Personalized Medication Dosing Using Volatile Data Streams

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1: Massachusetts Institute of Technology; 2: Massachusetts General Hospital,; 3: Emory University

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Introduction

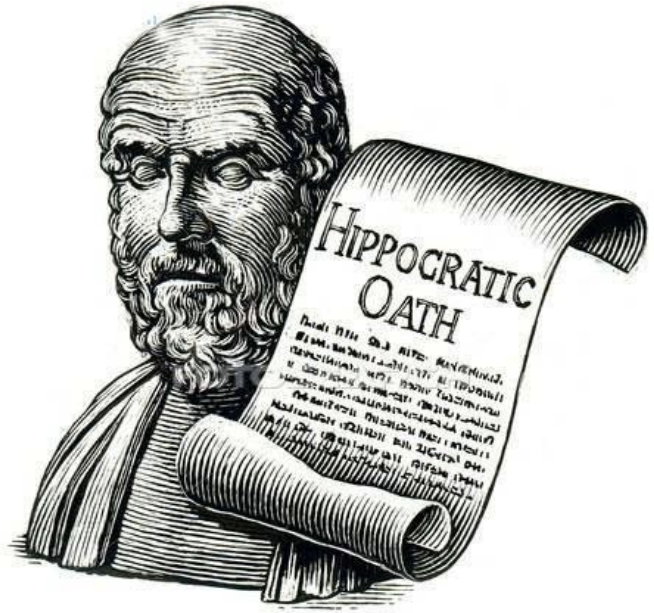
Personalized medicine:
A brief history

- 460BC: Personalized medicine was envisioned by Hippocrates
- 1990-2003: A surge of interest in personalized medicine following the human genome project
- 2017: FDA approves record number of personalized medicines

Allen Frances, M.D., Contributor
Allen Frances MD is Professor Emeritus of Psychiatry and former Chair at Duke University

Patient-Centered Vs. Lab-Centered 'Personalized Medicine'

07/24/2017 01:12 pm ET | **Updated** Jul 24, 2017



"It is more important to know the patient who has the disease than the disease the patient has." — Hippocrates

Allen Frances, MD, Professor of Psychiatry, Duke University

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PMC PERSONALIZED MEDICINE COALITION

NEWS

FDA Approves Record Number of Personalized Medicines in 2017

But what is “personalization”

Personalized medicine:
Two approaches

- Static personalization is often performed at the level of demography
  (e.g. gender, weight)

- Dynamic personalization begins with demography, and becoming more patient-specific as better data and responses to treatment are collected
  (e.g. anesthesia control)

Drug Dosage Recommendations[1] (3)

Table. 4.4

Dose in mg/kg (maximum dosage in parentheses)							
Drug	Adults/Children[2]			Daily	1 time/week[3]	2 times/ week[3]	3 times/ week[3]
EMB[4]	Adults	Weight	40-55 kg	14.5-20 mg/kg (800 mg)		36.4-50 mg/kg (2000 mg)	21.8-30 mg/kg (1200 mg)
			56-75 kg	16-21.4 mg/kg (1200 mg)		37.3-50 mg/kg (2800 mg)	26.7-35.7 mg/kg (2000 mg)
			76-90 kg	17.8-21.1 mg/kg (1600 mg)		44.4-52.6 mg/kg (4000 mg)	26.7-31.6 mg/kg (2400 mg)
	Children			15-20 mg/kg (1000 mg)		50 mg/kg (2500 mg)	

Ethambutol Dosing Suggestions

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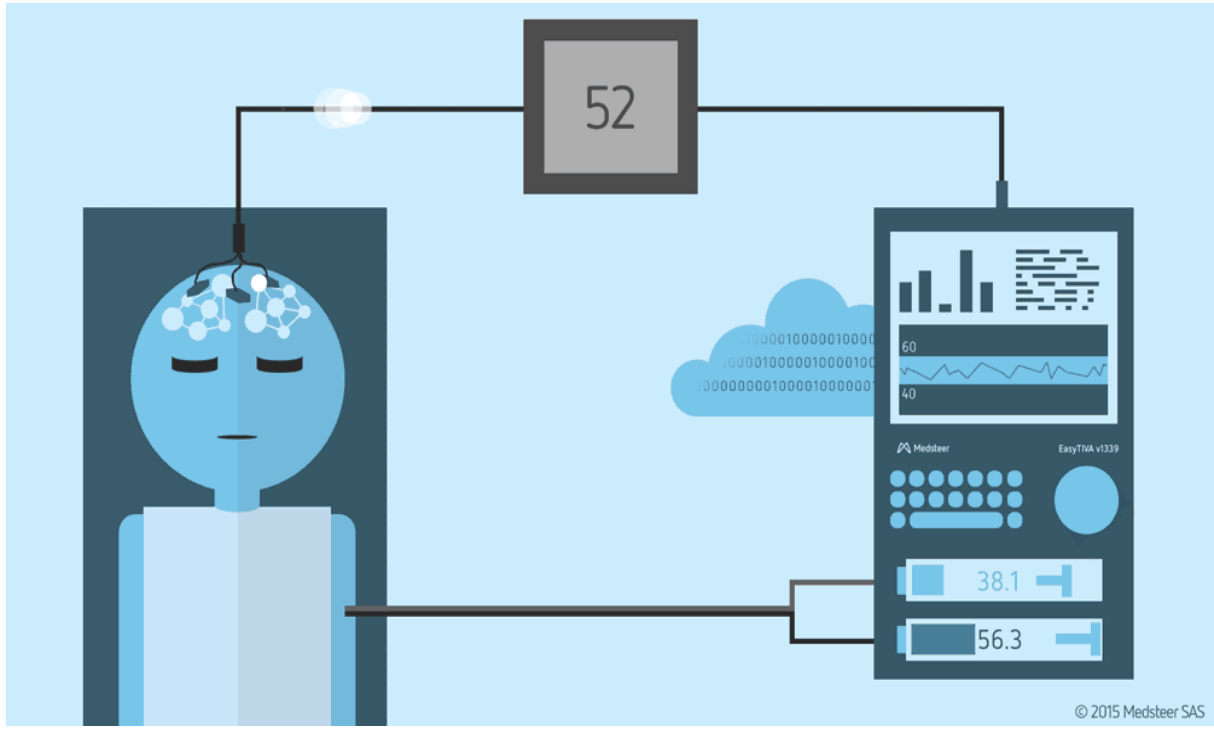

Source: Medsteer, http://medsteer.com/

Personalized medicine:
Needs deployable approaches

- Patients and providers have been slow to adopt personalized medicines, or alter established behaviors
- Solutions must work under real-world, imperfect conditions
- Translational impact will require interpretable approaches that integrate with provider and patient workflows to address high-value problems

The Limits of Personalized Medicine

A new study suggests that knowing their genetic risk of disease doesn't motivate people to change their behavior.

TIMOTHY CAULFIELD | MAR 16, 2016 | HEALTH

SCIENTIFIC AMERICAN.

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MEDICINE

A Very Personal Problem

Now personalized genetic medicine offers tests to avoid dangerous drug reactions—yet doctors are reluctant to use them

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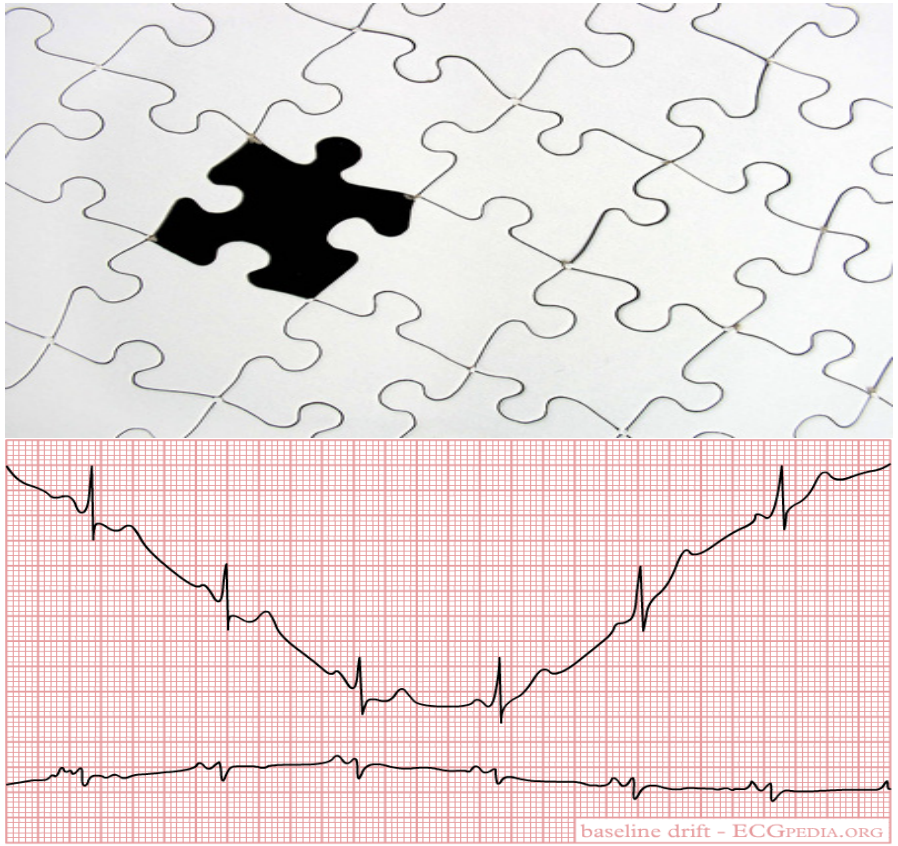
Missing Data



Artifacts

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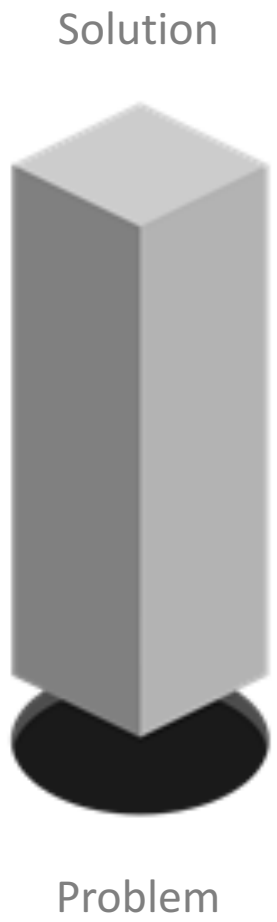

Personalized medicine:
High value problem

- Medication dosing

- Errors are responsible for ~400,000 preventable hospital deaths each year

- Over- or under- dosing can
  - Extended hospital stay,
  - Require follow-up interventions,
  - Incur additional morbidity.

