Enhanced Sampling Techniques

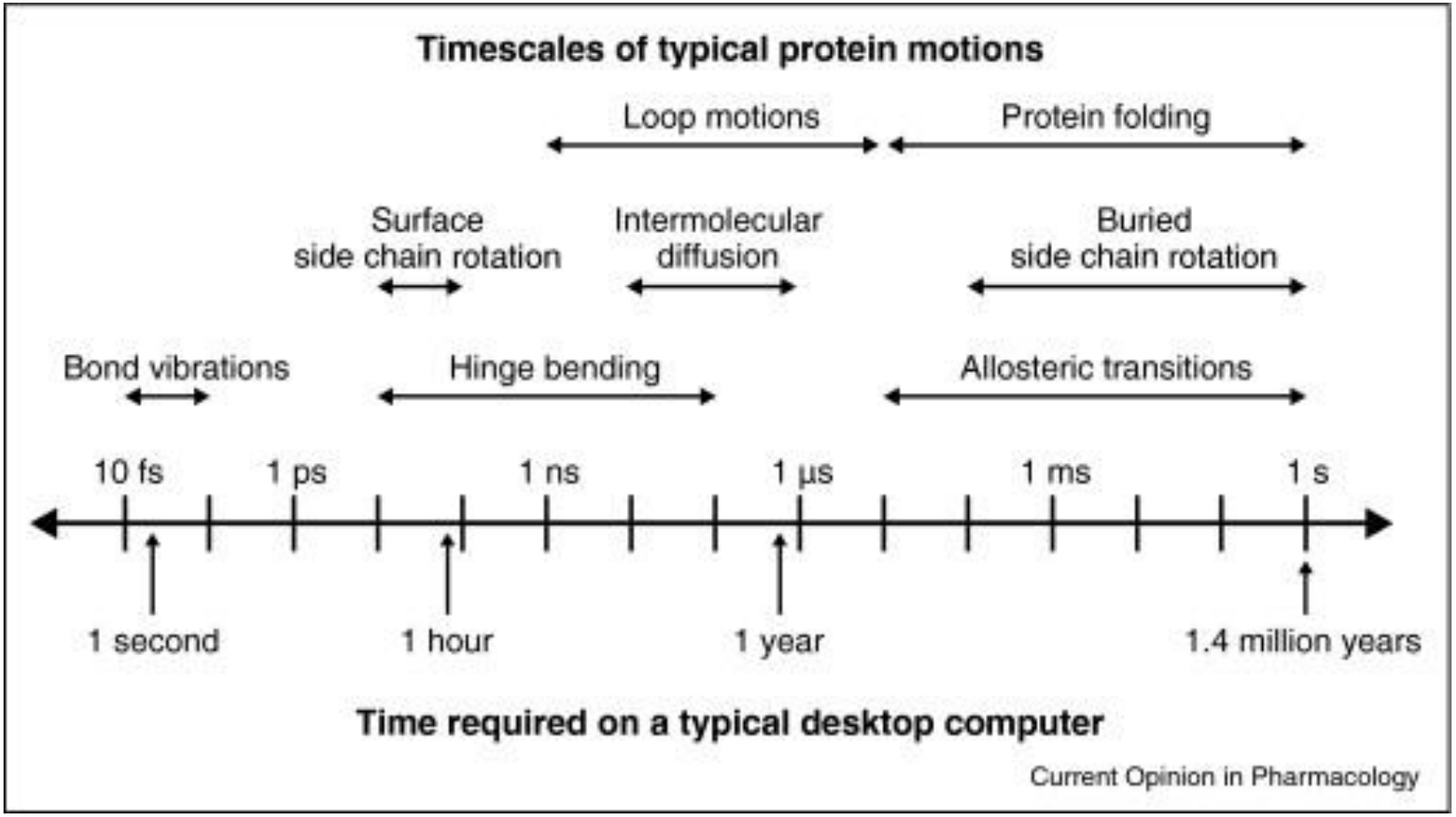
https://wkkrqsriursybsor-zippykid.netdna-ssl.com/wp-content/uploads/2014/10/costco-samples.jpg

QMMM Study Group
October 5th, 2018
Anthony Bogetti

References

- Zwier, M. and Chong, L. Reaching biological timescales with all-atom molecular dynamics simulations. *Curr. Opinion in Pharma.* 10: 6, 2010, 745-752
- Zuckerman, DM. and Chong LT. Weighted Ensemble Simulation: Review of Methodology, Applications, and Software. *Annu Rev Biophys. 2017. 46, 43-57.*

Biological Timescales



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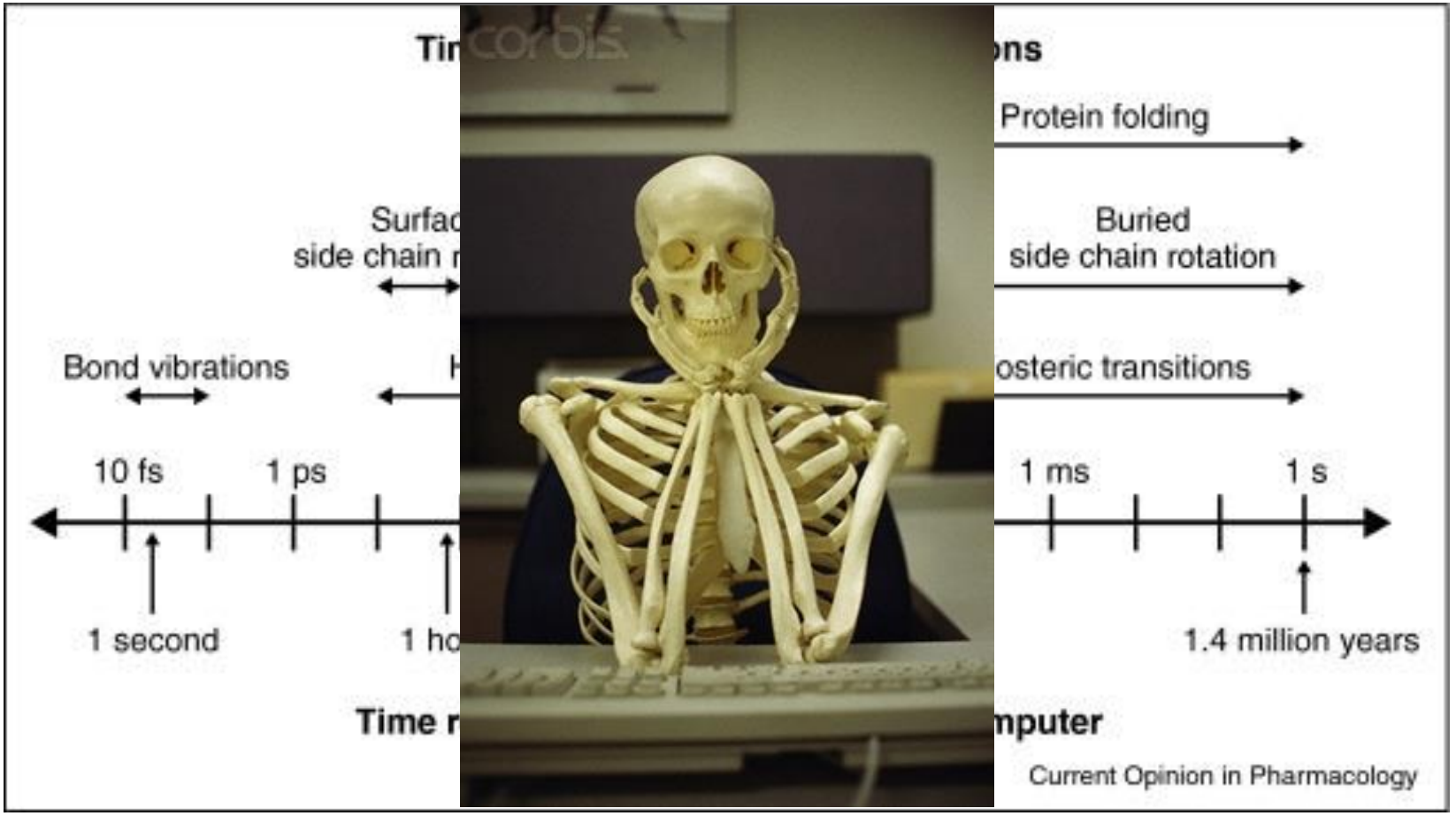

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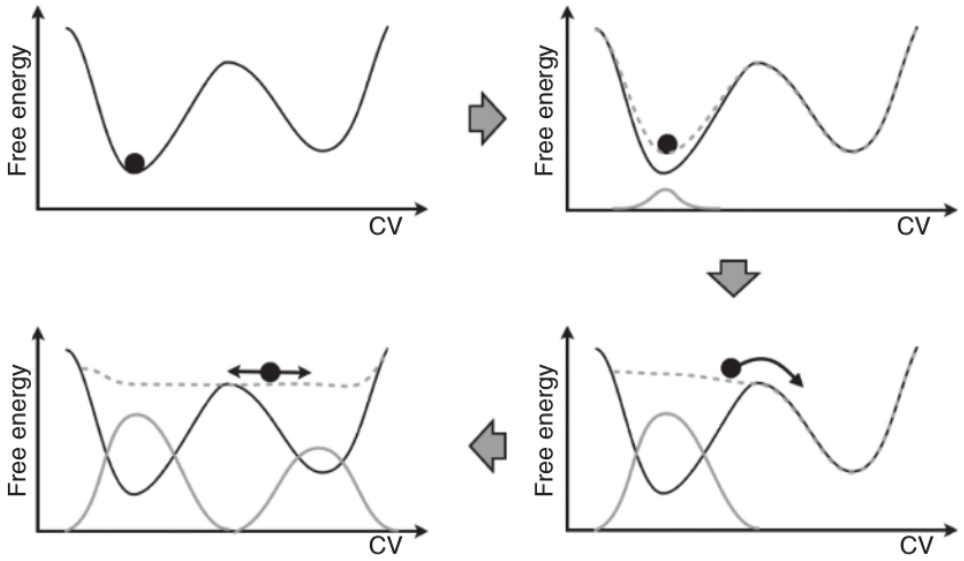
Separation of Timescales

- A central assumption of all ES techniques is that events are rare and waiting times between events are long
- How can the long wait times be eliminated?

http://blog.tutorhub.com/wp-content/uploads/2013/06/shutterstock_68955784.jpg

Altering the Energy Landscape

- Some techniques will alter the free energy landscape of a process to capture a rare event sooner.
- Examples include metadynamics (pictured below) and steered MD



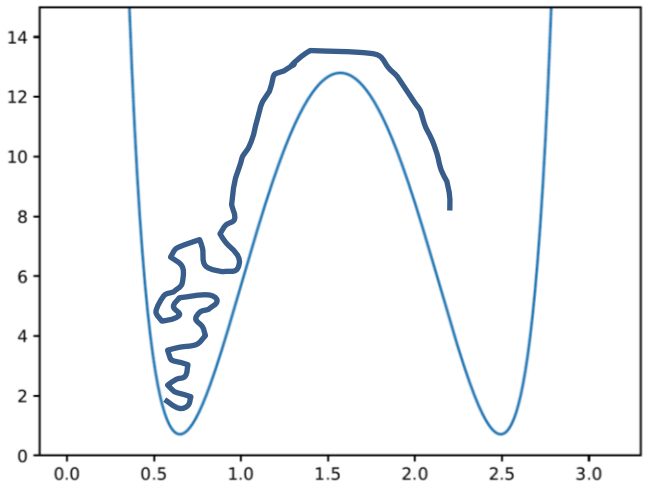
http://www.parrinello.ethz.ch/research/metadynamics/_jcr_content/par/fullwidthimage/image.imageformat.fullwidth.1393180090.png

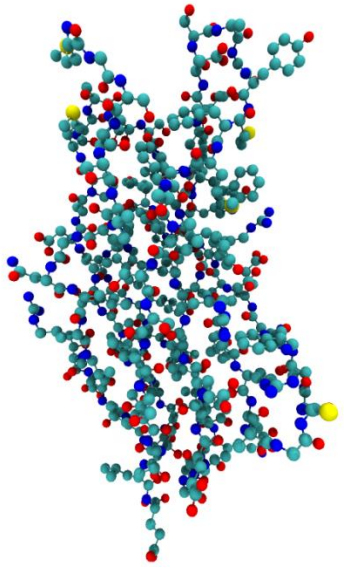
Altering the Energy Landscape

- Some techniques will alter the free energy landscape of a process to capture a rare event sooner.
- Examples include metadynamics (pictured below) and steered MD
- This can be useful for exploring the *thermodynamics* of a process, but what if we are interested in *kinetics*?

