HARVARD
School of Engineering
and Applied Sciences

Reinforcement Learning for Healthcare

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Harvard University

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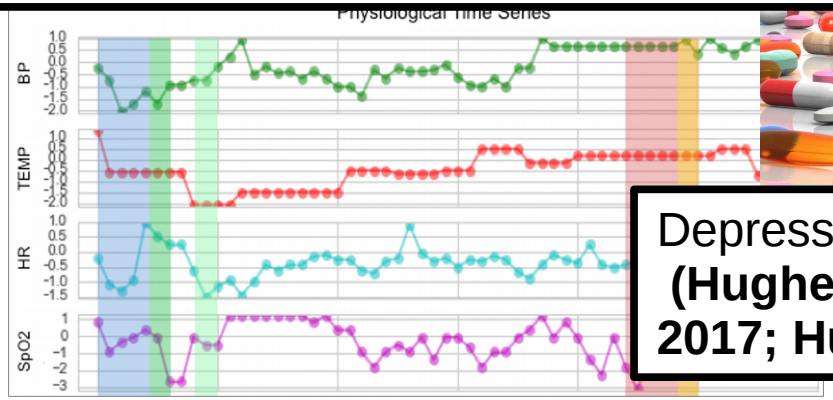
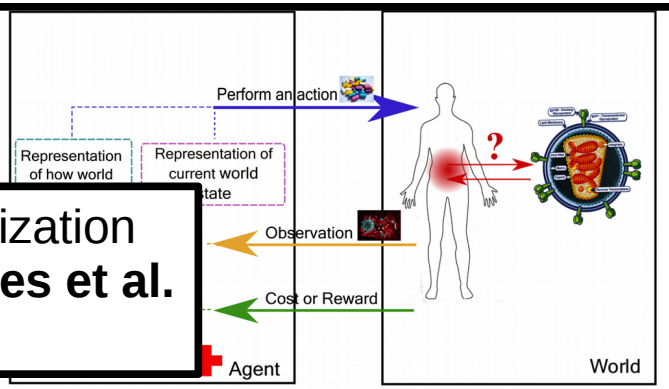
Our Lab: ML Towards Effective, Interpretable Health Interventions

Predicting and Optimizing Interventions in ICU (**Wu et al. 2015; Ghassemi et al. 2017; Peng 2018; Raghu 2018; Gottesman 2018**)



HIV Management Optimization **(Parbhoo et al., 2017, Parbhoo et al. 2018)**



Depression Treatment Optimization **(Hughes et al., 2016; Hughes et al. 2017; Hughes et al. 2018)**

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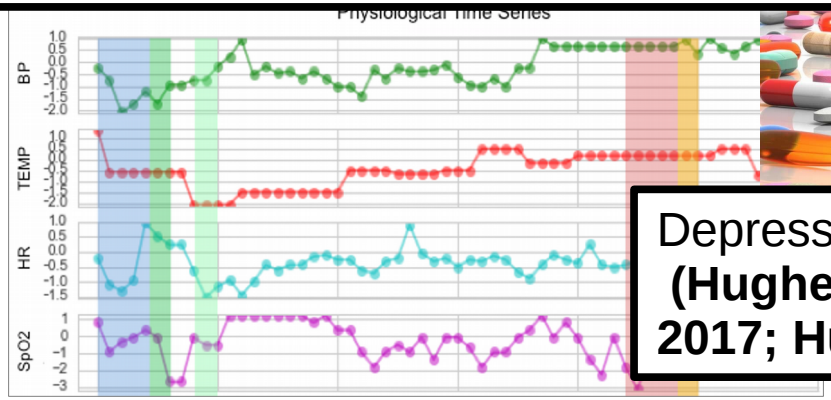

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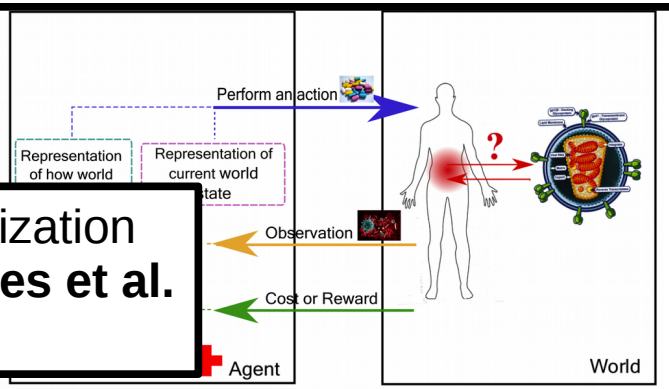
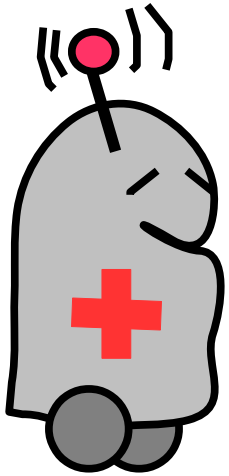


Depression Treatment Optimization **(Hughes et al., 2016; Hughes et al. 2017; Hughes et al. 2018)**

Today: How can reinforcement learning help solve problems in healthcare?

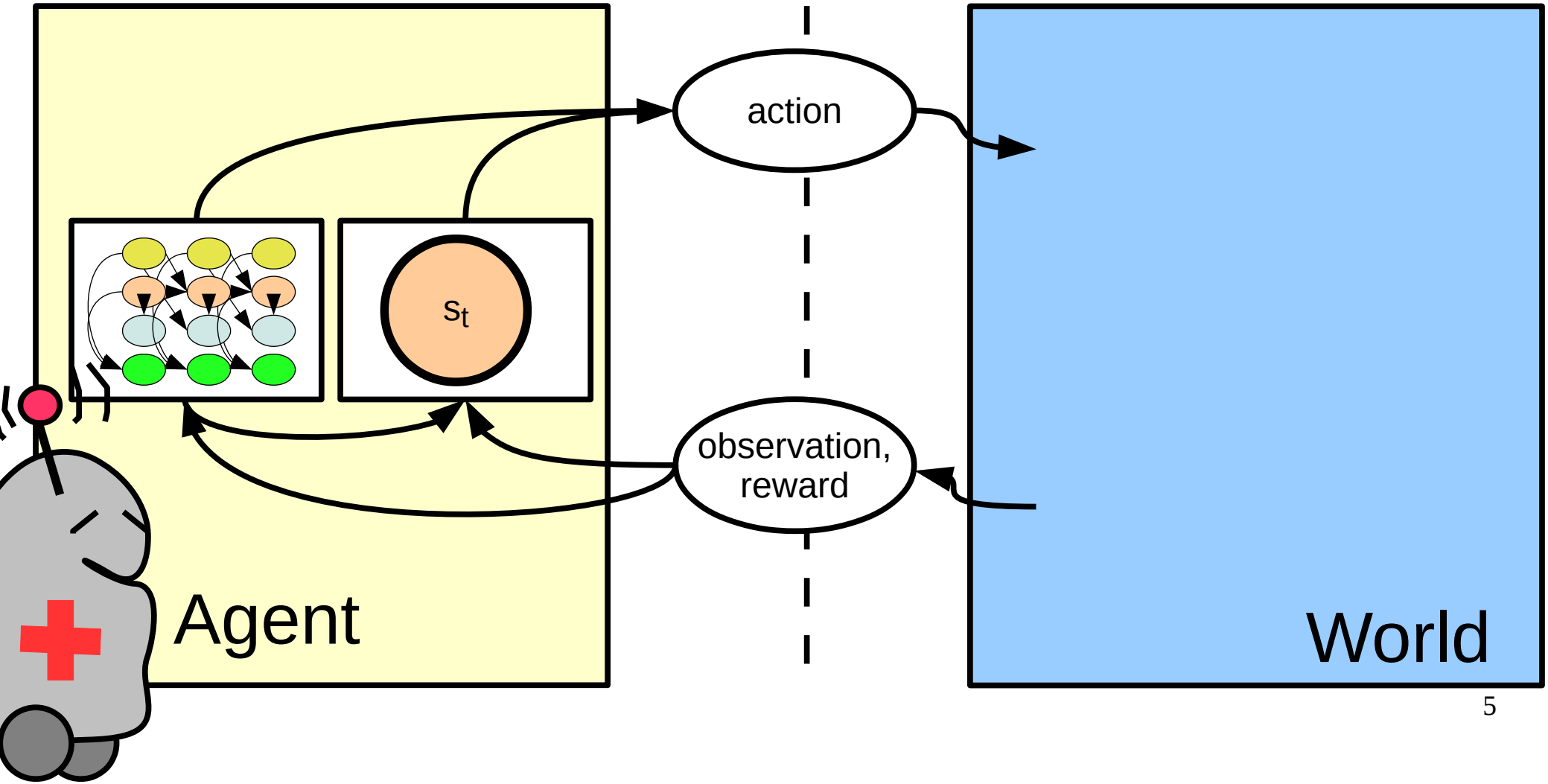
How reinforcement learning can help solve problems in healthcare

- Some health problems are effectively “one-off” (Does this image have a tumor? Will this depression med work?)
- Others involve reasoning about a series of decisions
  - Choosing meds for HIV (prevent drug resistance)
  - Choosing ICU interventions (short vs. longterm effects)



