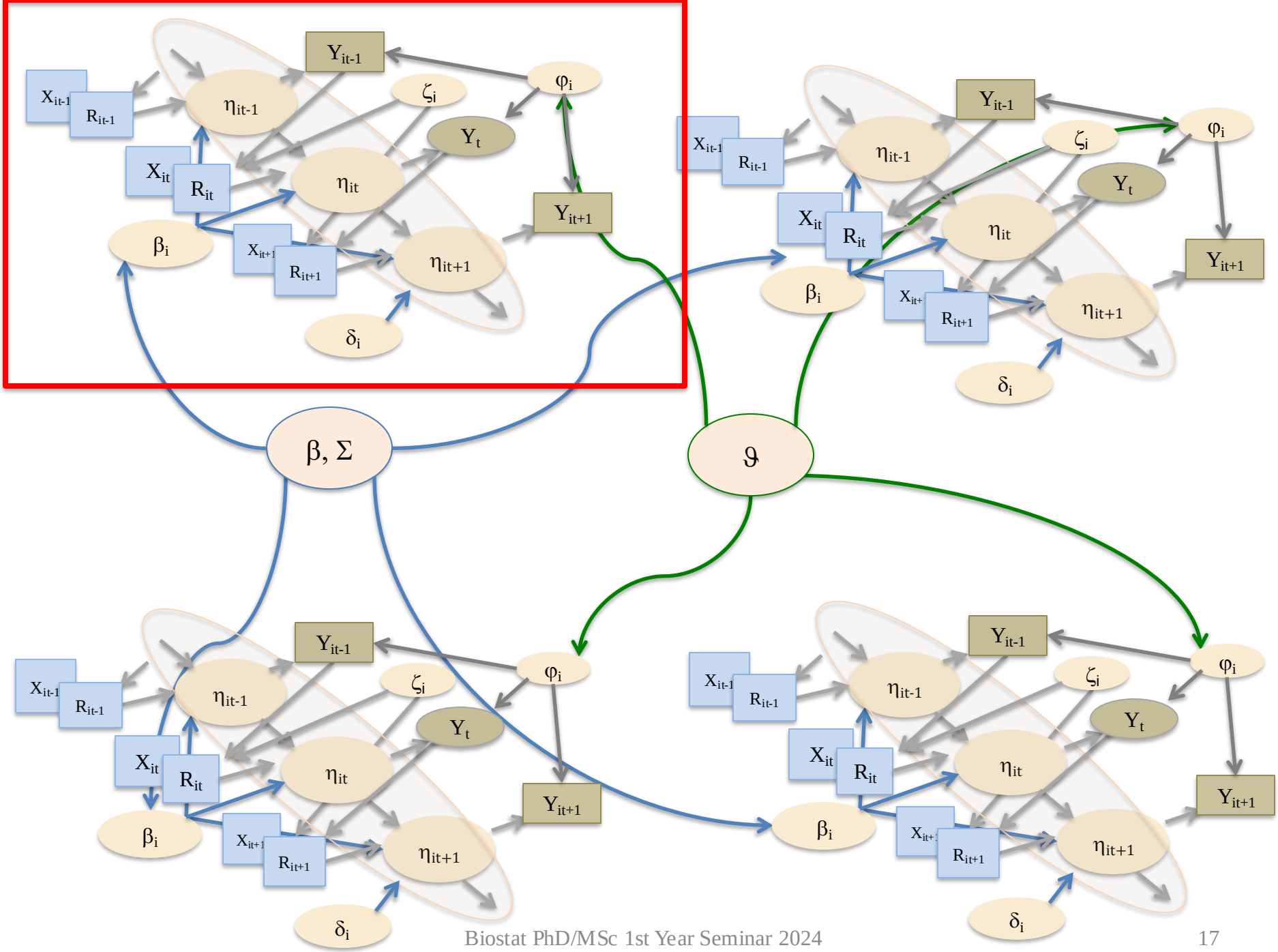
Observations (Y) that Inform about Health State through Coefficients (φ_i)

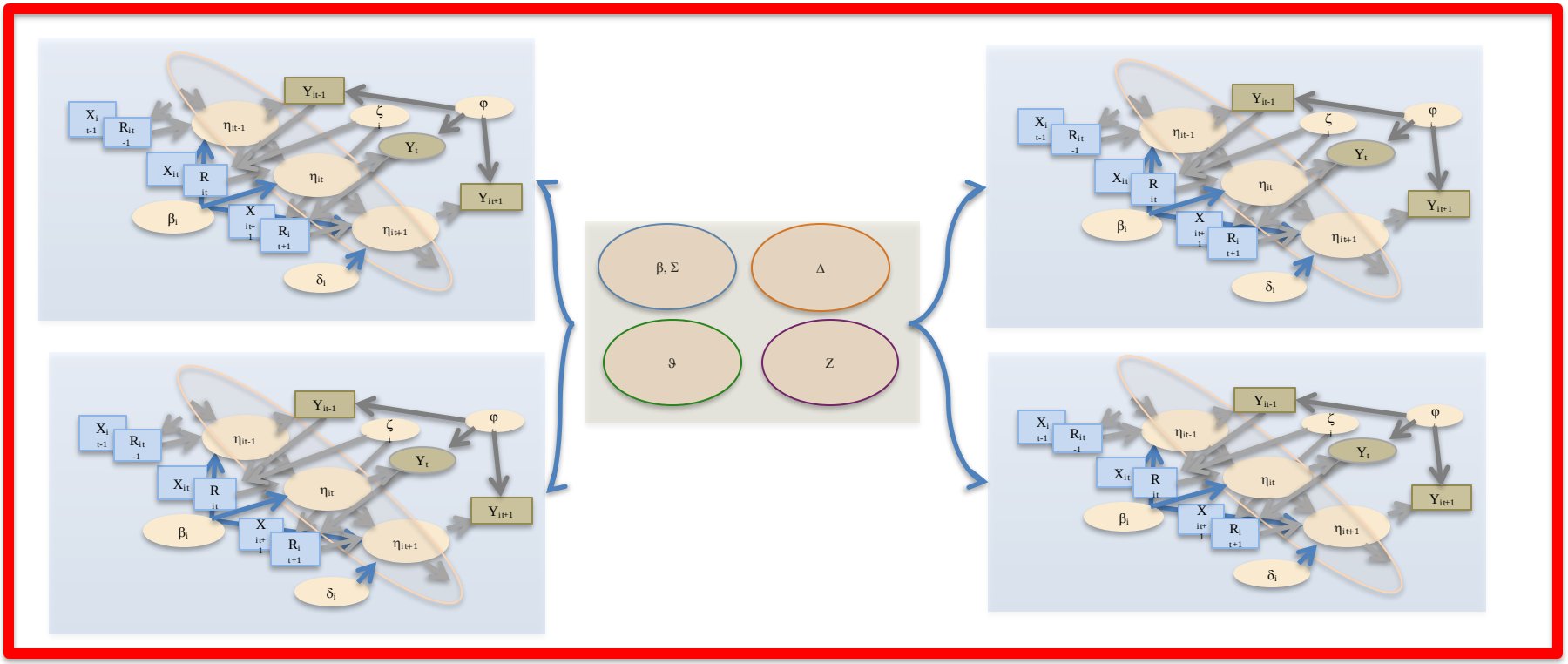


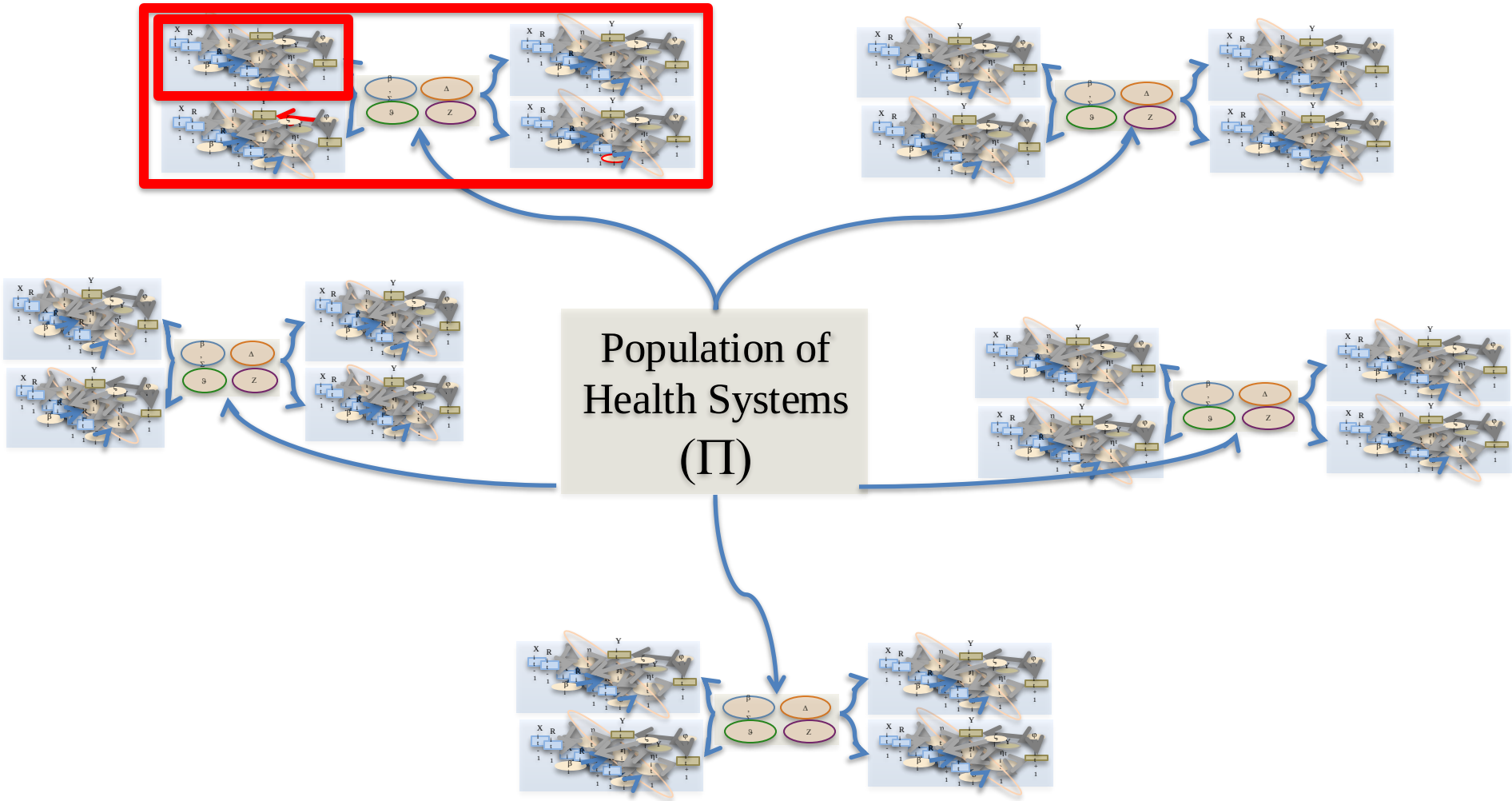
Treatment Decisions Depend on **Past Measured** Outcomes through Parameters (ζ_i)




Y_{it-1}
φ_i
X_{it-1}
R_{it-1}
η_{it-1}
ζ_i
Y_t
X_{it}
R_{it}
η_{it}
Y_{it+1}
β_i
X_{it+1}
R_{it+1}
η_{it+1}
δ_i