Path (Rare Event) Sampling

- Find the detailed dynamics of pathways between metastable states
- Kinetic observables can be determined
- Examples include transition path sampling, forward flux sampling and weighted ensemble.





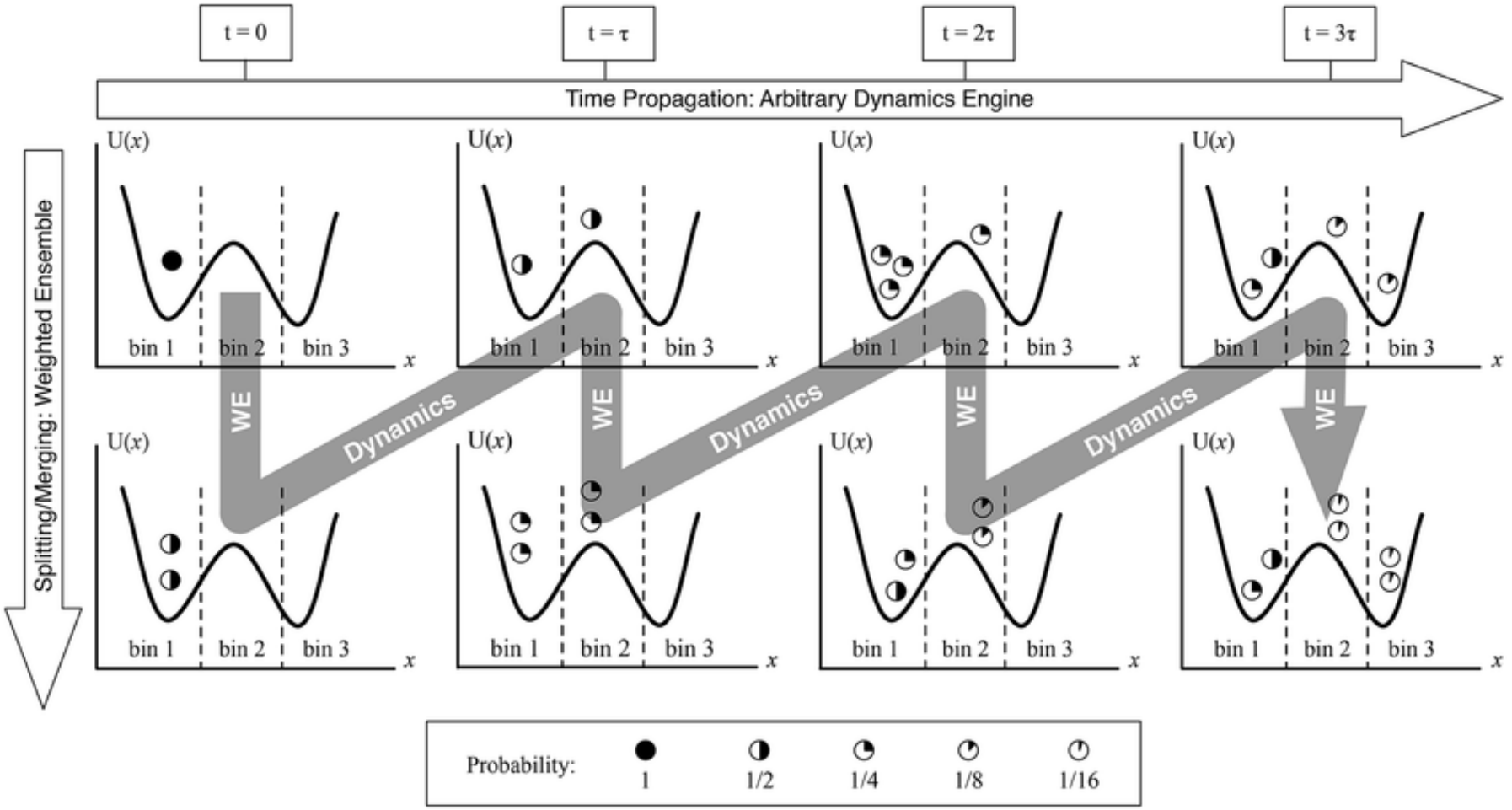
Weighted Ensemble

- Take your configuration space (determined largely by one or more **order parameters**) and divide it up into **bins**
- Start a fixed number of simulations in a bin (called **walkers**), propagate dynamics for each walker
- Assign walkers to bins based off of their calculated order parameter
- Every **iteration**, propagate dynamics and assign to bins

Weighted Ensemble

- Each walker (individual simulation) has a certain probability associated with it (starts with a probability of 1)
- There is a limit to the number of walkers that can be in a bin
- If there are more walkers in a bin than the target count, walkers are **merged** (probabilities are combined)
- If there are fewer than the target count, walkers are **split** (probabilities are divided)
- **Splitting and merging is the key to WE**

Weighted Ensemble



https://www.researchgate.net/profile/Robert_Murphy3/publication/292991222/figure/fig9/AS:341601621692426@1458455581570/Weighted-ensemble-algorithm-One-initial-trajectory-is-iteratively-resampled-until-its.png

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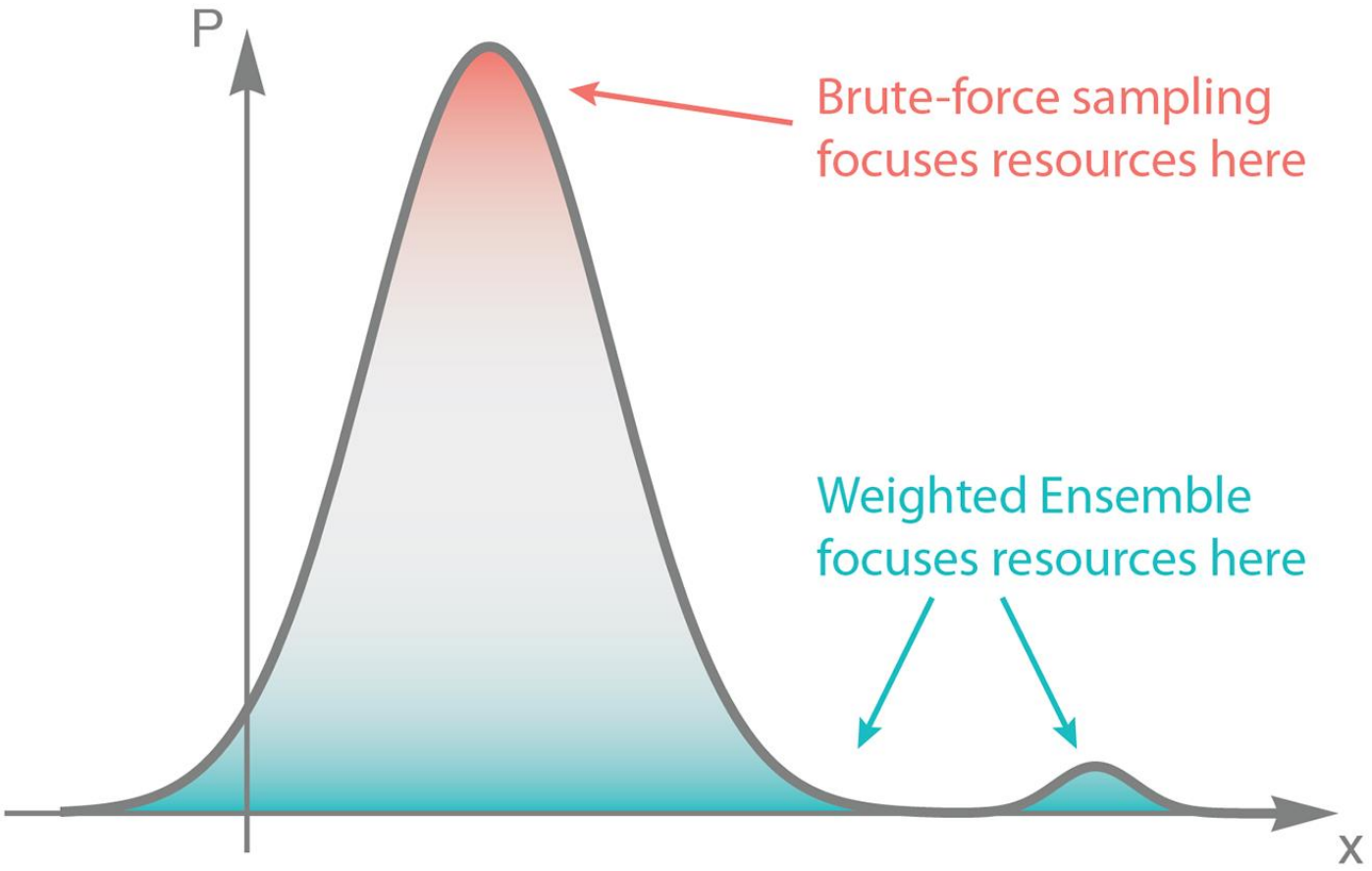
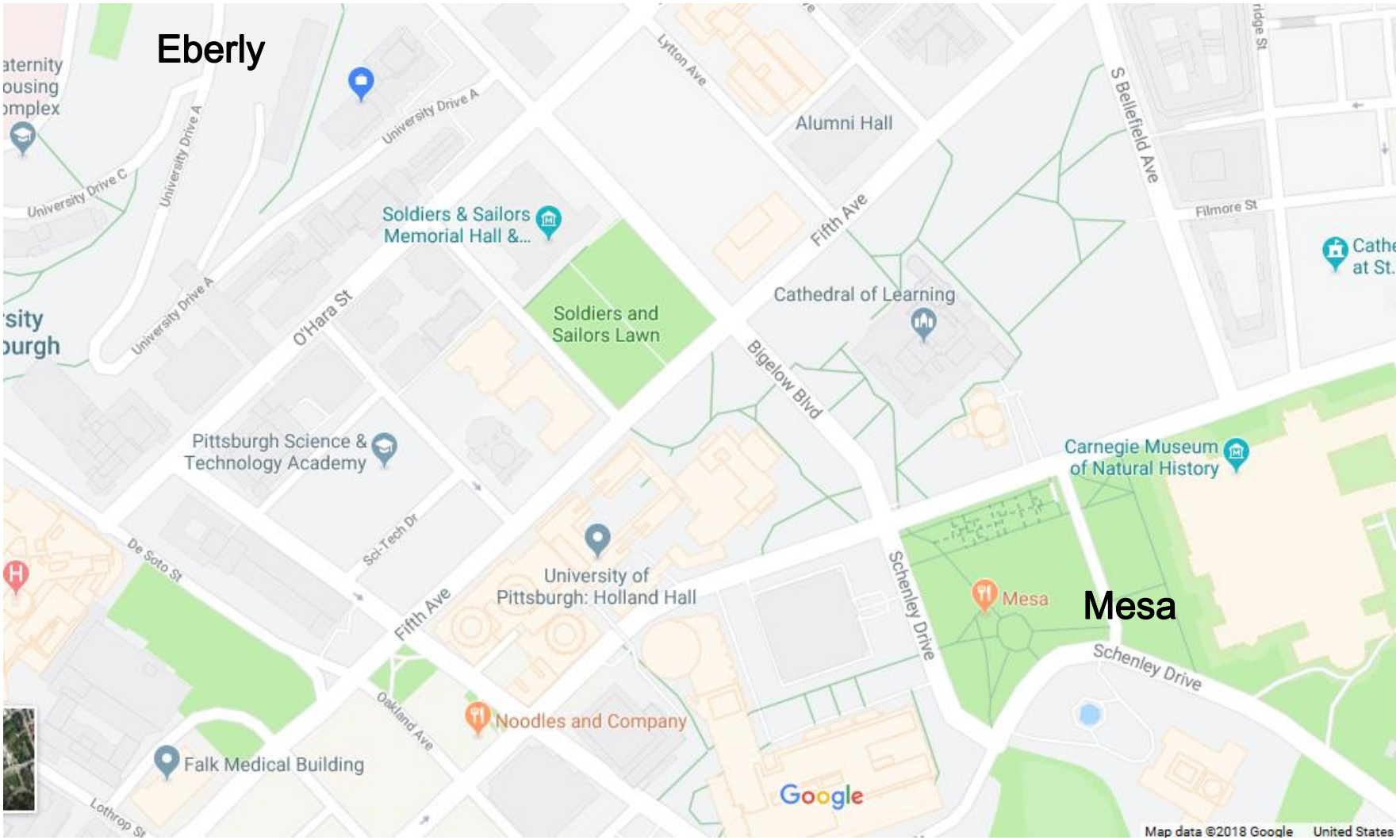


