REINFORCEMENT LEARNING FOR MOLECULE GENERATION

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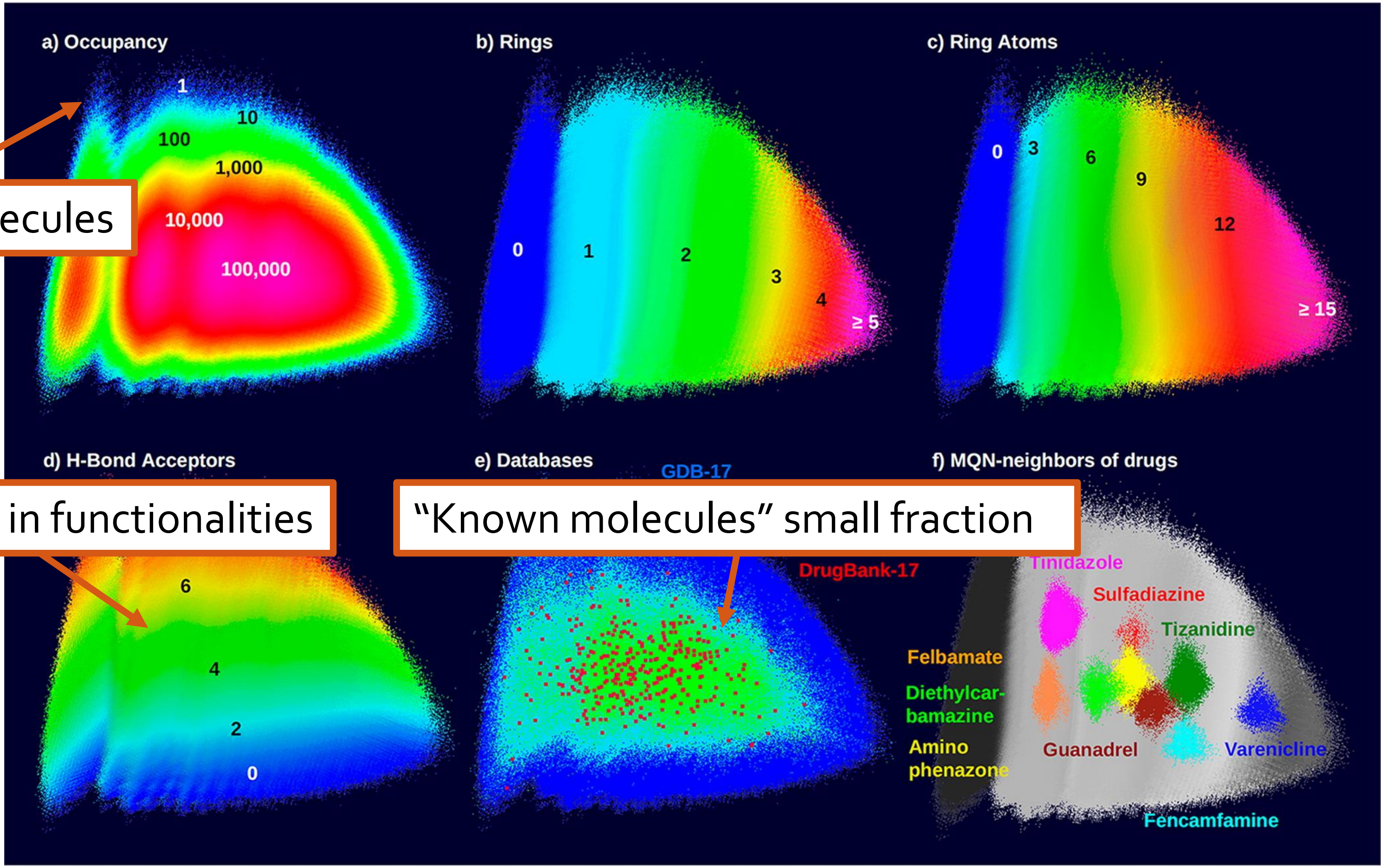
Chemical space is enormous