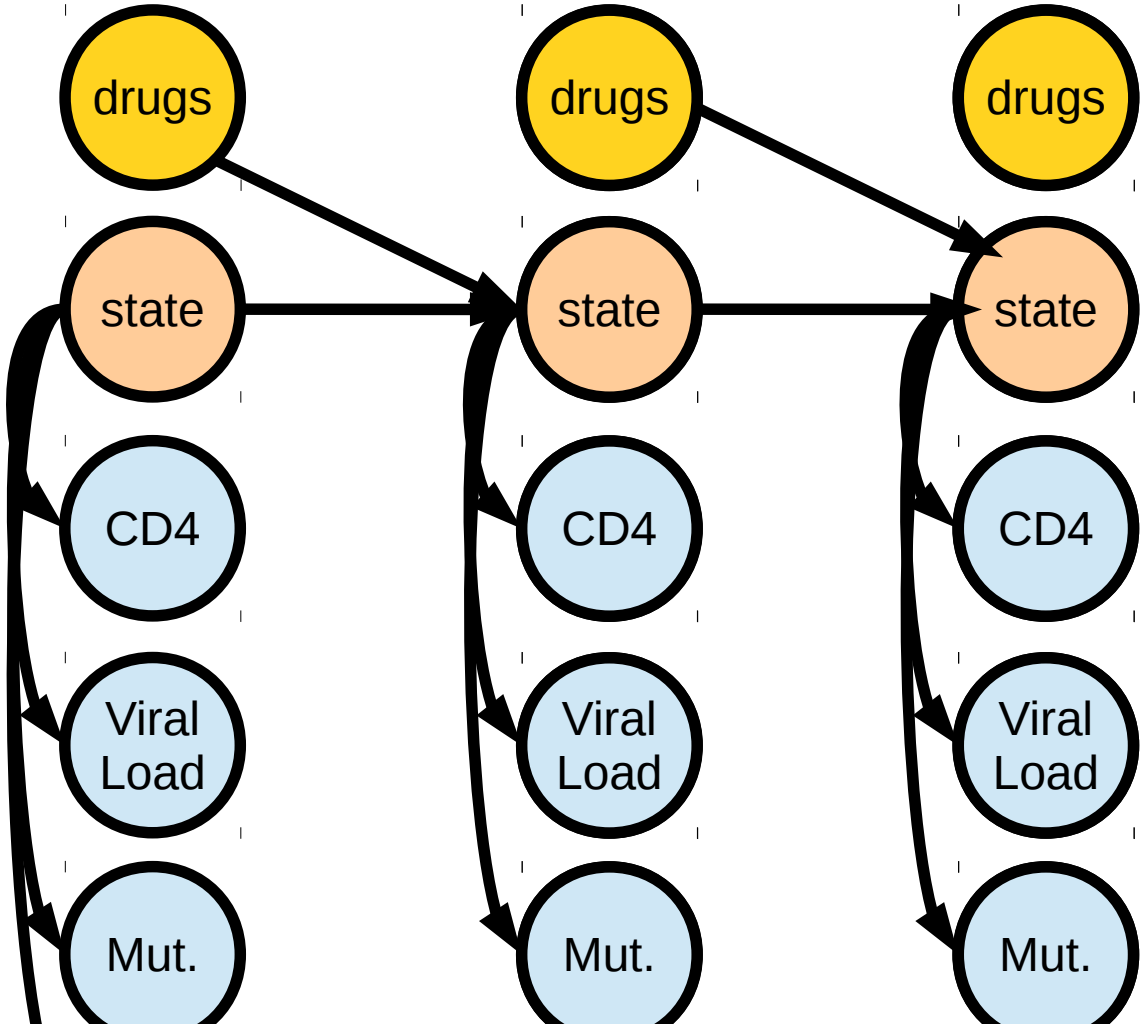
RL can help us think about sequential decisions!

Reinforcement Learning: Formalizing the Problem



Model-based RL for HIV Management

Solves the long-term problem (e.g. Ernst 2005; Parbhoo 2014; Marivate 2015), often in simulation/simplified settings.



Rewards:

If $V_t > 40$:

$r_t = -.7 \log V_t + .6 \log T_t - .2|M_t|$

Else:

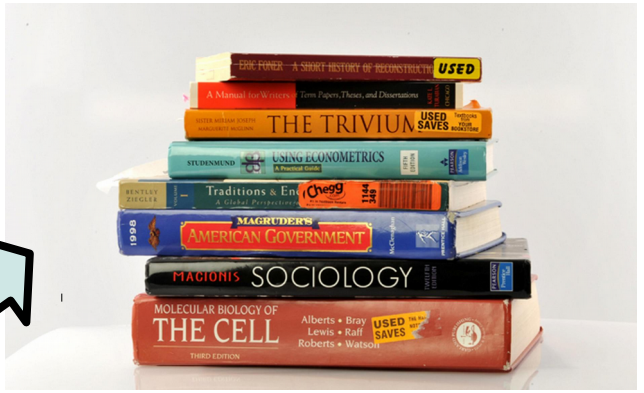
$r_t = 5 + .6 \log T_t - .2|M_t|$

Does it work??

Several works on model-based optimization of HIV treatment (e.g. Ernst 2005; Parbhoo 2014; Marivate 2015), none state of the art...

Drawback of model-based approaches

?



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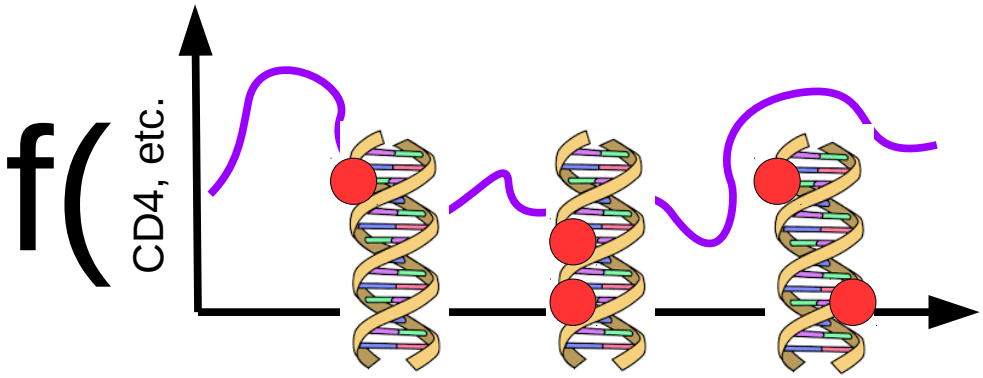
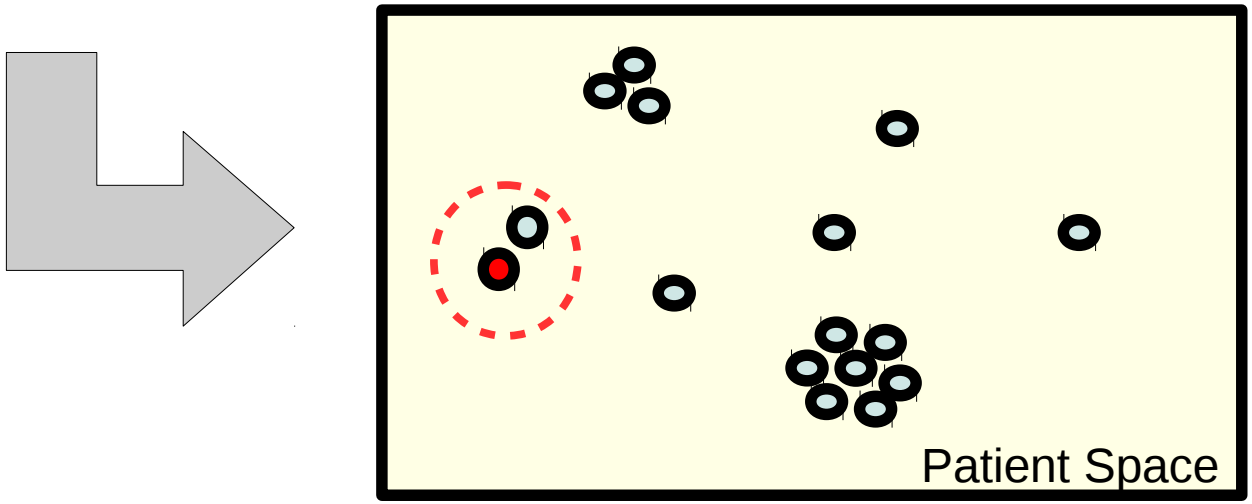
Alternative: Kernel-based Predictions

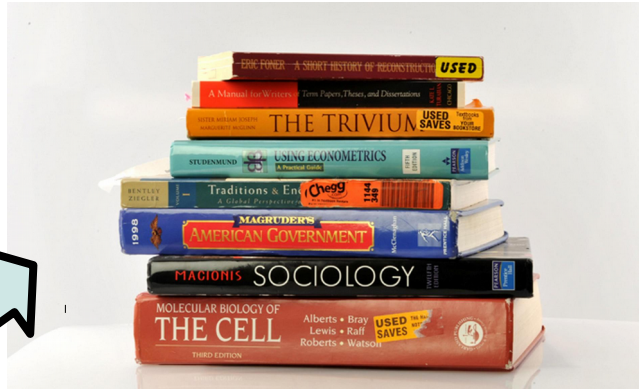
Use the full patient history to predict immediate outcomes (e.g. Bogojeska 2012), but often ignore long term effects.





Drawback of neighbor-based approaches

?