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Personalized medicine: Our study goal

- A personalized medication dosing policy for a common anticoagulant, heparin

- Provide an **initial dose** based on static demographics

- Provide **subsequent doses** based on real-time, noisy data stream

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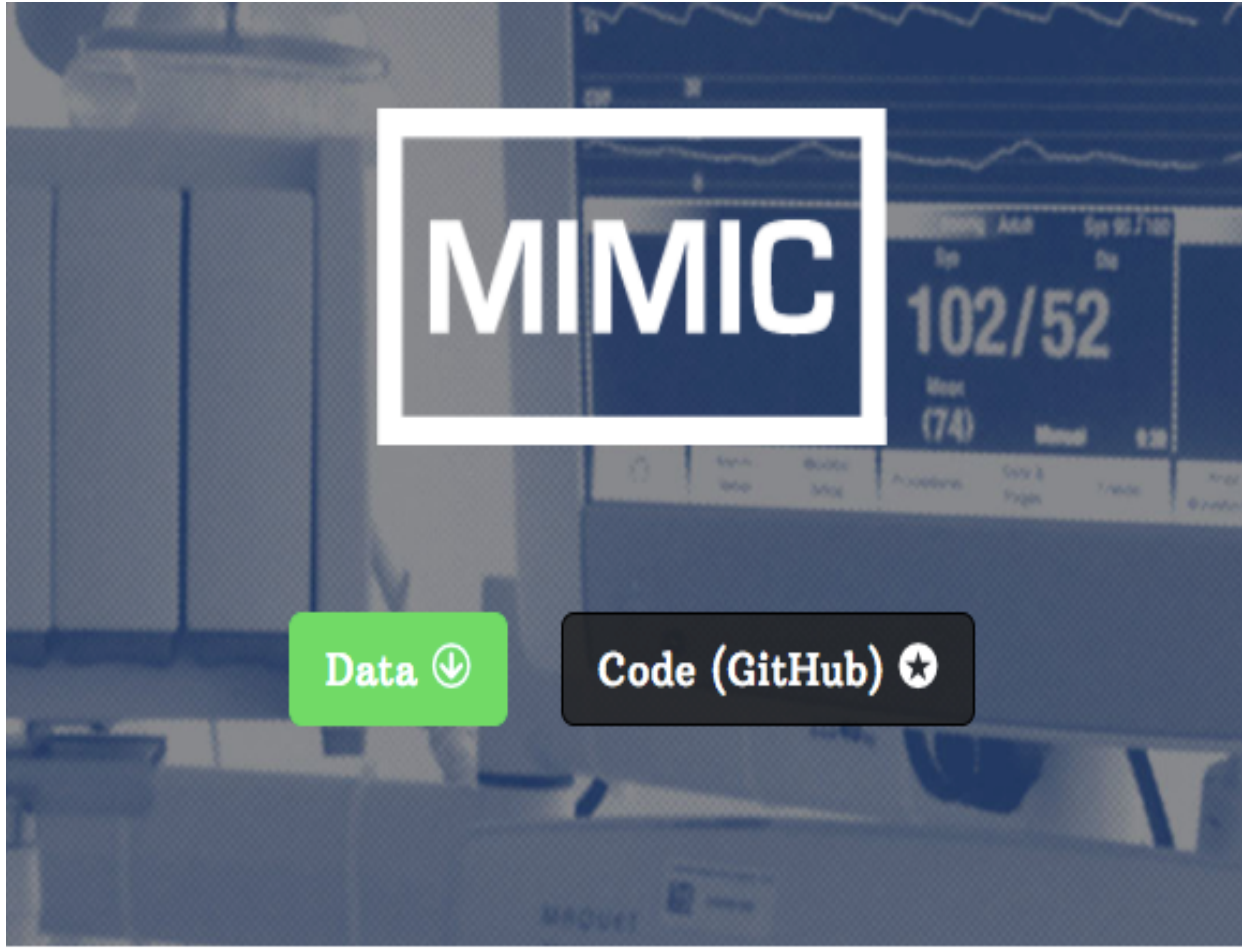
Methods

The data

- We extracted 4,470 patients from MIMIC who received intravenous UFH infusions during their ICU stay

- MIMIC is a de-identified, publicly available EMR archive of 40,000+ unique ICU admissions between 2001 - 2016.



If you use MIMIC data or code in your work, please cite the following publication:

MIMIC-III, a freely accessible critical care database. Johnson AEW, Pollard TJ, Shen L, Lehman L, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, and Mark RG. Scientific Data (2016). DOI: 10.1038/sdata.2016.35.
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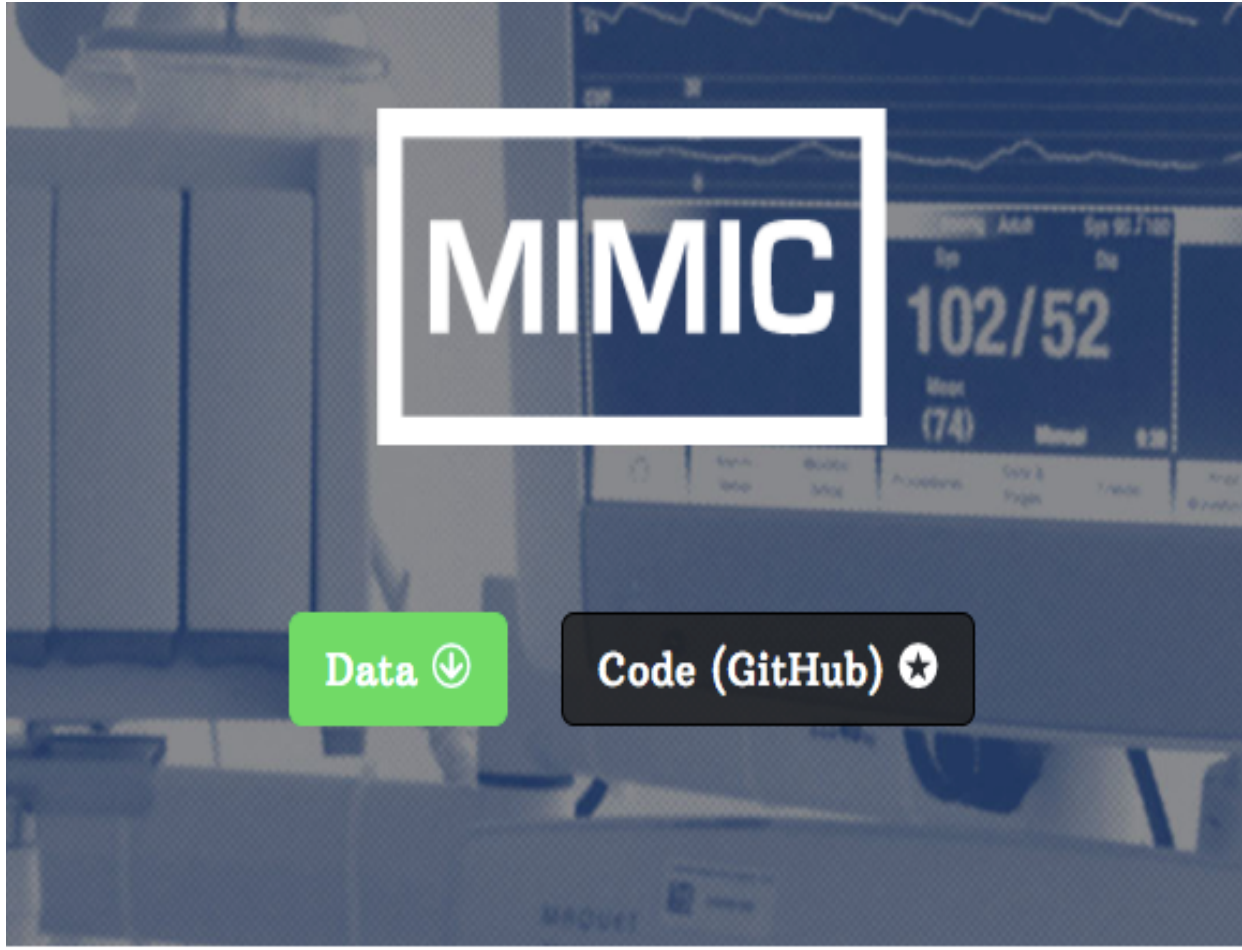

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The outcome

- Clinicians dose heparin, wait 6-12 hours, measure anticoagulation, then adjust dose as needed

- Goal is to obtain a therapeutic level of anticoagulation as quickly as possible, as indicated by aPTT

- aPTT may be categorized into one of three **states: therapeutic, sub-therapeutic, and supra-therapeutic**

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Clinical Features

- We extracted all features that are believed to confound the relationship between UFH and aPTT

Features (N= 9684)	Mean	Standard Deviation	Missing Data (%)
Static Features			
Age	68.01	14.91	0.00
Gender (%Male)	58	-	0.00
ICU Type (%Surgical)	35	-	0.00
Ethnicity (%White)	69	-	0.00
End Stage Renal Disease (%)	3	-	0.00
Pulmonary Embolism (%)	9	-	0.00
Continuously Measured Features			
Heparin Dose (units/kg)	11.79	4.11	6.88
White Blood Cell Count	12.26	6.35	6.23
Creatinine	1.58	1.48	5.18
Carbon Dioxide	24.61	4.67	5.69
Heart Rate (Mean)	84.81	17.12	0.01
Glasgow Coma Score	12.40	3.63	0.02
Hematocrit	31.50	4.65	4.27
Hemoglobin	10.63	1.66	6.45
Platelet Count	226.76	118.29	5.10
Urea	31.72	23.45	6.03
Temperature (F)	98.28	2.71	7.05
International Normalized Ratio	1.50	1.10	7.03
Prothrombin Time	15.22	3.99	0.12
Peripheral Capillary Oxygen Saturation	97.24	2.65	0.01

Clinical Features

- Static features are single measures that don't change over time

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- Age, gender, etc.

