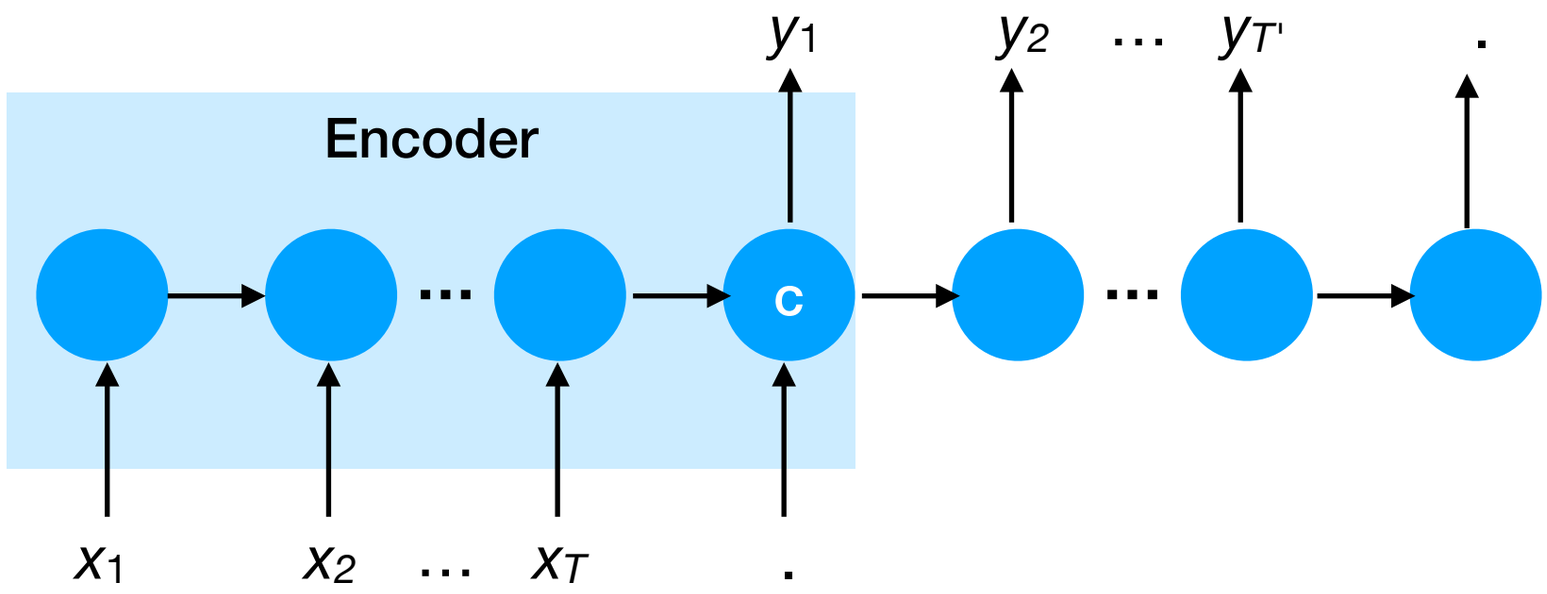
CS/DS 541: Class 21

Jacob Whitehill

seq2seq models

Sequence-to-sequence translation model (seq2seq)

- Recall the seq2seq model from Sutskever et al. (2014) in which the "context" **c** (that encapsulates the meaning of the input sentence) is the last hidden state of the encoder:



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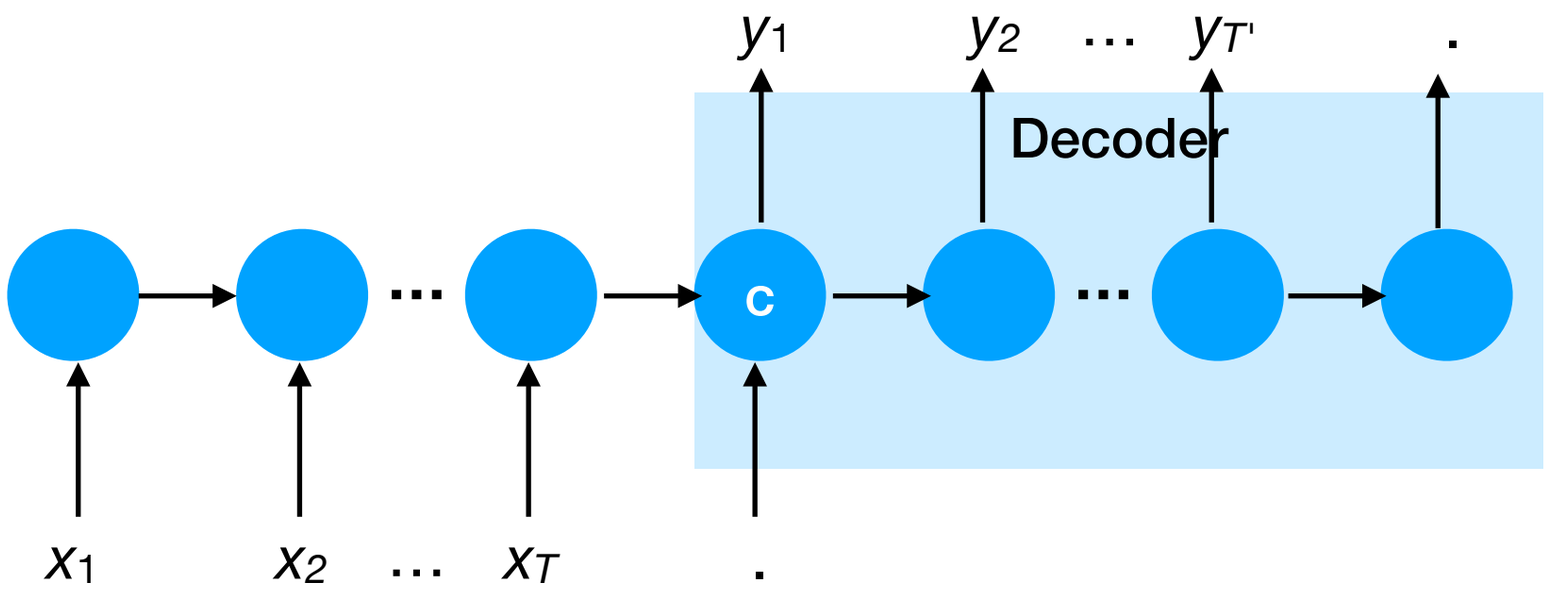
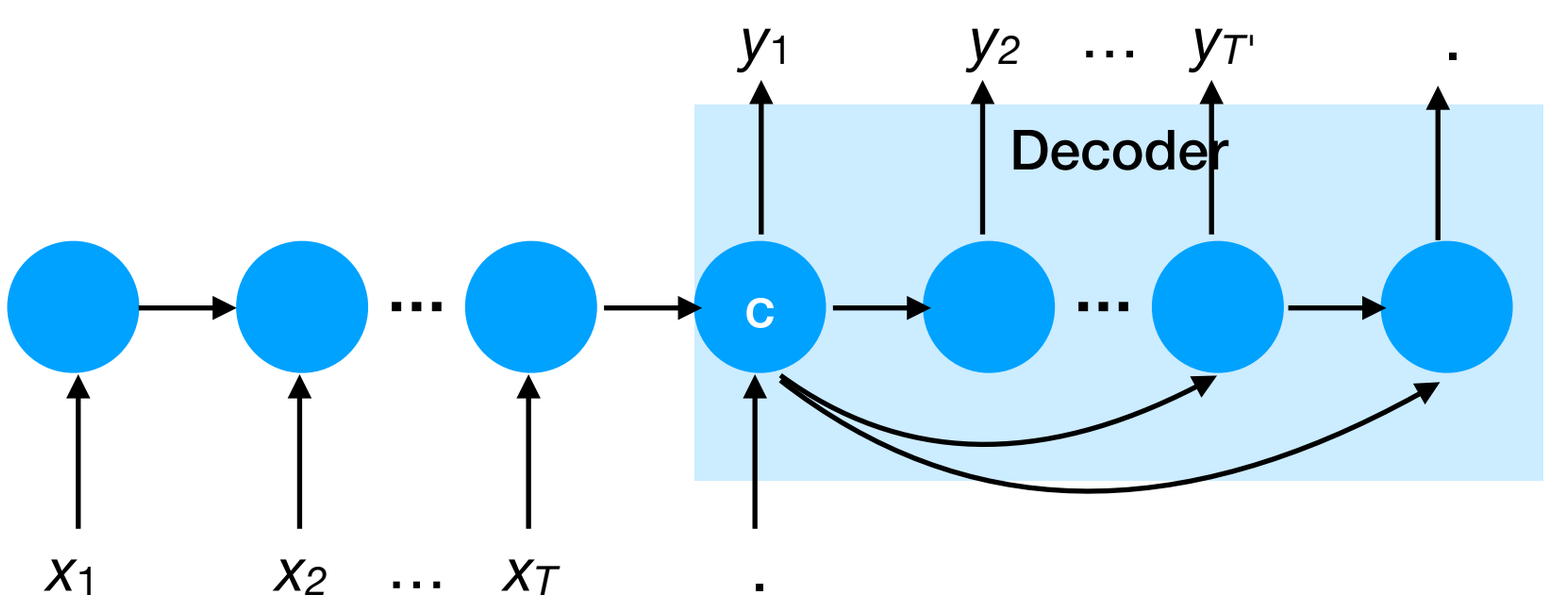


seq2seq models with context

- As an alternative to this model (Cho et al. 2014), we can feed **c** explicitly to *all* timesteps of the decoder:



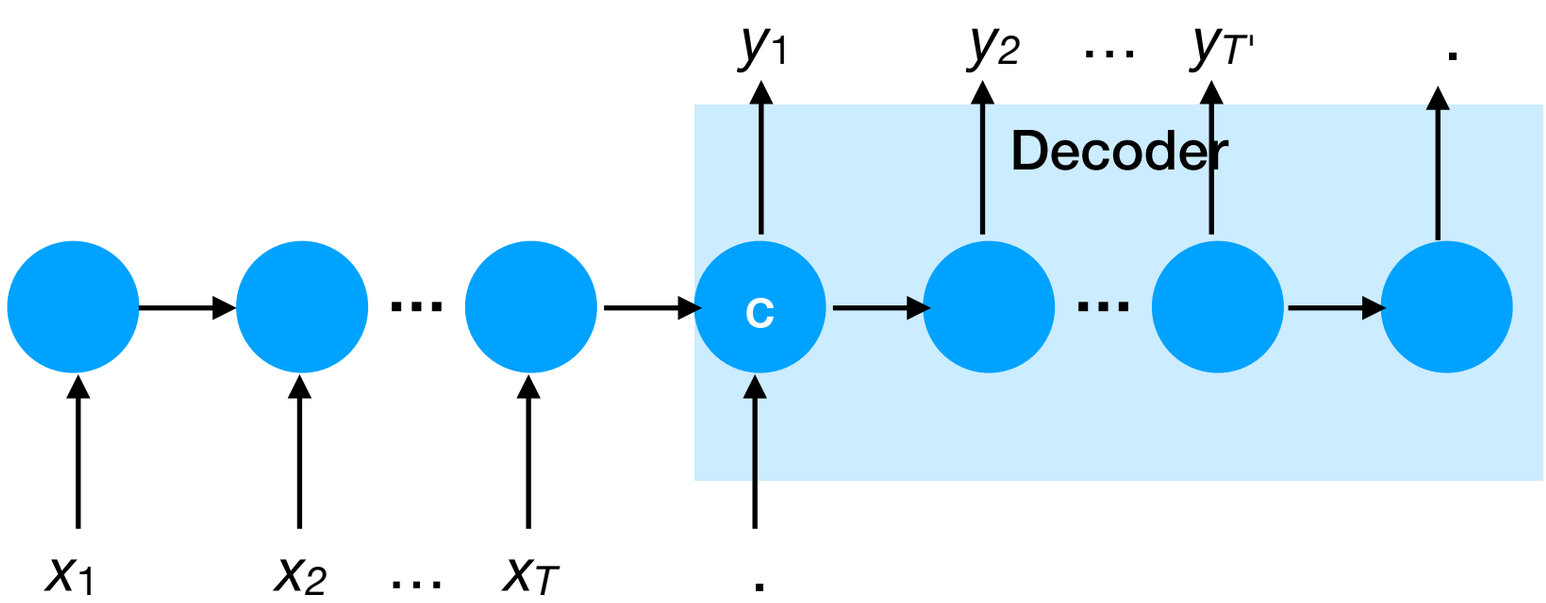
Neural attention models

Attention models

- Seminal paper:
  - Bahdanau et al. 2015

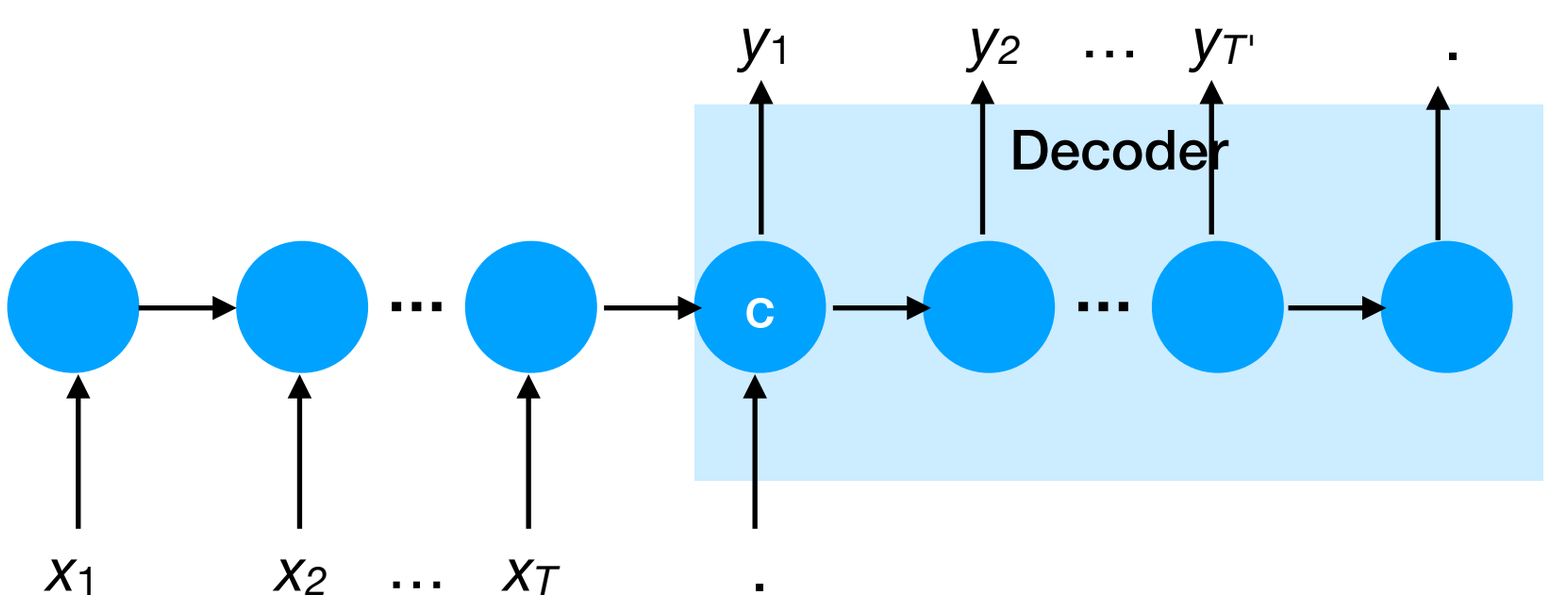
seq2seq models

- While elegantly simple, seq2seq networks may struggle to fit all information about **x** into a single vector **c**.



Attention models

- Intuitively, some subsequences of the input may be more relevant than others when producing a particular output symbol y_t.



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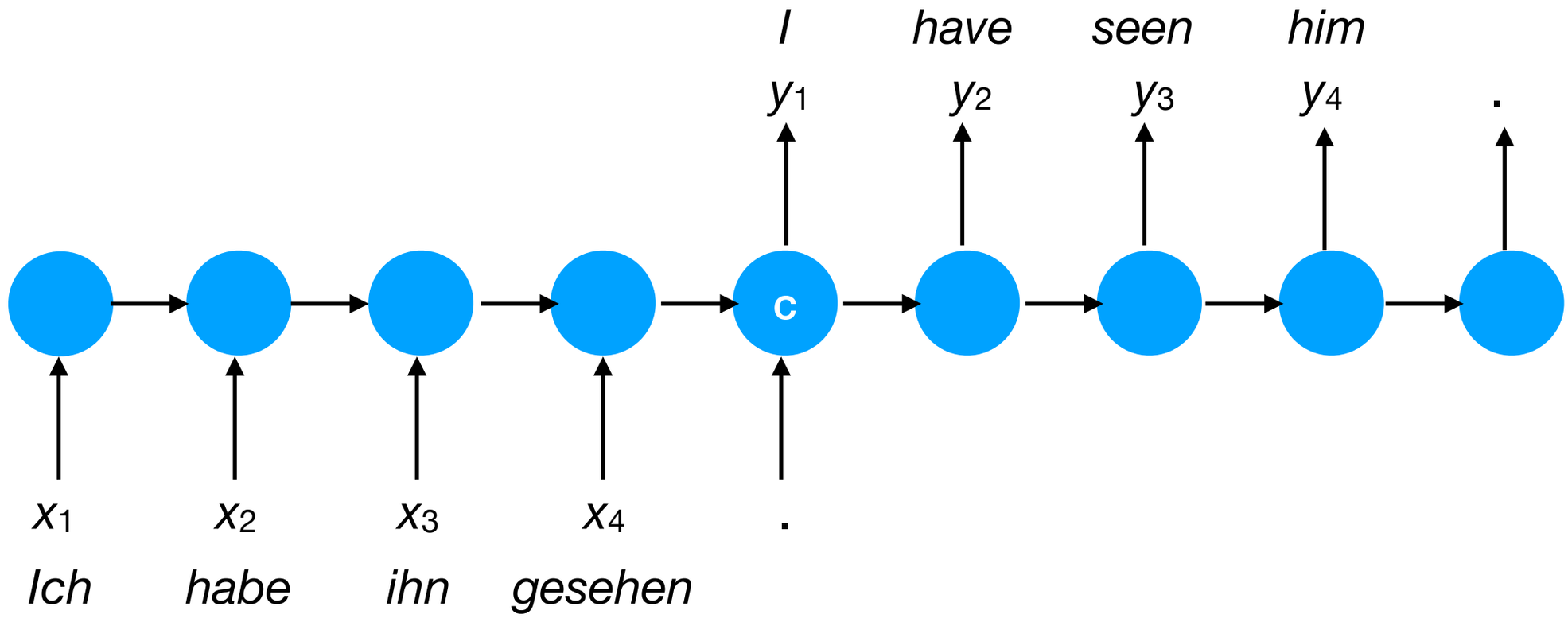

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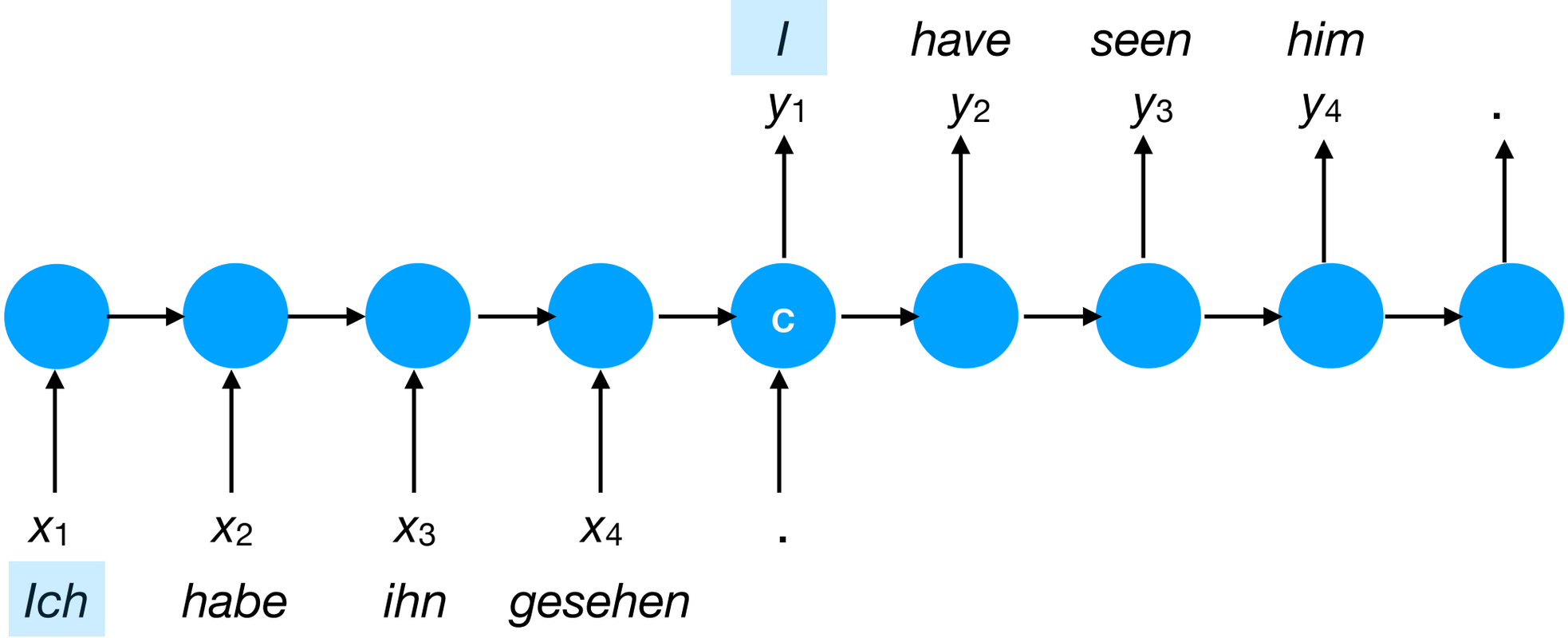