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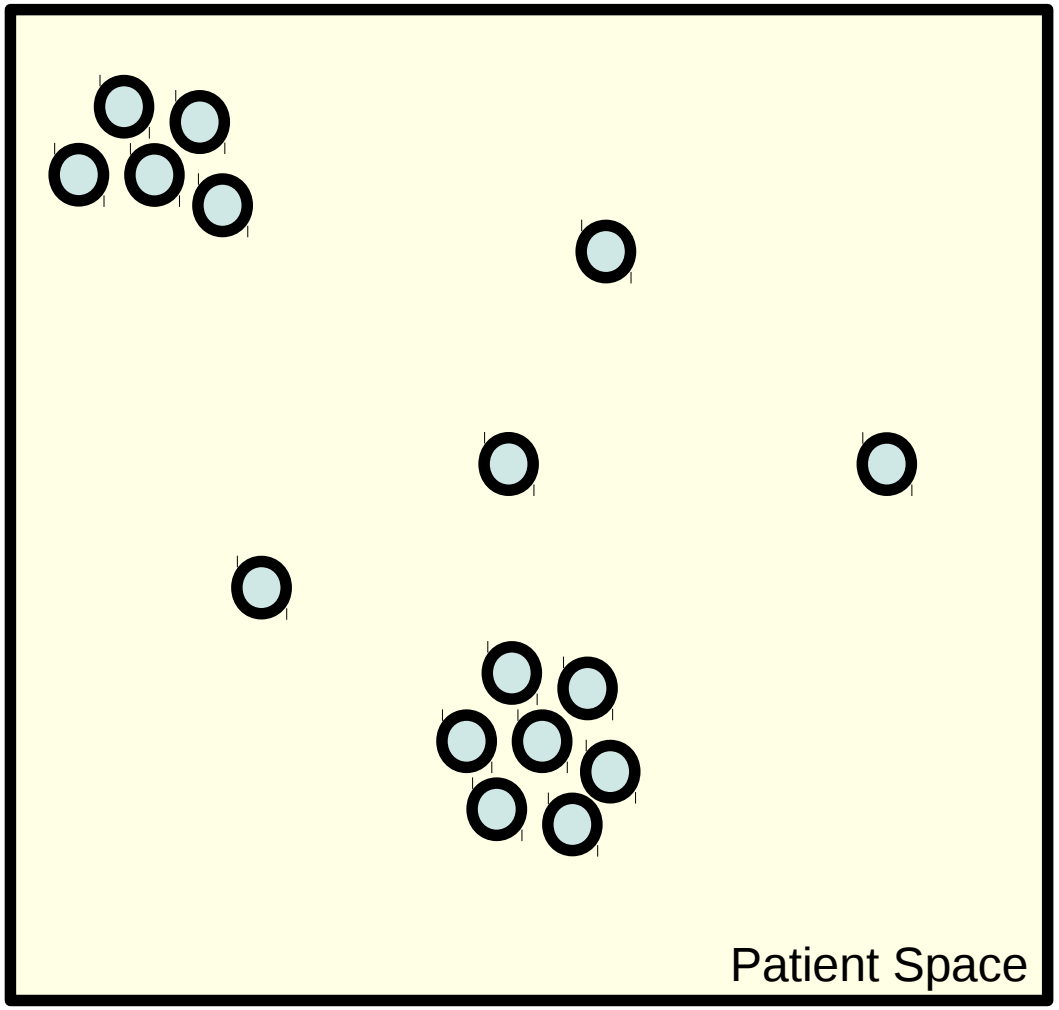
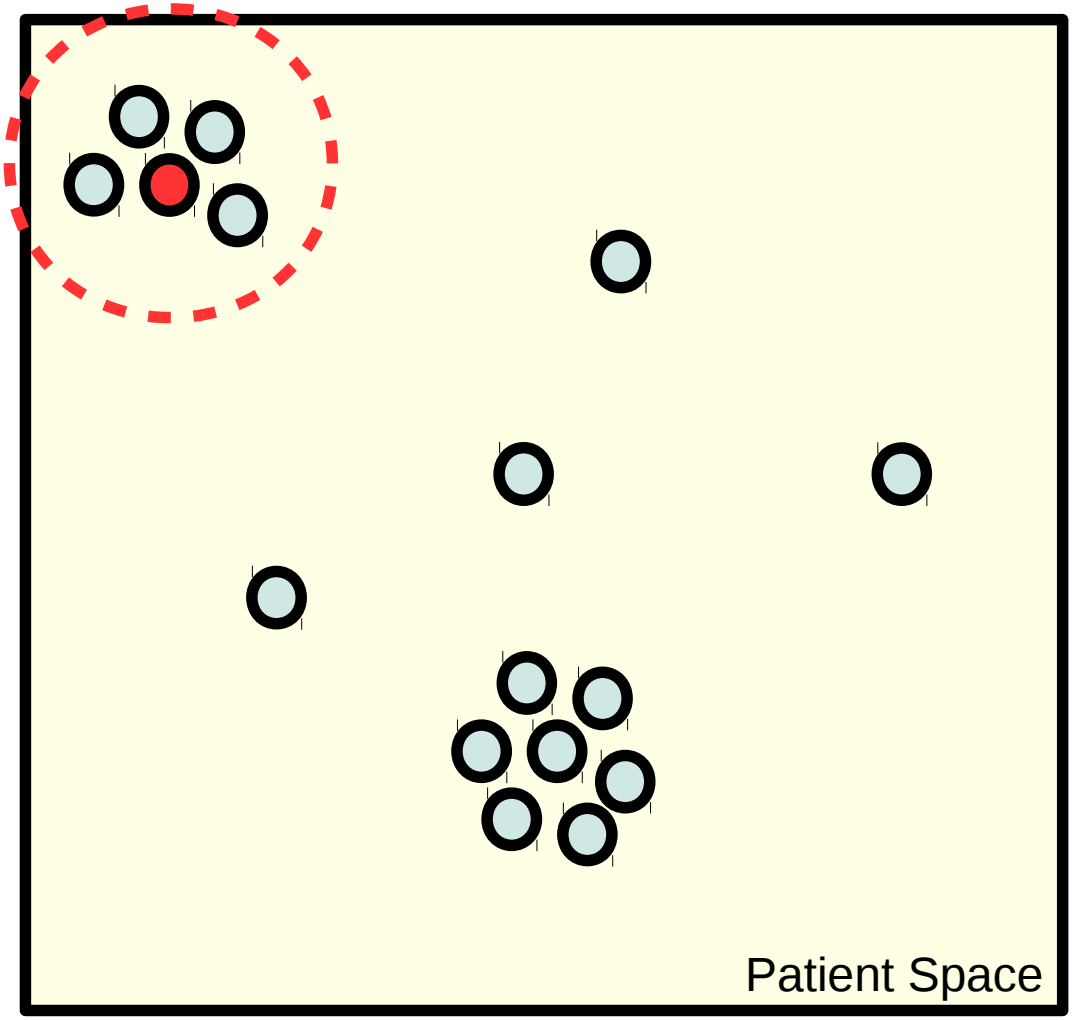
Our insight: Models and kernels have complementary strengths!



Our insight: Models and kernels have complementary strengths!

Patients in clusters may be best modeled by their neighbors



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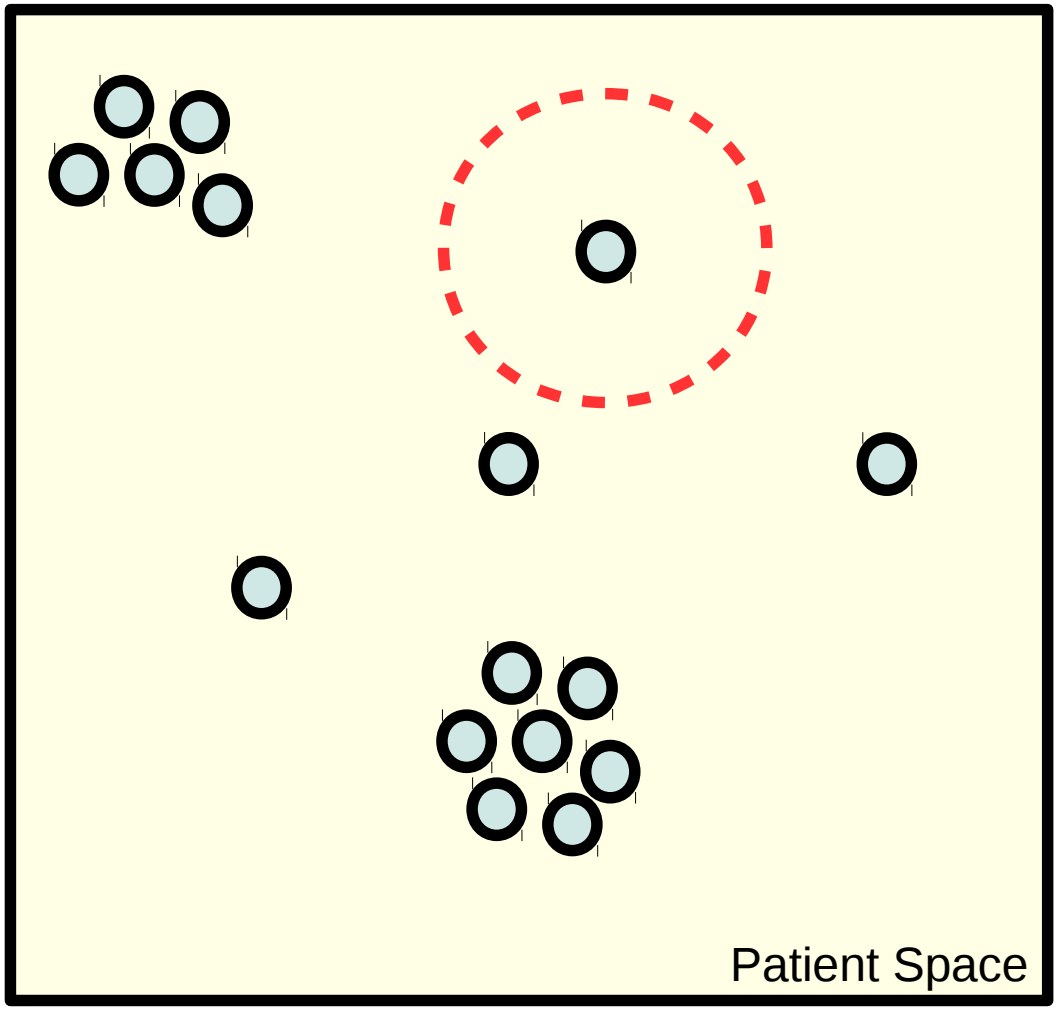
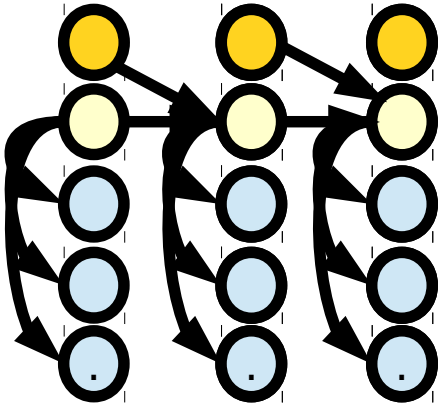
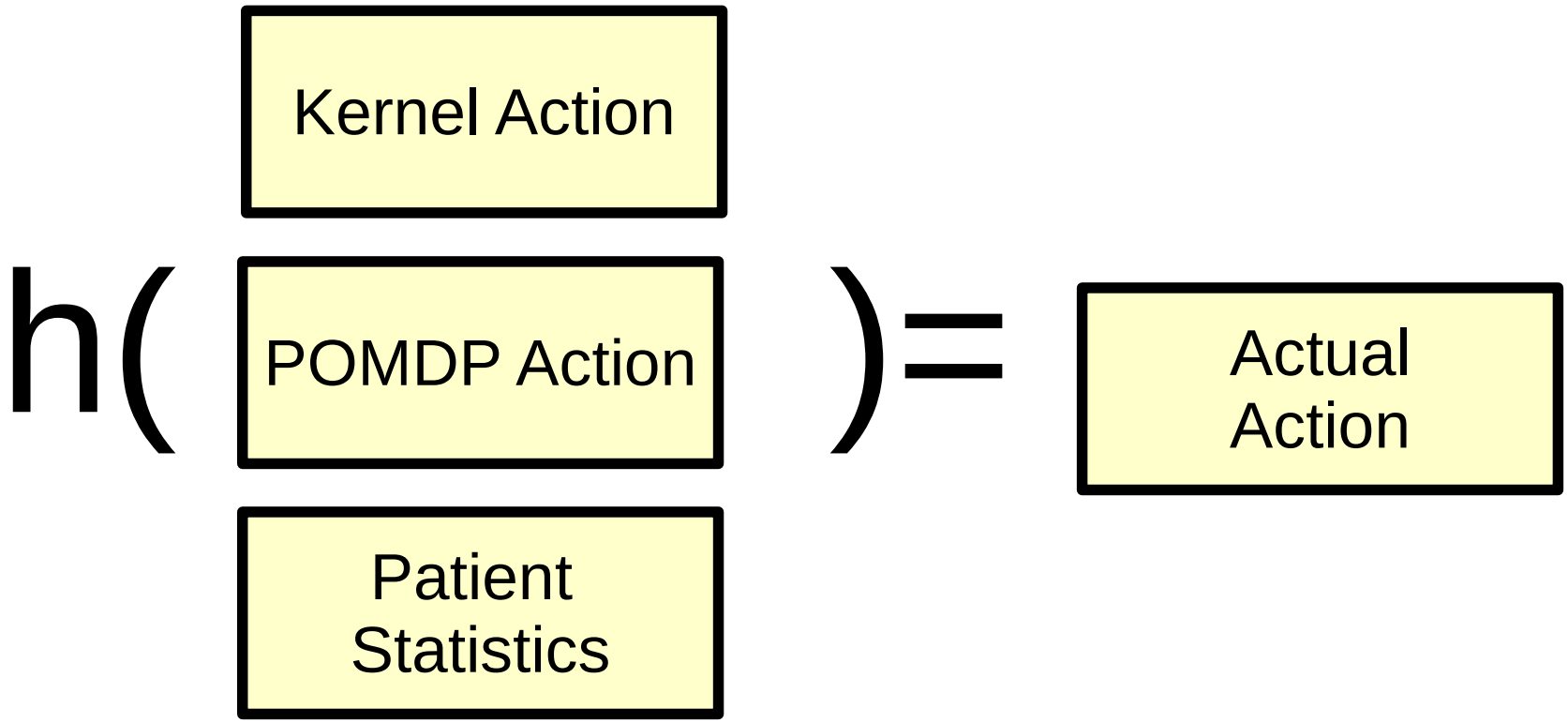


Patients without neighbors may be better modeled with a model



Key Idea: Combine!