Searching through even small fraction of "all molecules" is impractical



1.6 x 10^{11} molecules

Wide variety in functionalities

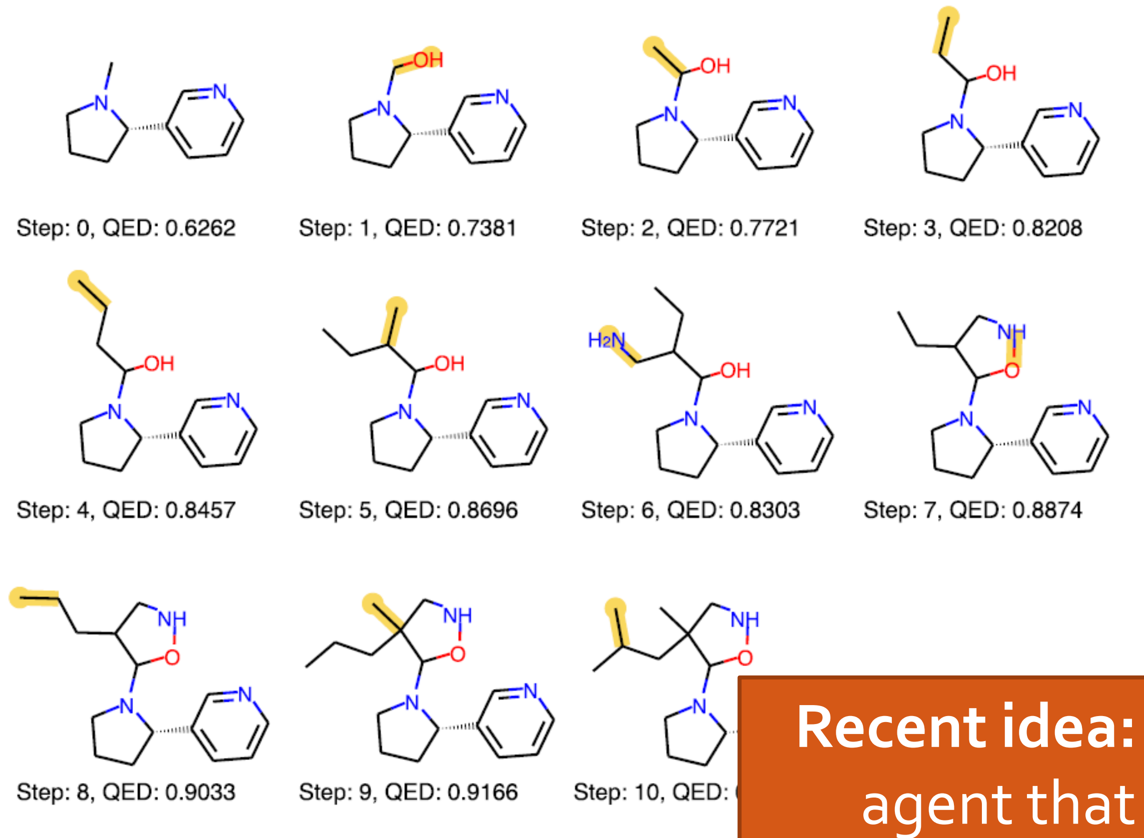
"Known molecules" small fraction

Fig: Ruddigkeit et al. JCIM. (2013)

We need a way to sample through space efficiently

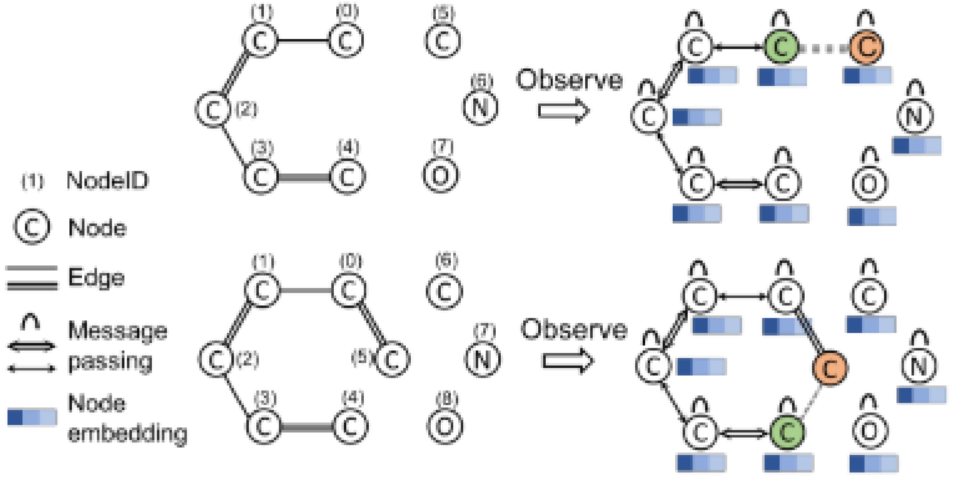
Using RL to sample chemical space

Example #1: MolDQN



Ref: [Zhou et al. Sci Rep. (2019)]