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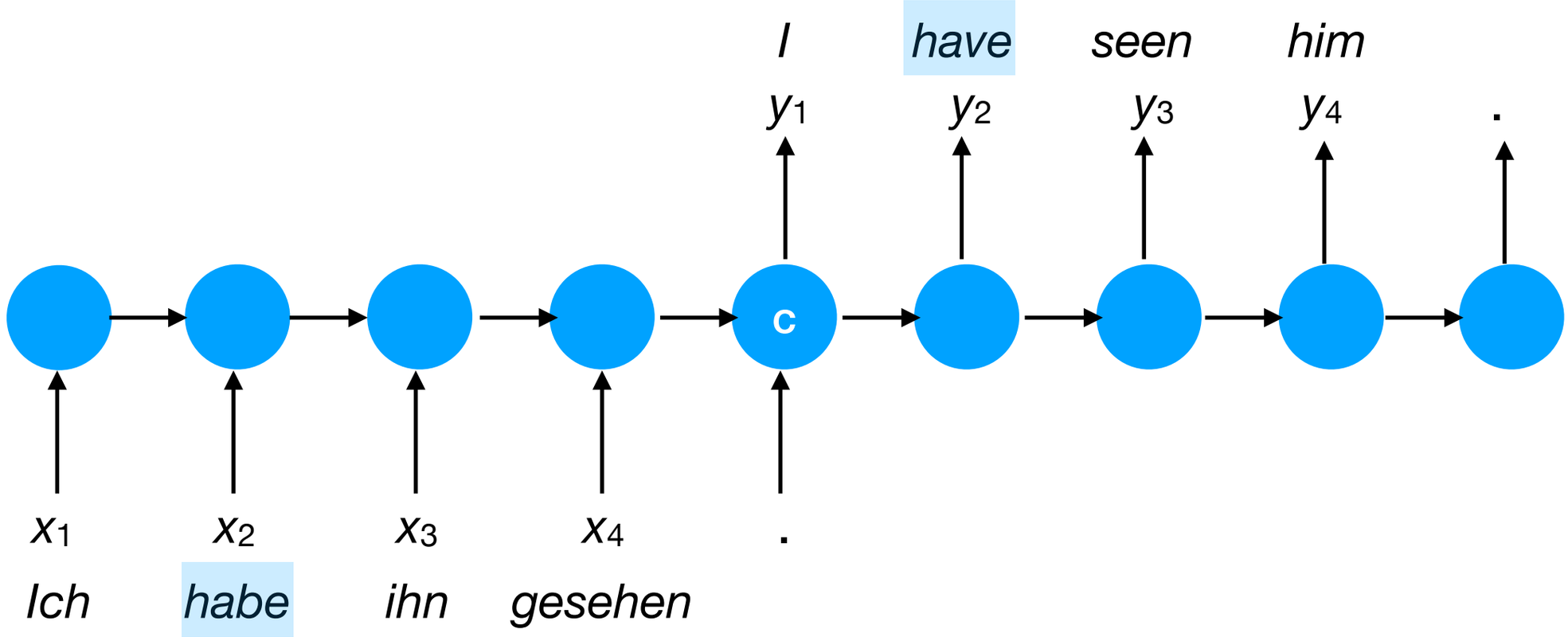

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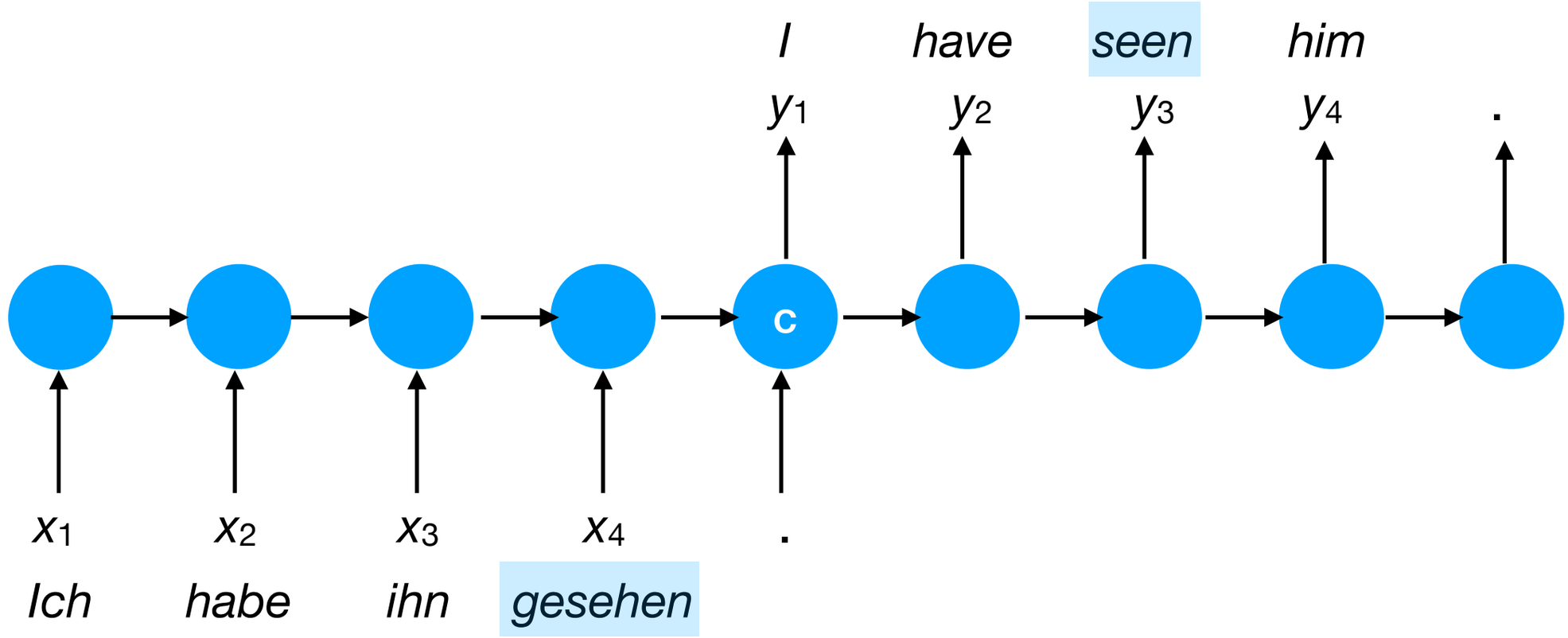

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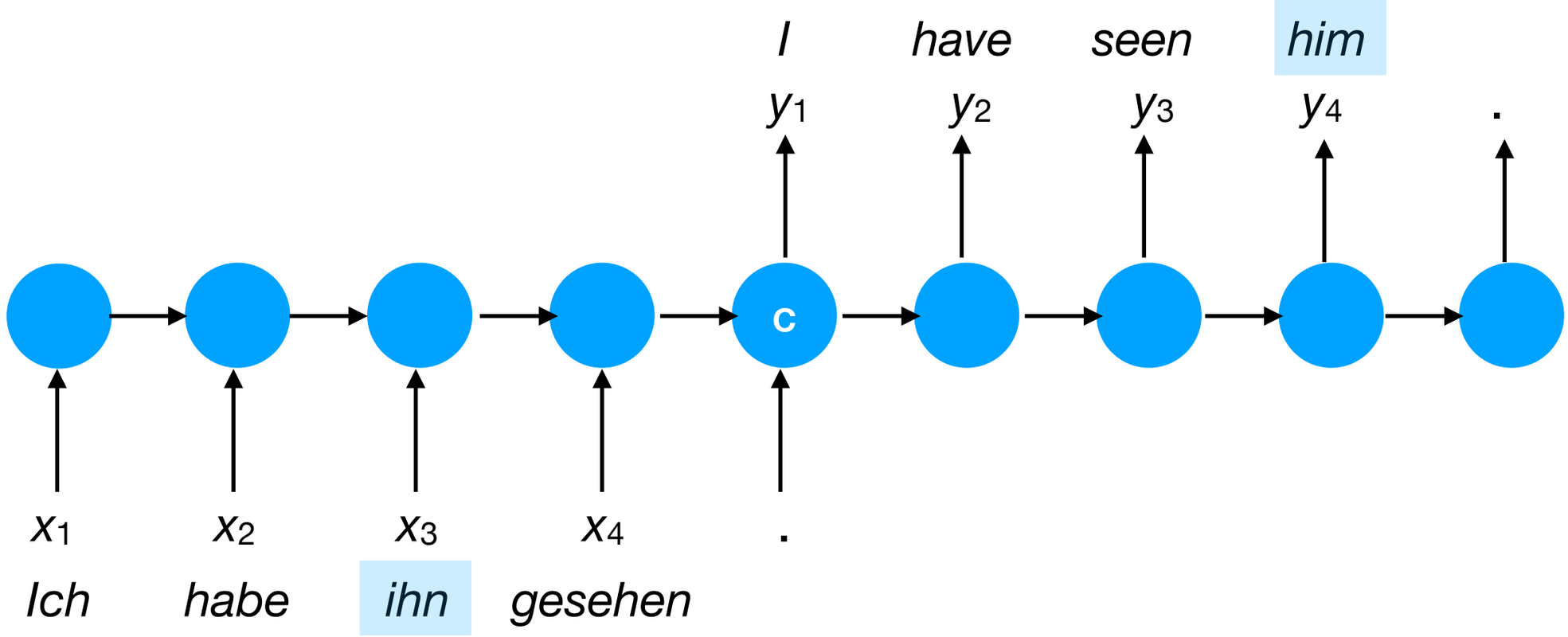
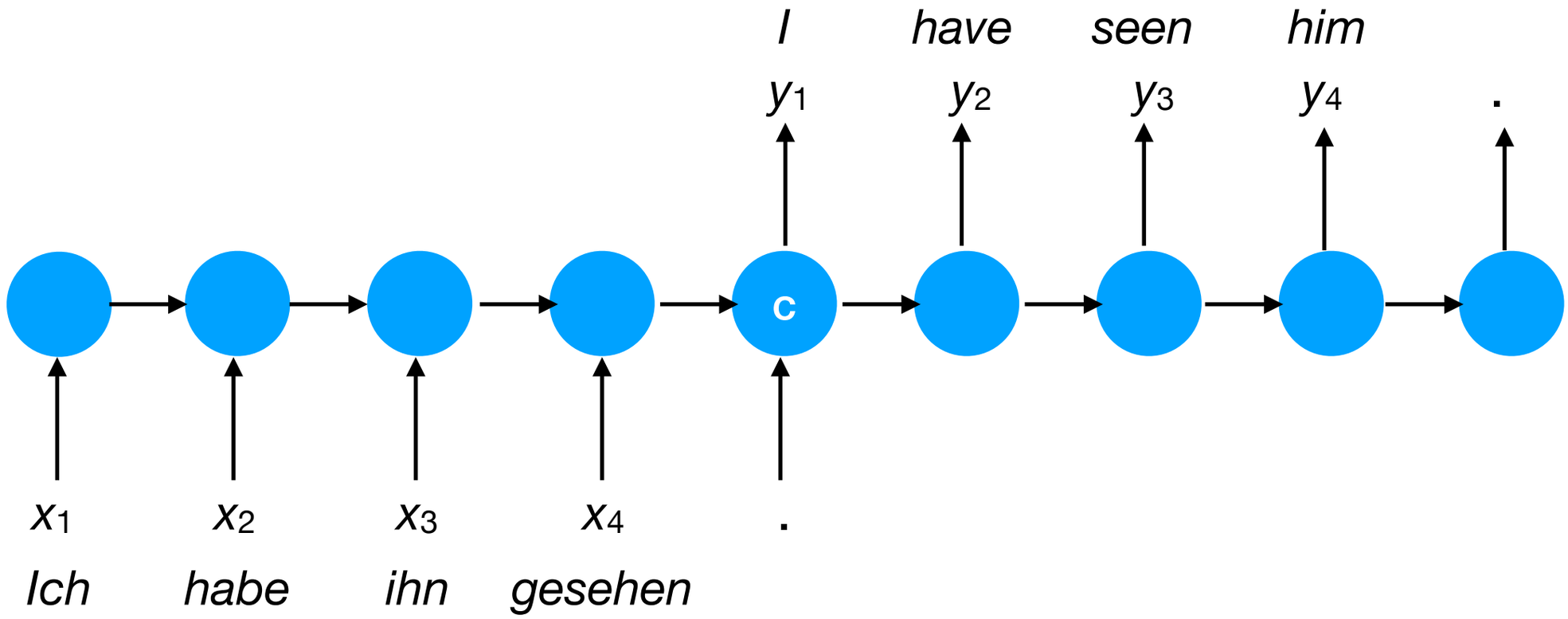