https://journals.plos.org/ploscompbiol/article/figure/image?id=10.1371/journal.pcbi.1004611.g002&size=large

An Example “Simulation”



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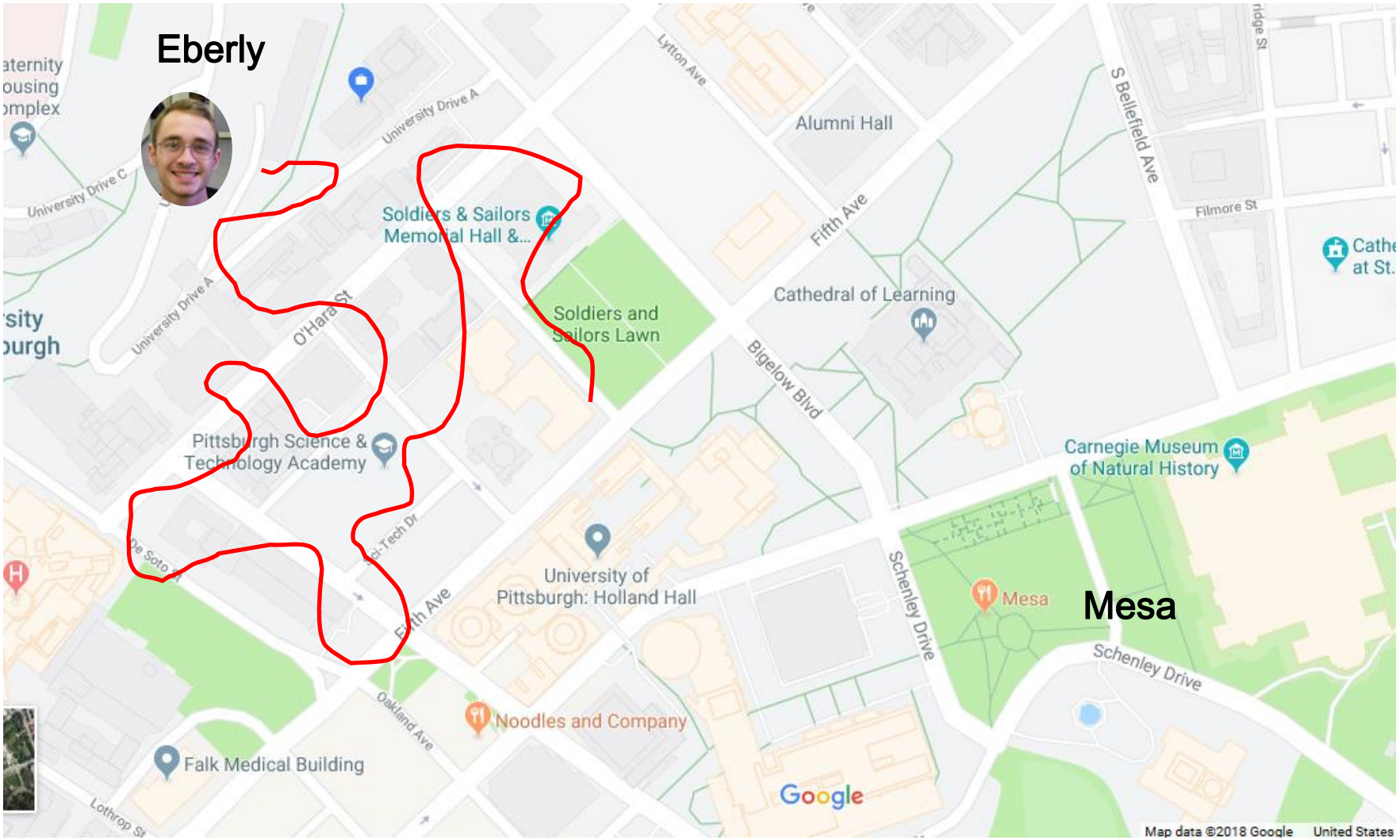

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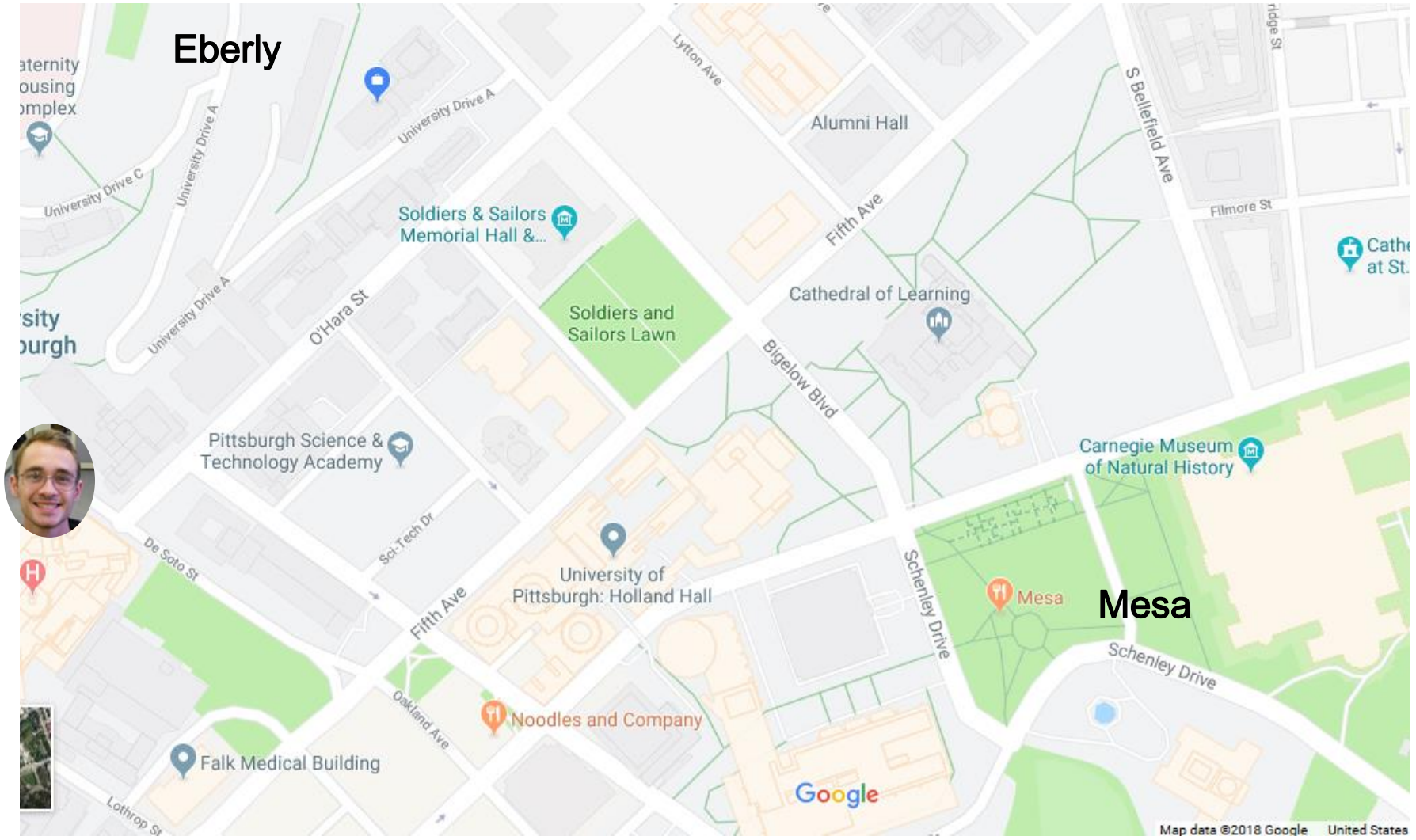