Does it work??

- 32,960 patients from EU Resist Database; hold out 3,000 for testing.
- Observations: CD4s, viral loads, mutations
- Actions: 312 common drug combinations (from 20 drugs)

Approach	DR Reward
Random Policy	-7.31 ± 3.72
Neighbor Policy	9.35 ± 2.61
Model-Based Policy	3.37 ± 2.15
Policy-Mixture Policy	11.52 ± 1.31

*Mixture chooses POMDP about 30% of the time.

Parbhoo et al., AMIA 2017

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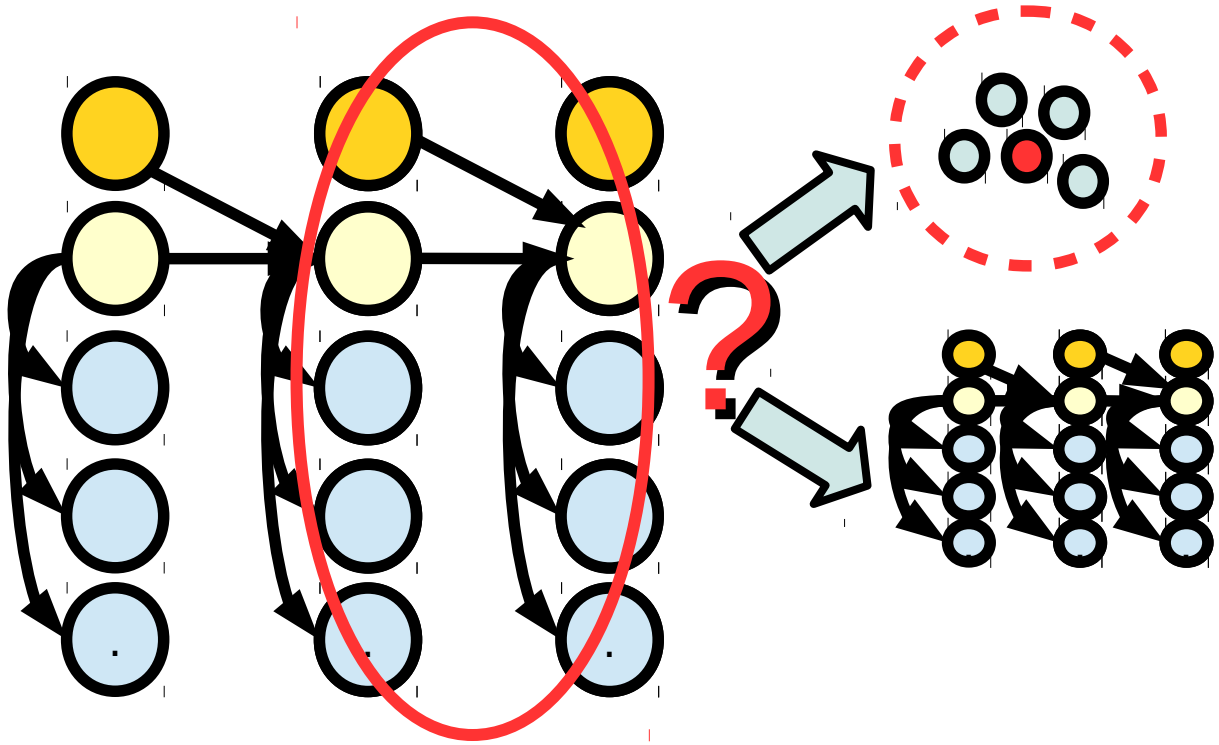
Extension: Putting the mixing in the model.



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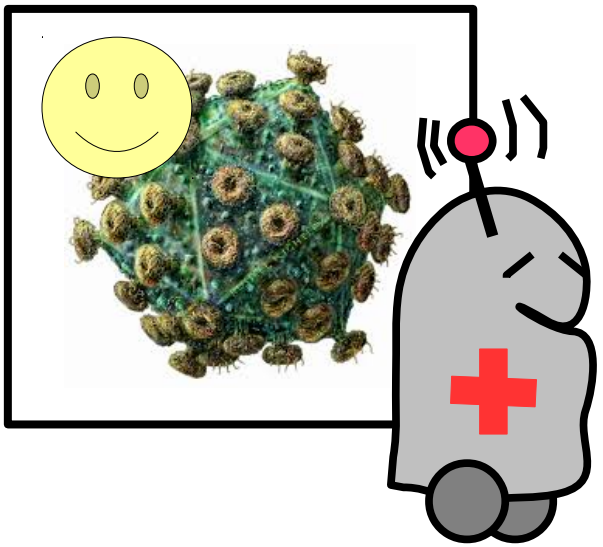
Where next?



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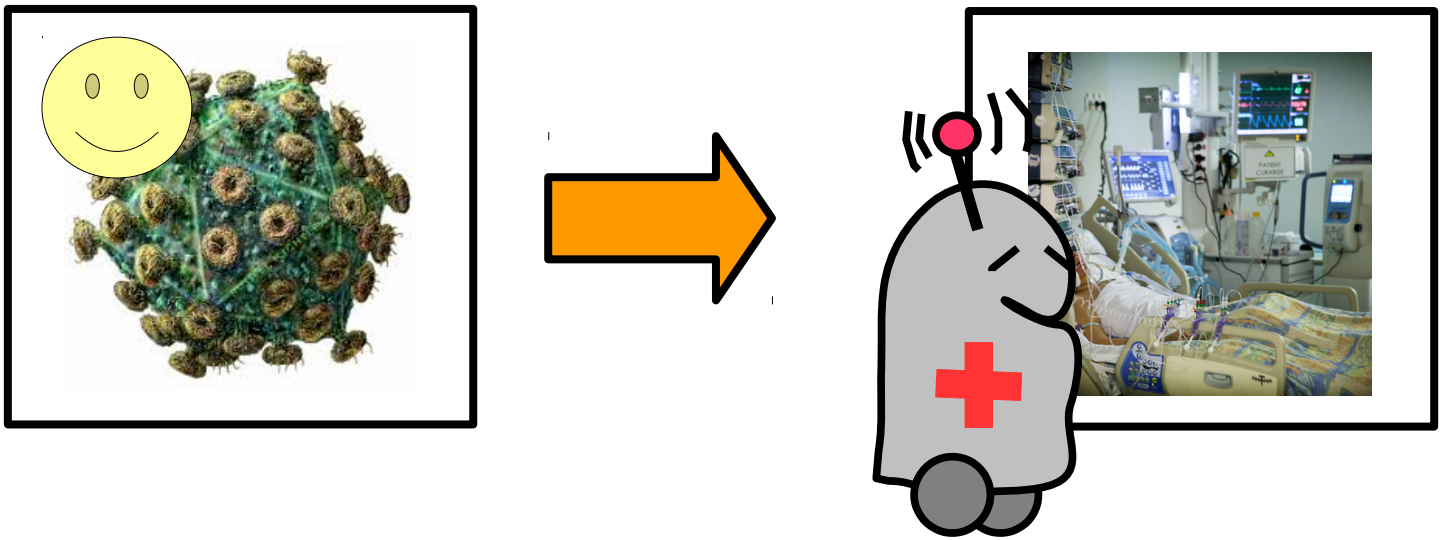
What about the ICU?



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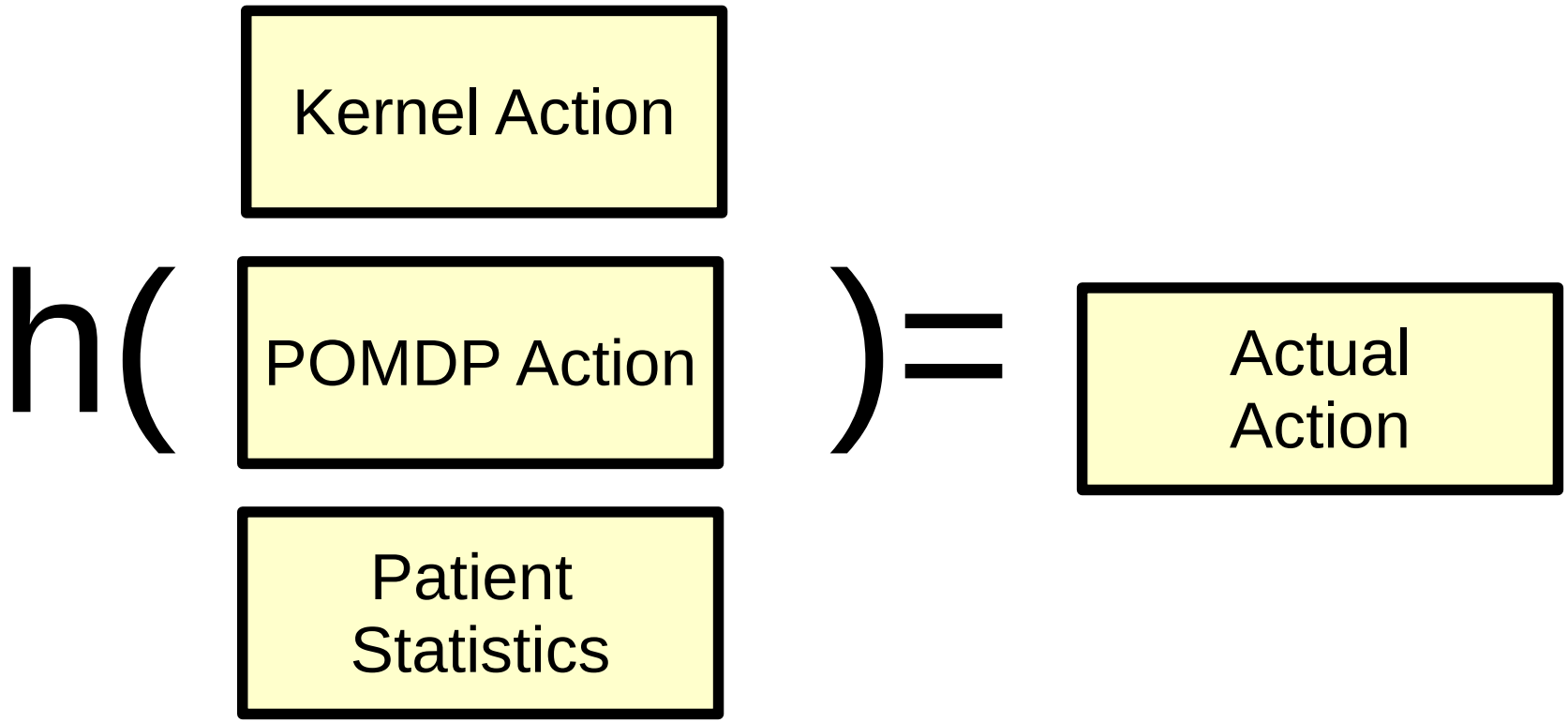
Managing Sepsis in the ICU

- Cohort of 15,415 patients with sepsis from the MIMIC dataset (same as Raghu et al. 2017); contains vitals and some lab tests.
- Actions: focus on vasopressors and fluids, used to manage circulation.
- Goal: reduce 30-day mortality; rewards based on probability of 30-day mortality:

$$r(o, a, o') = -\log \frac{f(o')}{1 - f(o')} f(o') + \log \frac{f(o)}{1 - f(o)}$$

Peng et al., AMIA 2018

Can we apply the same idea?