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- Static features are single measures that don't change over time
- These features are routinely collected (no missing data)

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Clinical Features

- Continuously measured features change over time
- Heparin dose is one of these features

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- Continuously measured features change over time
- Among several

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Clinical Features

- Continuously measured features change over time
- The value of these features are occasionally missing, or for some patients unmeasured

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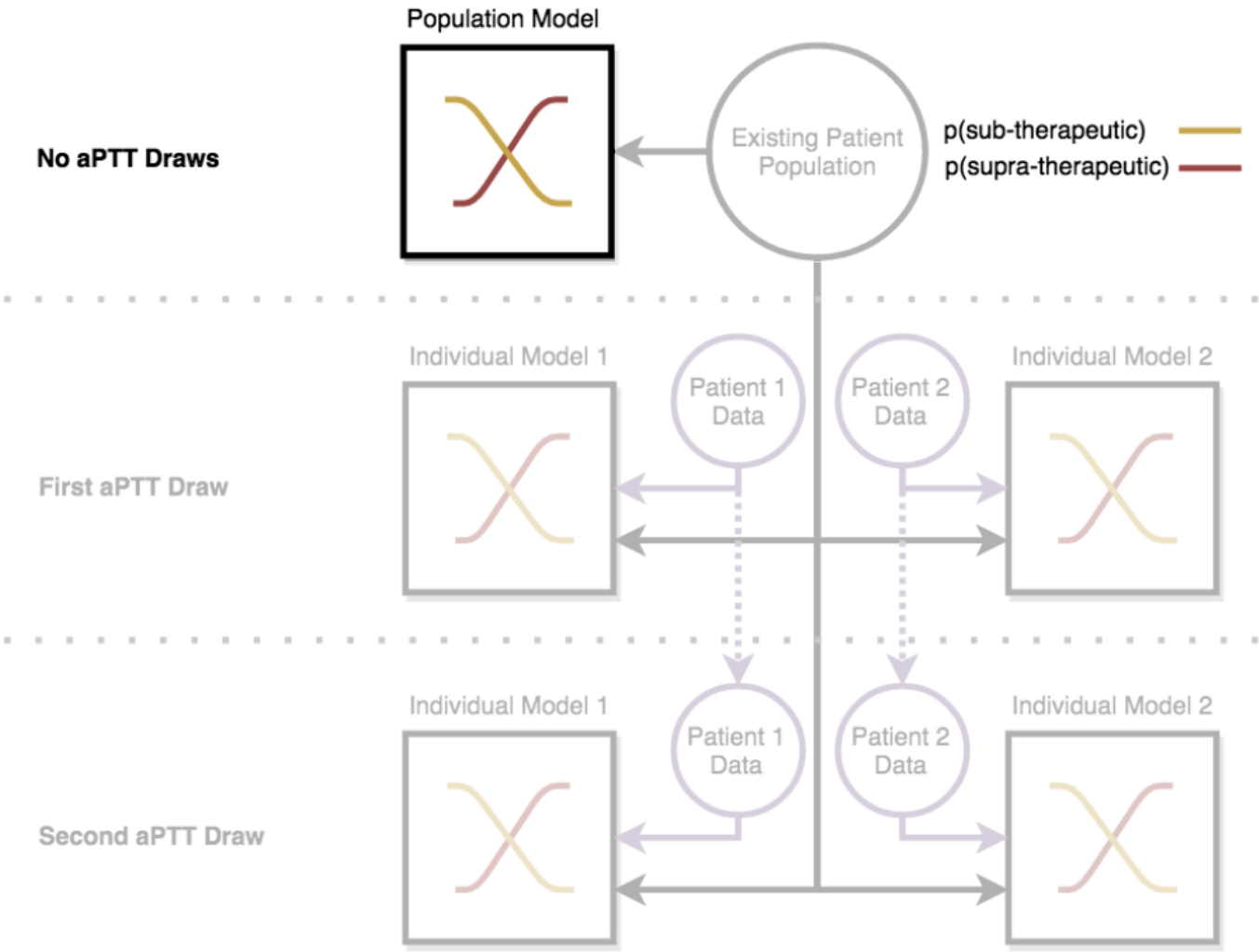
Proposed Approach

- Multinomial logistic regression (MNR) where model features and parameters are re-estimated for each patient, at each aPTT draw using a weighted combination of the data from
  - a population of existing patients, and
  - the individual patient's real-time data stream



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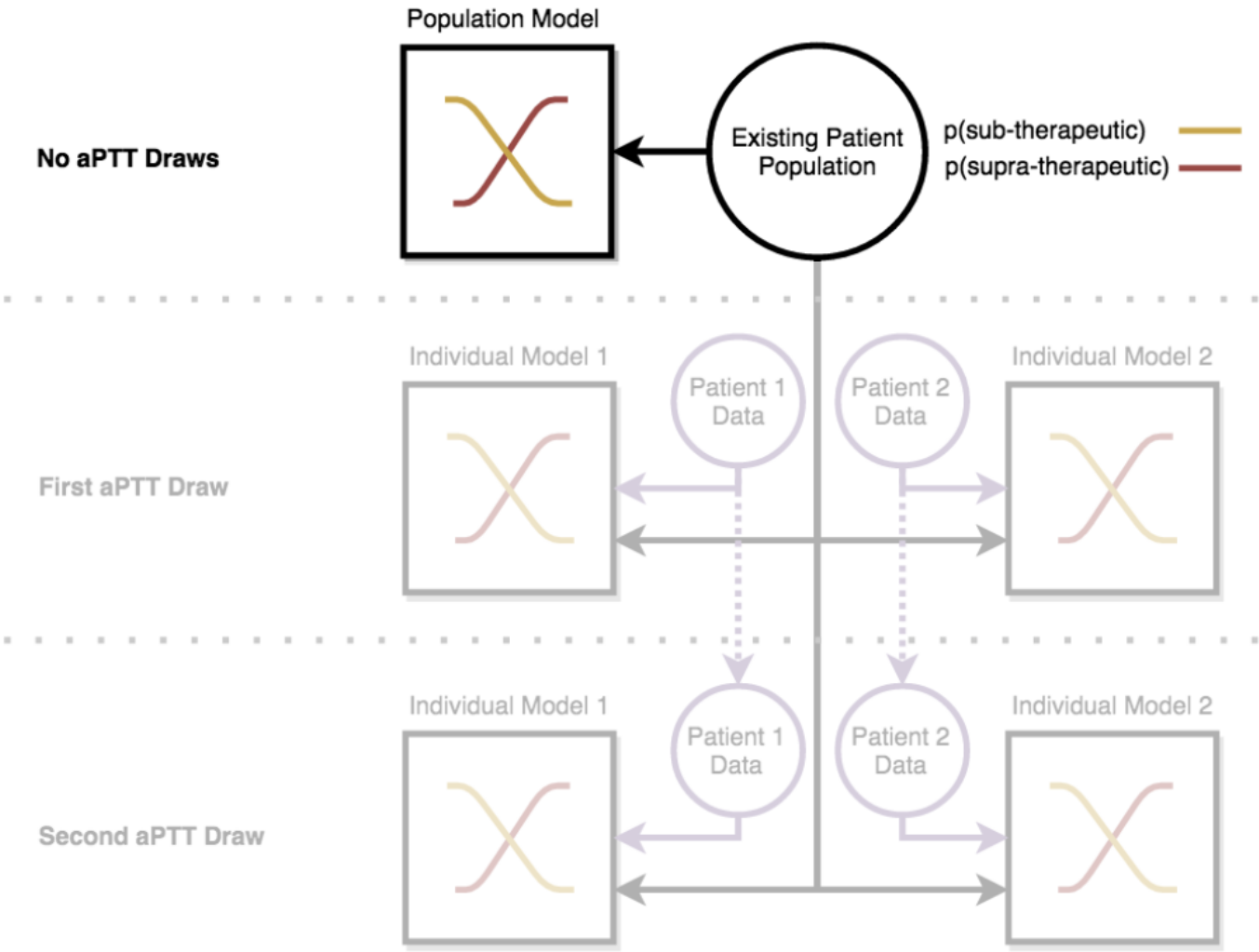