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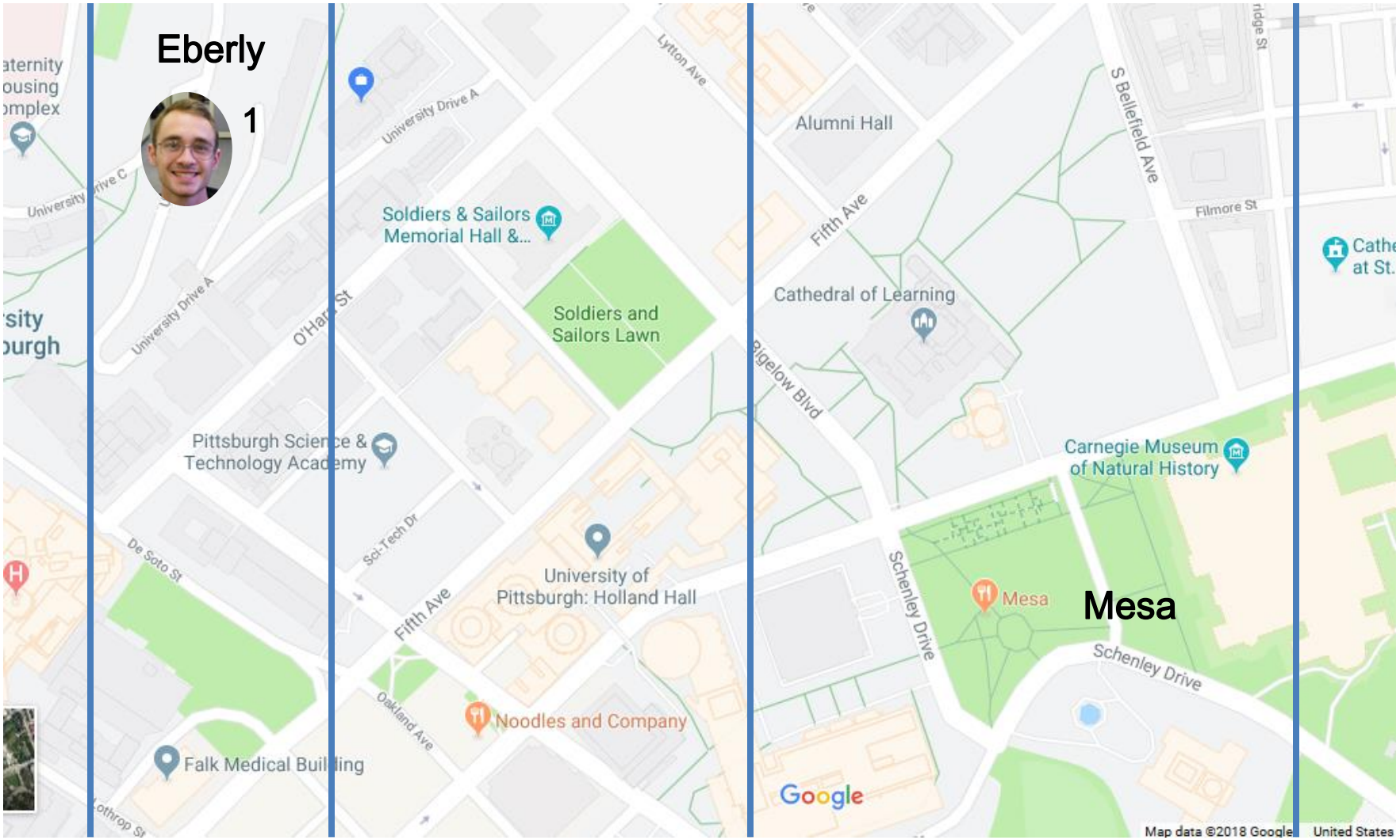

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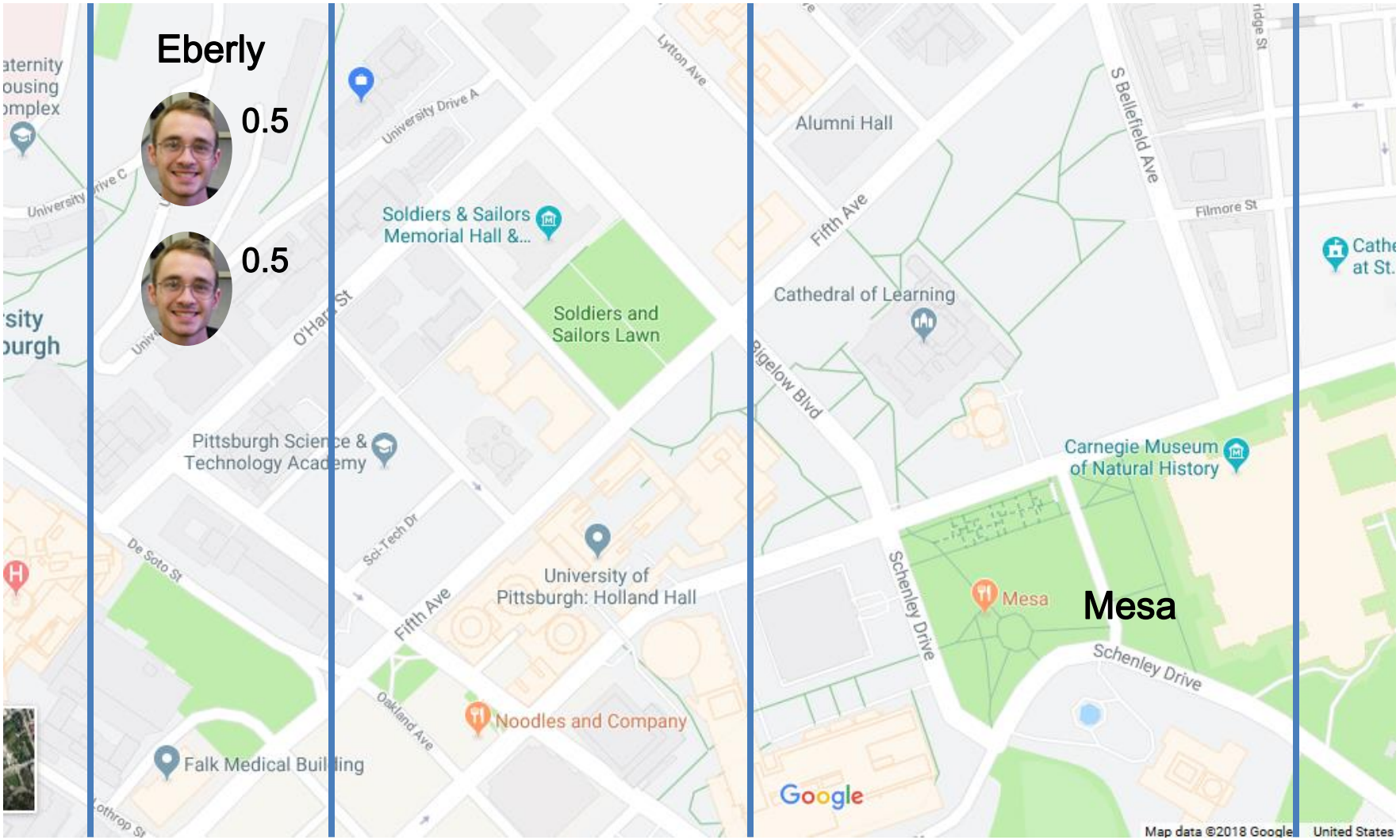

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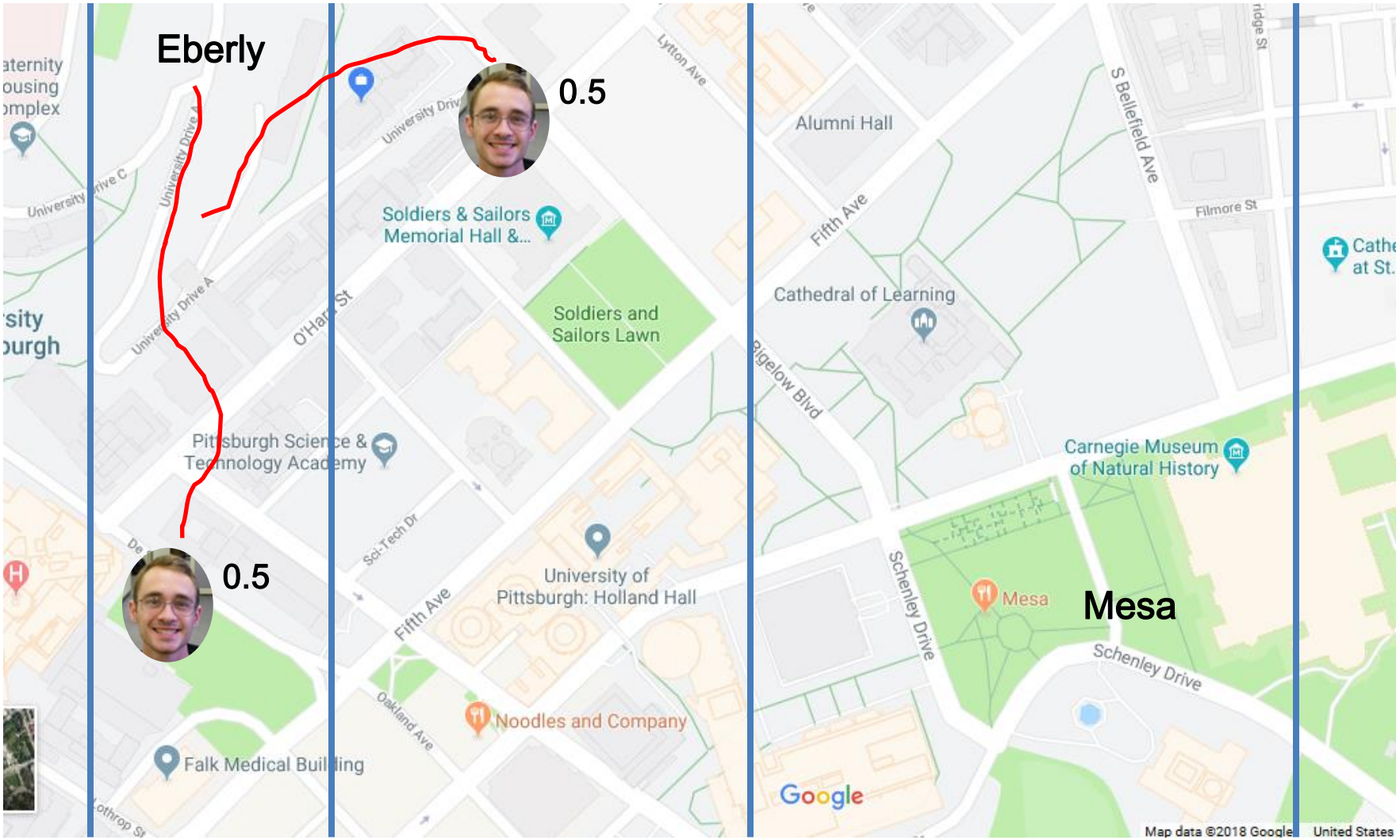