Y_{it-1}
X_{it-1}
R_{it-1}
η_{it-1}
ζ_i
φ_i
Y_t
X_{it}
R_{it}
η_{it}
Y_{it+1}
β_i
X_{it+1}
R_{it+1}
η_{it+1}
δ_i
β, Σ
ϑ

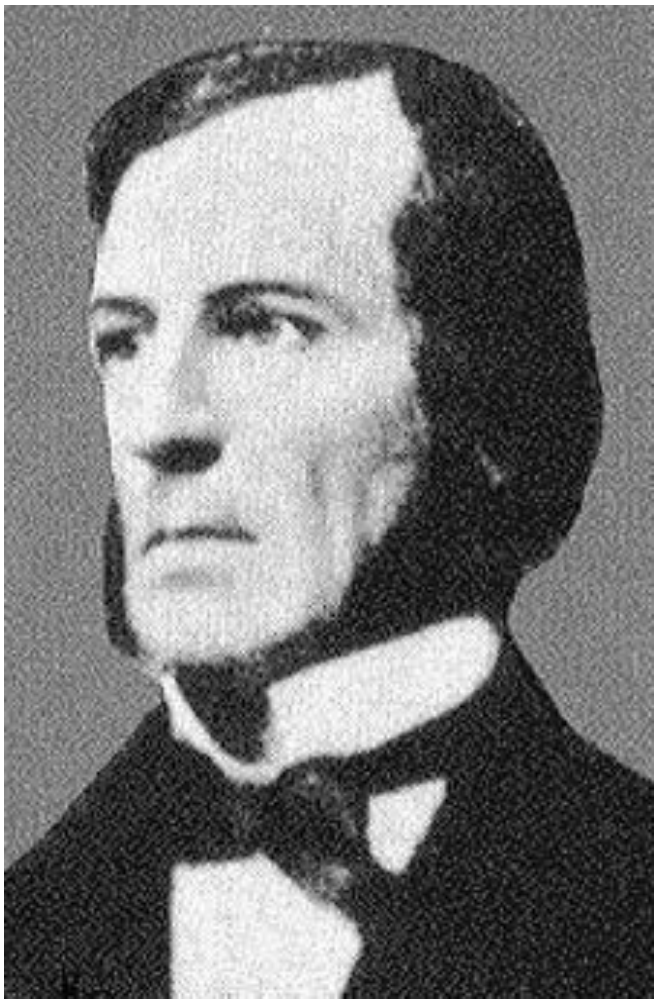

β, Σ
Δ
ϑ
Z


Population of Health Systems (Π)

Comments

- Formalism to make inferences about a single individual's health state, trajectory, and likely treatment effect.
- Address questions by combining individual's data with data on a reference population of others within and beyond her system.
- Make predictions and observe outcomes for model improvement
- Explicit reliance on informative priors where appropriate!
- A positive step from current practice?

Boole -to- Bayes



George Boole

Thomas Bayes

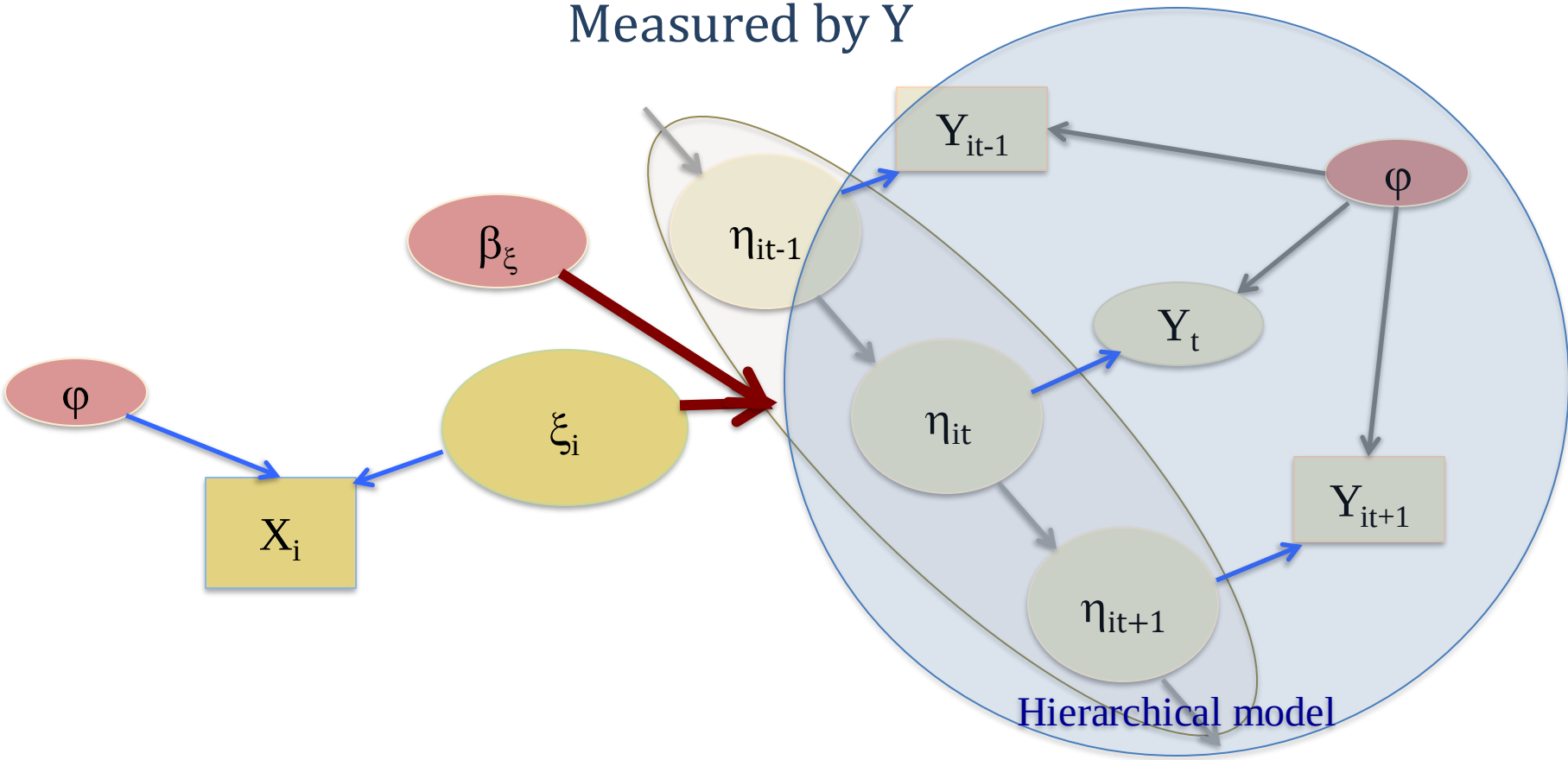
Bouillabaisse

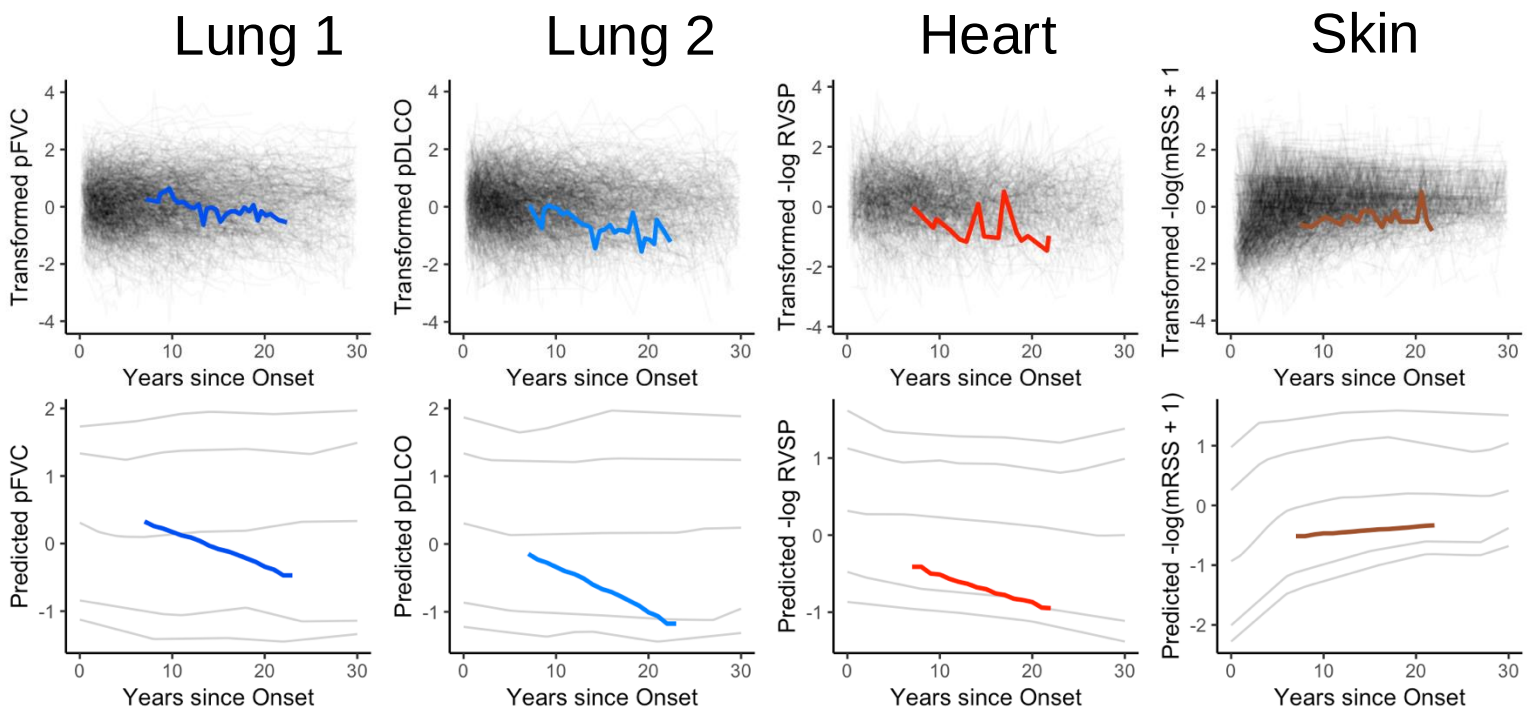
Bayes to von Neumann ?