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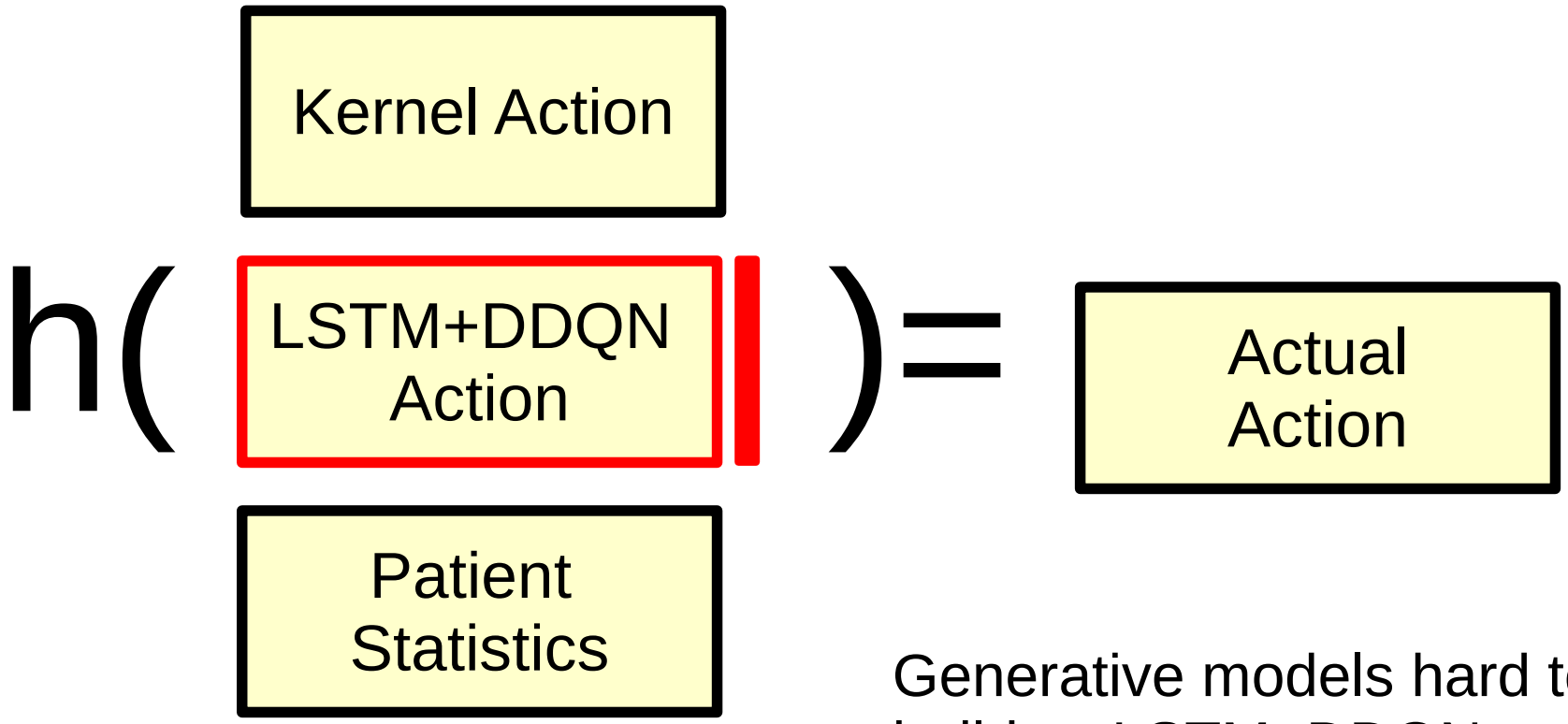
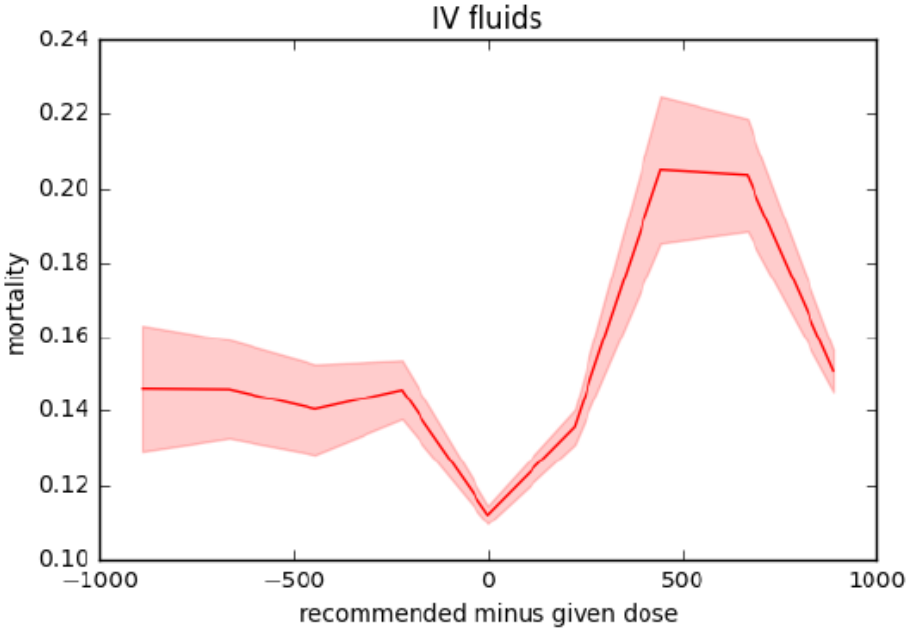


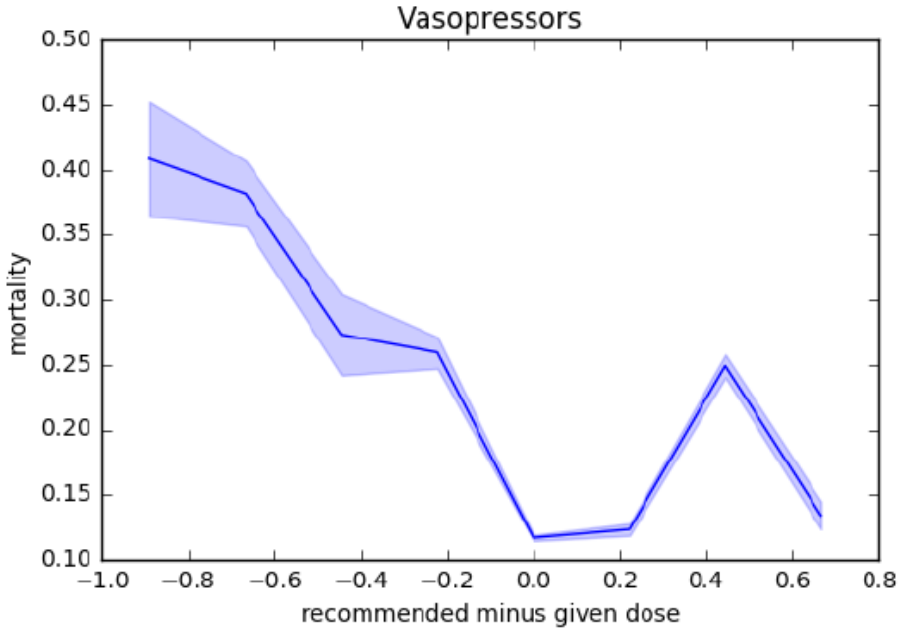
Generative models hard to build → LSTM+DDQN

LSTM+DDQN suggests never-taken actions → hard cap.

Again, Mixtures do best!

	Physician	Kernel	DQN	MoE_{V_d,Q_d}	MoE_{V_b,Q_b}
non-recurrent encoded	3.76	3.73	4.06	3.93	4.31
recurrent encoded	3.76	4.46	4.23	5.03	5.72