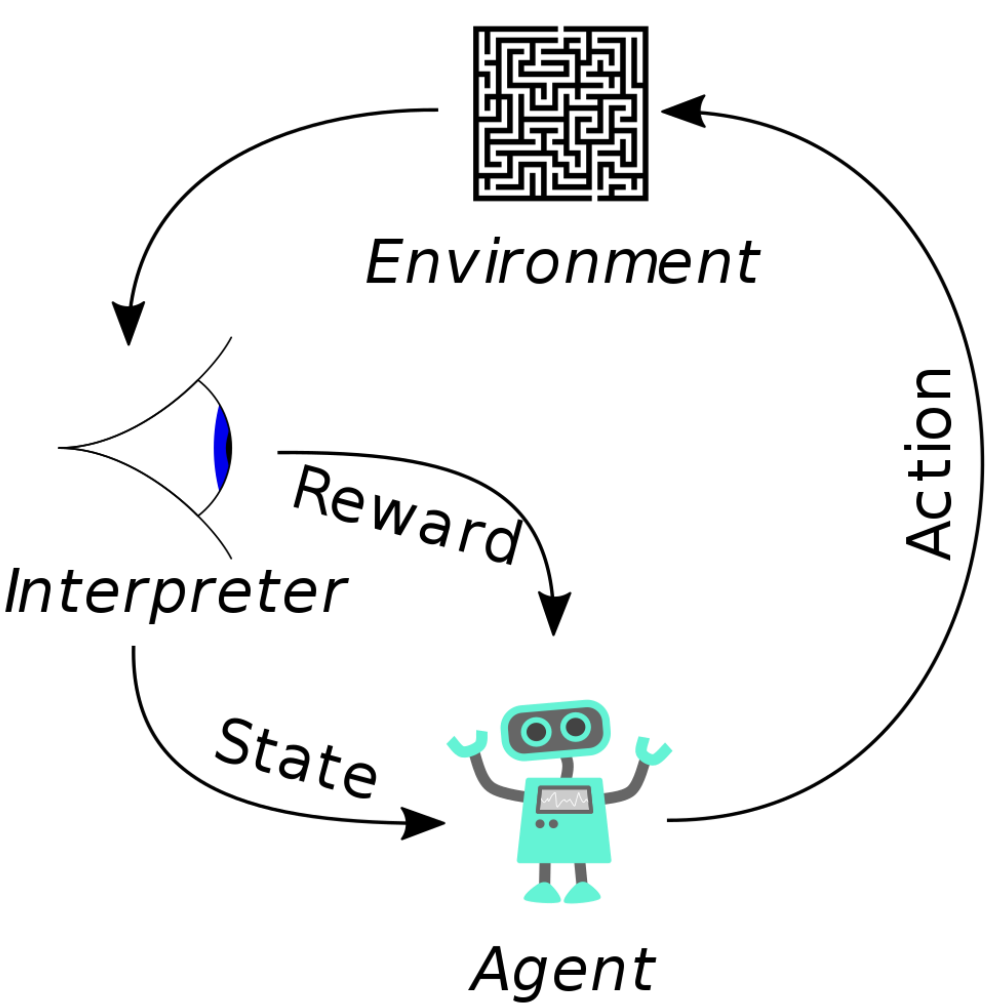
Example #2: GCPN

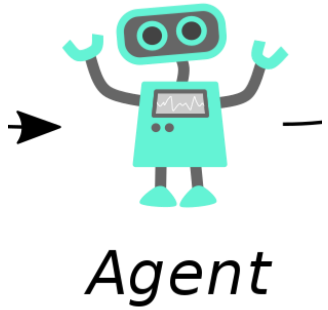


Ref: [You et al. NuerIPS. (2018)]

Recent idea: Make an intelligent agent that builds molecules

What is reinforcement learning?





The agent operates using a policy:

$$\pi(s, a) = \mathrm{P}(\mathrm{a}|\mathrm{s})$$

that produces a distribution of possible actions given the state

Our goal is to learn a policy that "optimizes reward"

How do we learn that policy?

Problem: You cannot just measure policy*

What can we measure?

The "reward" (R) for taking a certain action (a) in state (s)

How can we get those measurements? Interacting with the environment!
Making actions over many *steps* with the algorithm over many *episodes*, guided by the current policy (*rollout*)

New Problem: Ok, so we now have a dataset of many different (s, a, R). Now what?

*Not always true, you could decide an expert (e.g., humans) make optimal policy decisions

Simple Method: “Policy Gradient”

Idea: Update your policy ($\pi_\theta(s, a)$) to make good actions more often

Math*: $\theta \leftarrow \theta + \alpha \nabla_\theta \log \pi_\theta(\boldsymbol{a_t}, \boldsymbol{s_t}) \boldsymbol{V_t^*}$

$\boldsymbol{a_t}$ and $\boldsymbol{s_t}$ are things we measure directory

$\boldsymbol{V_t^*}$ is based on the ($\boldsymbol{r_t}$) rewards we measure for future steps

$$V_t = \sum_{i=0}^{n} \gamma^i r_{t+i}$$

subtracted from the “average reward”: $V_t^* = V_t - \mathbb{E}[V_t]$

so that good actions get positive and bad actions get negative rewards

*this equation is not arbitrary; it has a proof. See Chris Yoon’s excellent blog posts

A less-simple method: Actor Critic

Idea: Learn a better value function, one that looks <u>infinitely</u> far in the future

Math*: $\theta \leftarrow \theta + \alpha \nabla_\theta \log \pi_\theta(\boldsymbol{a_t}, \boldsymbol{s_t}) \boldsymbol{Q}_w(s_t, a_t)$