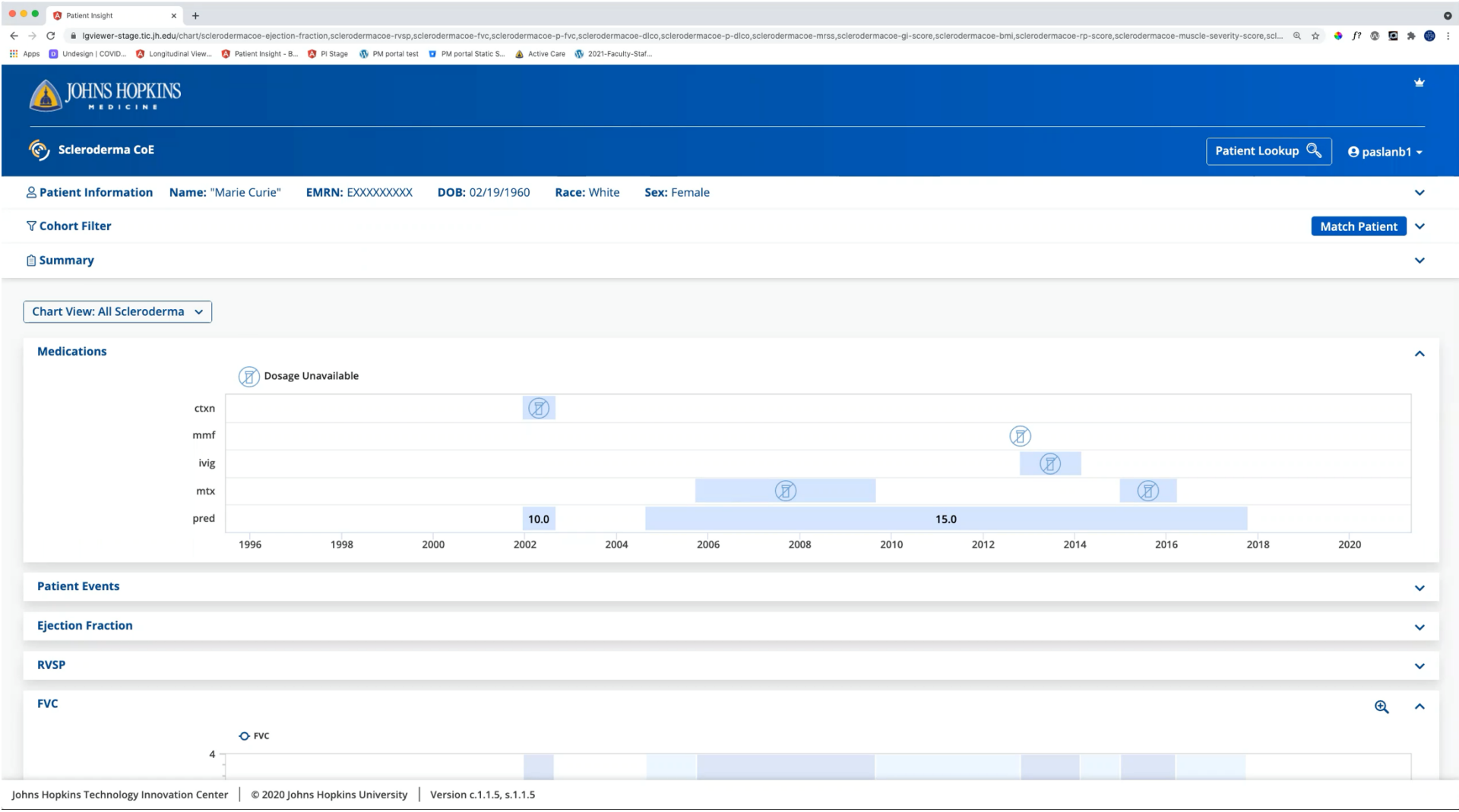
Thomas Bayes

John von Neumann

Disease Mechanism ξ, Measured by X, Causes Health Trajectory η, Measured by Y




Lung 1
Lung 2
Heart
Skin
Transformed pFVC
Transformed pDLCO
Transformed -log RVSP
Transformed -log(mRSS + 1
Predicted pFVC
Predicted pDLCO
Predicted -log RVSP
Predicted -log(mRSS + 1)
Years since Onset


Patient Insight
lgviewer-stage.tic.jh.edu/chart/sclerodermacoe-ejection-fraction,sclerodermacoe-rvsp,sclerodermacoe-fvc,sclerodermacoe-p-fvc,sclerodermacoe-dlco,sclerodermacoe-p-dlco,sclerodermacoe-mrss,sclerodermacoe-gi-score,sclerodermacoe-bmi,sclerodermacoe-rp-score,sclerodermacoe-muscle-severity-score,scl...
Apps
Undesign | COVID...
Longitudinal View...
Patient Insight - B...
PI Stage
PM portal test
PM portal Static S...
Active Care
2021-Faculty-Staf...
JOHNS HOPKINS MEDICINE
Scleroderma CoE
Patient Lookup
paslanb1
Patient Information
Name: "Marie Curie"
EMRN: EXXXXXXXXX
DOB: 02/19/1960
Race: White
Sex: Female
Cohort Filter
Match Patient
Summary
Chart View: All Scleroderma
Medications
Dosage Unavailable
ctxn
mmf
ivig
mtx
pred
10.0
15.0
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
Patient Events
Ejection Fraction
RVSP
FVC
FVC
4
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Causal Inference using Multivariate Generalized Linear Mixed-Effects Models with Longitudinal Data

Yizhen Xu, Jisoo Kim, Laura K. Hummers, Ami A. Shah, Scott Zeger

March 3, 2023

2 Notation and Model

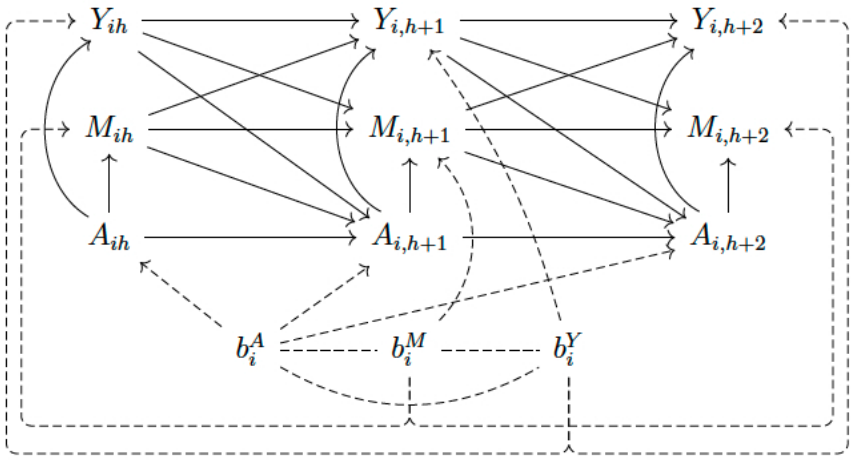


Figure 1: Directed acyclic graph (DAG) for the generalized linear mixed model displaying temporal order of the observed variables and time-invariant unmeasured heterogeneity in both treatment assignment and biomarker dynamics. Baseline characteristics V_i is excluded from the figure for simplicity.

$$
\begin{aligned}
Y_{it}|(M_{it}=1) =& \phi_1(\mathcal{H}_{it})\beta_1^Y + \phi_2(\mathcal{H}_{it})\phi_A(\overline{A}_{i,0:t})^T\beta_2^Y + b_{i0}^Y + e_{it}^Y \\
\text{logit}\{P(M_{it}=1)\} =& \phi_1(\mathcal{H}_{it})\beta_1^M + \phi_2(\mathcal{H}_{it})\phi_A(\overline{A}_{i,0:t})^T\beta_2^M + b_{i0}^M \\
\text{logit}\{P(A_{it}=1|A_{i,t-1}=0)\} =& \phi_1(\mathcal{H}_{it})\beta_1^A + b_{i0}^A
\end{aligned}
$$

where

$$
\begin{aligned}
(b_{i0}^Y, b_{i0}^M, b_{i0}^A)^T &\sim N(0, G), \\
\phi_1(\mathcal{H}_{it}) &= \{1, \tilde{Y}_{i,t-1}, V_i, B_i, ns(S_{it}, \nu_s), B_i \times ns(S_{it}, \nu_s)\}, \\
\phi_2(\mathcal{H}_{it})\phi_A(\overline{A}_{i,0:t})^T &= \{D(\overline{A}_{i,0:t}), V_i \times D(\overline{A}_{i,0:t}), B_i \times D(\overline{A}_{i,0:t}), I_{it} \times D(\overline{A}_{i,0:t})\},
\end{aligned}
$$

and we assume $\nu_s = 4$. Note that both the outcomes Y_{it} and confounders M_{it} are multivariate, i.e. Y_{it} and $M_{it} \in \mathbb{R}^3$. Specifically, $(b_{i0}^Y, b_{i0}^M, b_{i0}^A) \in \mathbb{R}^7$ and the covariance matrix $G \in \mathbb{R}^{7\times 7}$. Model

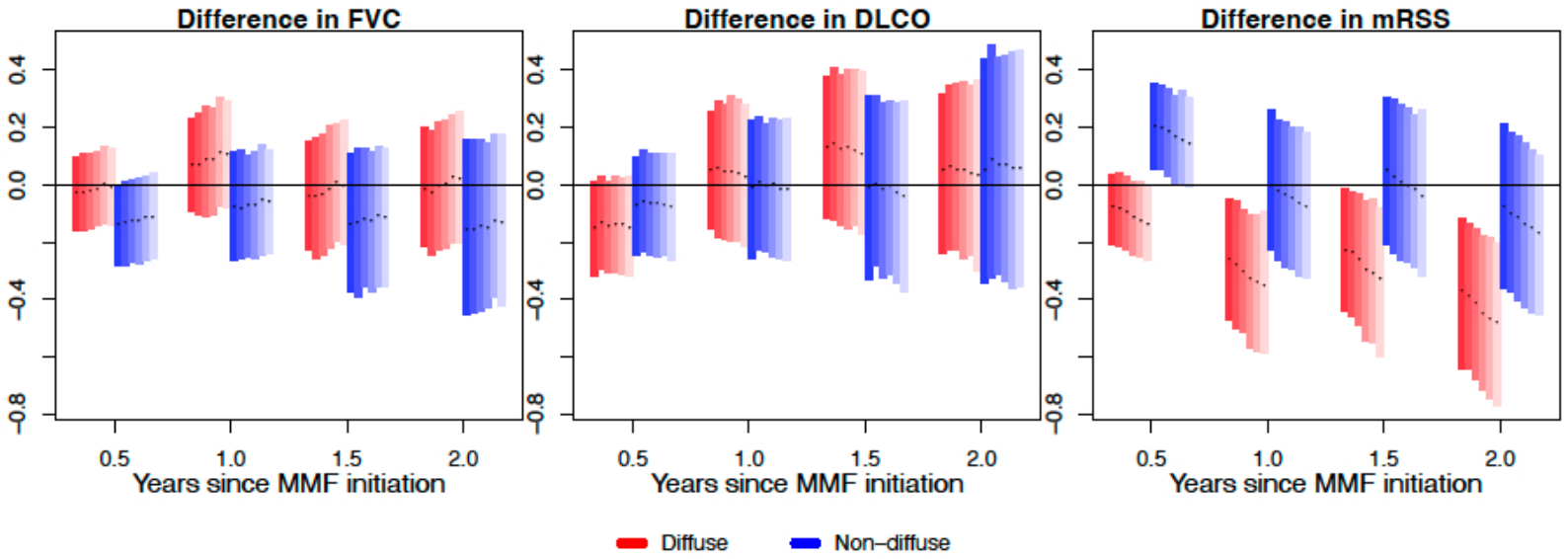


Figure 8: Application causal estimation by subgroup diffuse versus nondiffuse.