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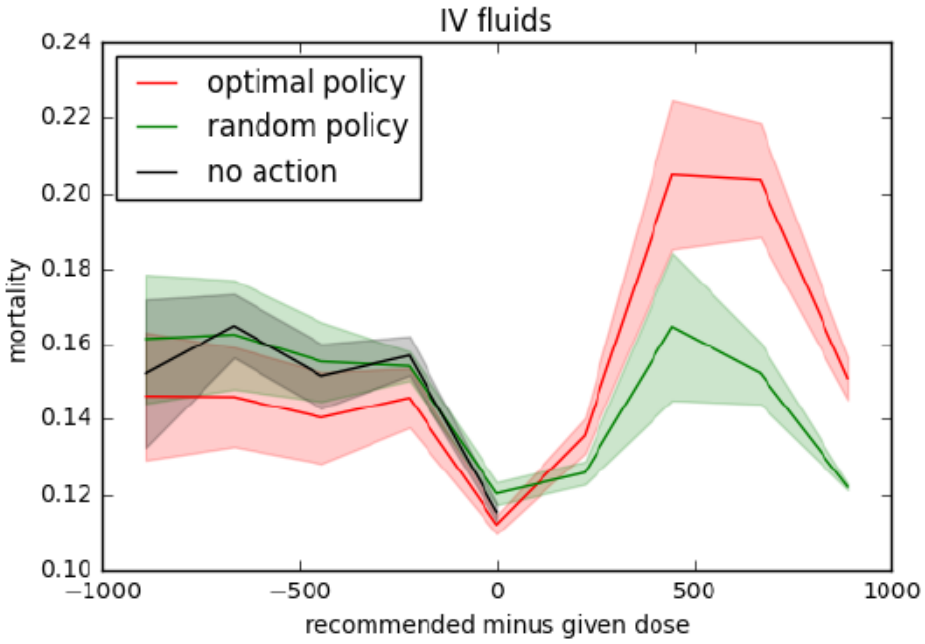
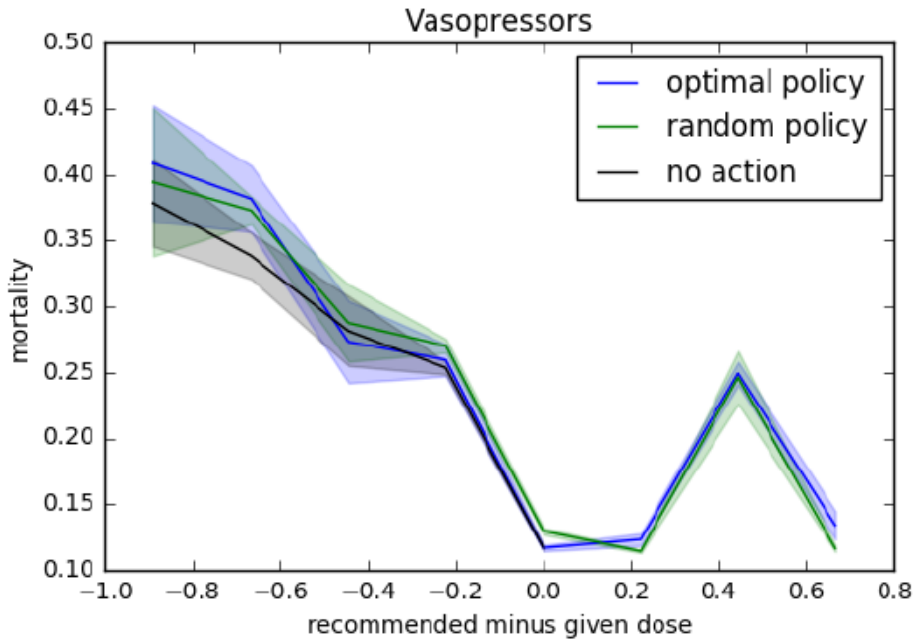
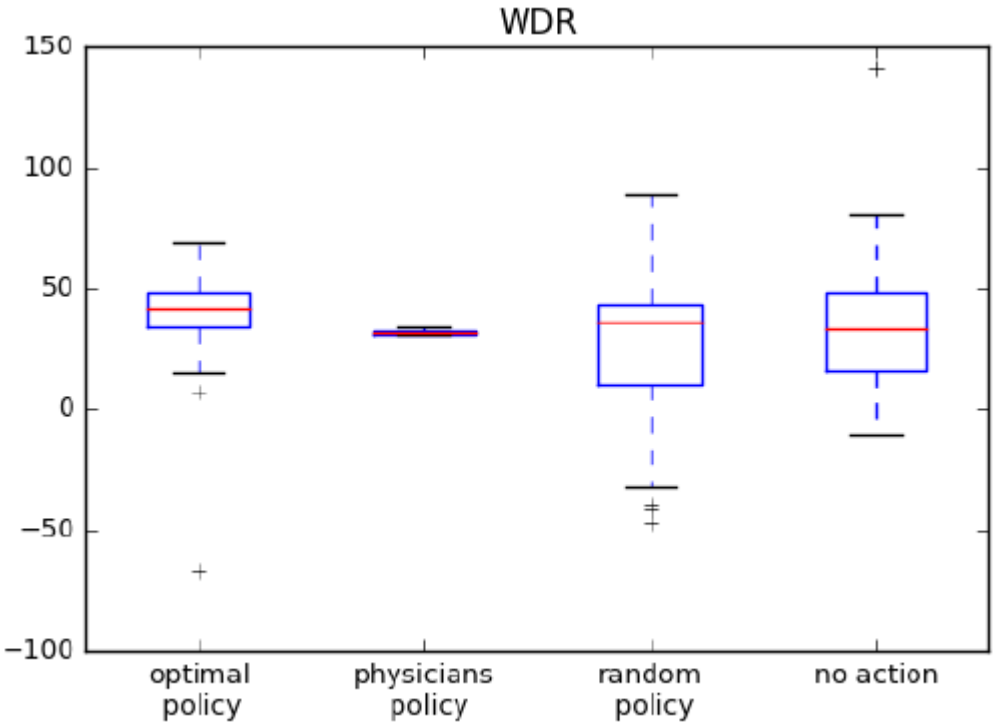




Evaluation Challenges: OPE

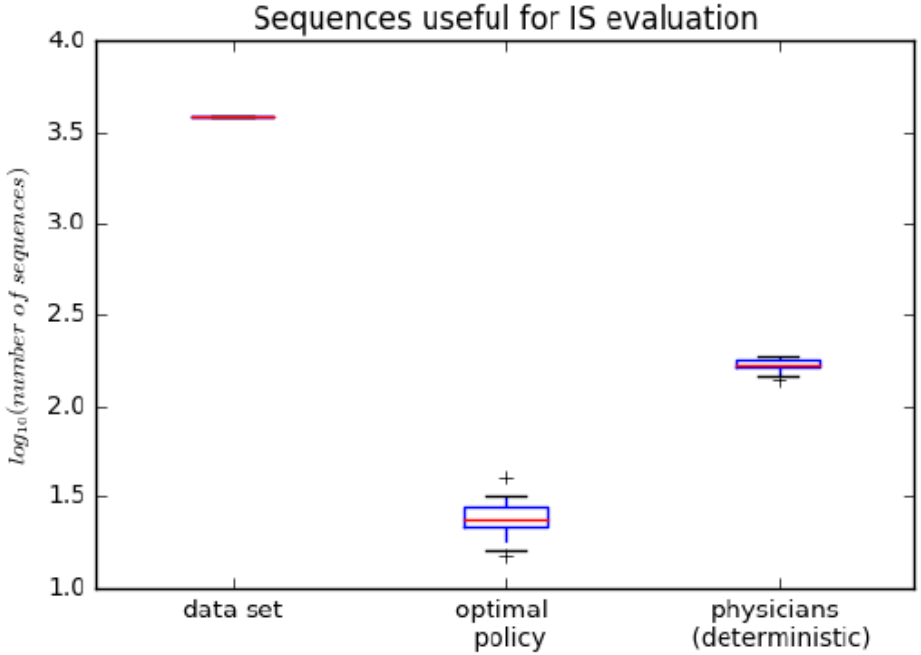
Statistical methods have high variance

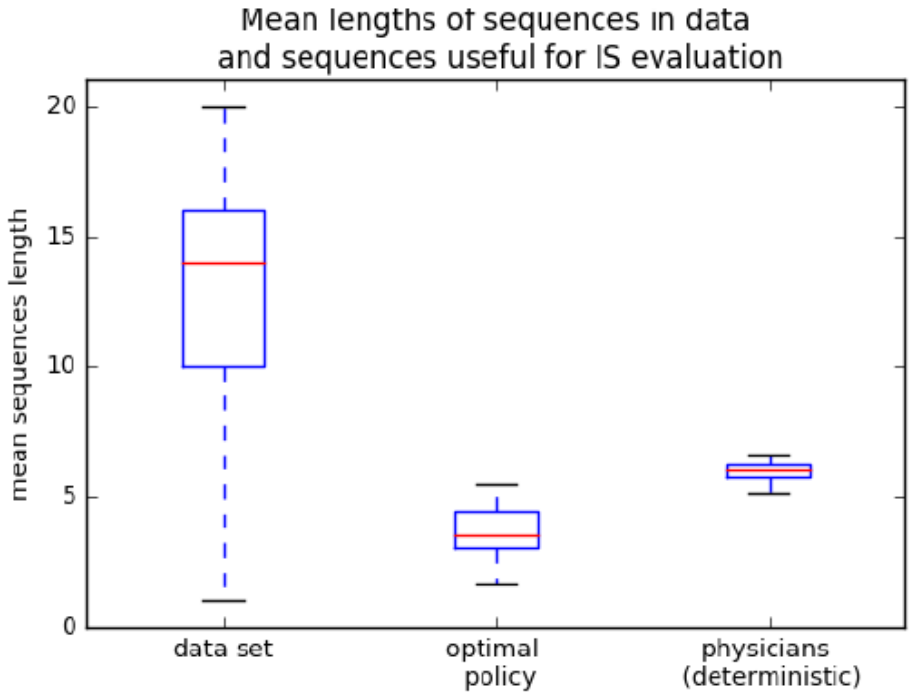


Gottesman et al. 2018, Raghu et al. 2018

Evaluation Challenges: OPE

They can select non-representative cohorts





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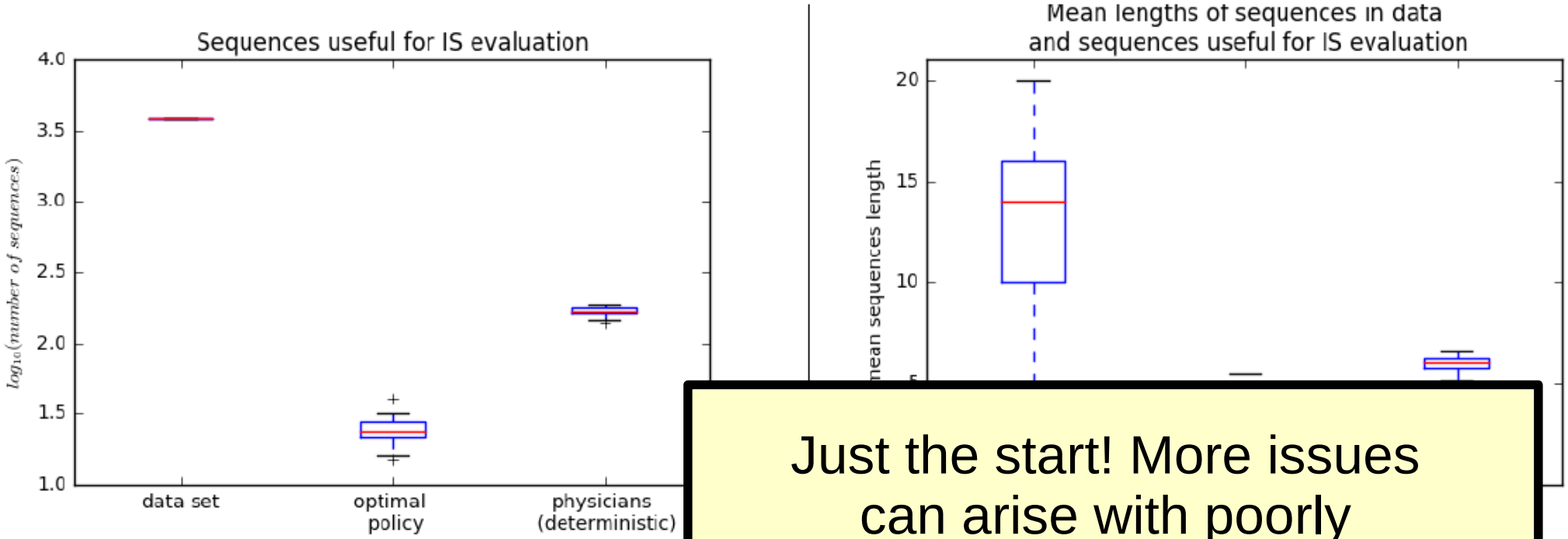


Just the start! More issues can arise with poorly estimated behavior policies, poor representation choices

So can we trust those results?

Positive Evidence: Replication

Our HIV results hold across two distinct cohorts.