We now have two models:

1. **Actor ($\boldsymbol{\pi_\theta(a_t, s_t)}$): Generates moves**
2. **Critic ($\boldsymbol{Q_w(a_t, s_t)}$):** Evaluates value of move

Train the "Critic" function by coming a "time-dependent" error from "Bellman Equation":

$$\delta_t = [\boldsymbol{r_t} + \gamma Q_w(\boldsymbol{s_{t+1}}, \boldsymbol{a_{t+1}})] - Q_w(\boldsymbol{s_t}, \boldsymbol{a_t})$$

Error is to make prediction of a moves' reward ($Q_w(\boldsymbol{s_t}, \boldsymbol{a_t})$)

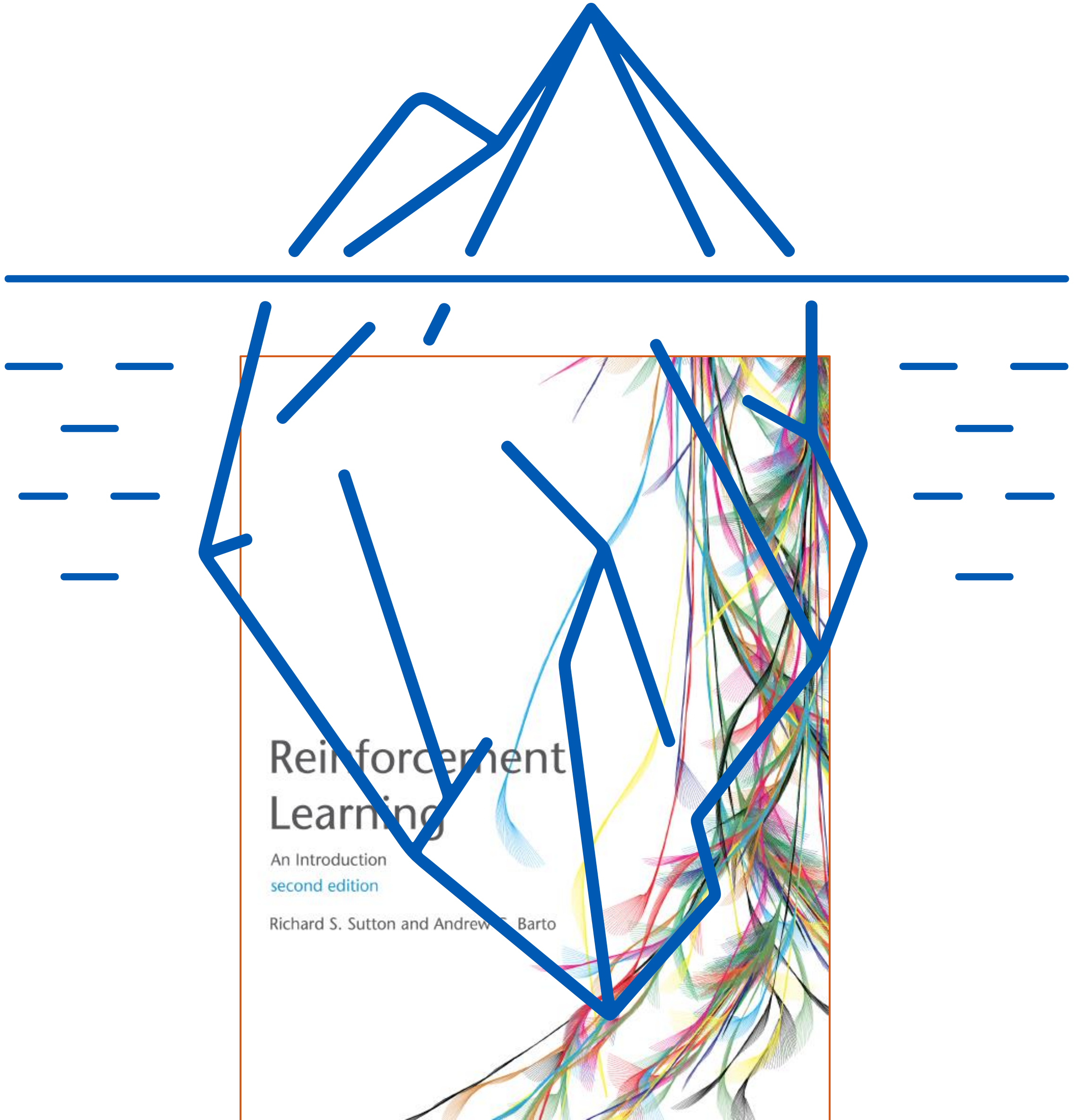
closer to value of the reward (r_t) plus a discounted (γ) value of next move ($Q_w(\boldsymbol{s_{t+1}}, \boldsymbol{a_{t+1}})$)*

Update the weights accordingly

$$w \leftarrow w + \alpha \delta_t \nabla_w Q_w(s_t, a_t)$$

*inductive relationship means after many updates, we achieve infinite lookahead
(step t+1 is influenced by t+2, t+2 by t+3, …)
See Chris Yoon's excellent blog posts

This lecture only scratches the surface



Today's lecture

A field with a [500+ page textbook]

Doing this in practice?