Covid-19

Department of Biostatistics All Hands on Deck

John Muschelli, Karen Bandeen Roche, **Mary Grace Bowring,** Martina Fu, **Yizhen Xu, Zitong Wang,** Mei-Cheng Wang; Jiyang Wen,

Jamie Perin, **Shannon Wongvibulsin,** Grant Schumock; Josh Betz; **Scott Zeger**

Many Clinical Scientific Colleagues

Brian Garibaldi, Amita Gupta, Matt Robinson; Antony Rosen; Eileen Scully;…

Question: *What is my risk of having severe disease given my current condition?*

- Predict risk of severe outcome from baseline and all intervening measures prior to t with 6-hourly updates
- Random Forest for Survival, Longitudinal and Multivariate (RF-SLAM) outcomes (Wongvibulsin, et al, 2019)
- Approximating tree to explain predictions to clinicians and patients (Wongvibulsin, et al, 2020)
- Severe Covid 19 Adaptive Risk Predictor (SCARP) (Wongvibulsin, et al, 2021)
- SCARP-lite implemented in JH Epic HER (Robinson, et al in 2021)

Results

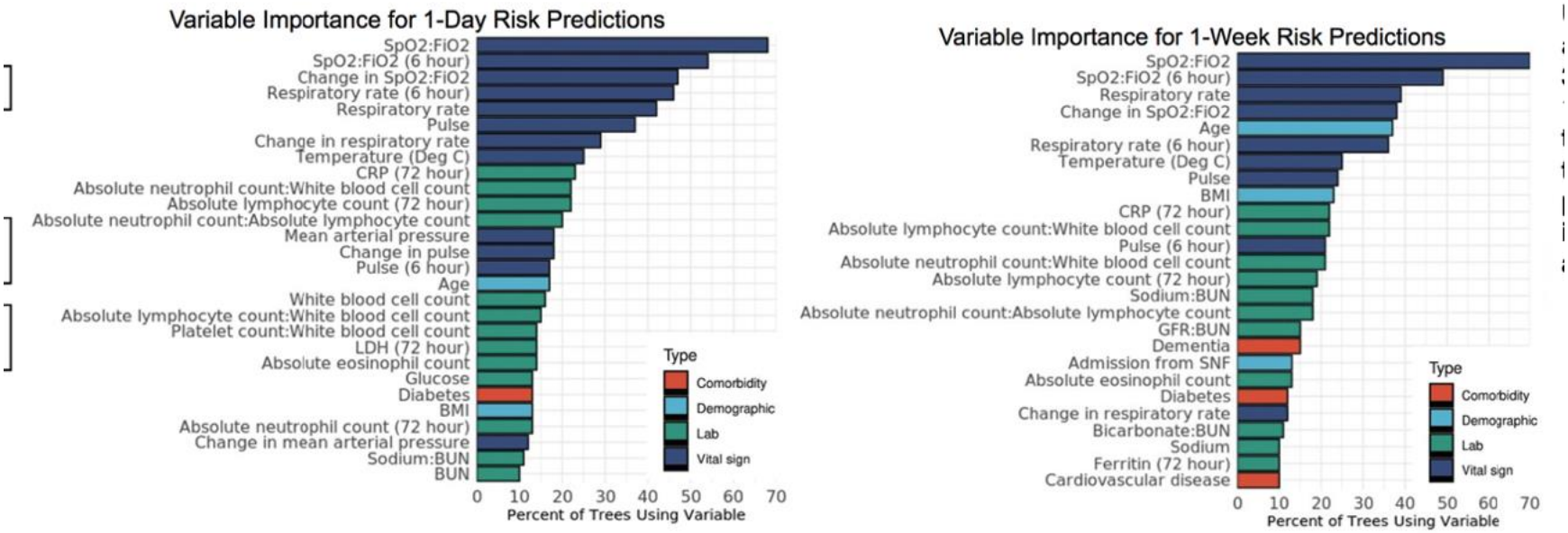
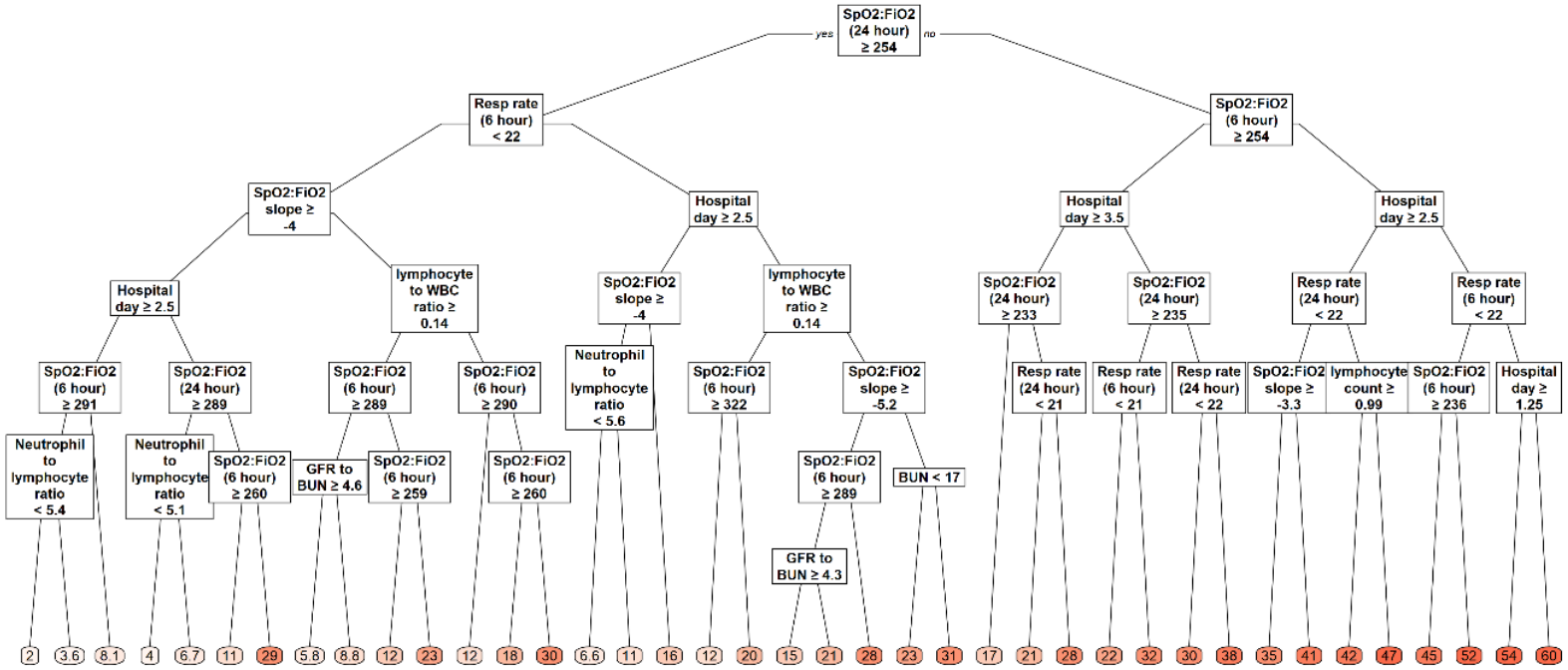
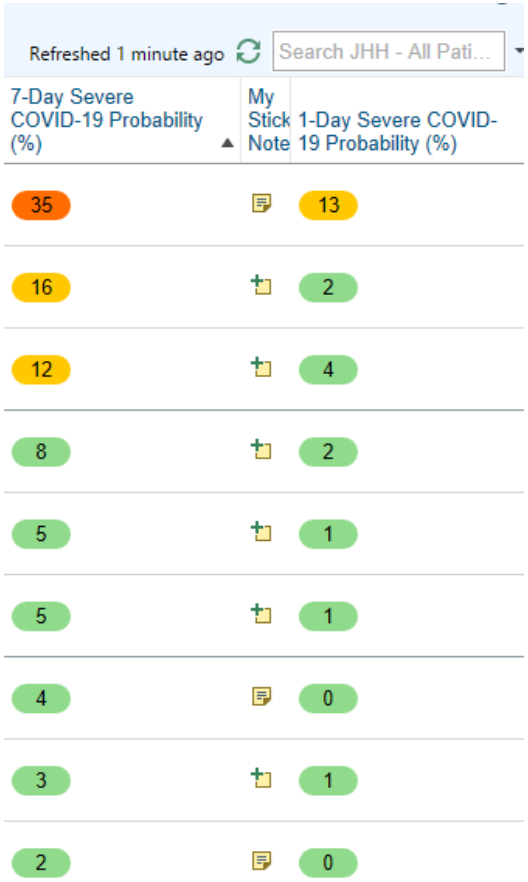


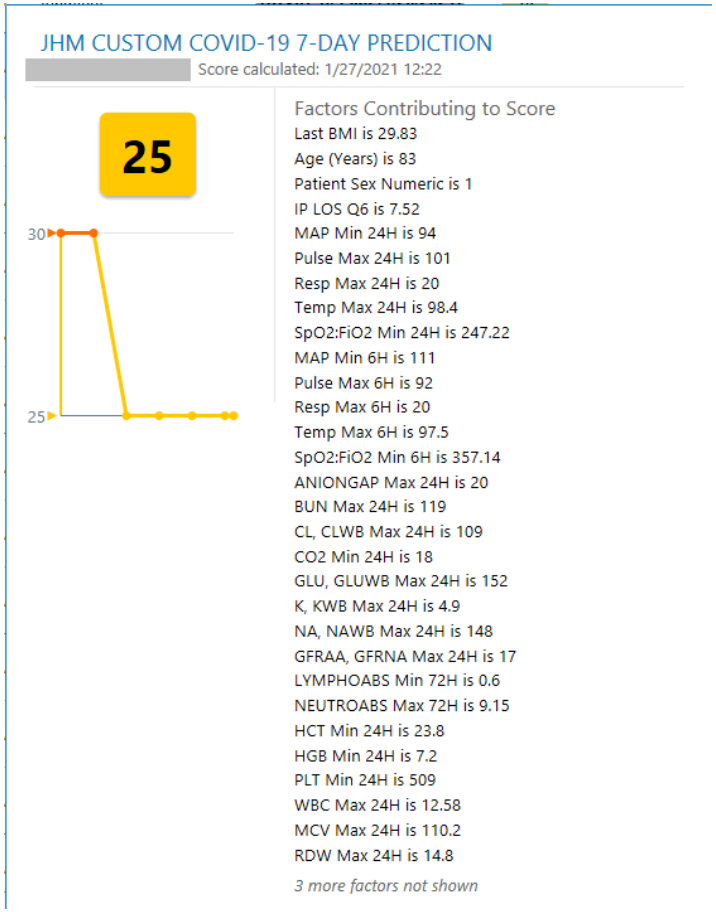
Figure 2: 1-Day risk prediction variable importance plot and 1-week risk prediction variable importance plot: The percentage of trees incorporating each of the variables is used as a simple and interpretable measure of variable importance. The variables used by 10% or greater of the trees are shown in the plots. Note: values for labs and vital signs correspond to values in the past 24 hours unless otherwise specified (e.g., 6 hour indicates that the value corresponds to the past 6 hours).