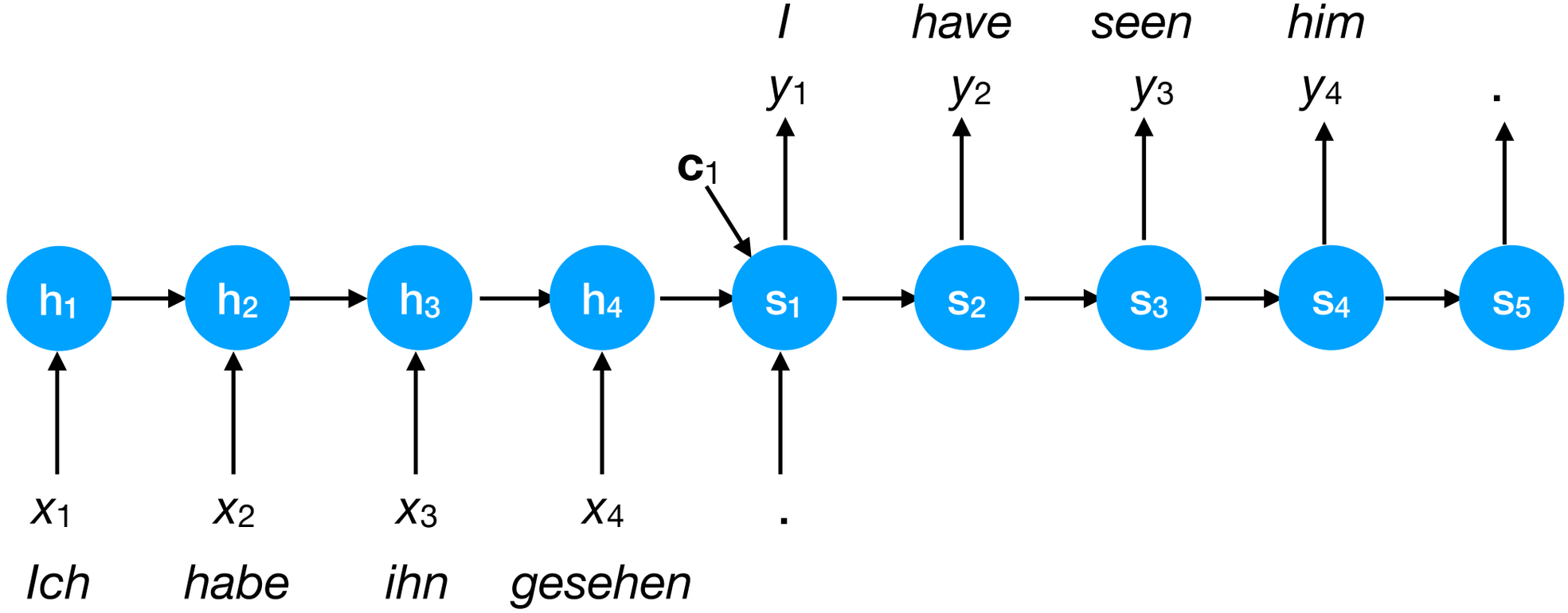
Attention models

- How can we focus the network's **attention** on the **most relevant inputs** when deciding each of the outputs?



Varying context

- Bahdanau et al. (2015) proposed making the context depend on the particular output y_t: Instead of a fixed $\mathbf{c}$, we compute a different $\mathbf{c}_t$ for each output timestep t.



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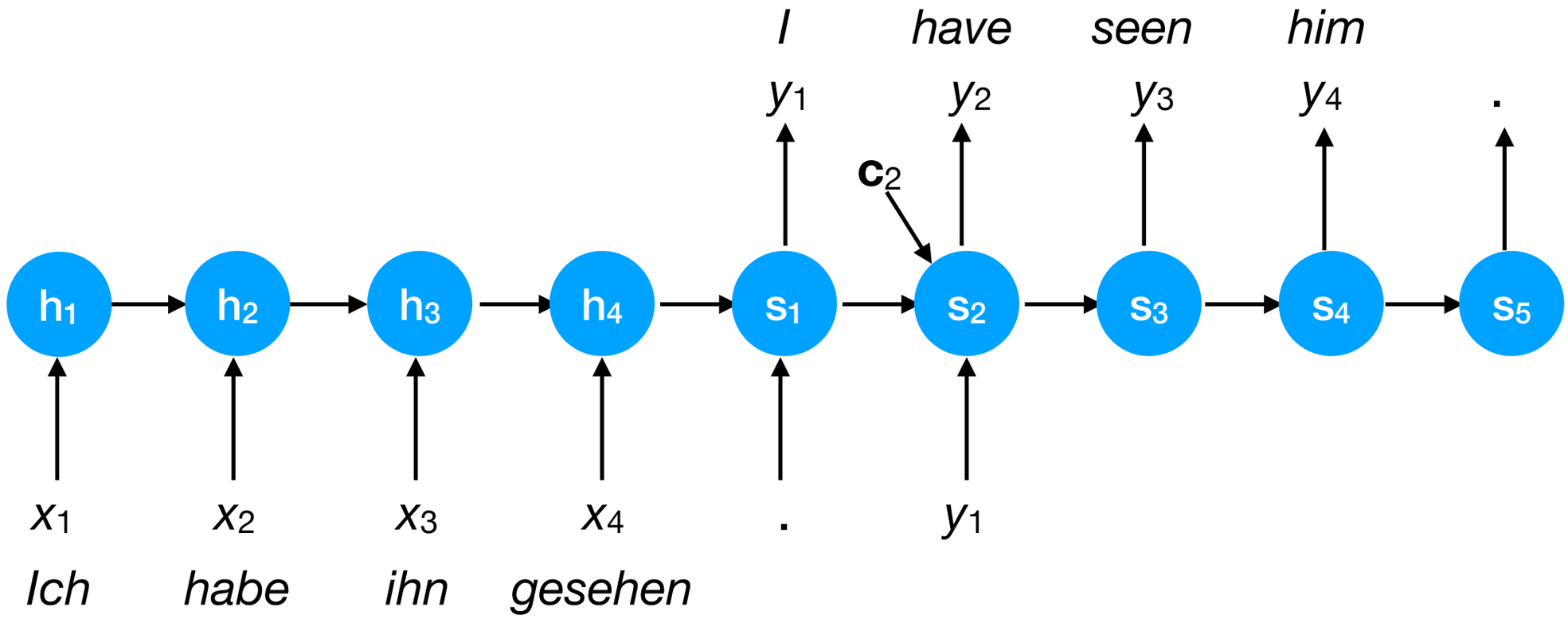

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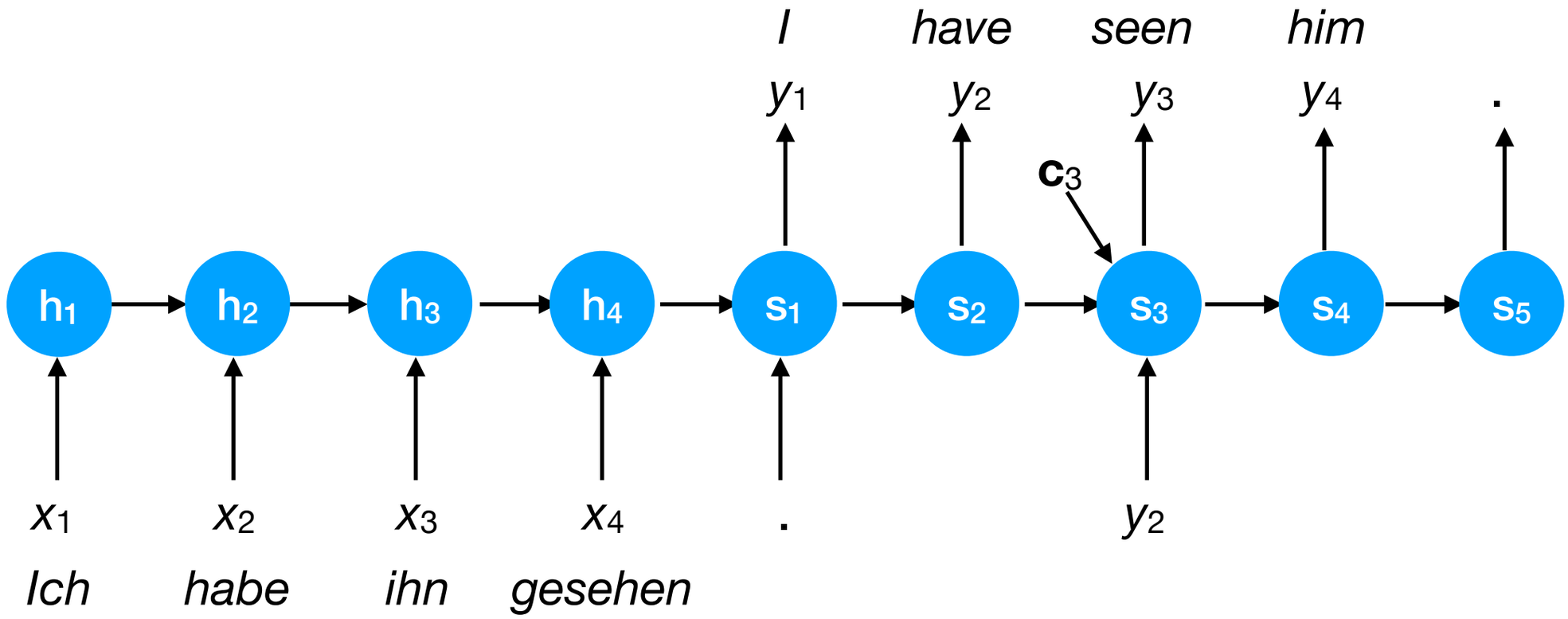