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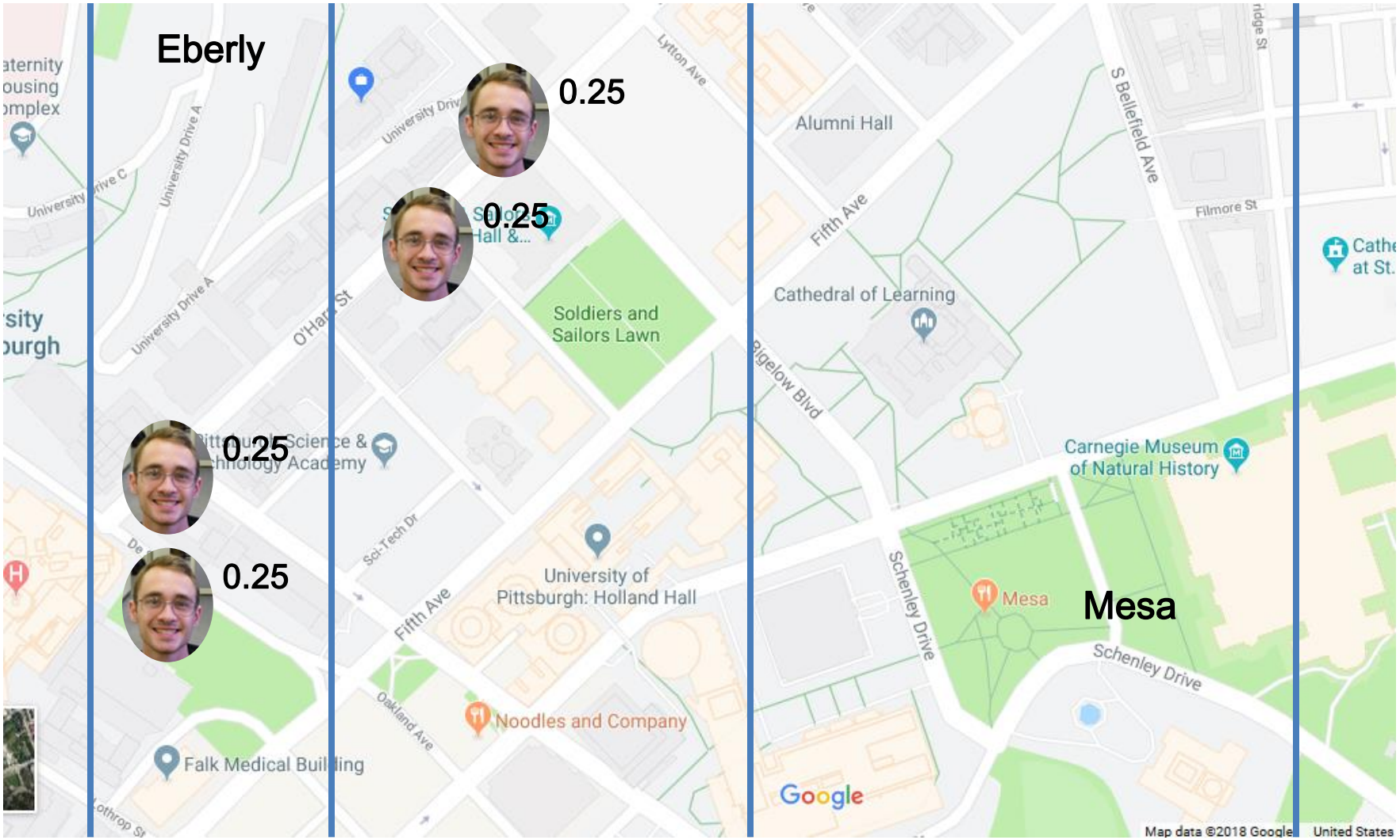

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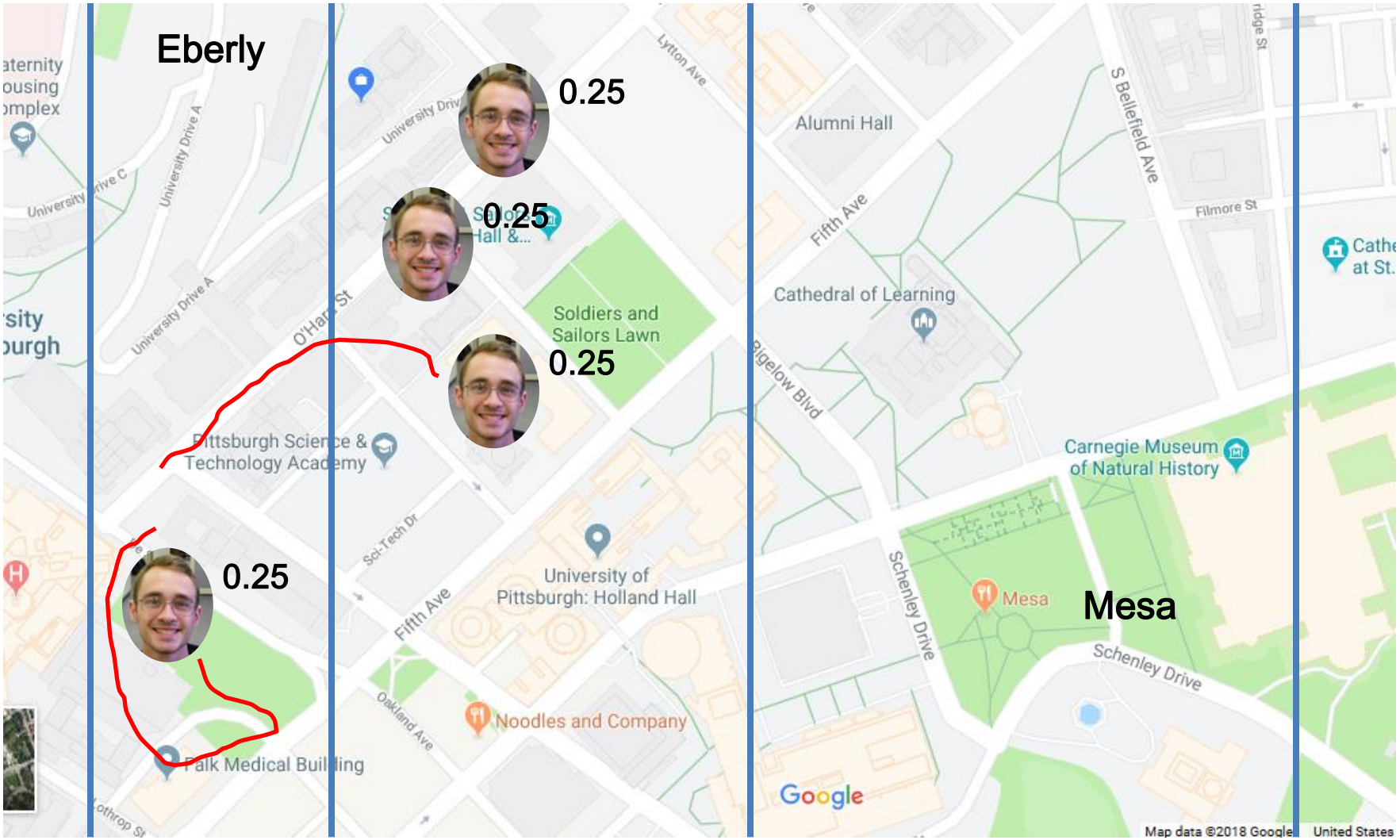

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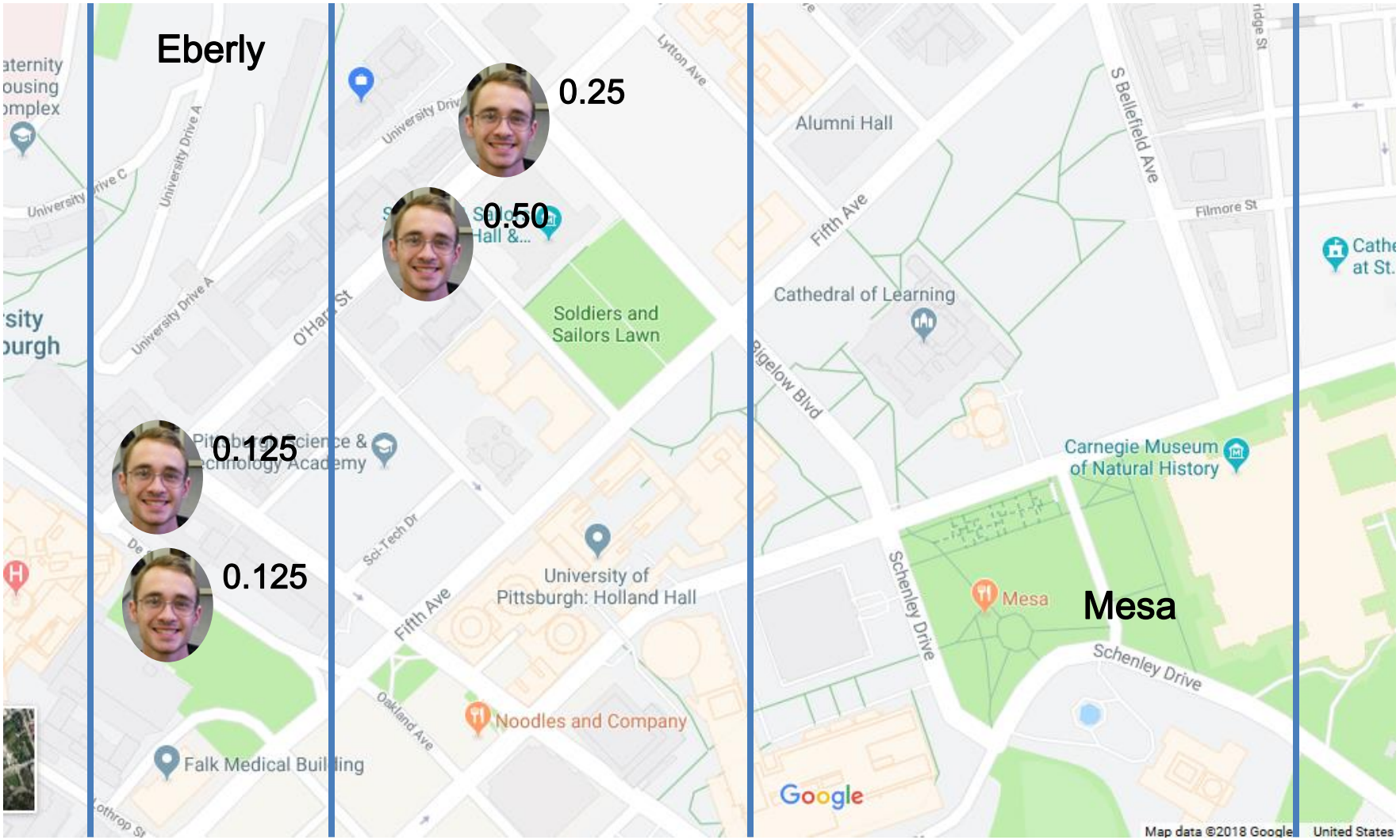