Several interdependent choices:

- **Training Algorithm:** How are we going to express and learn a policy?
- **Environment:** How do we define the state and actions for an environment?
- **Learnable Functions:** How do we represent state and actions? What models to use?

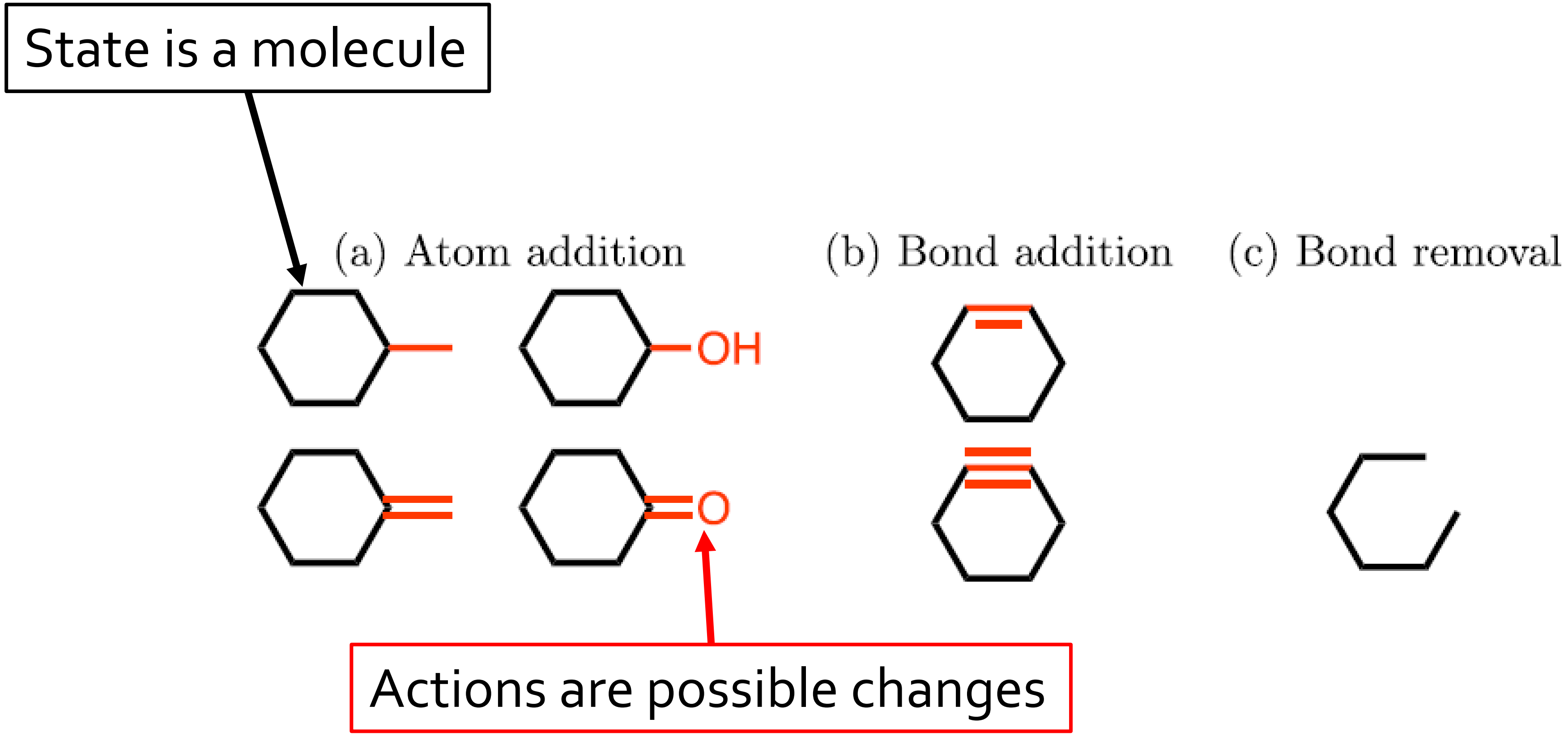
EXAMPLE #1: MOLDQN

Ref: Zhou et al. Sci Rep. (2019)

How do I train it? “Deep Q-Learning”

	Human	Math
What is the “Q function”?		
	“Q” is the value of an action at a certain state	$Q(s, a) = \mathrm{E}_\pi[\sum r_t]$
	Action with best Q is the best choice	$\pi^*(s) = \arg\max_a Q(s, a)$
How do I train it?		
	Minimize the “lookahead/Bellman equation,”	$l(\theta) = \mathrm{E}\left(f_l\left(y_t - Q(s_t, a_t)\right)\right)$
	which updates value to match reward + Q value of the next step	$y_t = r_t + \max_a Q(s_{a+1}, a)$