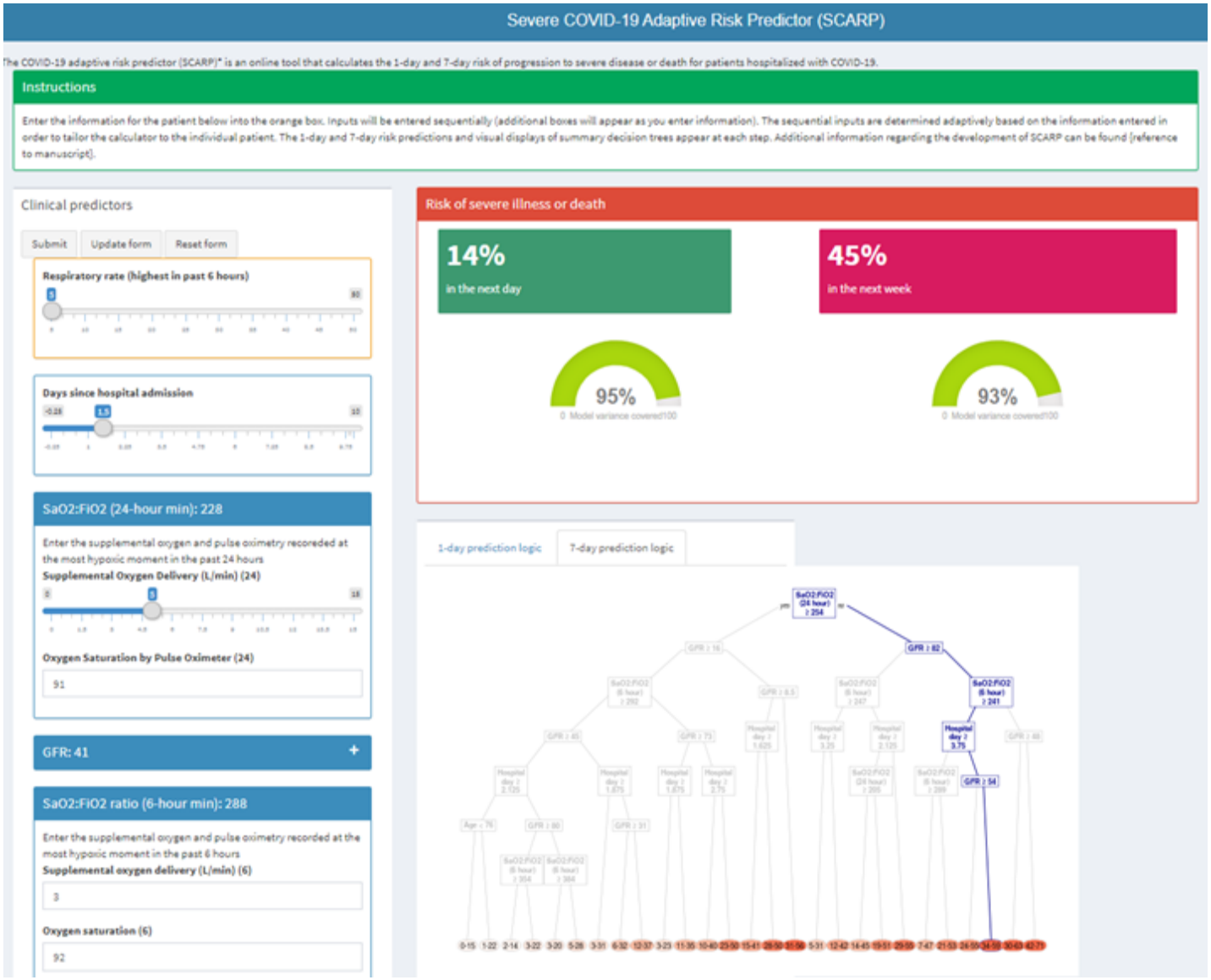
Summary of RF-SLAM predictions



Summary tree of RF-SLAM predictions of 1-week risk of severe disease or death. The predicted probabilities are expressed in the terminal nodes and shaded according to lowest risk (0%) to highest risk (100%) prediction


Refreshed 1 minute ago
Search JHH - All Pati...
7-Day Severe COVID-19 Probability (%)
My Stick Note
1-Day Severe COVID-19 Probability (%)
35
13
16
2
12
4
8
2
5
1
5
1
4
0
3
1
2
0

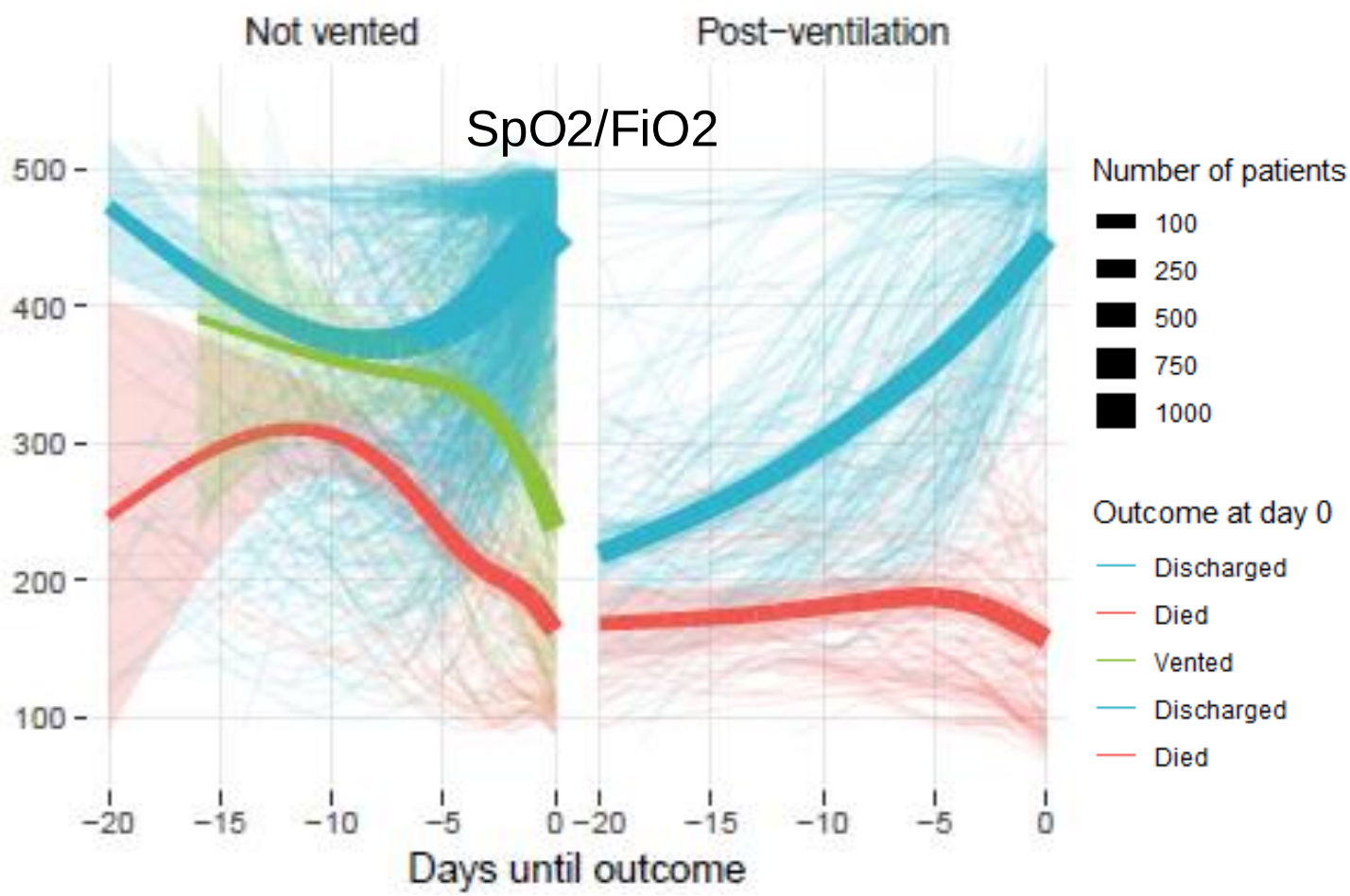

JHM CUSTOM COVID-19 7-DAY PREDICTION
Score calculated: 1/27/2021 12:22
25
30
25
Factors Contributing to Score
Last BMI is 29.83
Age (Years) is 83
Patient Sex Numeric is 1
IP LOS Q6 is 7.52
MAP Min 24H is 94
Pulse Max 24H is 101
Resp Max 24H is 20
Temp Max 24H is 98.4
SpO2:FiO2 Min 24H is 247.22
MAP Min 6H is 111
Pulse Max 6H is 92
Resp Max 6H is 20
Temp Max 6H is 97.5
SpO2:FiO2 Min 6H is 357.14
ANIONGAP Max 24H is 20
BUN Max 24H is 119
CL, CLWB Max 24H is 109
CO2 Min 24H is 18
GLU, GLUWB Max 24H is 152
K, KWB Max 24H is 4.9
NA, NAWB Max 24H is 148
GFRAA, GFRNA Max 24H is 17
LYMPHOABS Min 72H is 0.6
NEUTROABS Max 72H is 9.15
HCT Min 24H is 23.8
HGB Min 24H is 7.2
PLT Min 24H is 509
WBC Max 24H is 12.58
MCV Max 24H is 110.2
RDW Max 24H is 14.8
3 more factors not shown


Severe COVID-19 Adaptive Risk Predictor (SCARP)
The COVID-19 adaptive risk predictor (SCARP)* is an online tool that calculates the 1-day and 7-day risk of progression to severe disease or death for patients hospitalized with COVID-19.
Instructions
Enter the information for the patient below into the orange box. Inputs will be entered sequentially (additional boxes will appear as you enter information). The sequential inputs are determined adaptively based on the information entered in order to tailor the calculator to the individual patient. The 1-day and 7-day risk predictions and visual displays of summary decision trees appear at each step. Additional information regarding the development of SCARP can be found (reference to manuscript).
Clinical predictors
Submit
Update form
Reset form
Respiratory rate (highest in past 6 hours)
Days since hospital admission
SaO2:FiO2 (24-hour min): 228
Enter the supplemental oxygen and pulse oximetry recoreded at the most hypoxic moment in the past 24 hours
Supplemental Oxygen Delivery (L/min) (24)
Oxygen Saturation by Pulse Oximeter (24)
91
GFR: 41
SaO2:FiO2 ratio (6-hour min): 288
Enter the supplemental oxygen and pulse oximetry recorded at the most hypoxic moment in the past 6 hours
Supplemental oxygen delivery (L/min) (6)
3
Oxygen saturation (6)
92
Risk of severe illness or death
14%
in the next day
45%
in the next week
95%
93%
1-day prediction logic
7-day prediction logic

Question: Given my current state, what are my future risks of discharge, intubation or death; what are my expected biomarker trajectories for each outcome?

- Competing discrete hazards of (3) events on each future day (Project 1 approach)
- Retrospective longitudinal data analysis of multiple biomarkers *given event outcome* (define t=0 at event time) (Bowring, MG, Wang, Z et al, 2021)
- Bayes rule to calculate the probability of a future event given baseline and biomarker data until current time.