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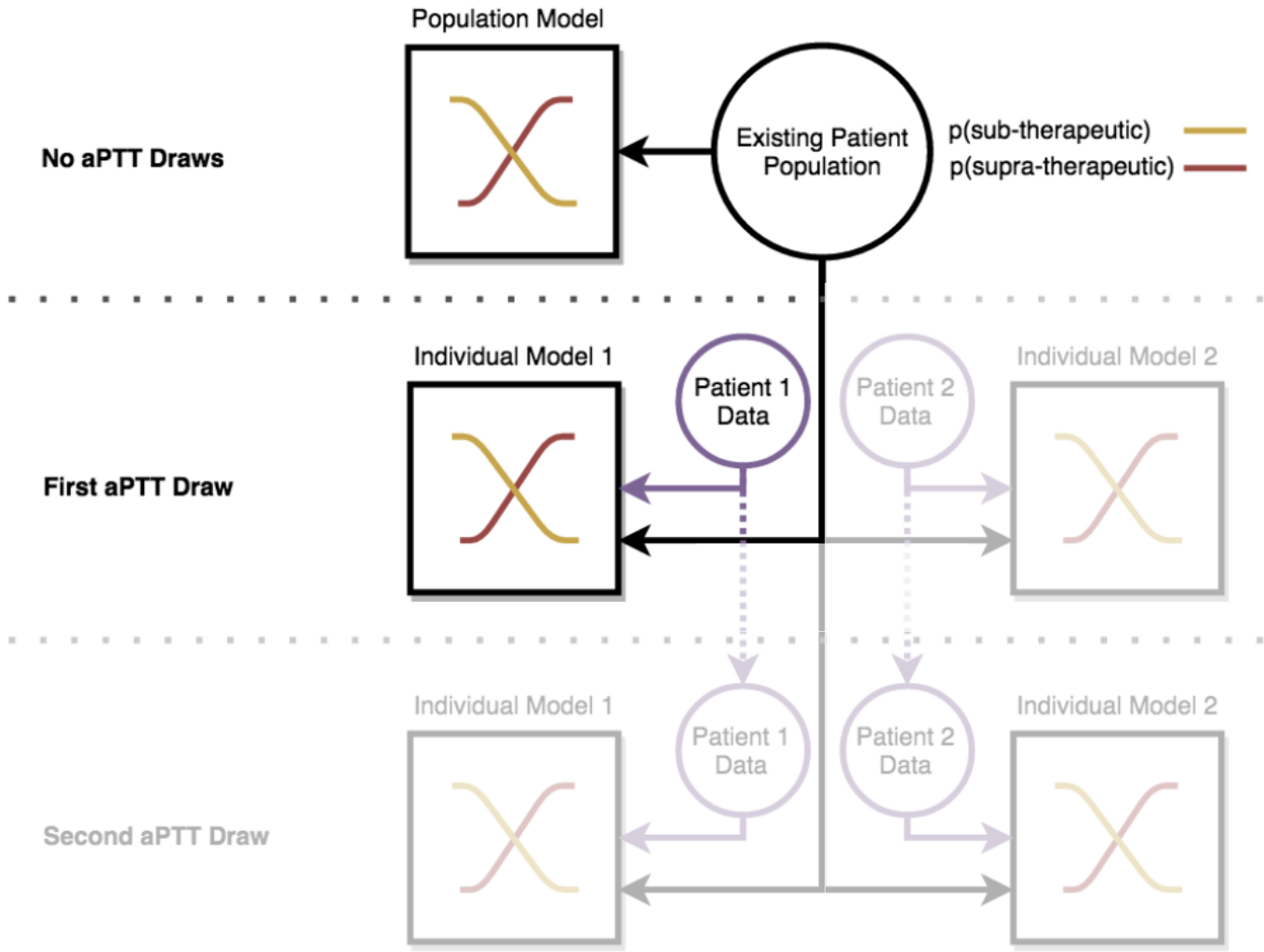

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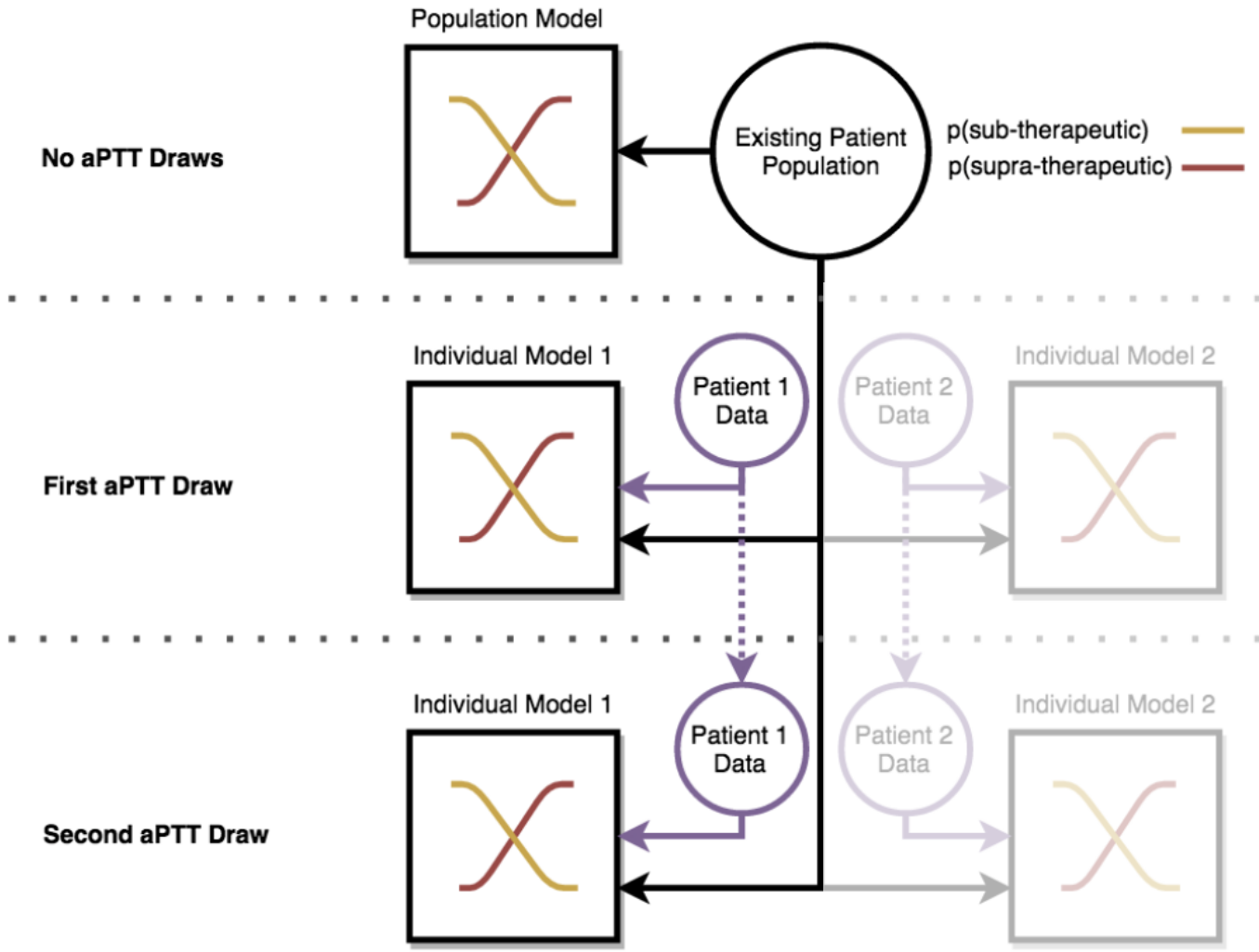

Method, formally:

State	Interval	Individual	Population
s	n	i	p

Data	Samples	Features	Outcome
X_i^n	r_i^n	c_i^n	$\mathbf{y}_i^n$
X_p^n	r_p^n	c_i^n	$\mathbf{y}_p^n$

Parameters	Data row (p)	Data row (i)
$\theta_{i,s}^n$	$\mathbf{x}_p^{(k)} y_p^{(k)}$	$\mathbf{x}_i^{(j)} y_i^{(j)}$

α γ	weighting hyper-parameters

Multinomial Logistic Regression, at each interval

$$p(y_i^n = s|\mathbf{x}_i^n, \theta_i^n) = \frac{e^{\mathbf{x_i}^\mathsf{T}\theta_{i,s}^n}}{\sum_{k=1}^{3} e^{\mathbf{x_i}^\mathsf{T}\theta_{i,k}^n}}$$

Where likelihood is a weighted combination of *p* and *i* data

$$\mathcal{L}(\theta_i^n) = \prod_{j=1}^{r_i^n} p(y_i^{(j)}|\mathbf{x}_i^{(j)}, \theta_i^n)^{\phi(n)} \times \prod_{k=1}^{r_p} p(y_p^{(k)}|\mathbf{x}_p^{(k)}, \theta_i^n)$$

Population versus individual data weight is time-dependent

$$\phi(n) = \frac{\alpha}{1 + e^{-(\gamma_0 + \gamma_1 * n)}}$$

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$$\mathcal{L}(\theta_i^n) = \prod_{j=1}^{r_i^n} p(y_i^{(j)}|\mathbf{x}_i^{(j)}, \theta_i^n)^{\phi(n)} \times \prod_{k=1}^{r_p} p(y_p^{(k)}|\mathbf{x}_p^{(k)}, \theta_i^n)$$

Population versus individual data weight is time-dependent

$$\phi(n) = \frac{\alpha}{1 + e^{-(\gamma_0 + \gamma_1 * n)}}$$

Method, formally:

P(supra) increases wrt dose; P(sub) decreases wrt dose; P(ther) is maximum when:

$$\frac{1}{1+e^{-(\beta_{i,o}^n d_i^n + \kappa_{i,o}^n)}} = \frac{1}{1+e^{-(\beta_{i,u}^n d_i^n + \kappa_{i,u}^n)}}, \quad find\ d_i^n$$

Yielding: $$d_i^n = \frac{\kappa_{i,u}^n - \kappa_{i,o}^n}{\beta_{i,o}^n - \beta_{i,u}^n}$$

Where:

	Heparin parameter	Non-heparin feature impact
over	$\beta_{i,o}^n$	$\kappa_{i,o}^n$
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Non-personalized baseline methods

- **Baseline 1: Multinomial logistic regression using static features**, without personalization
- **Baseline 2: Multinomial logistic regression using all features**, without personalization and excluding subjects with missing data (23.6%) of all patients
- **Baseline 3: Multilayer neural network.** Densely connected, feed-forward, two hidden layers, softmax output, ReLU activation, Xavier initialization, scaled conjugate gradient descent optimization, grid search topology selection.
- **Baseline 4: Reinforcement learning via deterministic policy network**. We defined the state, action, and rewards as follows: (1) State: aPTT and laboratory measures (2) Actions: maintain dose, increase dose, decrease dose. (4) Rewards: proportional to the aPTT error.