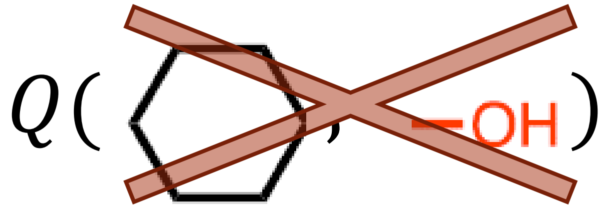
What is the environment?



What are the functions?

What they don't do: Represent current molecule and action separately

How do you represent a bond addition, deletion or atom addition in the same way!?

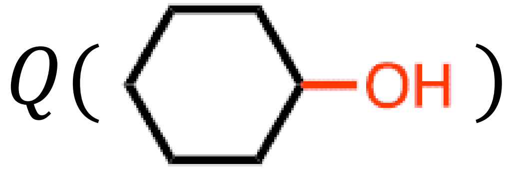


Theory aside:

1. Q-learning takes pairs of state (s) and action (a)
2. State + action do not always predict the next state (s′)
3. Unless the process is deterministic (same state, same action, same result)

Simplification: Use the next state (a whole molecule) [An easy task]

They chose Morgan fingerprints with multi-layer perceptions



EXAMPLE 2: GRAPH CONVOLUTIONAL POLICY NETWORK (GCPN)

Ref: You et al. NuerIPS. (2018)

How do I train it? PPO (at a High-Level)

High-level Goal: Maximize taking 'advantageous moves'

$$L(\theta) = \mathbb{E}_t\left[\min\left(r_t(\theta)\hat{A}_t, \text{clip}(r_t(\theta), 1-\epsilon, 1+\epsilon)\hat{A}_{\boldsymbol{t}}\right)\right]$$

where $r_t(\theta) = \frac{\pi_\theta(a_t, s_t)}{\pi_{\theta_{old}}(a_t, s_t)}$

Adjust θ so that $\pi(s, a)$ becomes bigger for advantageous moves

Hard part is defining the "Advantage Function" ($\widehat{\mathrm{A}}_{\mathrm{t}}$)

$$\hat{A}_t = \delta_t + (\gamma\lambda)\delta_{t+1} + \cdots + (\gamma\lambda)^{T-t+1}\delta_{T-1}$$

where $\delta_t = r_t + \gamma V(s_{t+1}) - V(s_t)$

Something we can compute

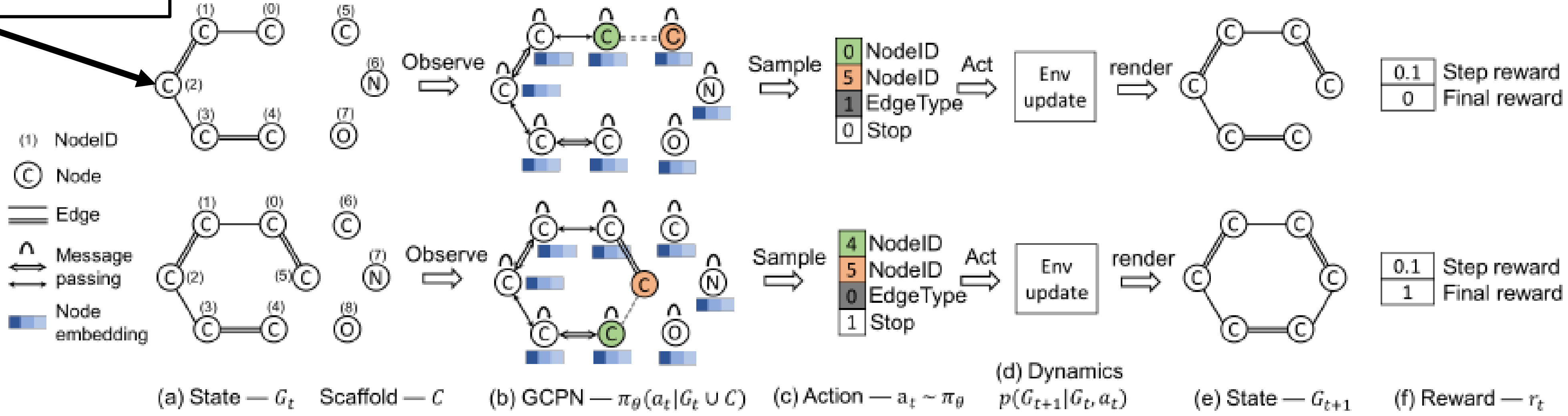
A function we can learn with similar "lookahead" approaches

Another "trick:" Keeping $\pi(a_t, s_t)$ diverse with an "entropy" prediction

Full details: Schman et al.