Longitudinal Data Analysis



Bowring MB, in press

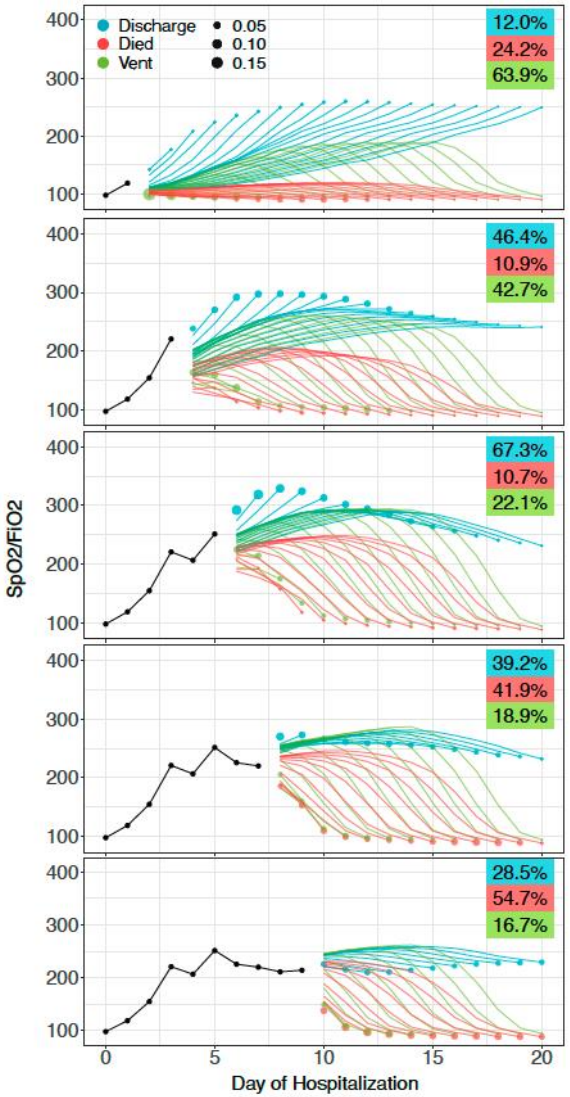


FIG 4. *Prediction capabilities of the retrospective model based on data from the first 2, 4, 6, 8 and 10 days of hospitalization for a given patient. Black lines represent the observed SpO2/FiO2 for the patient during hospitalization. Blue, red, and green lines indicate the predicted SpO2/FiO2 trajectories leading to discharge, death, or ventilation events respectively. The marker size at the end of each predicted trajectory indicates the probability of that event on that day given the past biomarker history. The probabilities of each event happening eventually (before day 20) are shown in the colored boxes on the right, with colors indicating event types.*

Statistical Challenges

1. Wrangling gigabytes of transactional EHR data into a longitudinal data set for thousands of patients; limitations of measurements
2. Brand new disease without a clinical evidence base
3. Observational, not experimental data

   …=> Treatments(i,t-1) => Outcomes(i,t) => Treatments(i,t) =>…

3. Outcomes comprise many biomarkers, major events and treatment choices
4. Competing risks of three major events: discharge, intubation, death
5. Significant fraction of deaths complicate off-the-shelf longitudinal data analysis approaches
6. Predictors are numerous and dynamic; many are irrelevant; need to find the important ones
7. Potentially useful results are unhelpful until translated into terms clinicians can understand to improve their decisions

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Thank you

Autoimmune Disease
Auto-antibody "Signature"

Jisoo Kim, Livia Casciola-Rosen, Antony Rosen,
Ami Shah, **Zhenke Wu, Scott Zeger**

Disease Mechanism (ξ_i) Causes Health Trajectory (η_{it})

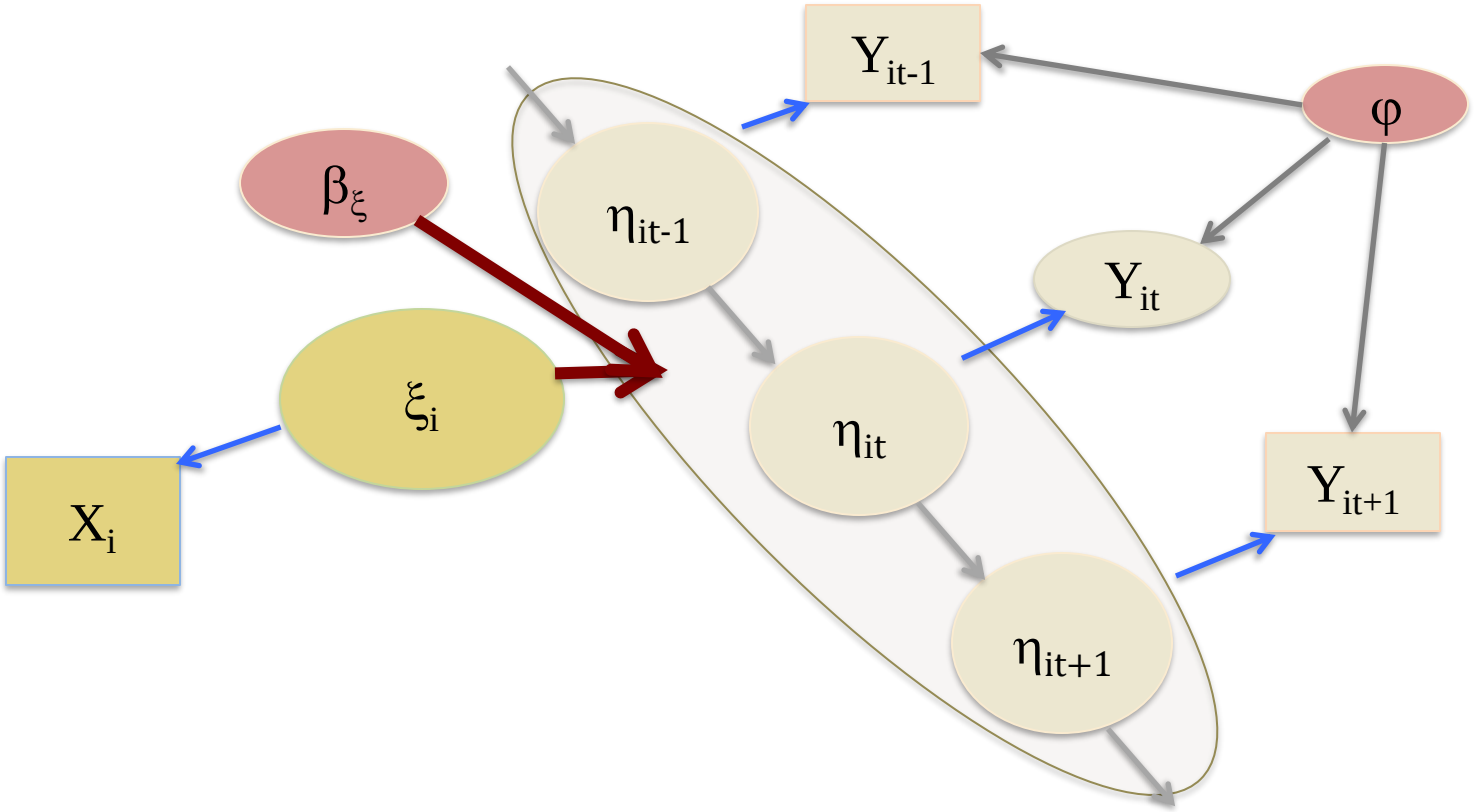
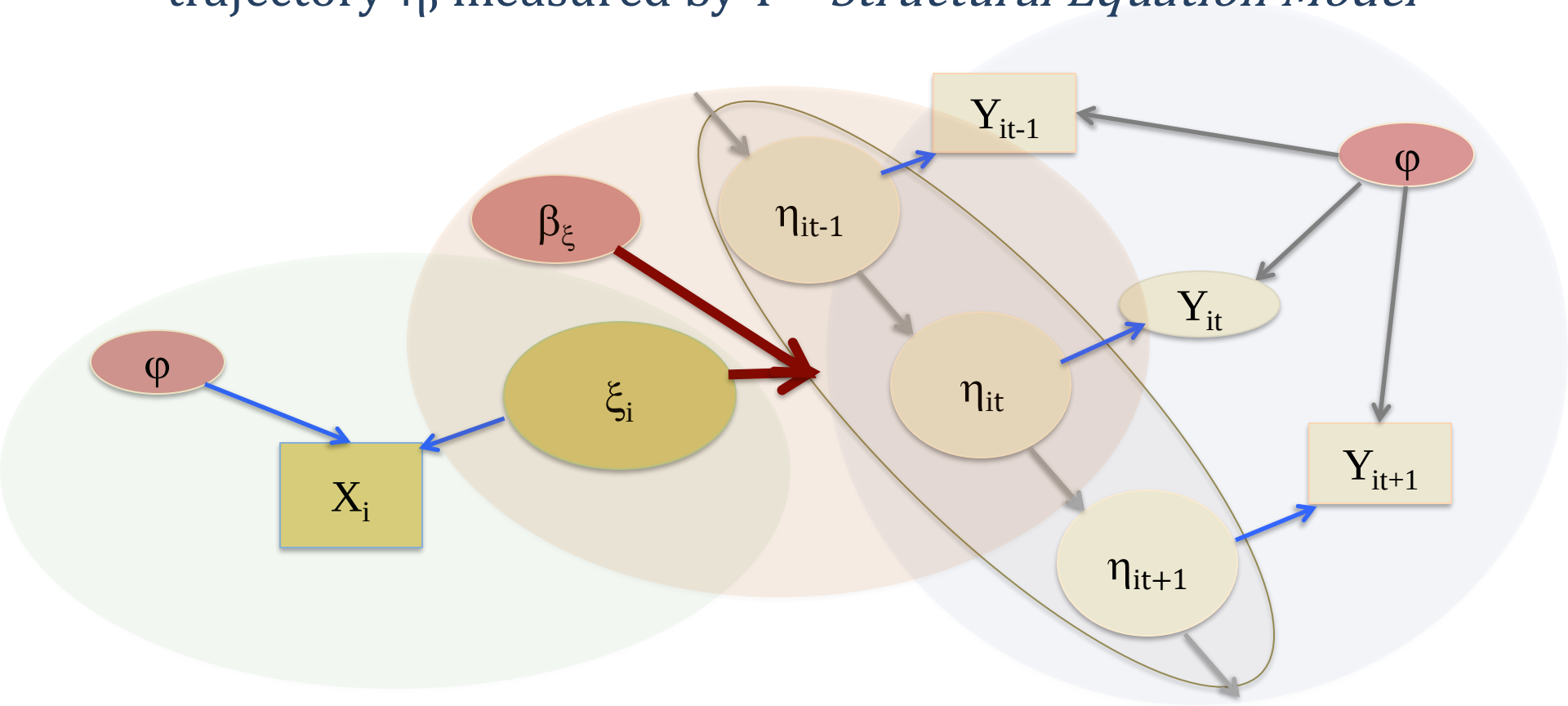
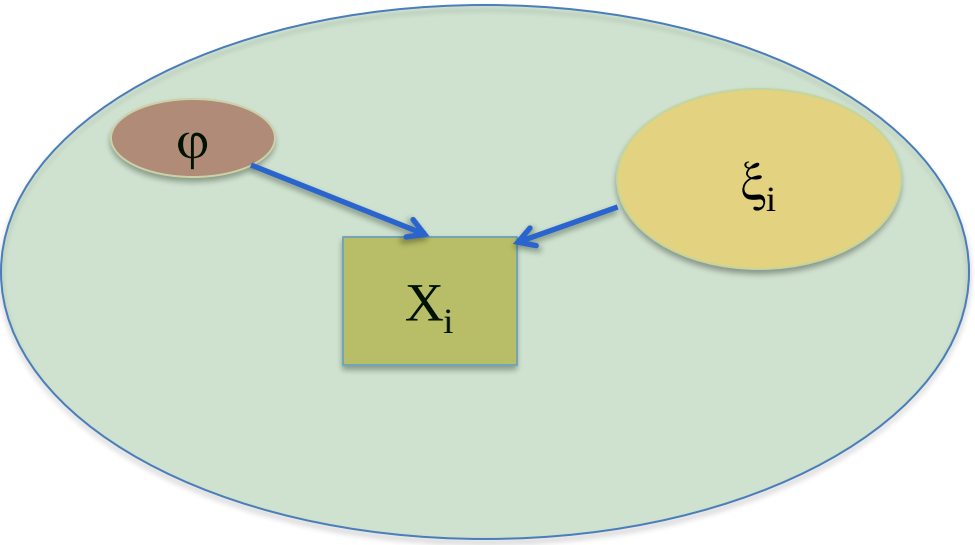