Features (N= 9684)	Mean	Standard Deviation	Missing Data (%)
Static Features			
Age	68.01	14.91	0.00
Gender (%Male)	58	-	0.00
ICU Type (%Surgical)	35	-	0.00
Ethnicity (%White)	69	-	0.00
End Stage Renal Disease (%)	3	-	0.00
Pulmonary Embolism (%)	9	-	0.00
Continuously Measured Features			
Heparin Dose (units/kg)	11.79	4.11	6.88
White Blood Cell Count	12.26	6.35	6.23
Creatinine	1.58	1.48	5.18
Carbon Dioxide	24.61	4.67	5.69
Heart Rate (Mean)	84.81	17.12	0.01
Glasgow Coma Score	12.40	3.63	0.02
Hematocrit	31.50	4.65	4.27
Hemoglobin	10.63	1.66	6.45
Platelet Count	226.76	118.29	5.10
Urea	31.72	23.45	6.03
Temperature (F)	98.28	2.71	7.05
International Normalized Ratio	1.50	1.10	7.03
Prothrombin Time	15.22	3.99	0.12
Peripheral Capillary Oxygen Saturation	97.24	2.65	0.01

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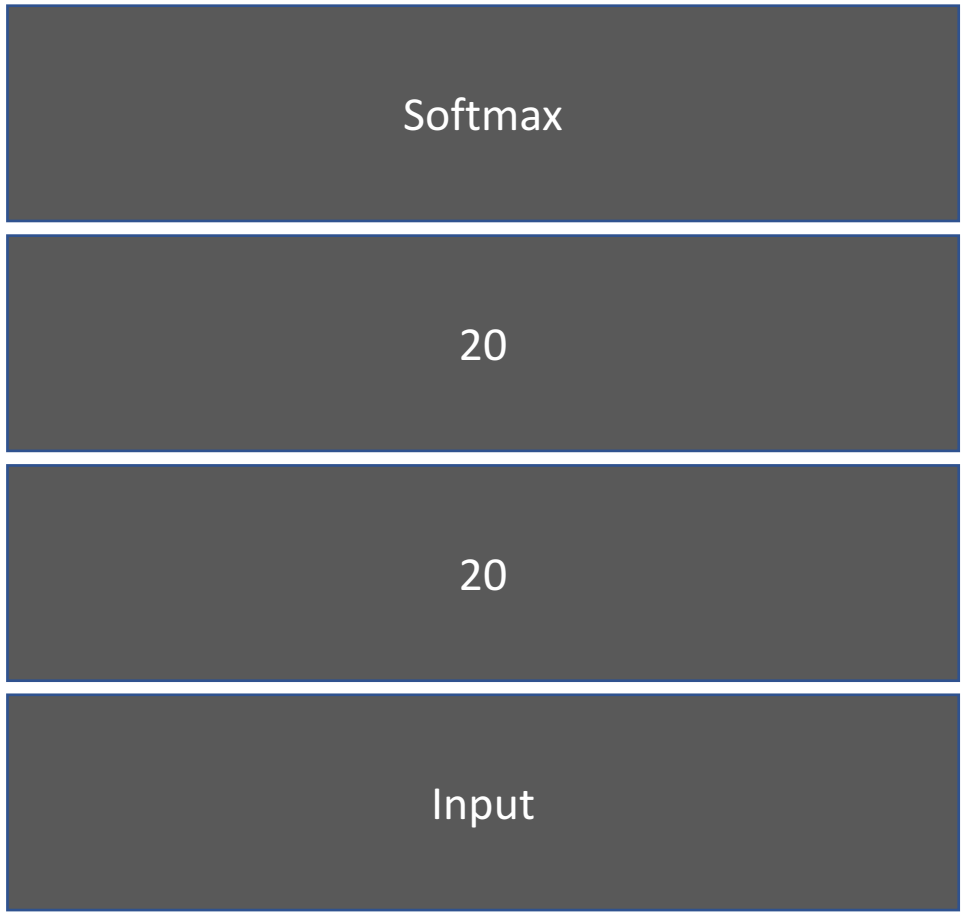

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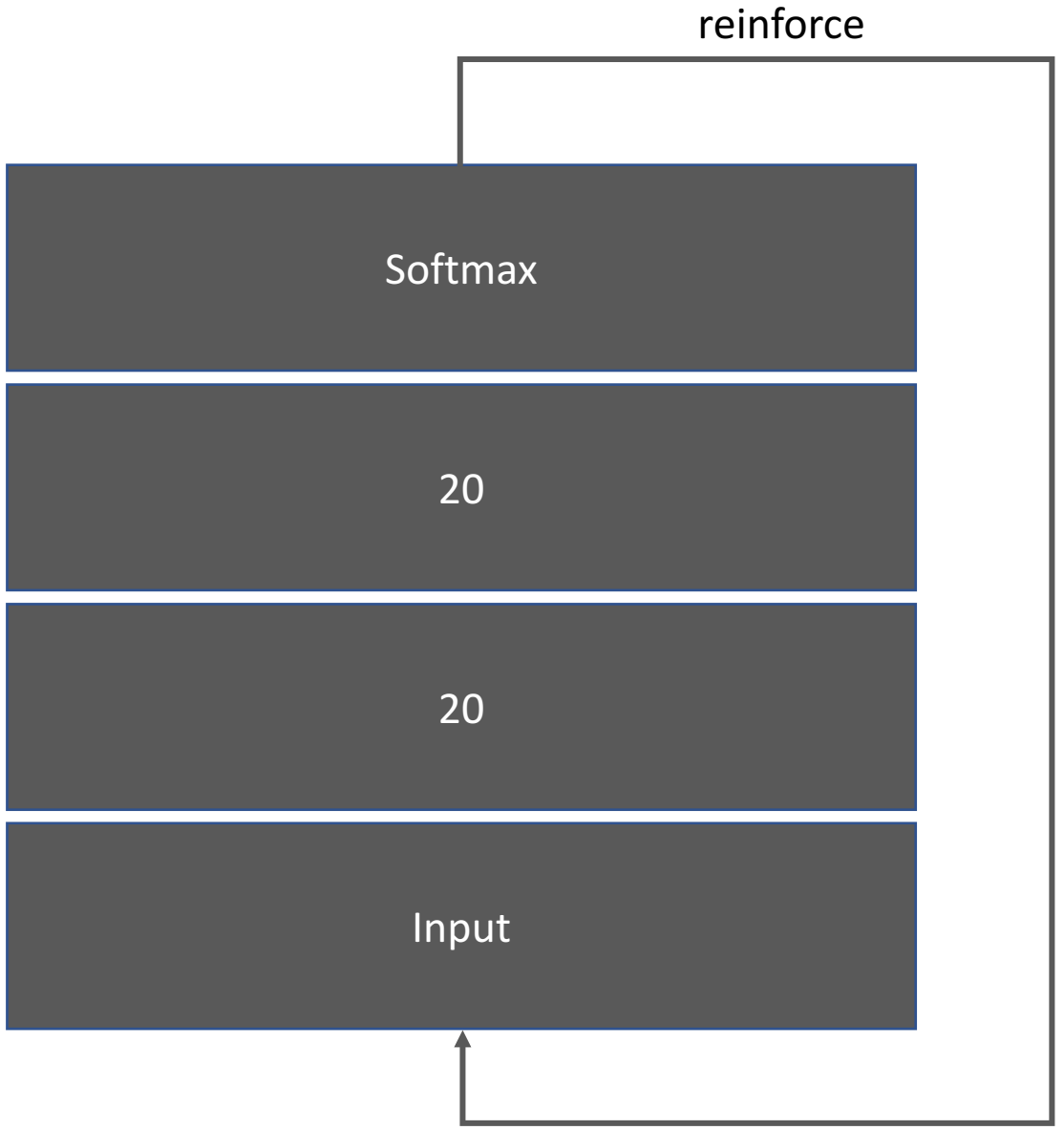
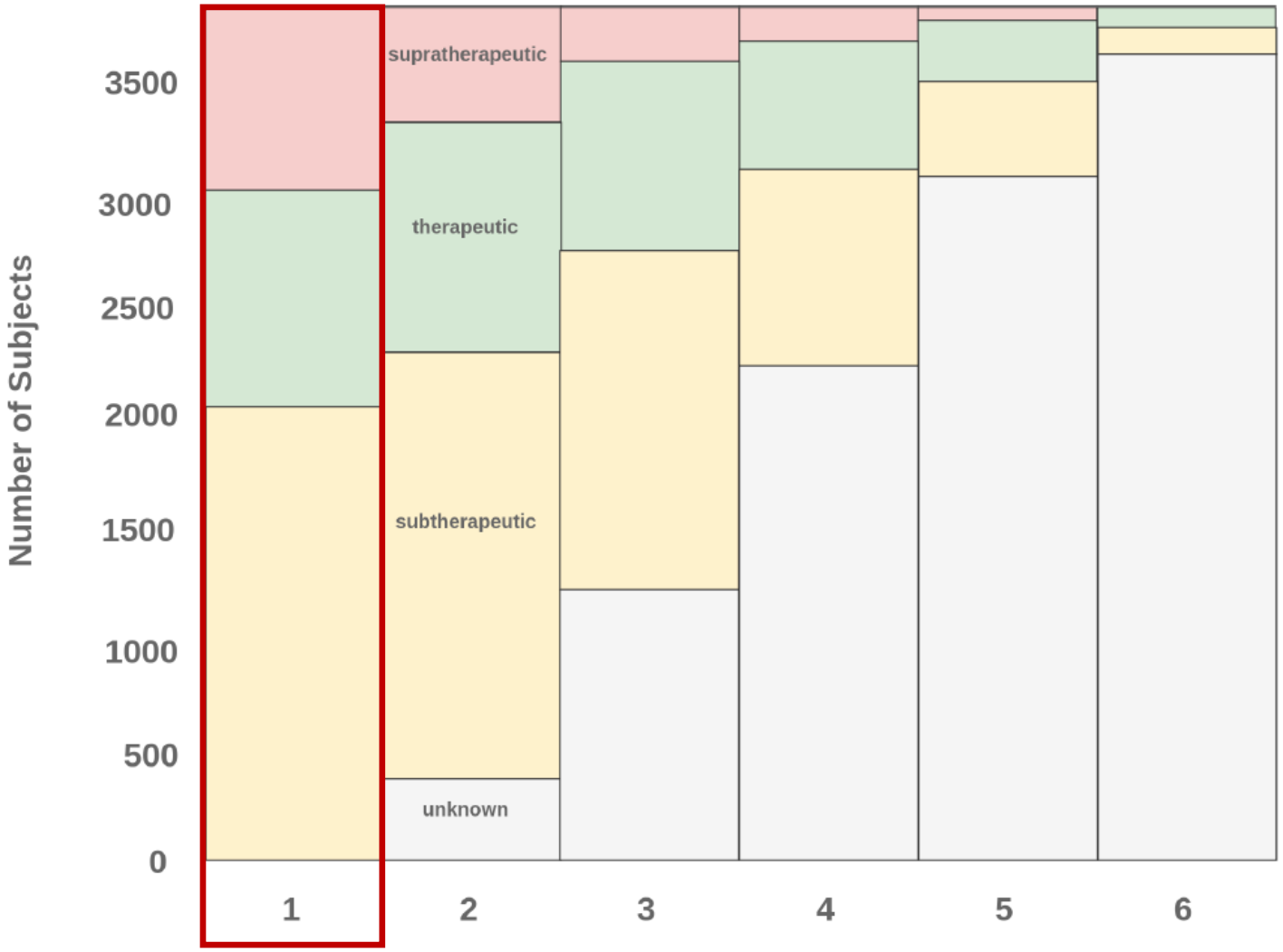


Results

Data characteristics

- UFH misdoing is consistently error-prone even after multiple aPTT draws (and consequent opportunities for dose adjustment).
- 80% of our sample stopped receiving aPTT draws after their fifth adjustment
- 5% of the 3,883 patient with recorded aPTT values had a sixth dose adjustment.