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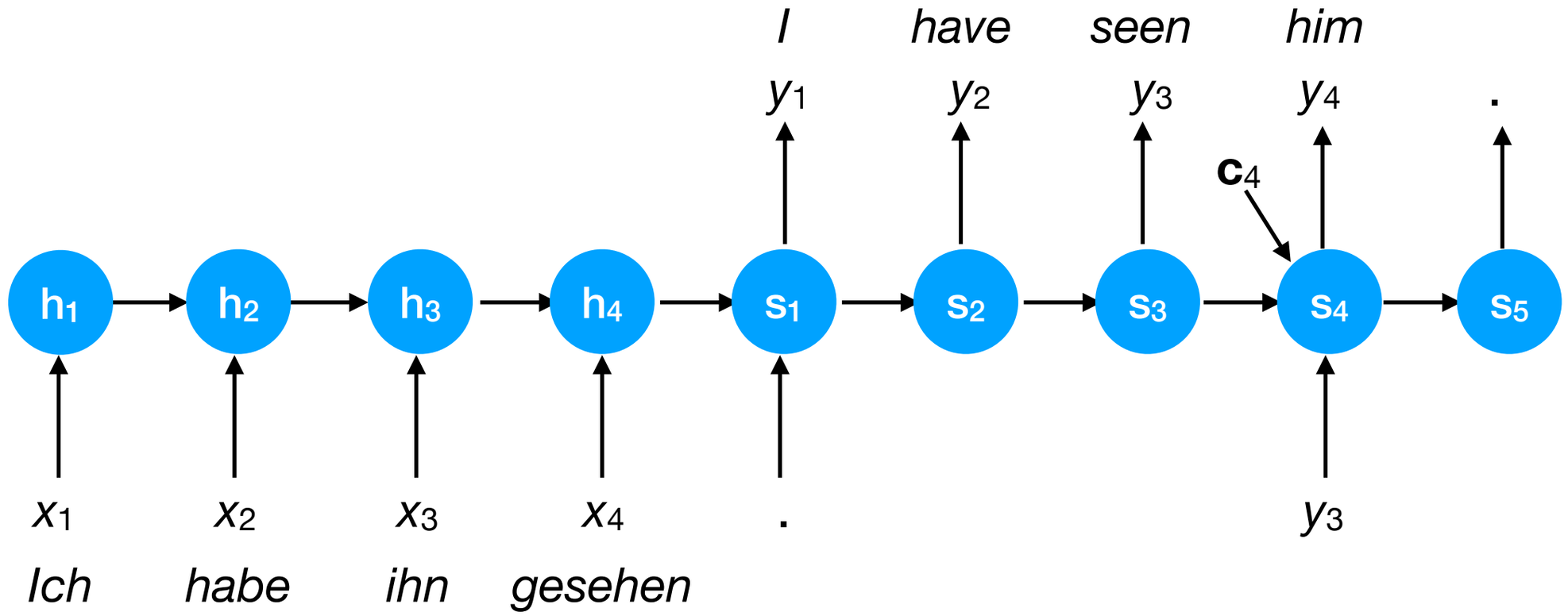
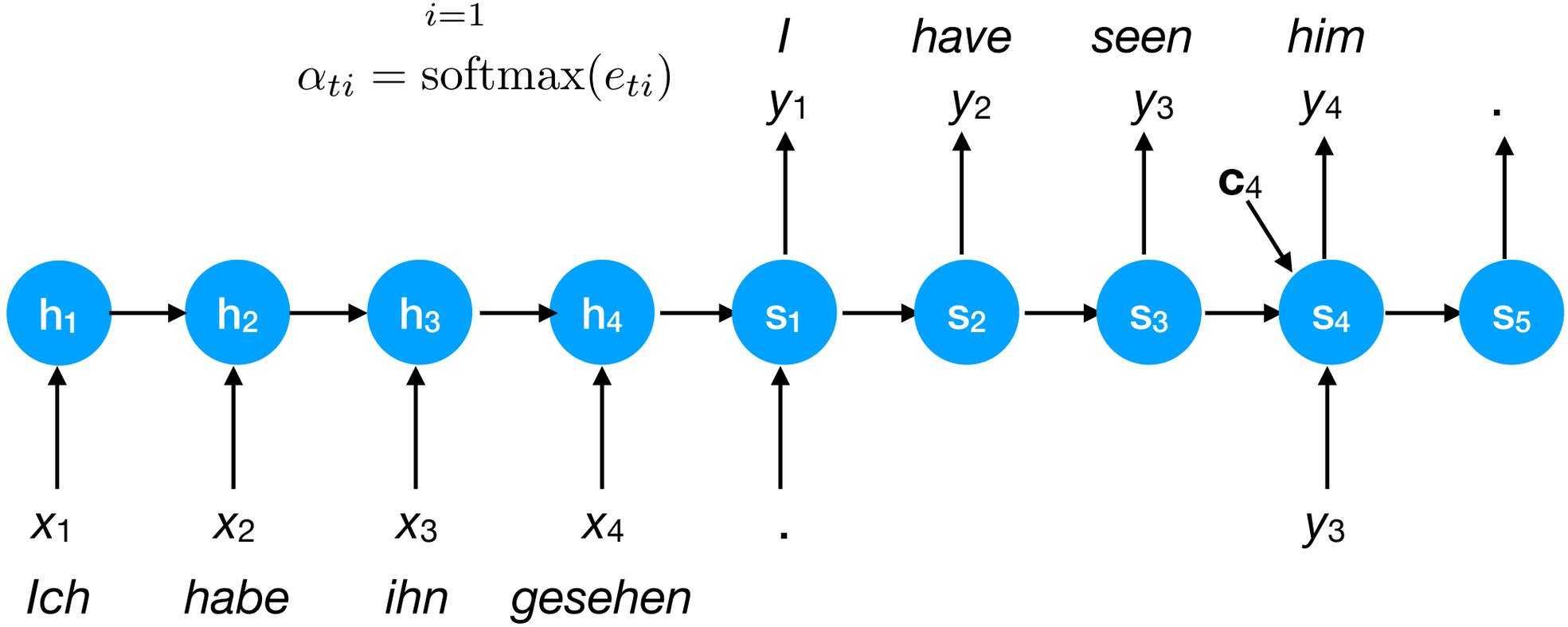


Attention weights

- Each $\mathbf{c}_t$ is a weighted sum of the hidden state sequence $\mathbf{h}_1, \ldots, \mathbf{h}_T$:

$$\mathbf{c}_t = \sum_{i=1}^{T} \alpha_{ti} \mathbf{h}_i$$

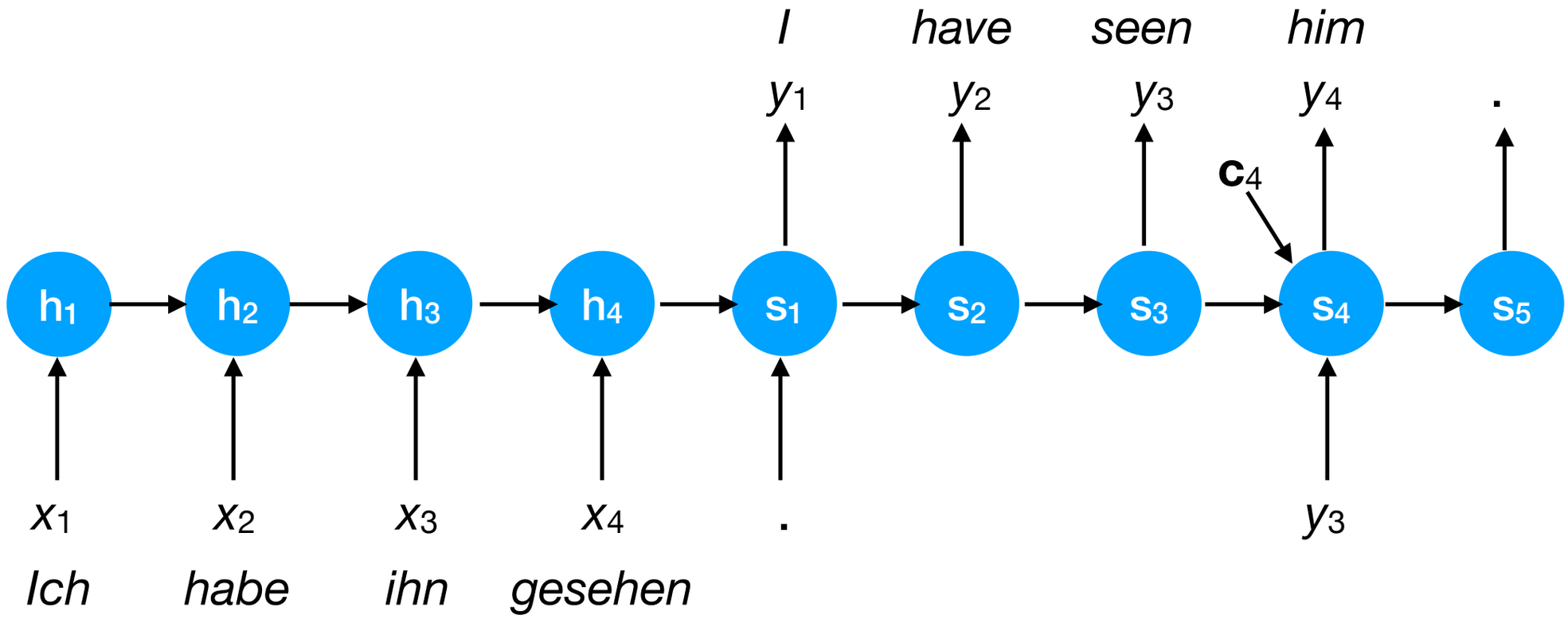
$$\alpha_{ti} = \mathrm{softmax}(e_{ti})$$



Attention weights

- Each e_{ti} is determined by the **alignment** between $\mathbf{s}_{t-1}$ and the sequence $\mathbf{h}_1, \ldots, \mathbf{h}_T$:

$$e_{ti} = a(\mathbf{s}_{t-1}, \mathbf{h}_i)$$

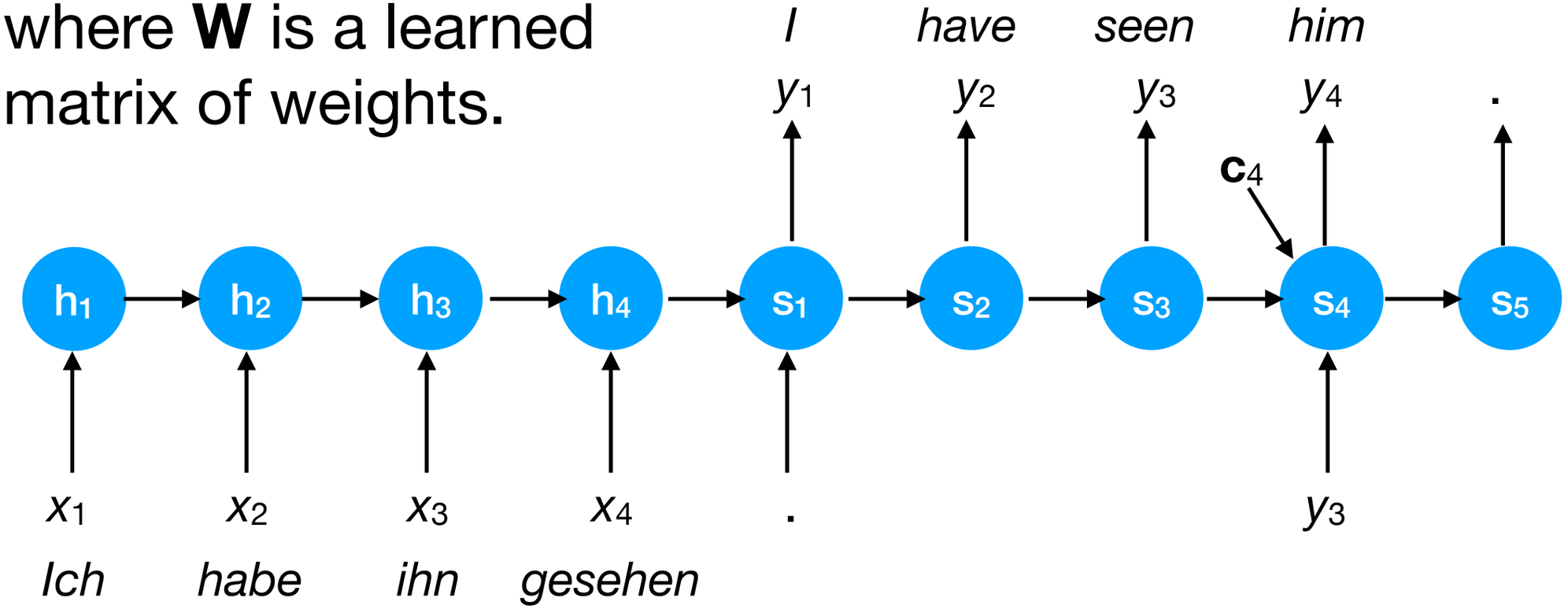


Alignment functions

- Various choices for *a* exist. One of the simplest is just a weighted dot product:

$$a(\mathbf{u}, \mathbf{v}) = \mathbf{u}^\top \mathbf{W} \mathbf{v}$$

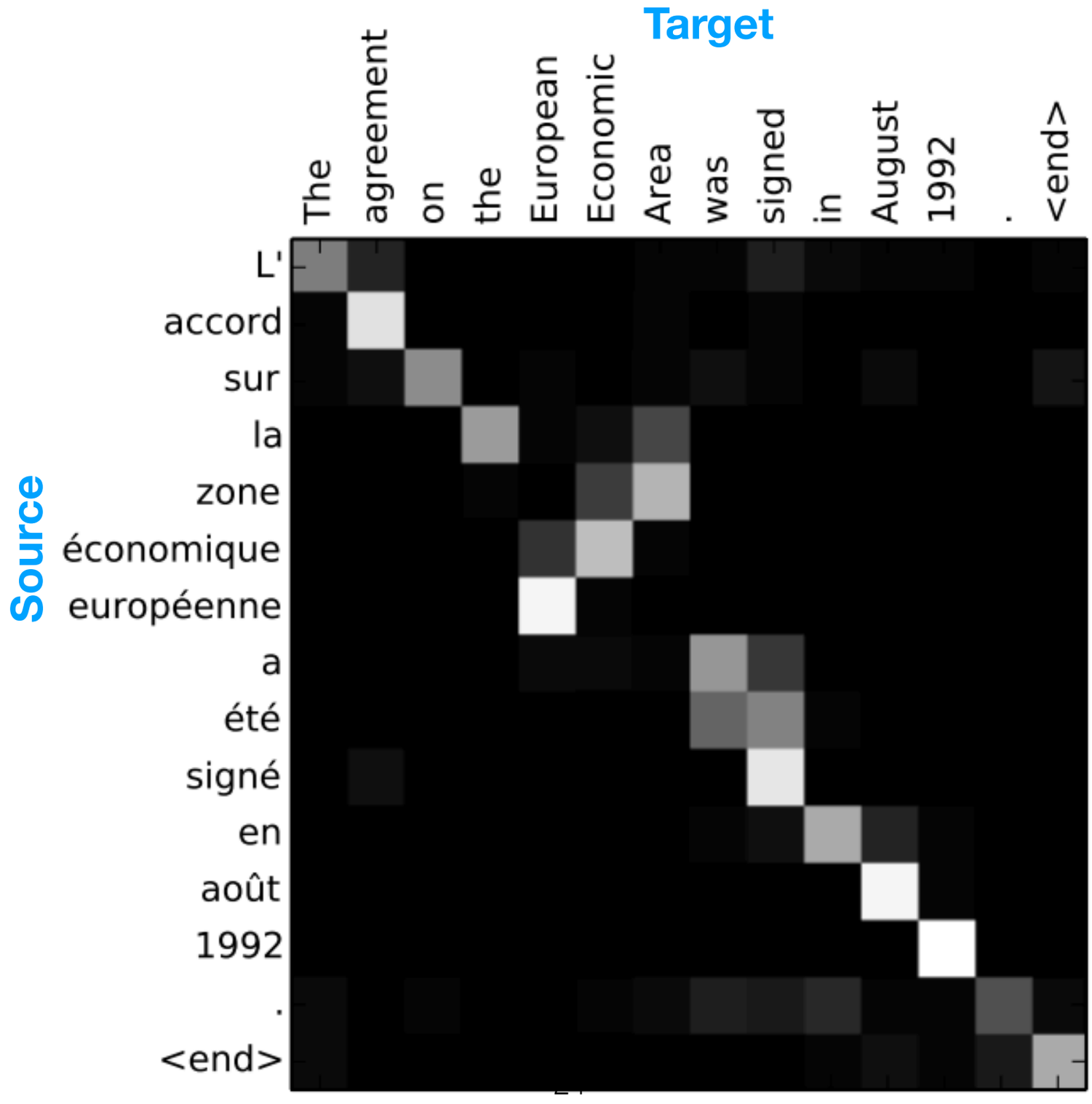
where **W** is a learned matrix of weights.



Results

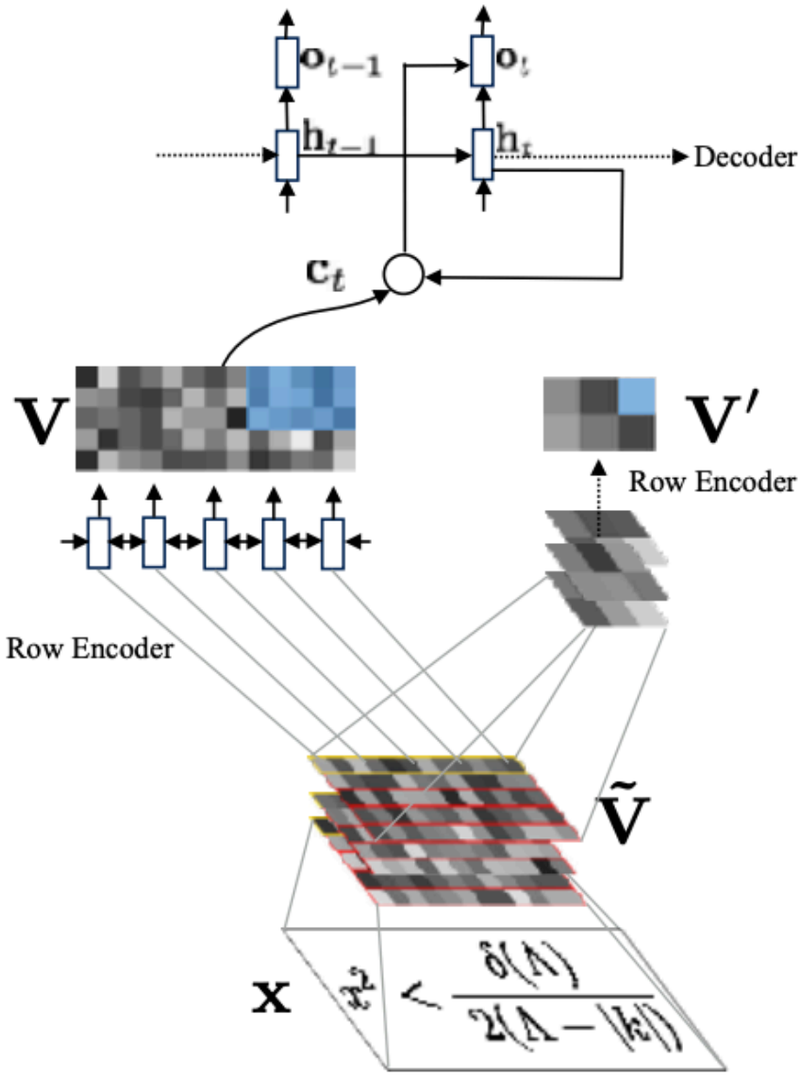
- By adding this **neural attention model** to the standard seq2seq model, the authors were able to achieve higher accuracy on standard machine translation benchmarks.