Figure 1. Disease mechanism ξ, measured by X, causes health trajectory η, measured by Y – *Structural Equation Model*



Disease Mechanism ξ, Measured by X, Causes Health Trajectory η, Measured by Y

Restricted latent class analysis => $[\xi|X]$ – Zhenke Wu



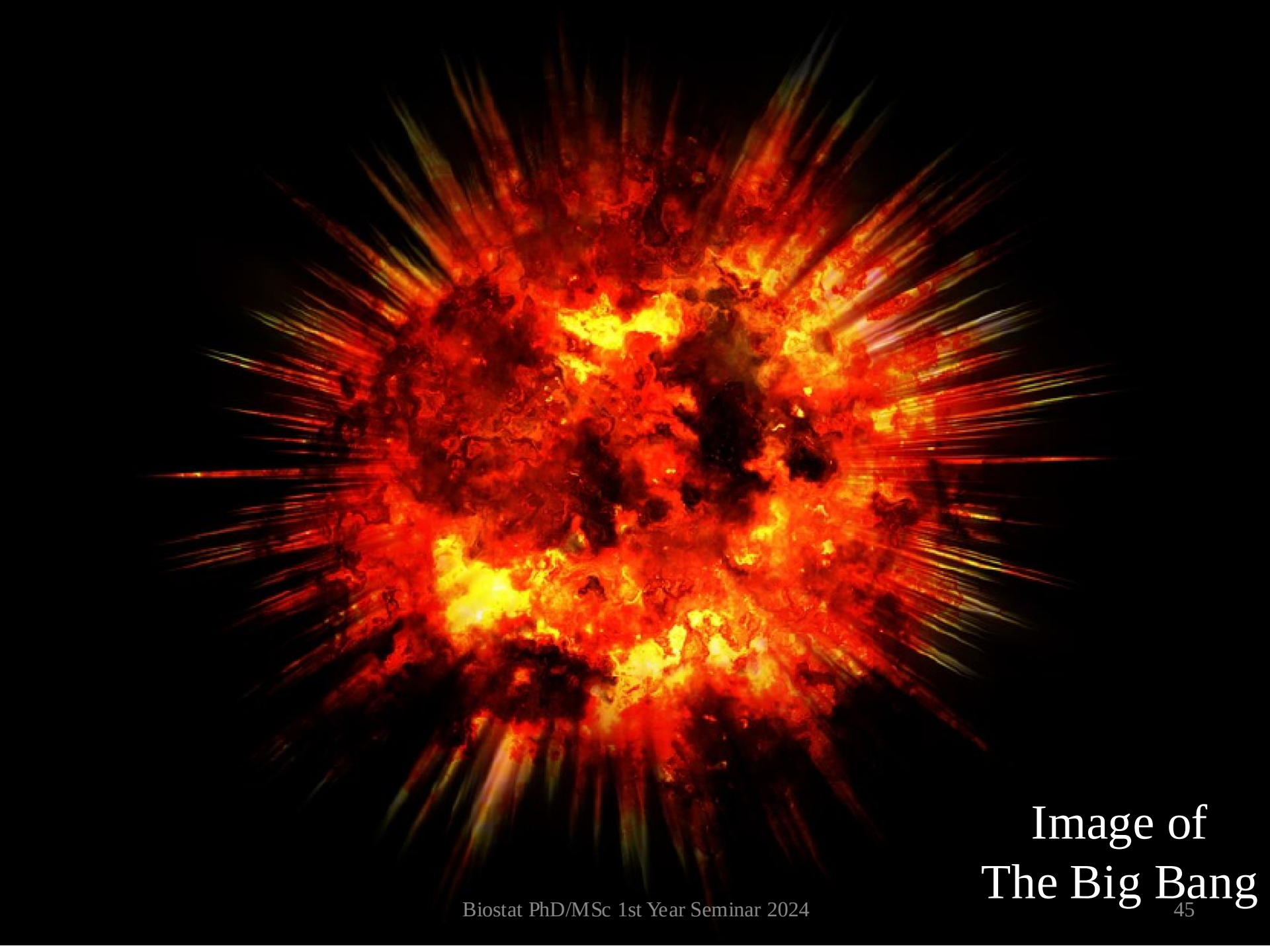
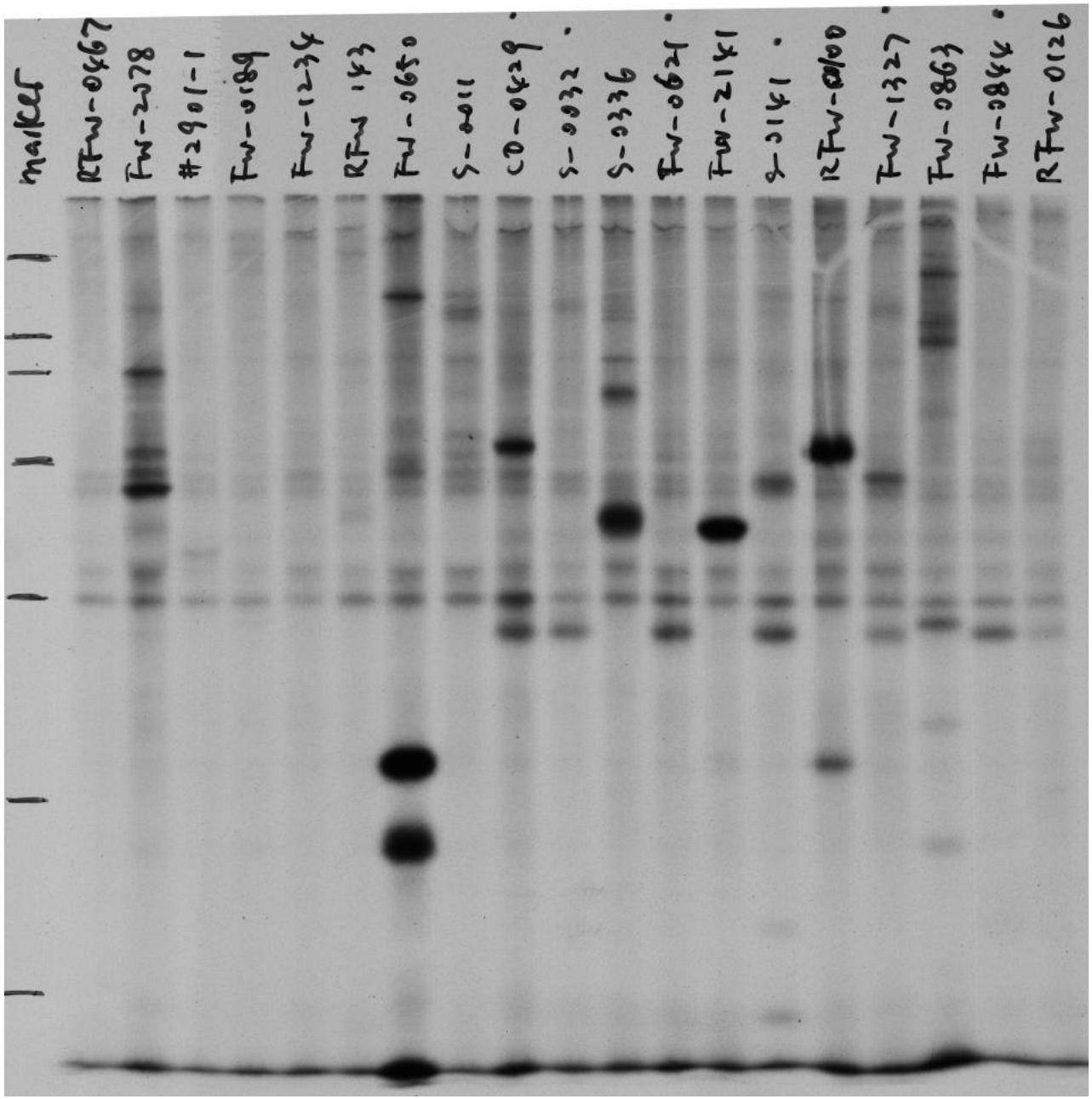
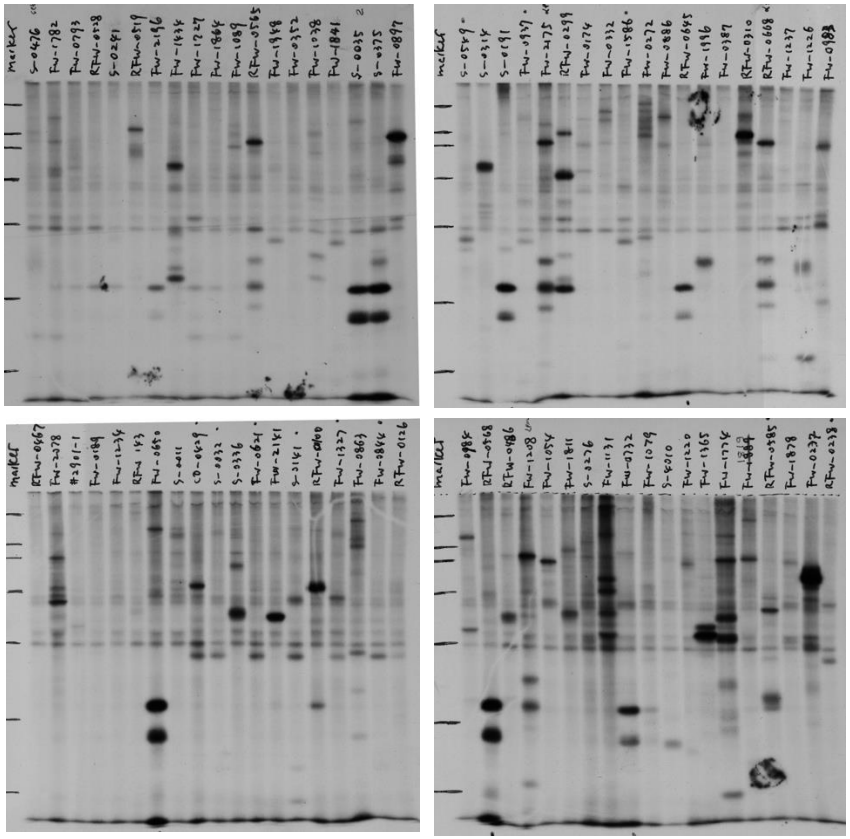