2/3 of patients mis-dosed

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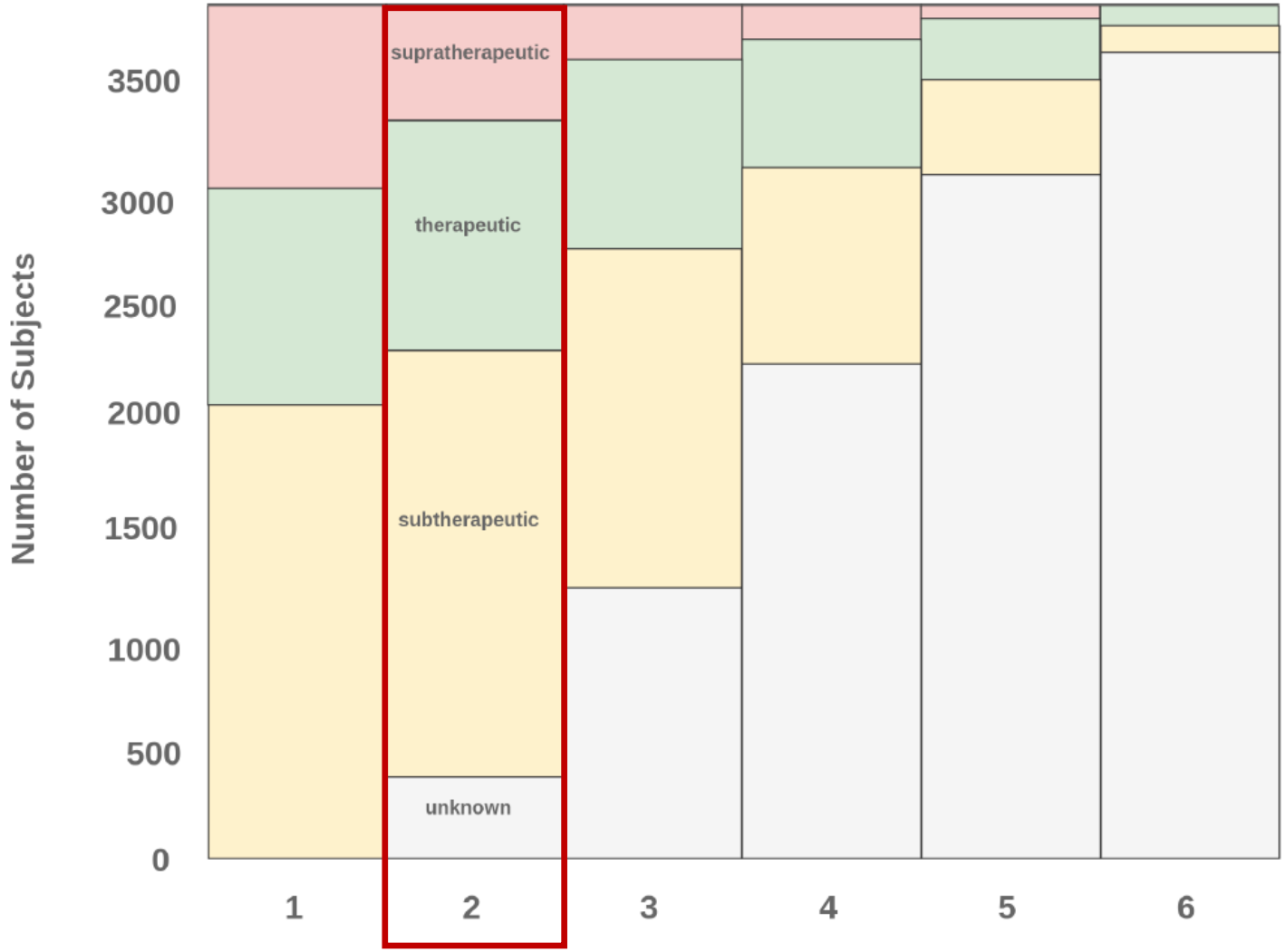

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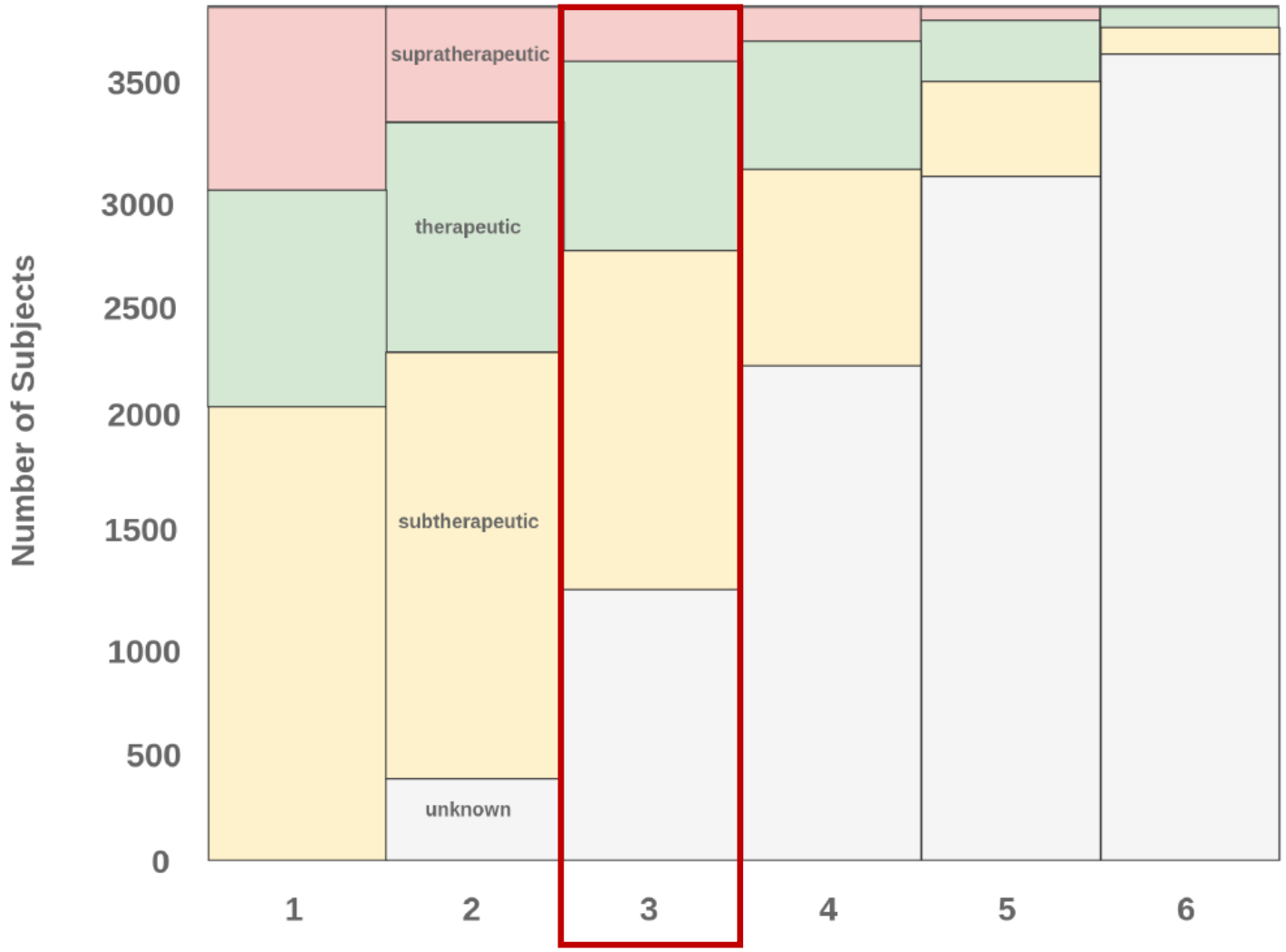