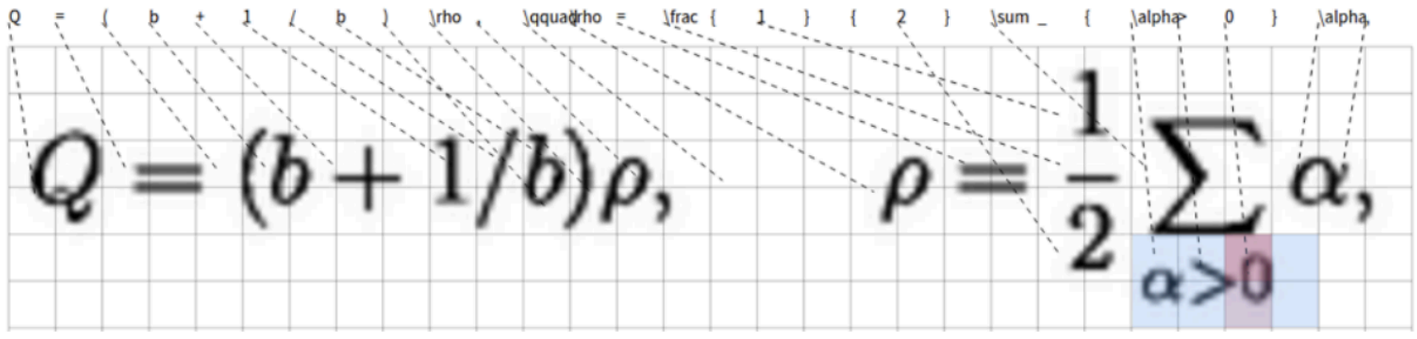
Example alignment



Another application: Image -> LaTeX

- Deng et al. 2017





Recurrent models of visual attention

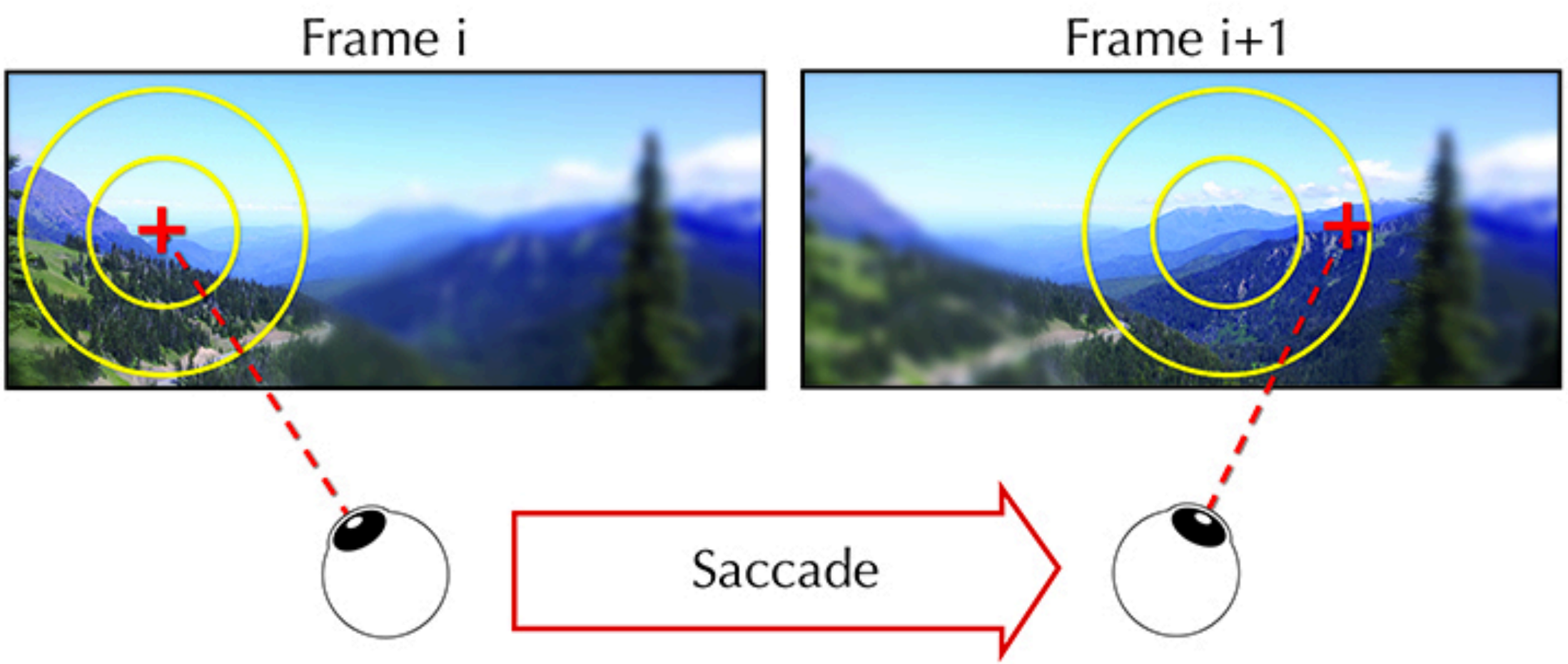
Mnih et al. 2014

Saccades and foveate human vision

- Humans transition the focus of their eye gaze through a sequence of **saccades** that help them concentrate on the most salient information in a visual scene.

Saccades and foveate human vision

- For any focal point on an image, humans' perception is **foveated**, i.e., the spatial resolution decreases as the distance to the focus increases.



https://research.nvidia.com/publication/2017-09_Latency-Requirements-for

Saccades and foveate human vision

- Saccades are a task-dependent method of human attention to visual scenes that varies over time.
- Mnih et al. 2014 explored a DL-based model of recurrent visual attention that implements a similar method.

Recurrent models of visual attention

- Consider a scenario in which a robot is interacting with its environment in order to maximize some long-term reward:

- At each time t:
  - The robot can **look** at a location l_t in the visual scene.
  - Based on the information it learns by looking, the robot **updates** its state representation h_t of the environment.
  - The robot **acts** with action a_t on the environment.
- The robot's goal is to choose actions so as to maximize the **return** $R(\tau)$ where $\tau=(a_1, \ldots, a_T, h_1, \ldots, h_T)$.

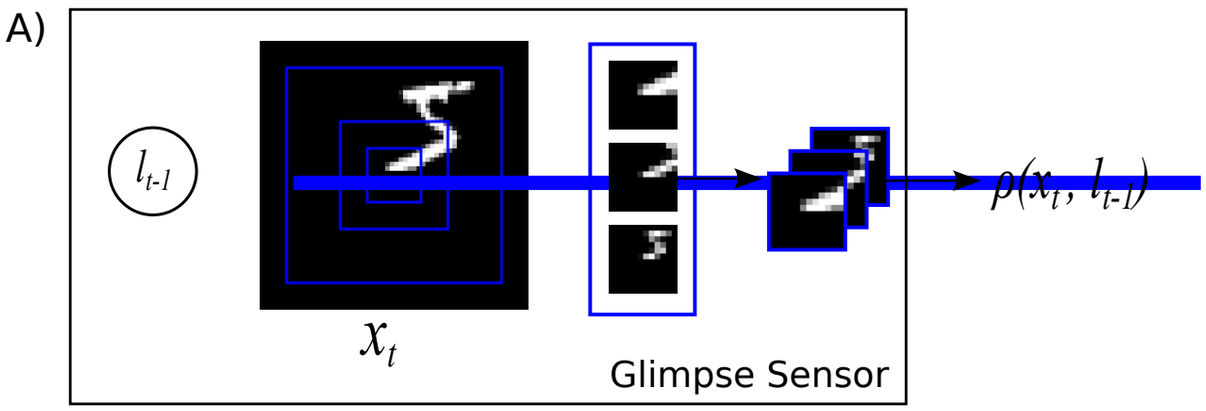
Example

- Consider a robot that picks items from a conveyor belt at a material recovery facility (MRF).

- The robot should look carefully at each item before deciding how to act (what to pick up, how to pick it up).

- The reward might be based on amount of sorted garbage, number of machine failures, etc.

Recurrent models of visual attention



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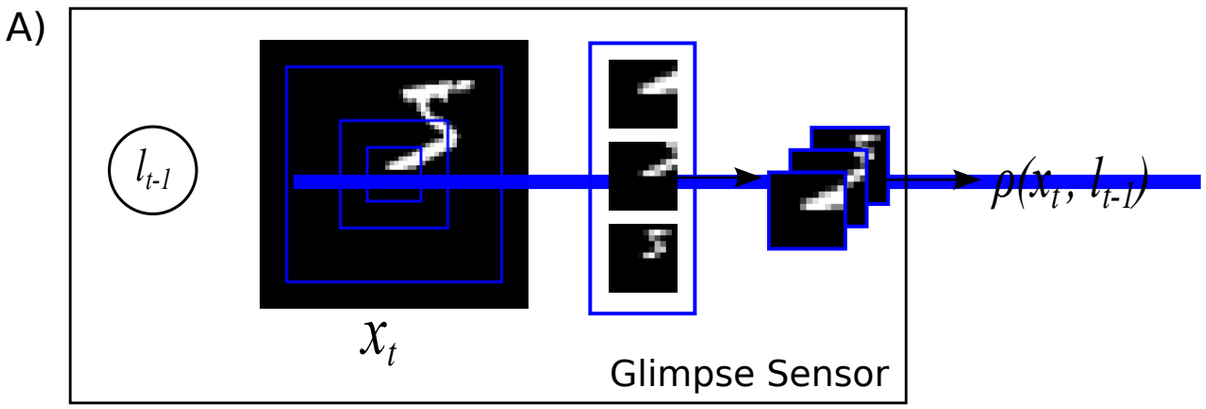