EU Resist

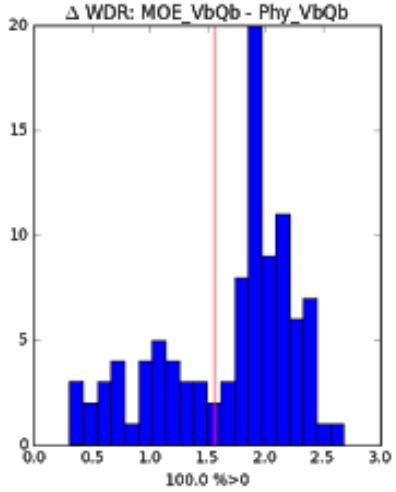
	Doubly Robust	Importance Sampling	Weighted Importance
Random Policy	–2.31 ± 1.42	–3.48 ± 1.36	–2.80 ± 1.27
Short-term Kernel	2.17 ±1.4	2.18 ±1.20	2.16 ±1.71
Long-term Kernel	9.47 ± 1.70	5.72 ± 1.81	6.97 ± 1.29
POMDP	6.04 ± 2.18	4.15 ± 2.28	6.67 ± 1.74
Mixture-of-experts	**11.83 ± 1.26**	**12.50 ± 1.19**	**11.07 ± 1.21**

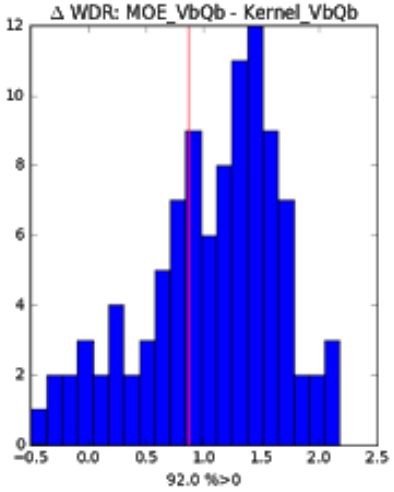
Swiss HIV Cohort

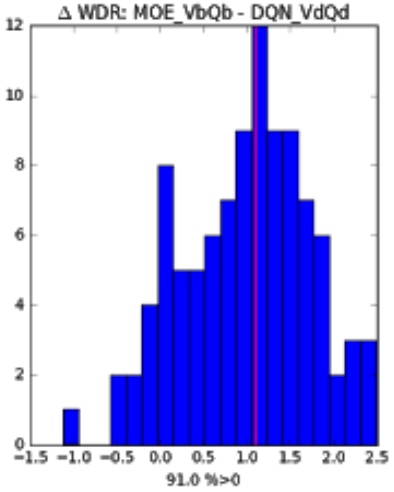
	Doubly Robust	Importance Sampling	Weighted Importance
Random Policy	–6.33 ± 3.47	–5.57 ± 2.17	–6.18 ± 3.24
Short-term Kernel	1.64 ±1.86	2.03 ±1.81	2.17 ±1.74
Long-term Kernel	9.67 ± 1.49	7.38 ± 1.72	7.64 ± 1.92
POMDP	5.46 ± 2.05	6.72 ± 2.88	7.76 ± 2.10
Mixture-of-experts	**10.73 ± 1.02**	**13.59 ± 1.57**	**11.83 ± 1.31**

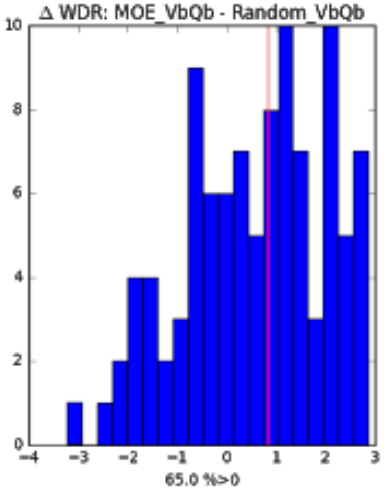
Positive Evidence: Sensitivity Analysis

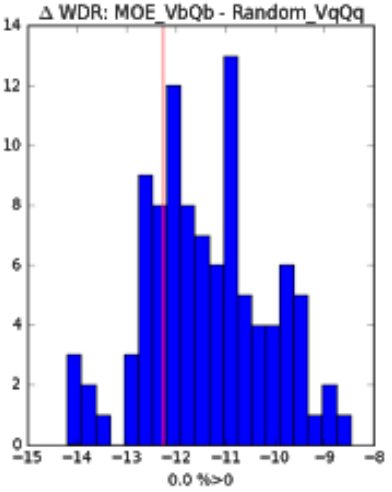
Sepsis: results hold with different control variates

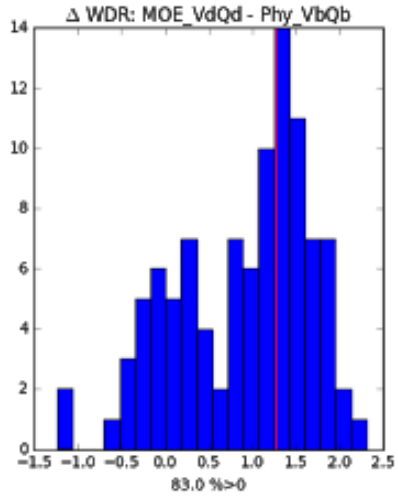


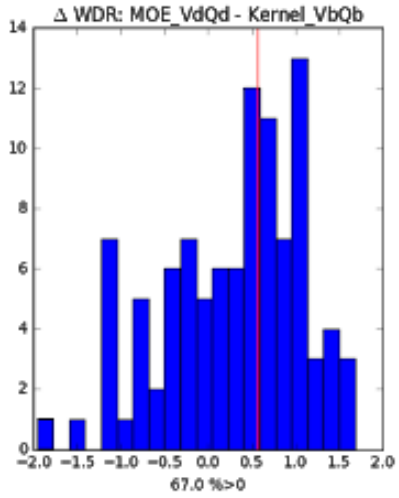


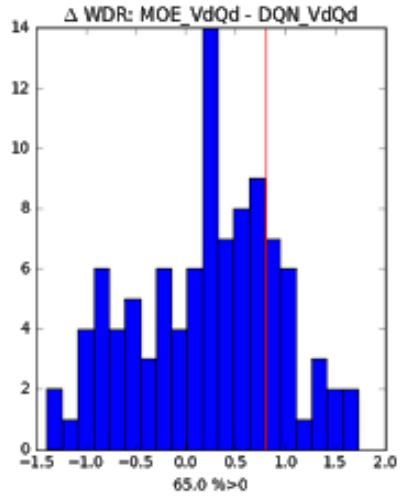


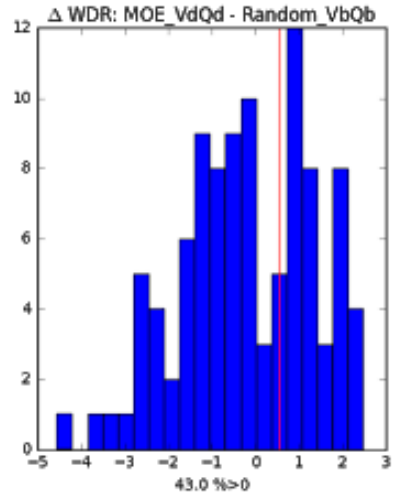


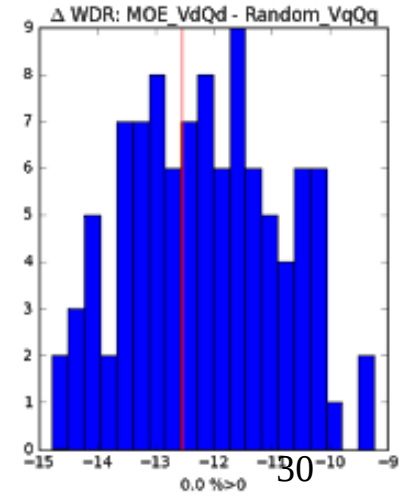












Positive Evidence: Expert Confirmation

- HIV: Checking against standard of care:

	NNRTIs	NRTIs	PIs	Fusion/Entry Inhibitors
First-line therapy	12 157	3 054	774	128
Second-line therapy	4 068	8 764	6 082	1 042

- As well as three expert clinicians:

	Clinician 1	Clinician 2	Clinician 3
Agree	18	15	13
Partially Agree	10	11	13
Disagree	2	4	4

Responsible RL in Healthcare

- Representation learning: are the essential variables at least used by clinicians being retained?
- Statistical evaluation: How large is the bias, variance in off-policy evaluation?
- Interpretation: Do clinicians find it valid?

Finally, remember that the ML will operate within the health system!

Responsible RL in Healthcare

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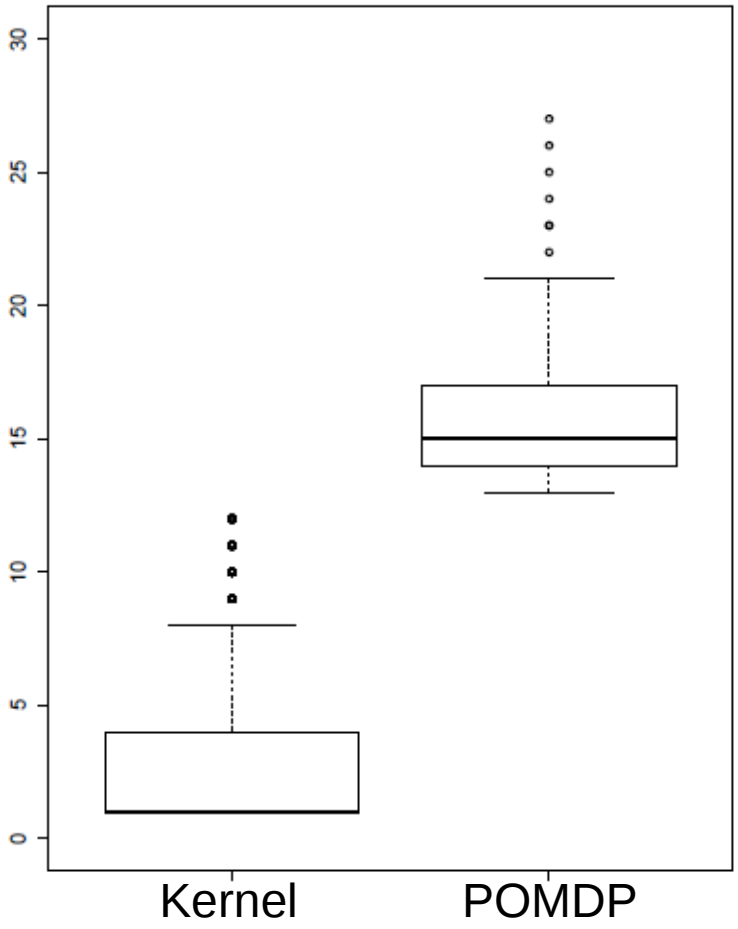
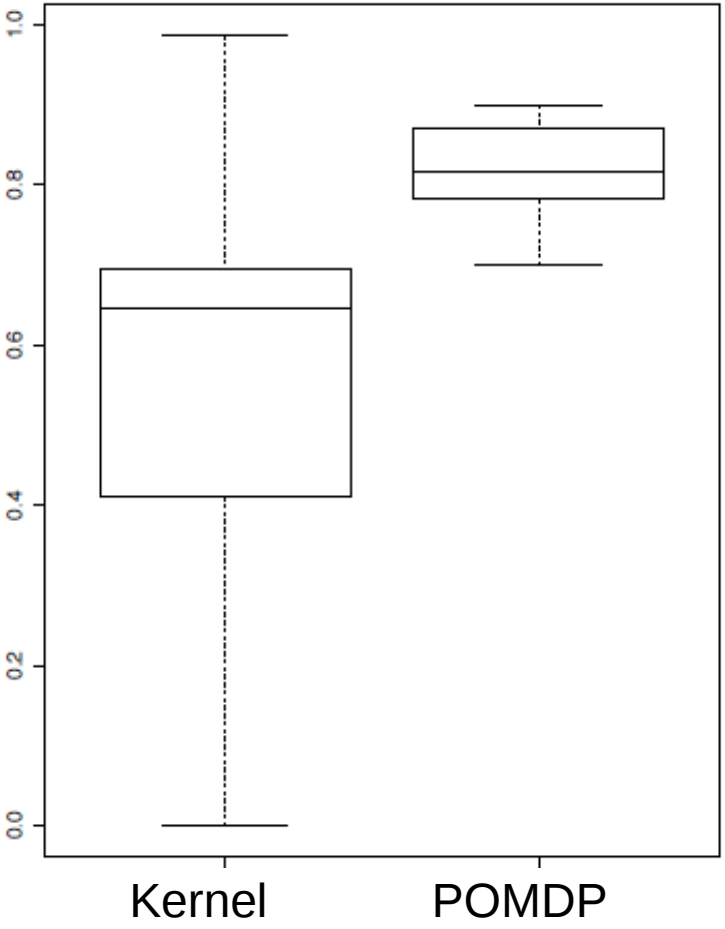
Plugs: MlforHC.org (ML for Health → ML + Clinical researchers)
JAMA Network Open (ML for Health → to clinicians)