Image of
The Big Bang

Autoantibody profiles in patient sera – immunoprecipitation readout

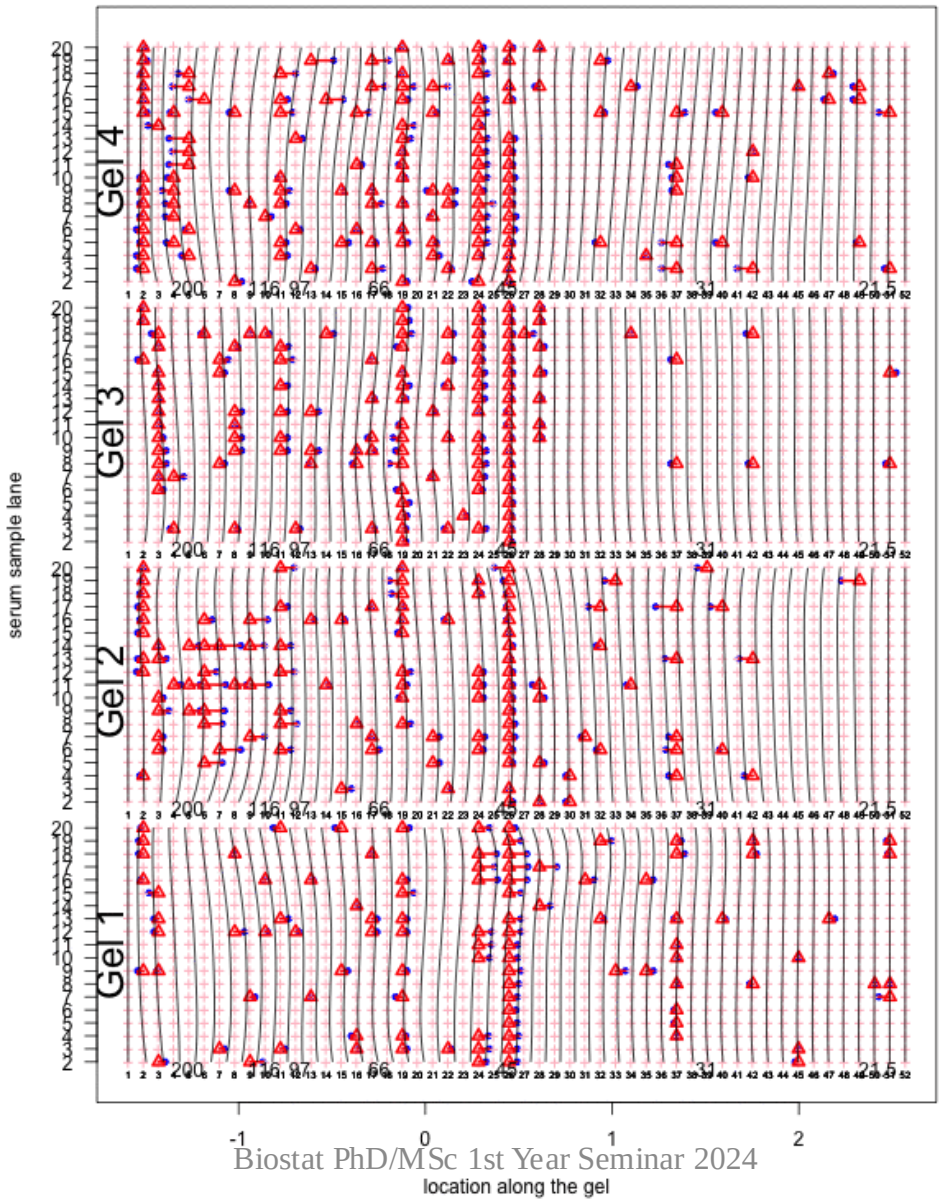


- 76 autoantibody patterns from patients with rheumatic disease & cancer
- all were negative for autoantibodies against prominent defined specificities

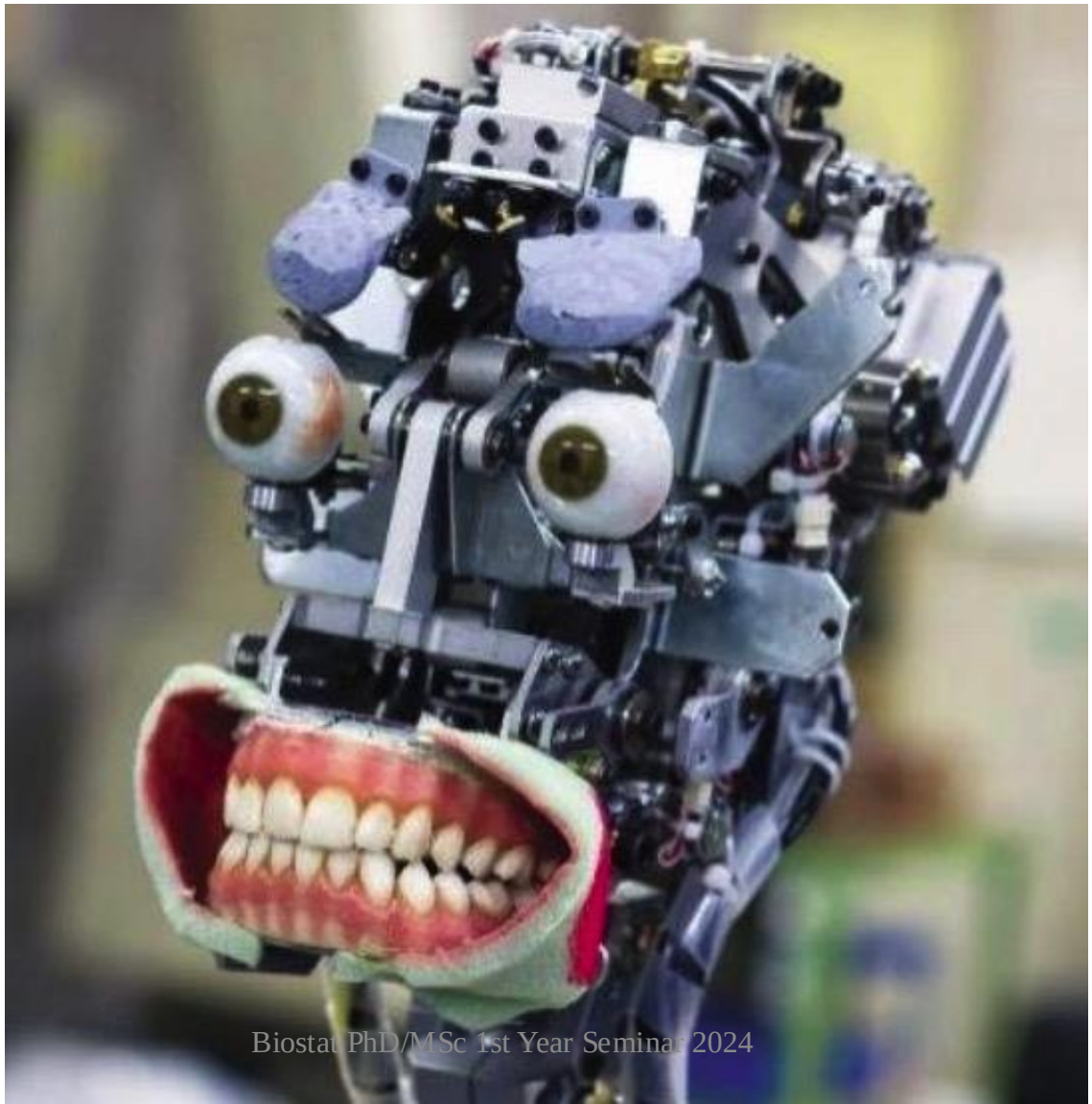


Bayes Rule to identify common autoantibody signatures?

Align the peaks

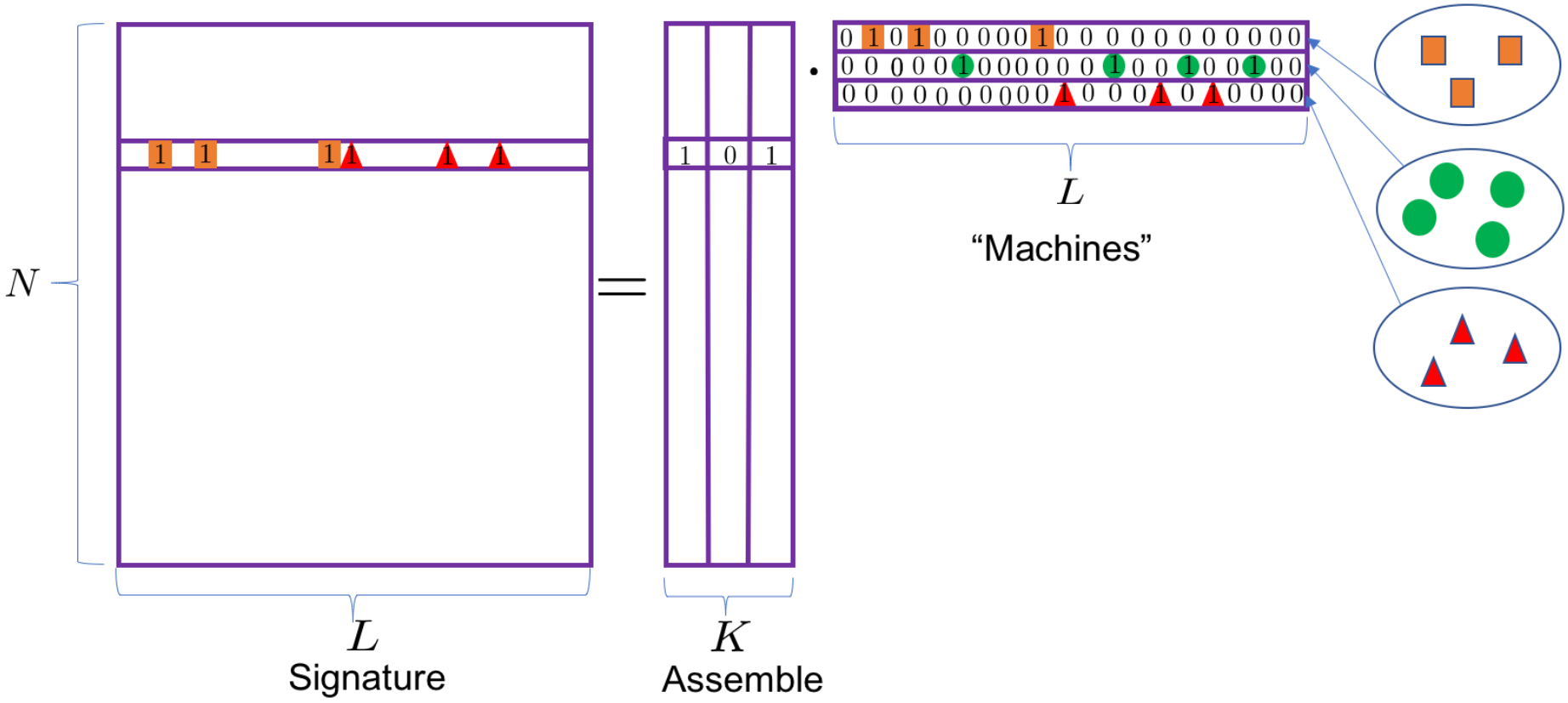


Cellular Machines Model – Machine is a set of proteins that do a cellular job; machines are targeted by the immune system



Clustering informed by the biology that antibodies target multiple components in complexes (intermolecular spreading)

$$\xi_i = \eta_i^{\top} \cdot Q$$



Preliminary clustering results based on machine models

Data: CTP negative sera

Method: Bayesian machine-based algorithm

Figure: Three estimated clusters (top three panels) with distinct enrichment of three distinct estimated machines (bottom panel)

Colored labels: red, blue, green - for clusters obtained by eyeballing; the algorithm is agnostic to them.