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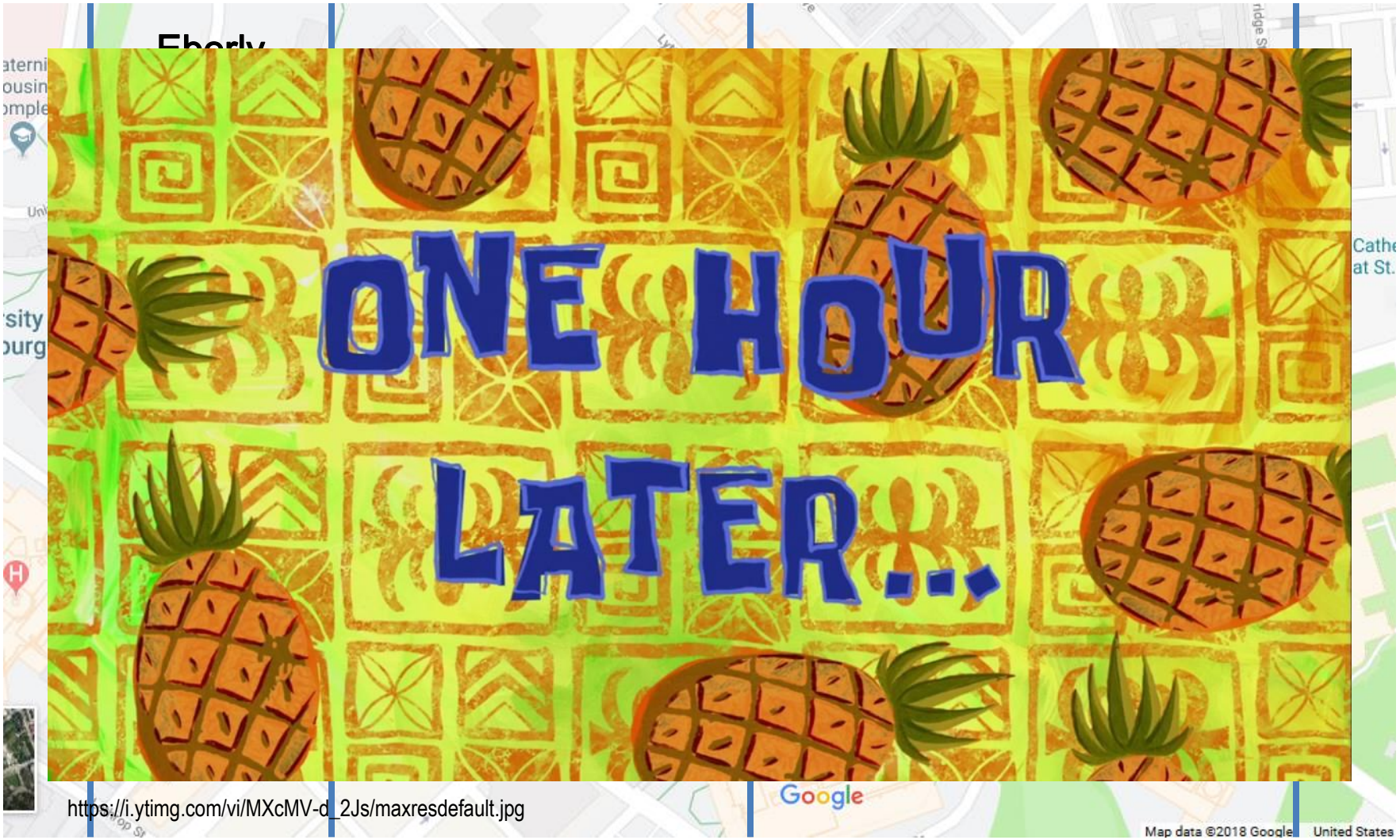

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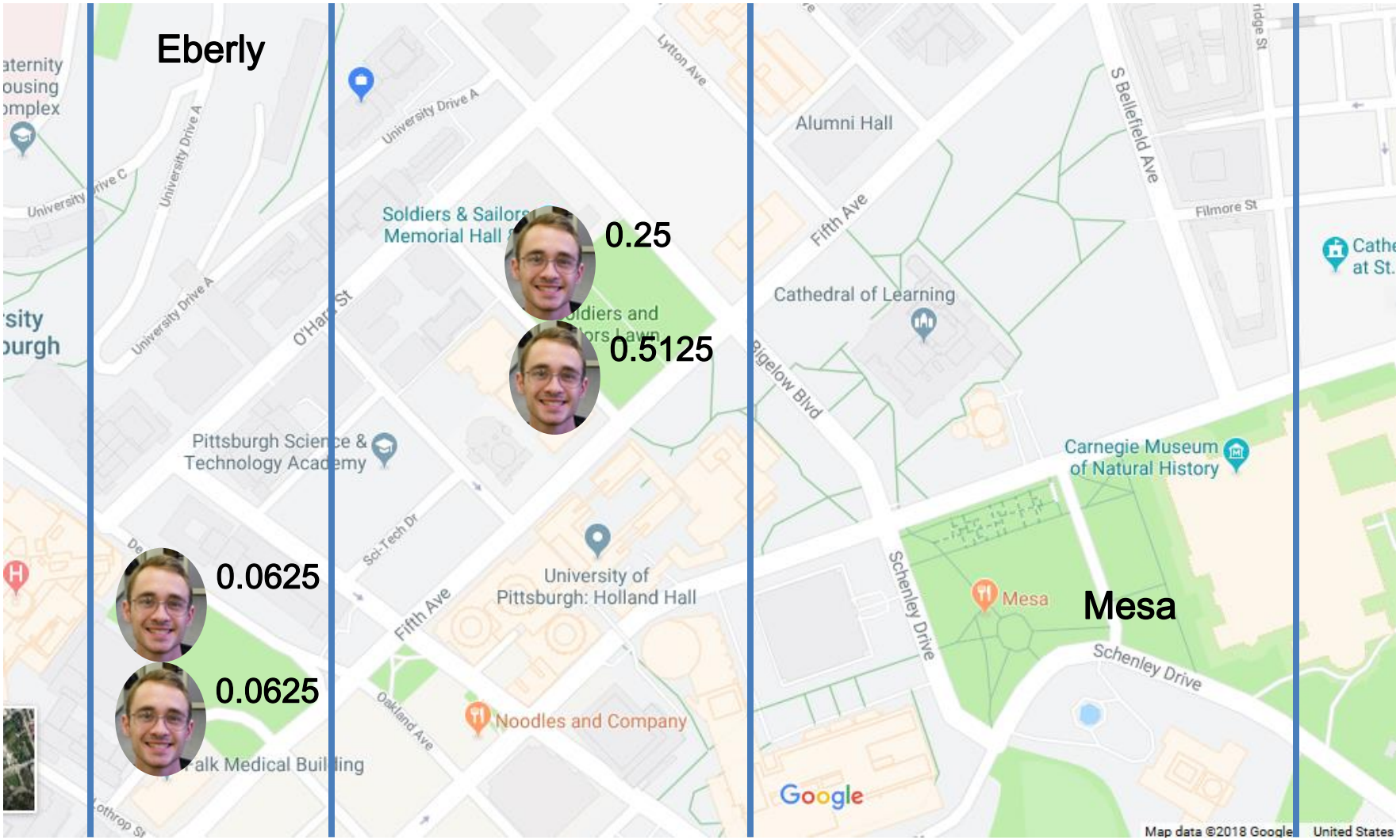

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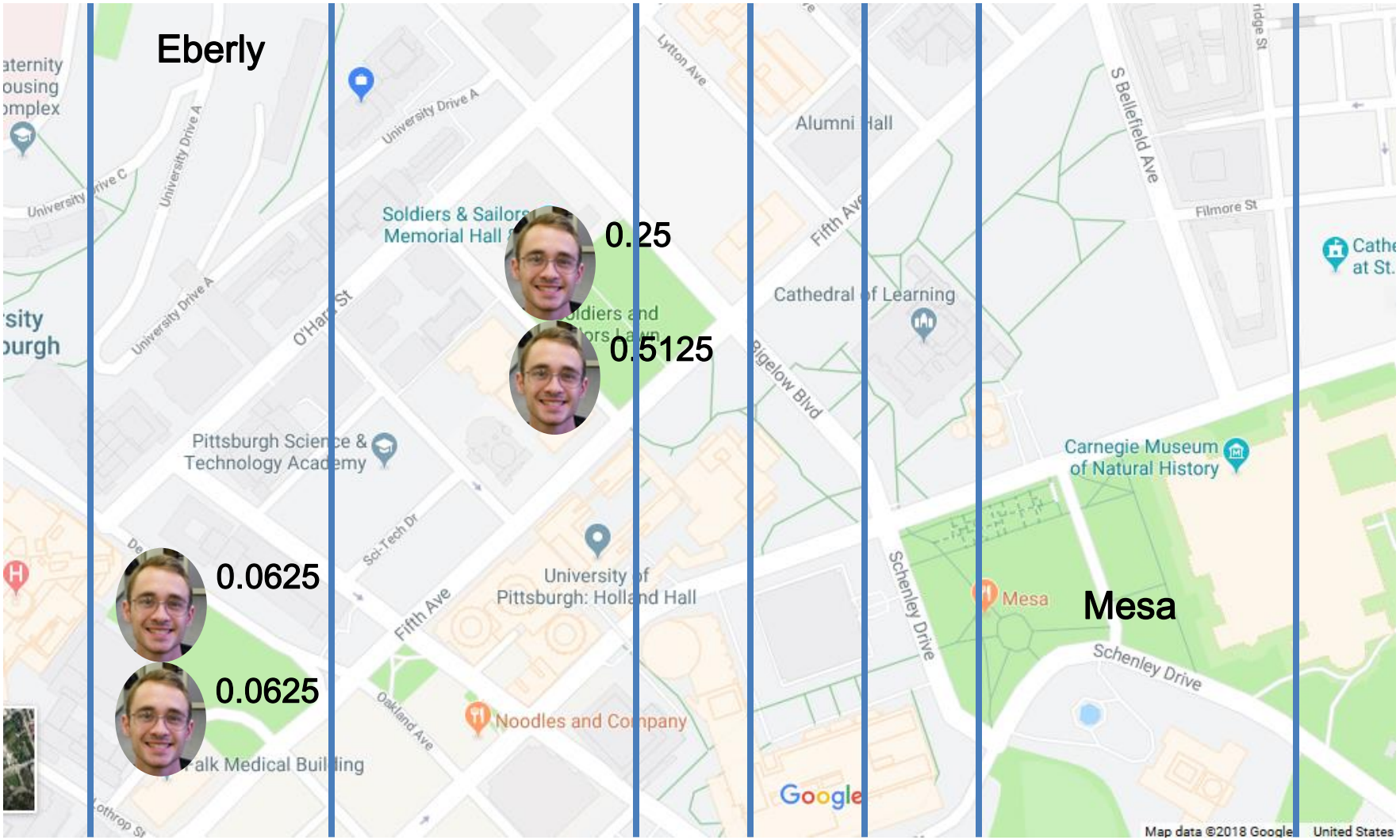