What does my environment look like?

State is a molecule



Actions are: Atom at beginning and end of bond, bond type and whether to stop

$$a_t = \text{CONCAT}(a_{\text{first}}, a_{\text{second}}, a_{\text{edge}}, a_{\text{stop}})$$

What are the functions?

Message passing networks (graph convolutions) are used to generate atom features (X)

$$f_{\text{first}}(s_t) = \text{SOFTMAX}(m_f(X)), \qquad a_{\text{first}} \sim f_{\text{first}}(s_t) \in \{0,1\}^n$$

First atom: Generate probability given atom features

$$f_{\text{second}}(s_t) = \text{SOFTMAX}(m_s(X_{a_{\text{first}}}, X)), \qquad a_{\text{second}} \sim f_{\text{second}}(s_t) \in \{0,1\}^{n+c}$$

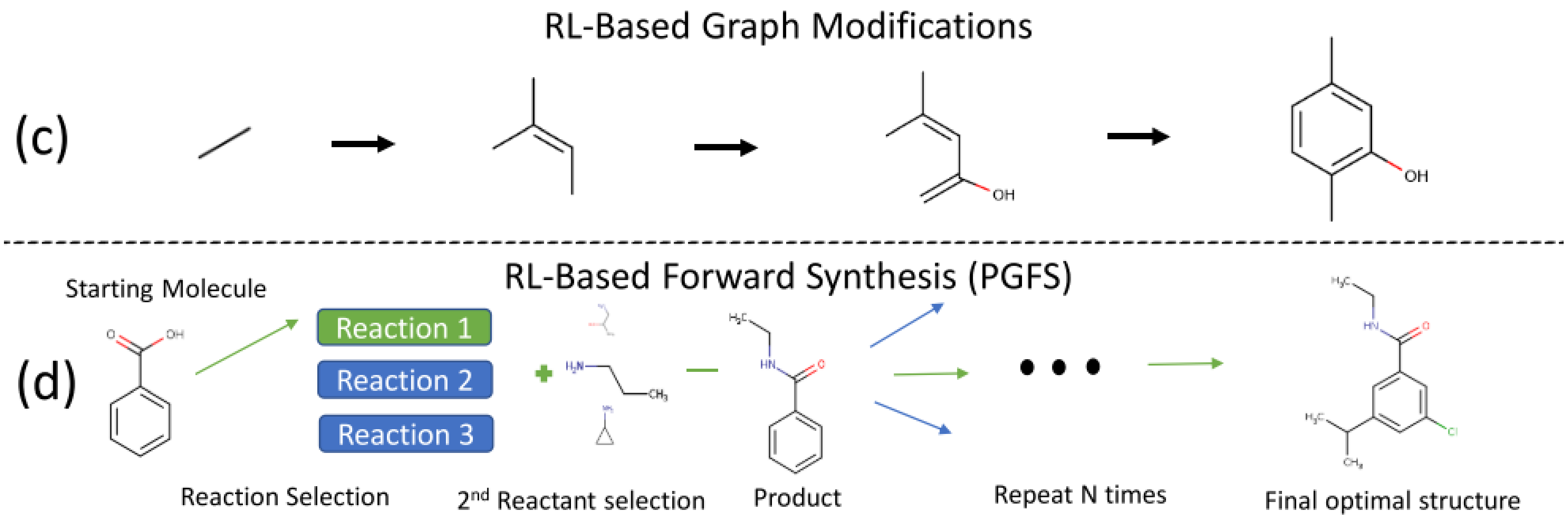
Second atom: Generate probability given first atom's features *and* all node features

$$f_{\text{edge}}(s_t) = \text{SOFTMAX}(m_e(X_{a_{\text{first}}}, X_{a_{\text{second}}})), \qquad a_{\text{edge}} \sim f_{\text{edge}}(s_t) \in \{0,1\}^b$$