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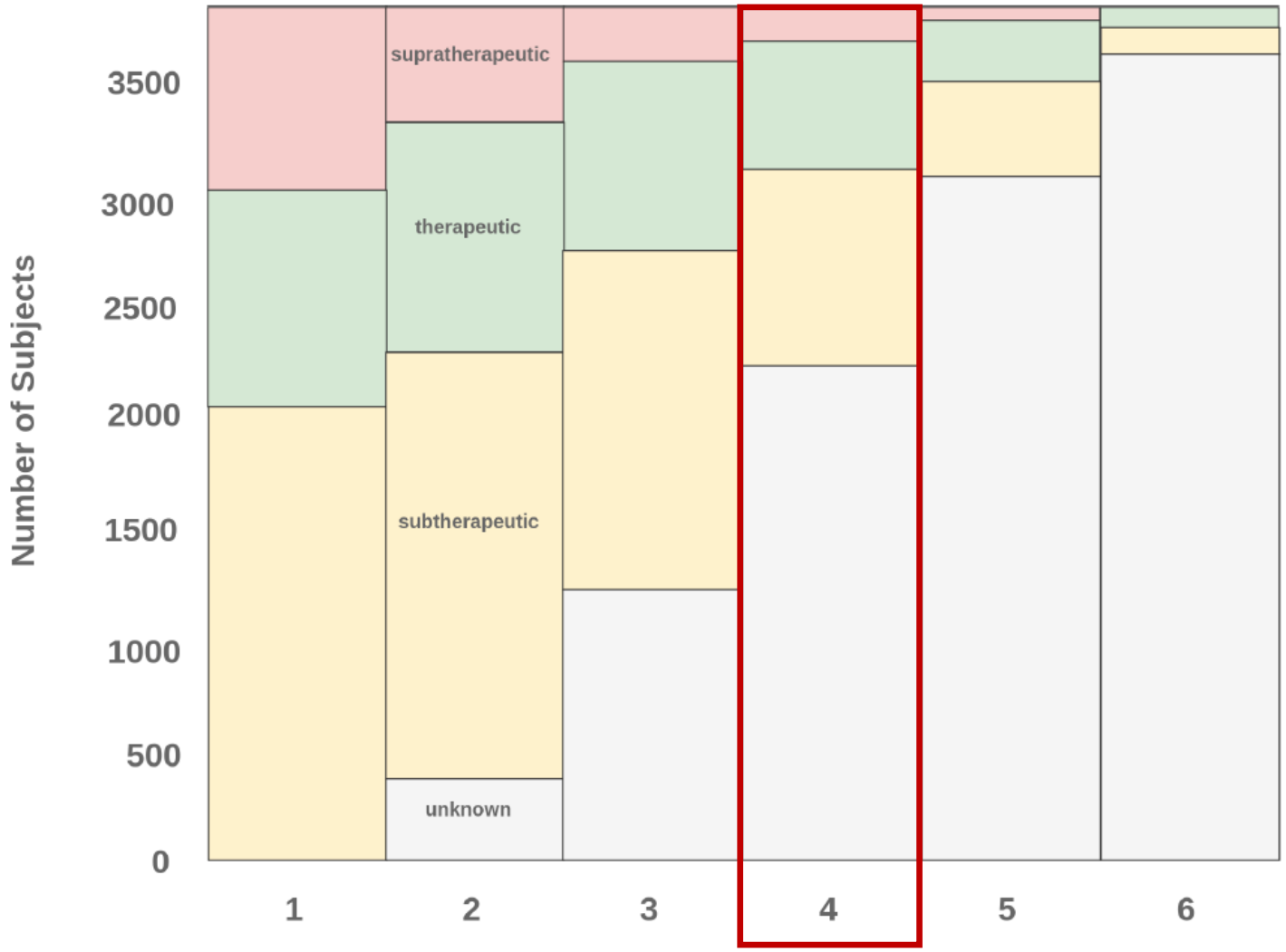

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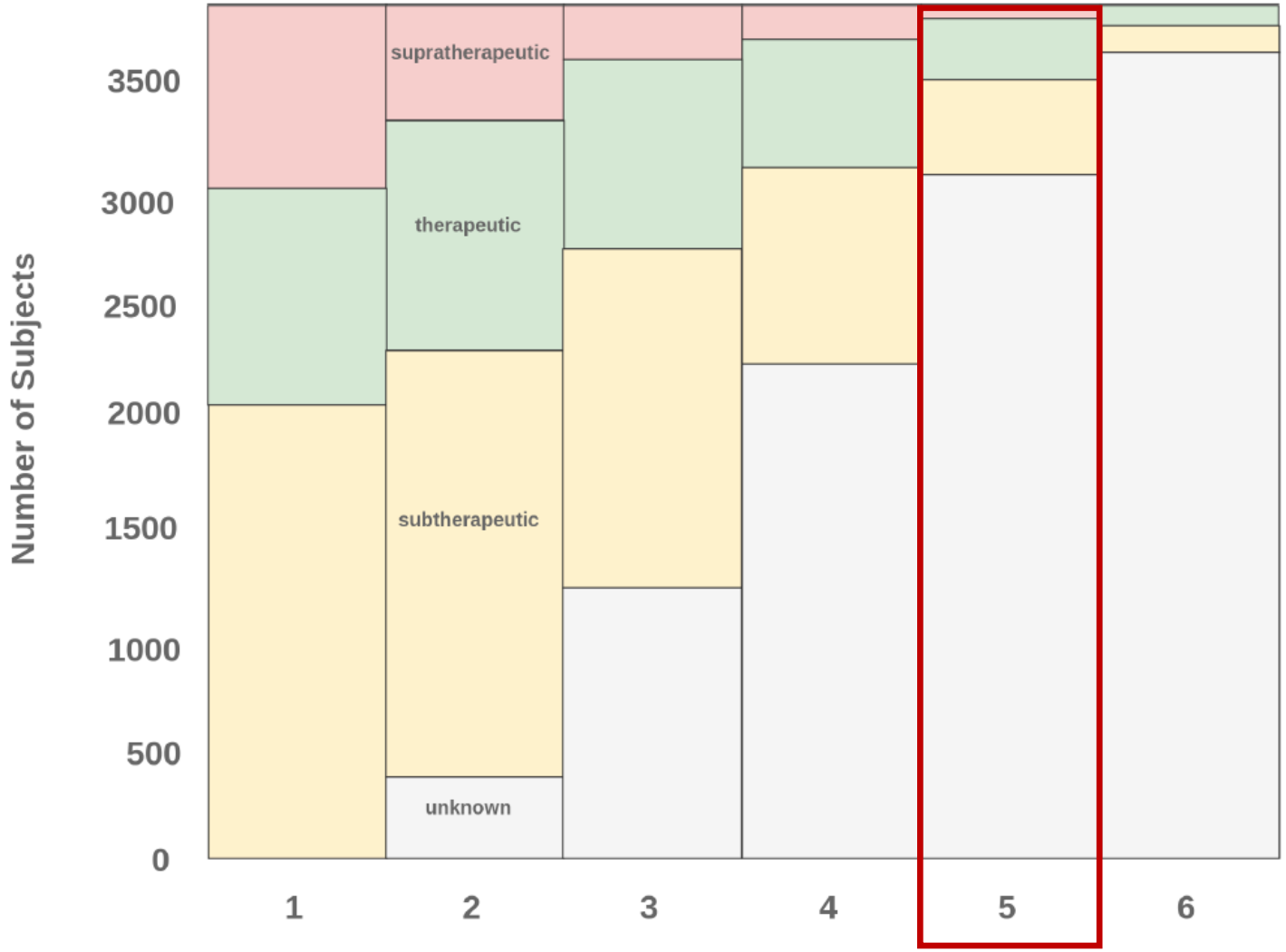

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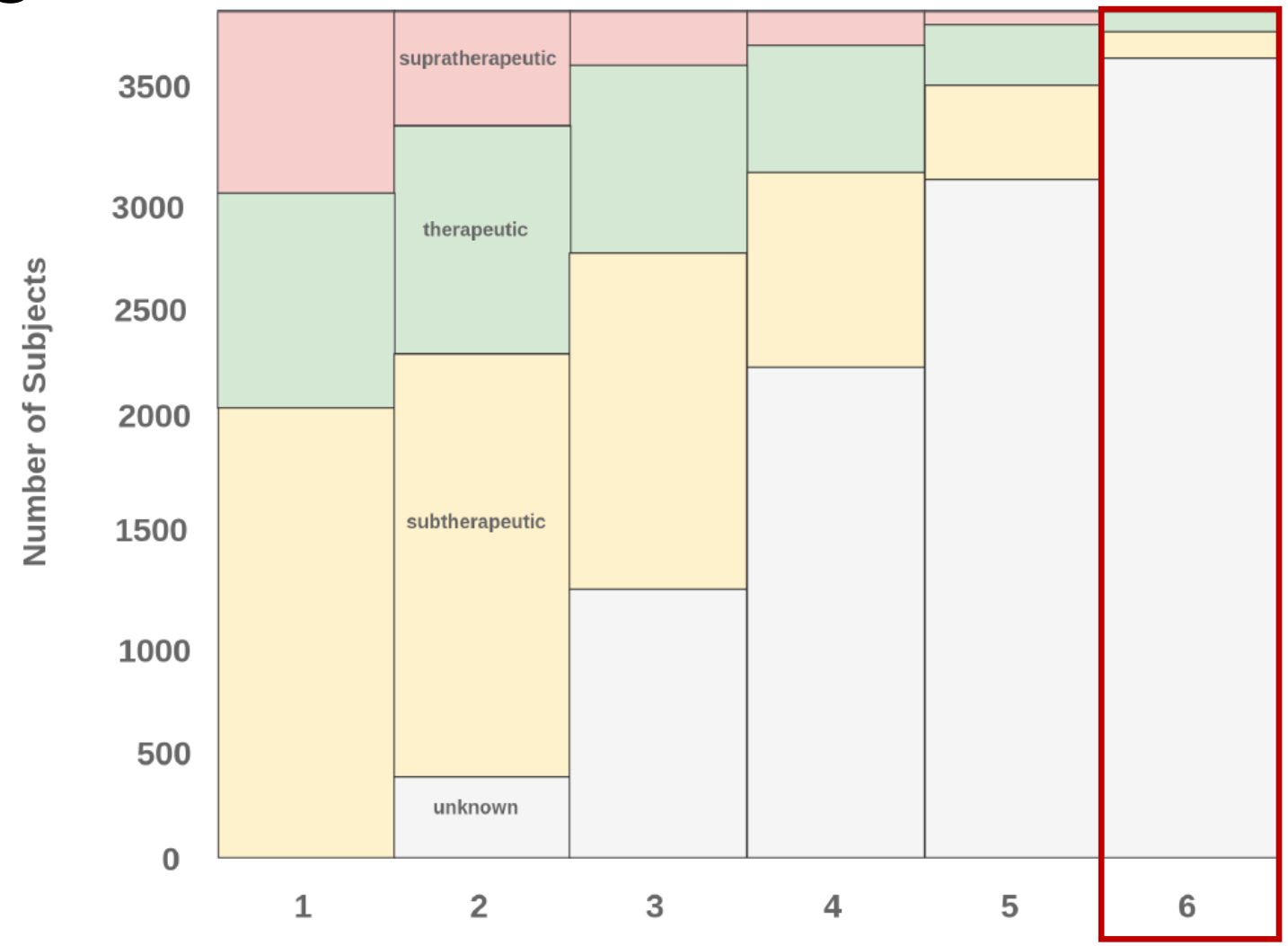