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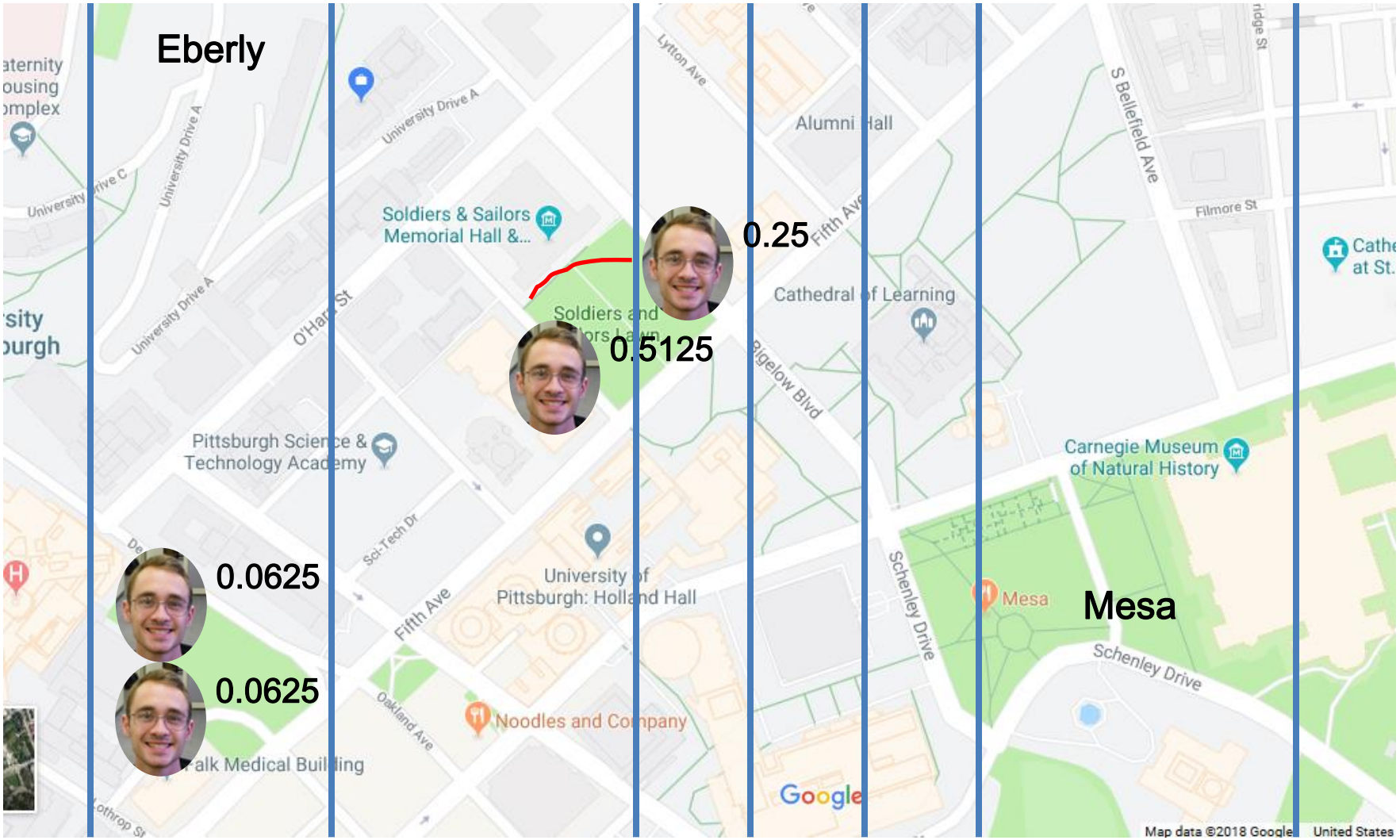

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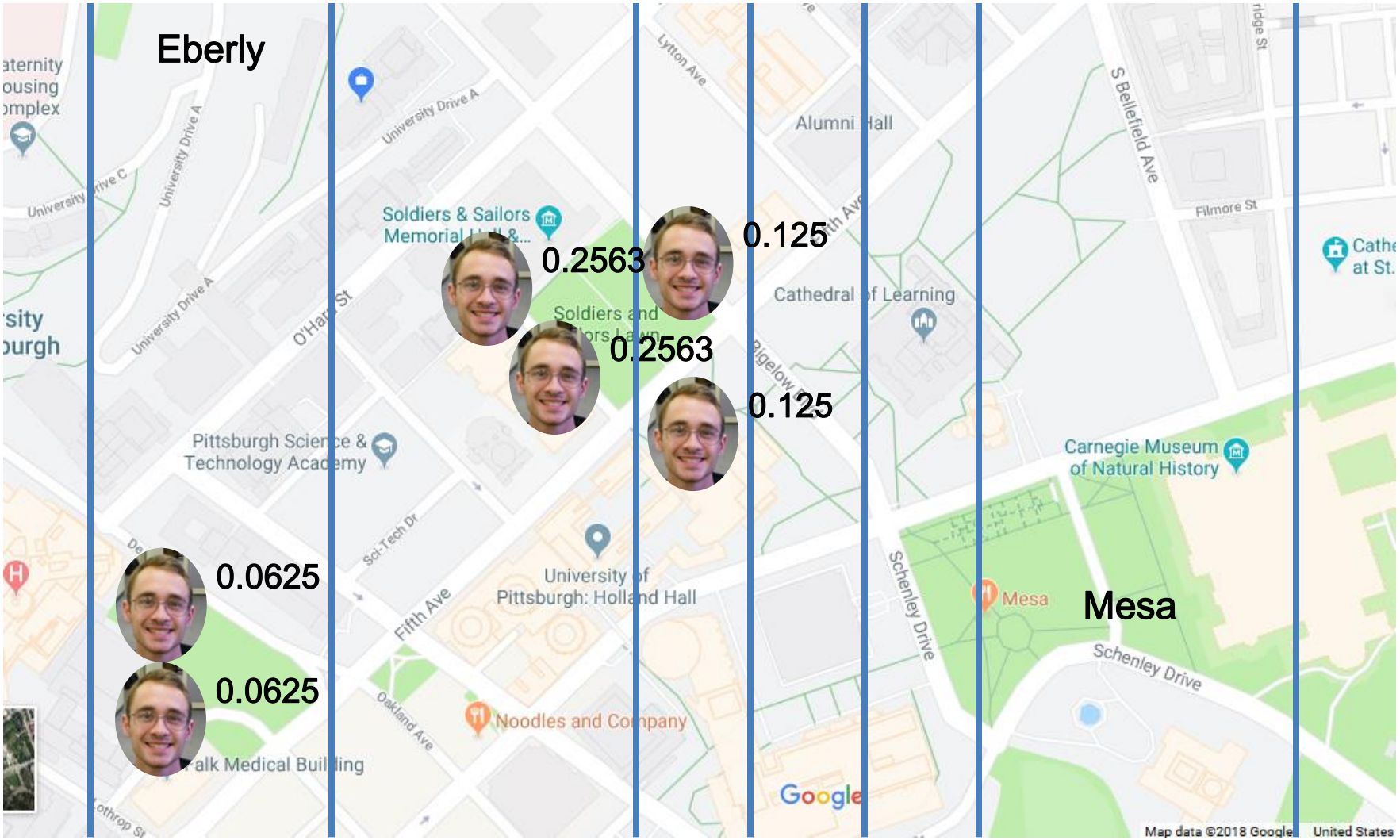

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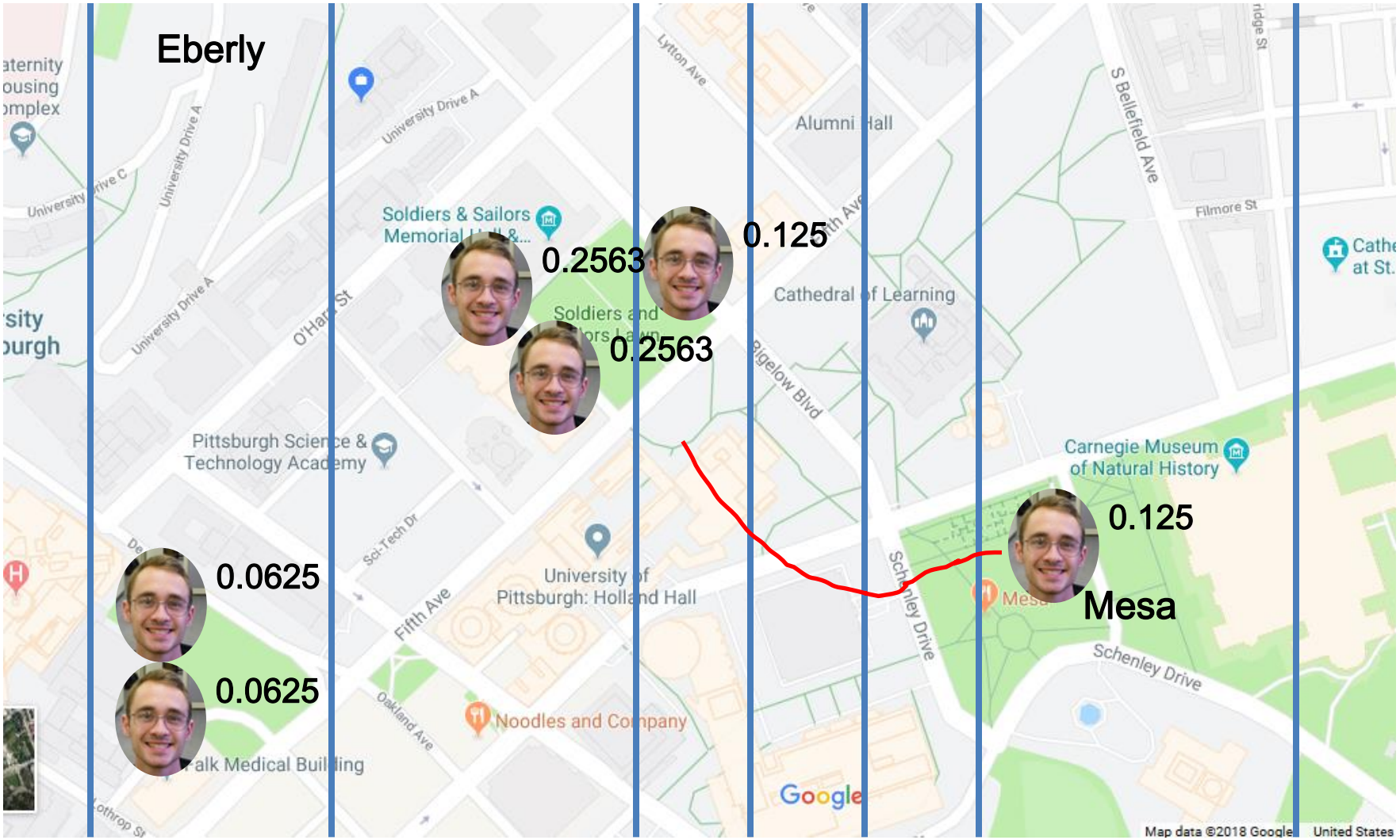
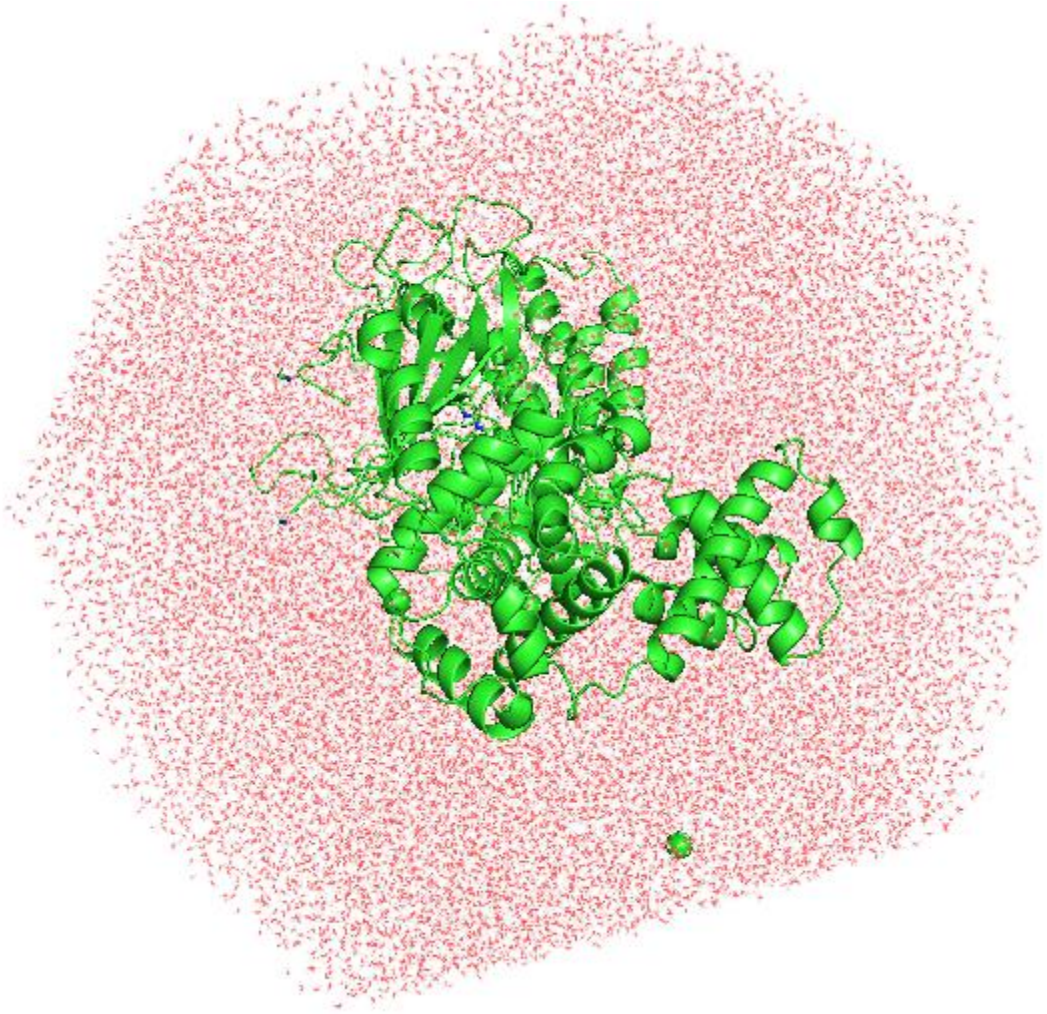