Bond type: Generate probabilities given features of first and second atom

Newer Iteration: Reaction-template guided RL

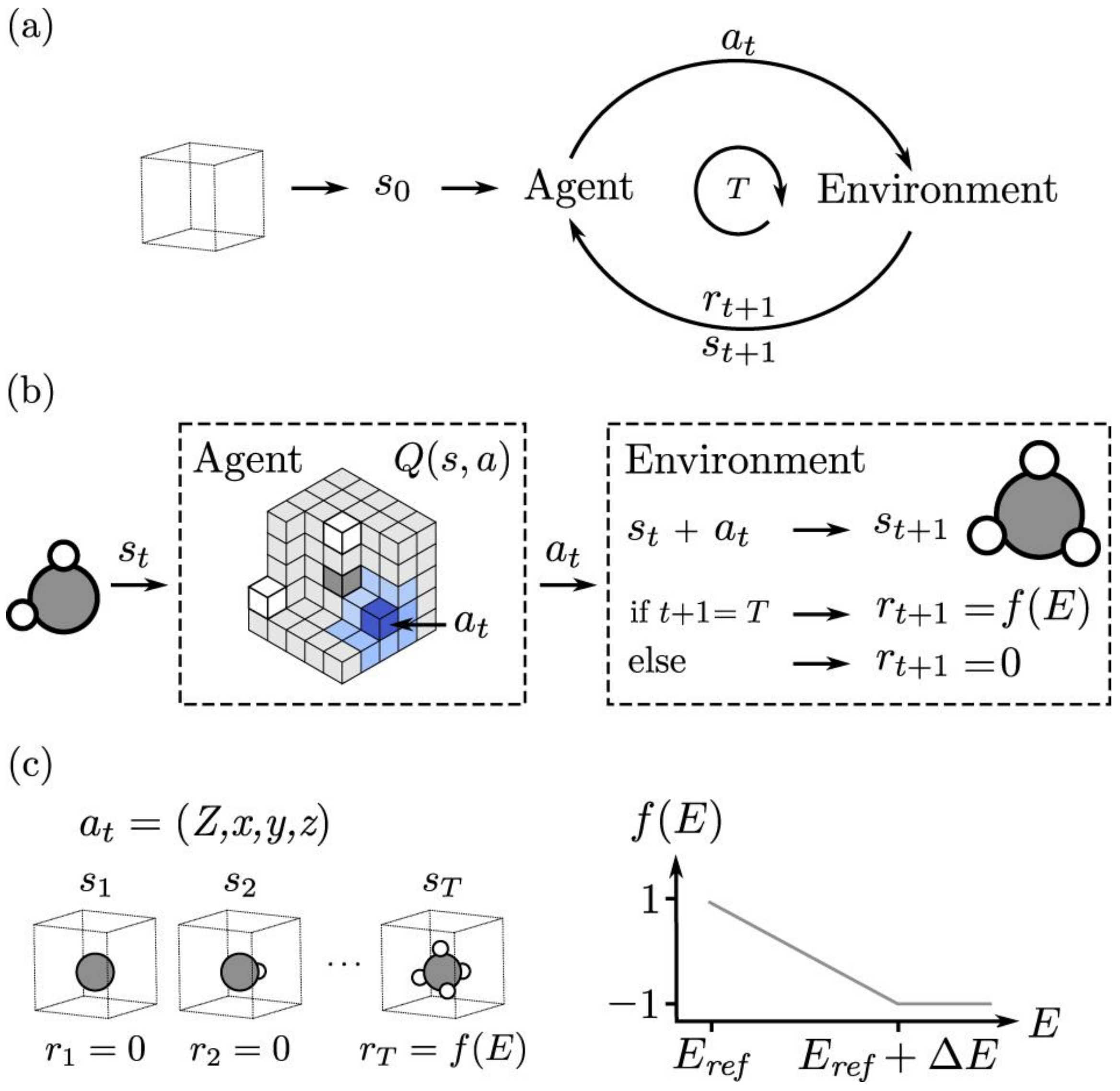
Or example methods chose moves as graph additions



Newer approaches limit choices by selecting reaction products

Ref: Gottipati et al. (2020)

Another Example: Q-Learning for Atomic Structures



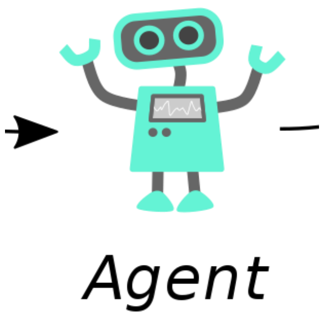
Ref: Meldgaard et al. JP:CM (2020)

Take Away Points

RL at a glance

Concept: Learn a policy by

1. interacting with an environment
2. adjusting based on rewards



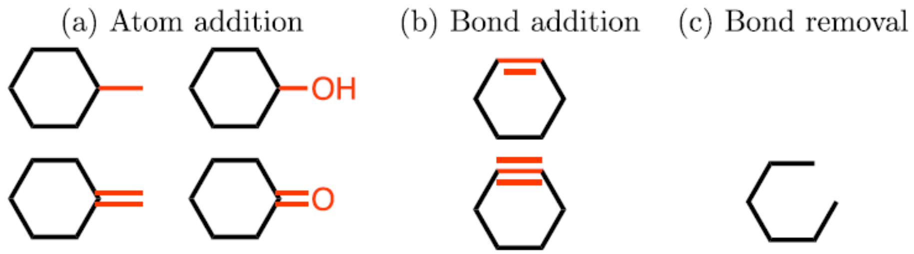
Difficult math:

Many ways to learn policy:

1. Q-learning
2. PPO
3. Actor critic
4. …

Making your own environment

1. Implement an environment



2. Choose learning policy

3. Make representations state and action, implement value/actor/critic/Q functions