Overall performance of personalized approach

- Highest overall accuracy (60%)
- Highest overall VUS (0.46), a 0.02 improvement over the RL approach
- 7.3% more likely to detect supra-therapeutic doses than the population model that didn’t exclude patients

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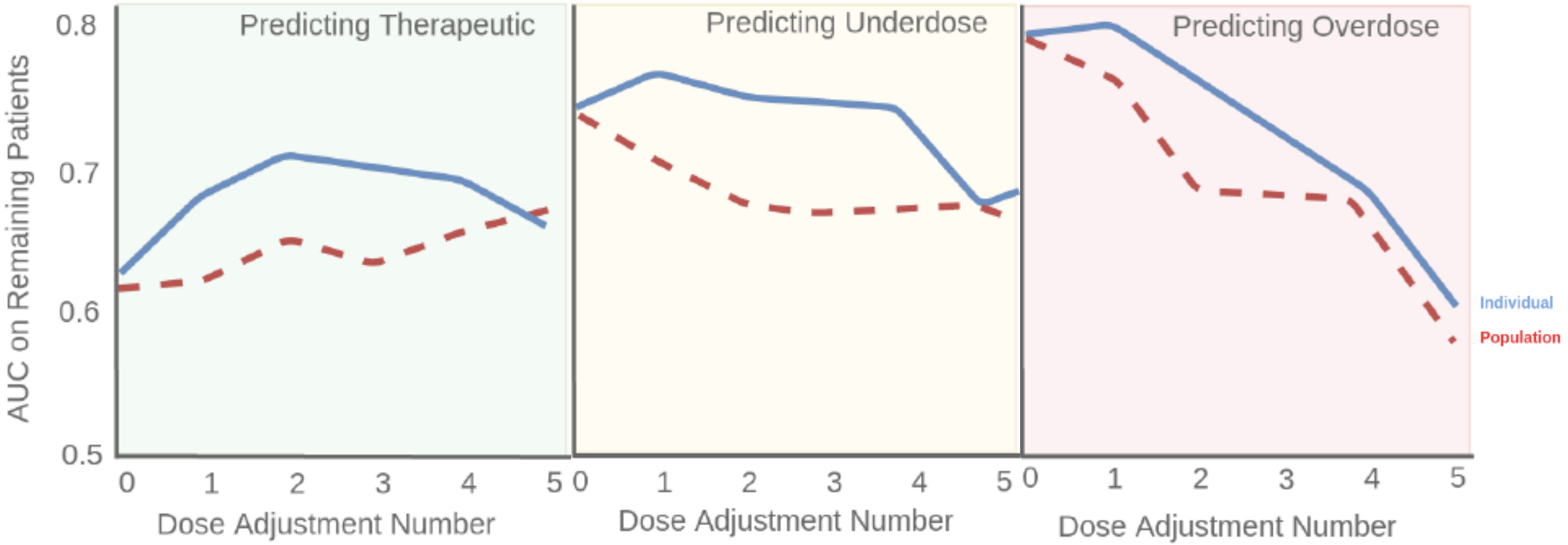
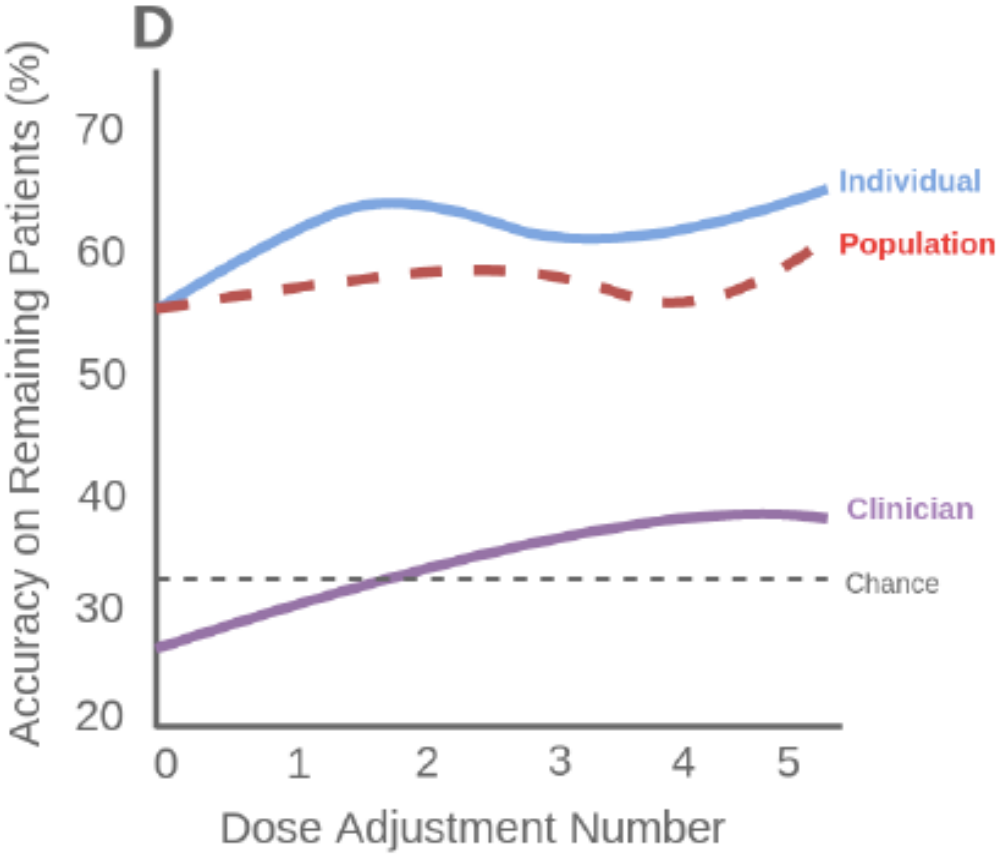
Temporal performance of personalized approach

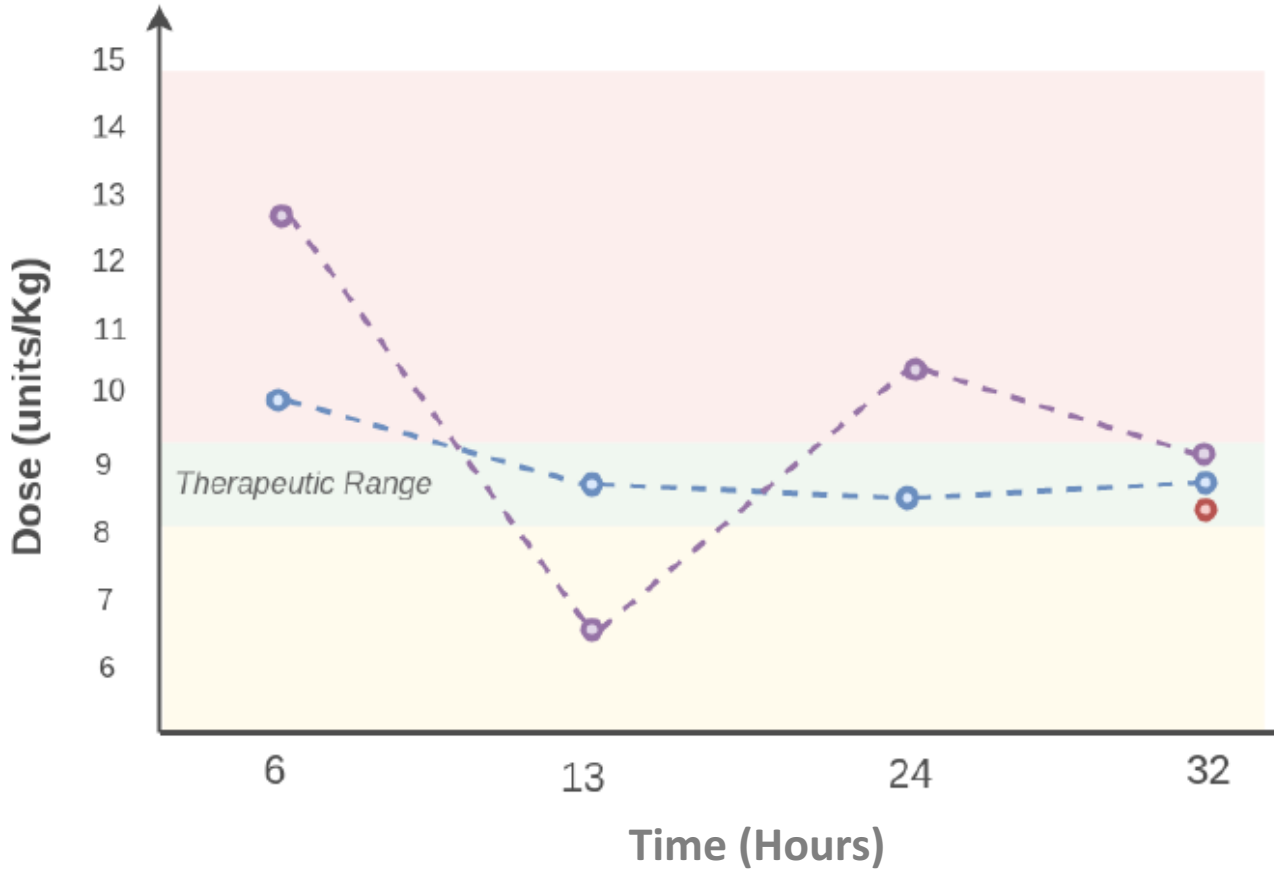
Our approach consistently outperformed the best comparable baseline across time



Temporal performance of personalized approach

Our approach might reduce errors, and bring patients to therapeutic aPTT, faster.





Conclusion and Future Direction

- Heparin dosing guidelines are based on population models
- Patient-specific modeling has the potential to improve performance
- We are working to deploy this algorithm within the BIDMC for real-world impact

Questions and Collaborations:

http://ghassemi.xyz