A “Real” Example



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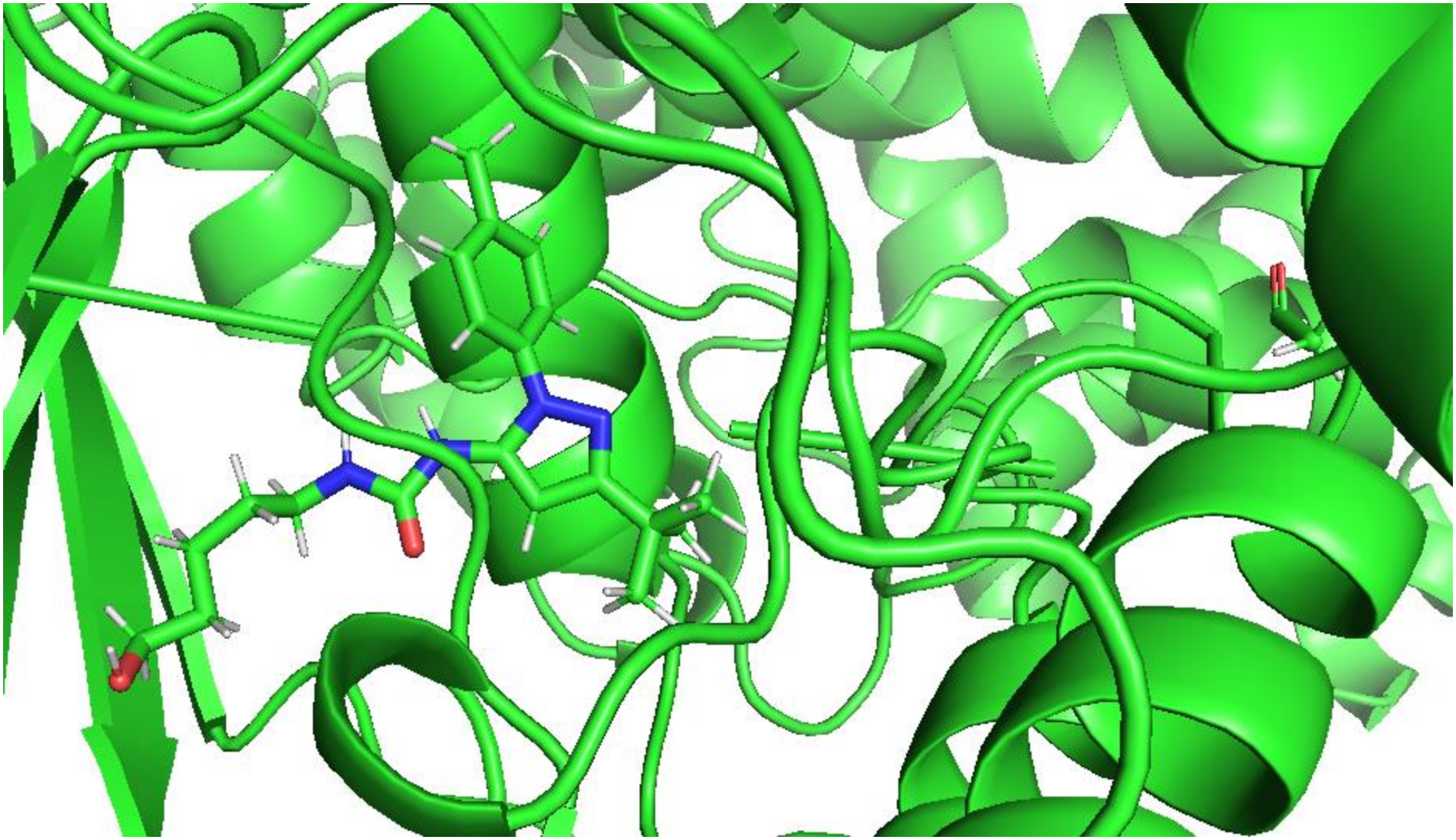

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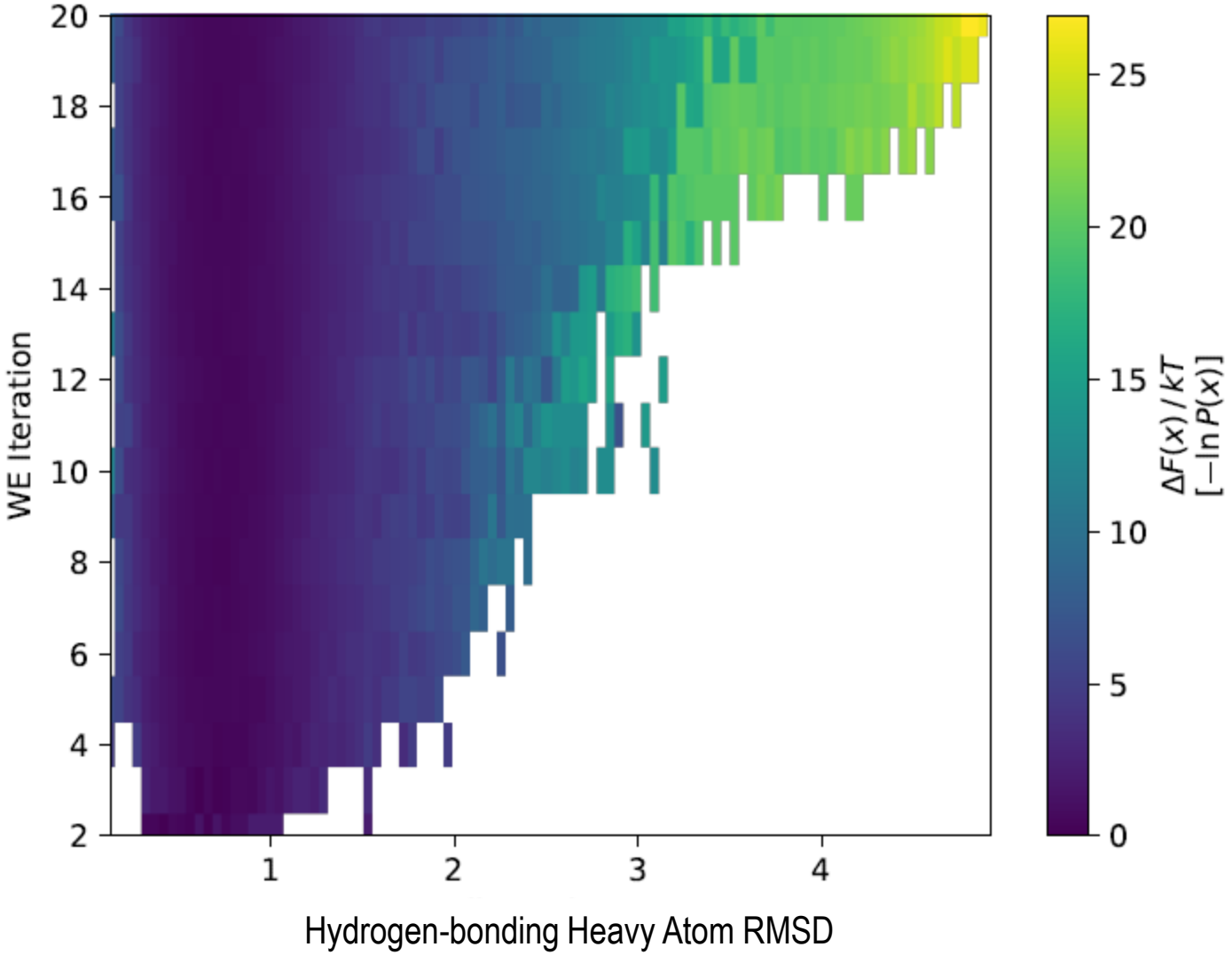

Complications

- It's really difficult to choose *good* parameters for WE (timestep of dynamics, binning scheme, order parameter, etc.)
- **One** event may not be representative of the **ensemble** of events
- Difficult to deal with error (bootstrapping)
- Target state may not be known
- Massive amounts of data are generated, it's very difficult to go back through and re-calculate something if forgotten

References

- Zwier, M. and Chong, L. Reaching biological timescales with all-atom molecular dynamics simulations. *Curr. Opinion in Pharma.* 10: 6, 2010, 745-752