And: Our hypothesis was correct! Model used when neighbors are far

History Length

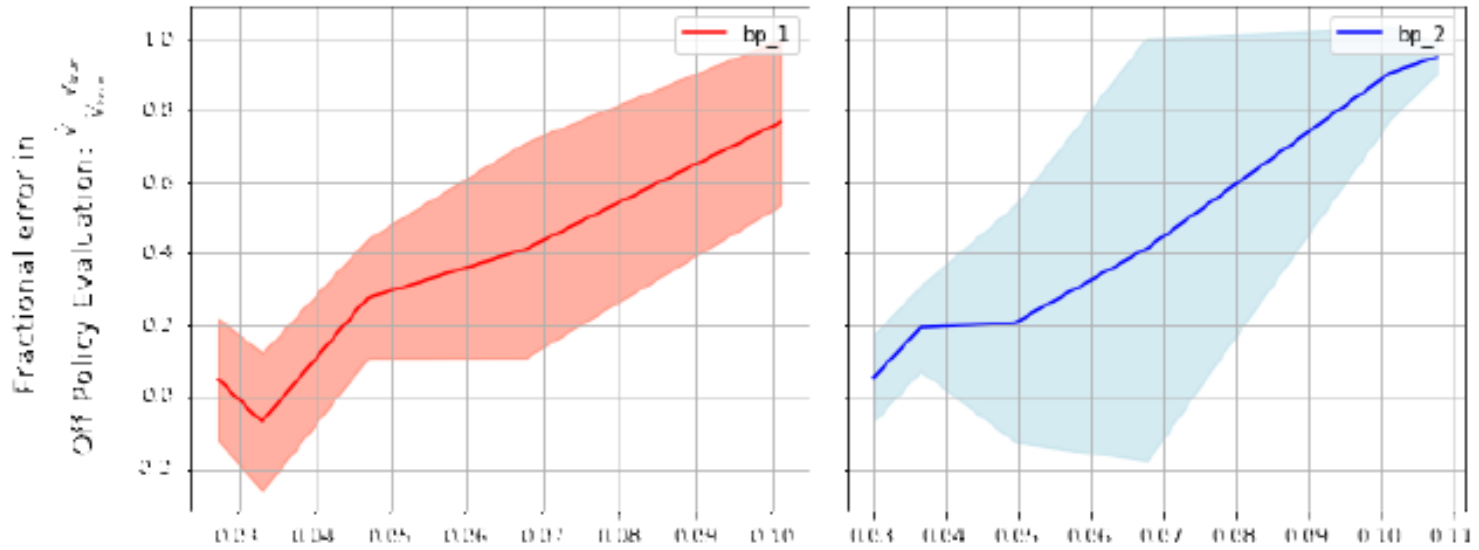


2nd Quantile Distance



Evaluation Challenges: OPE

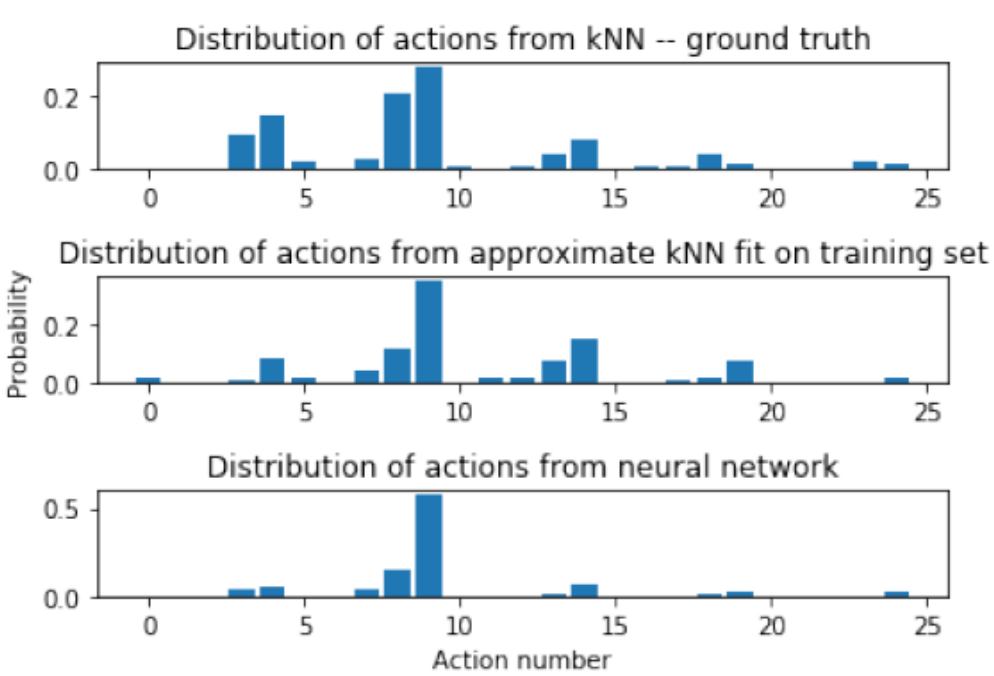
Toy problem: value estimate error grows with behavior policy estimate error



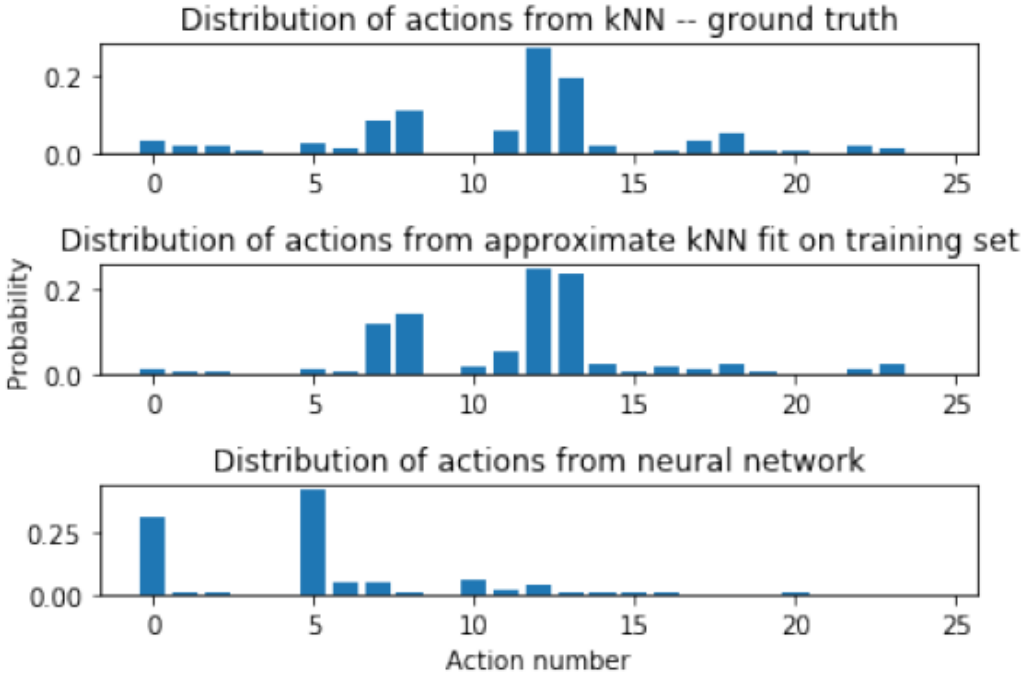
$$\mathrm{WDR}(D) := \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t w_i^t r_t^{H_i} - \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t (w_t^i \hat{Q}^{\pi_e}(S_t^{H_i}, A_t^{H_i}) - w_{t-1}^i \hat{V}^{\pi_e}(S_t^{H_i}))$$

Evaluation Challenges: OPE

Sepsis: Neural networks definitely not calibrated...



(a) Overconfident predictions



(b) Incorrect predictions

$$\mathrm{WDR}(D) := \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t w_i^t r_t^{H_i} - \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t\left(w_t^i \hat{Q}^{\pi_e}(S_t^{H_i}, A_t^{H_i}) - w_{t-1}^i \hat{V}^{\pi_e}(S_t^{H_i})\right)$$

Evaluation Challenges: OPE

kNN is more calibrated

Severity	LR	RF	NN	Approx kNN
0 - 4	0.249	0.214	0.213	**0.129**
5 - 9	0.269	0.254	0.246	**0.152**
10 - 13	0.309	0.309	0.399	**0.210**
14 - 23	0.356	0.337	0.426	**0.199**

Calibration helps

Behaviour Policy Model	MDP Approximate Model	MSE
Approximate kNN	Fitted Q Iteration	**3.05**
Approximate kNN	Kernel-based RL	6.54
Approximate kNN	Discrete SARSA	6.53
Neural network	Fitted Q Iteration	3.53
Neural network	Kernel-based RL	10.2

$$\mathrm{WDR}(D) := \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t w_i^t r_t^{H_i} - \sum_{i=1}^{I}\sum_{t=0}^{T}\gamma^t\left(w_t^i \hat{Q}^{\pi_e}(S_t^{H_i}, A_t^{H_i}) - w_{t-1}^i \hat{V}^{\pi_e}(S_t^{H_i})\right)$$

And even the best OPE can’t counteract bad modeling choices...

https://i0.wp.com/lipstickandlifesaving.com/wp-content/uploads/2017/03/img_9064.jpg