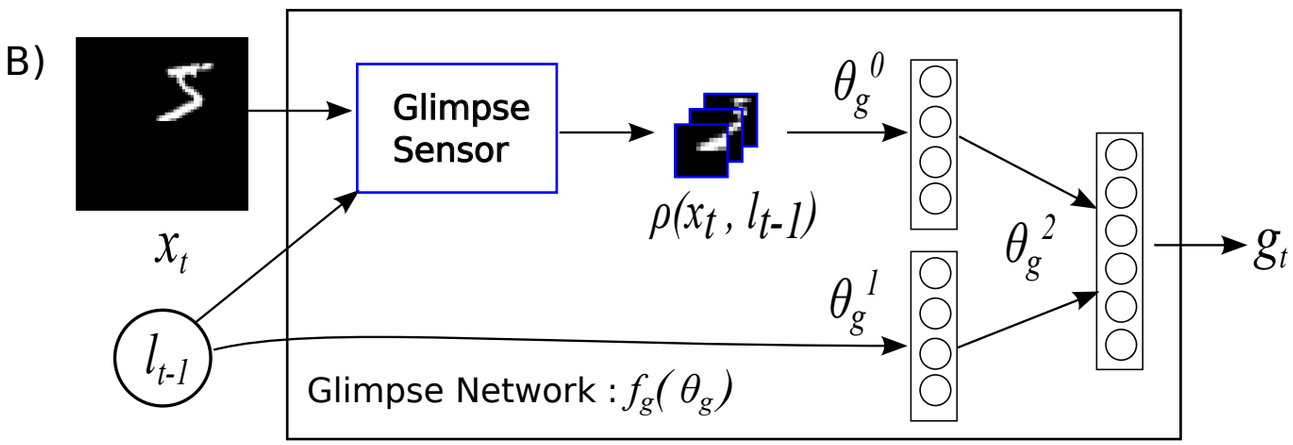

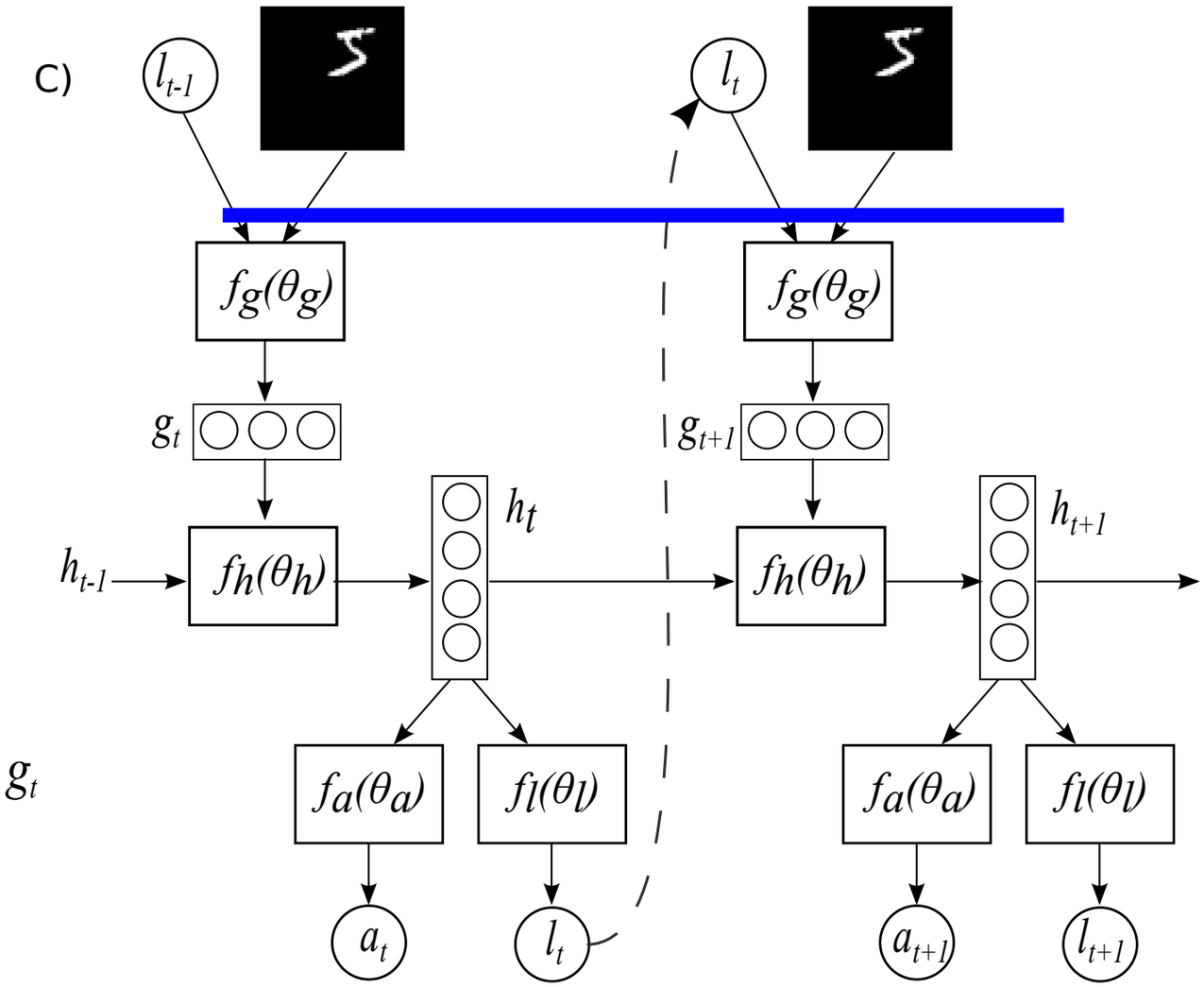

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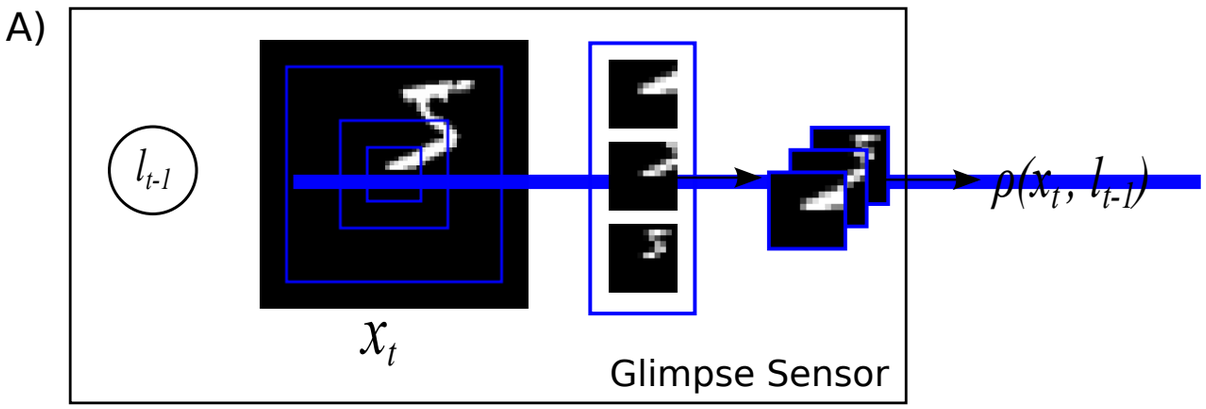
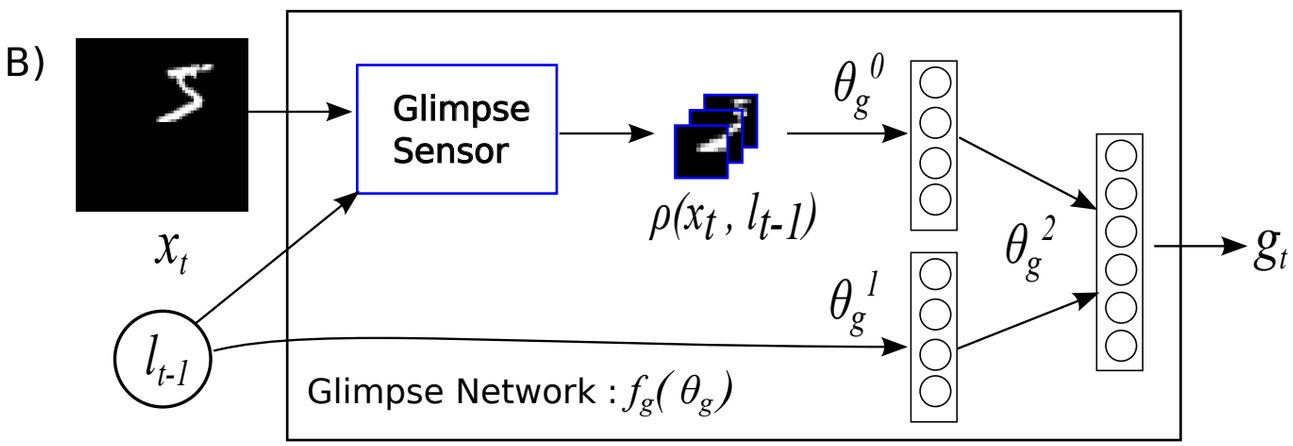
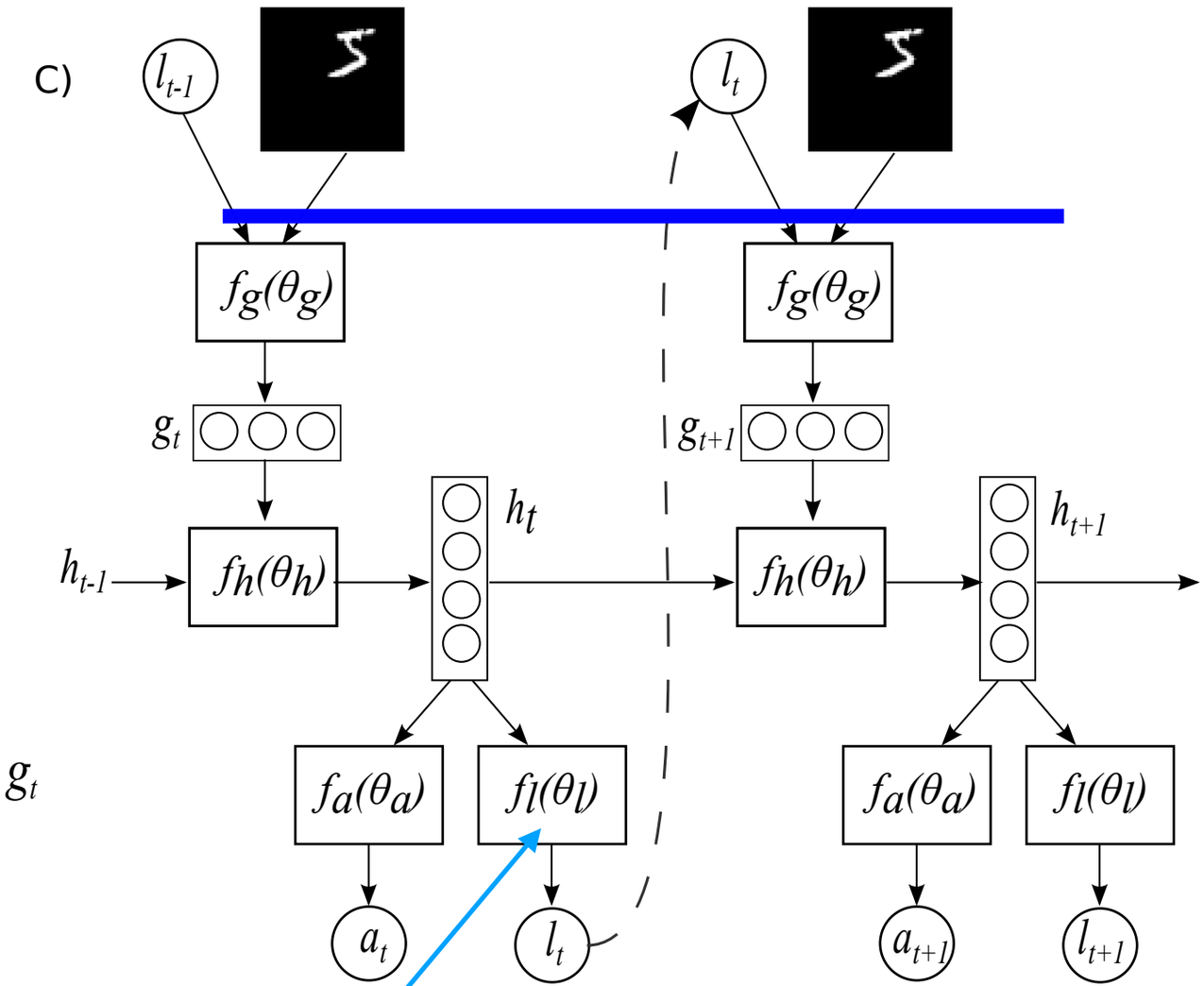
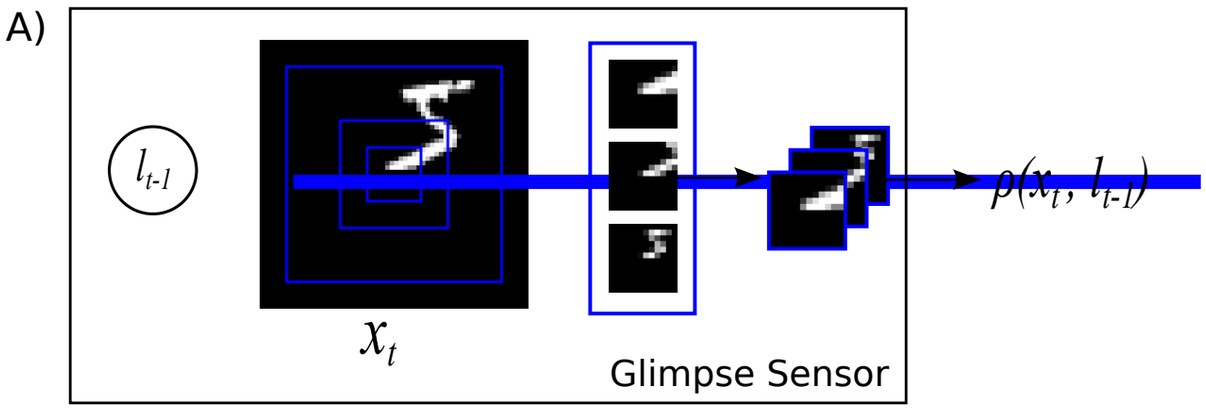


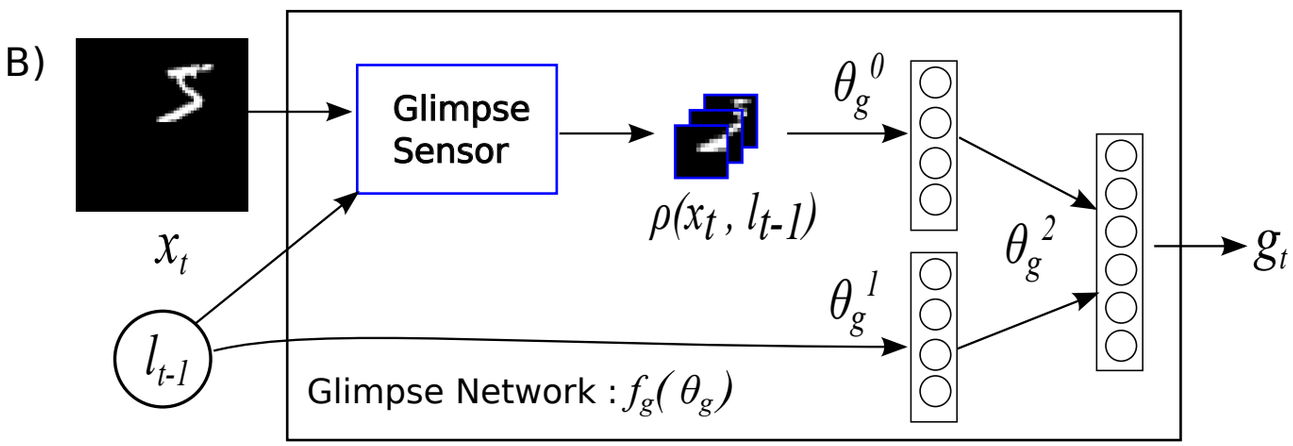


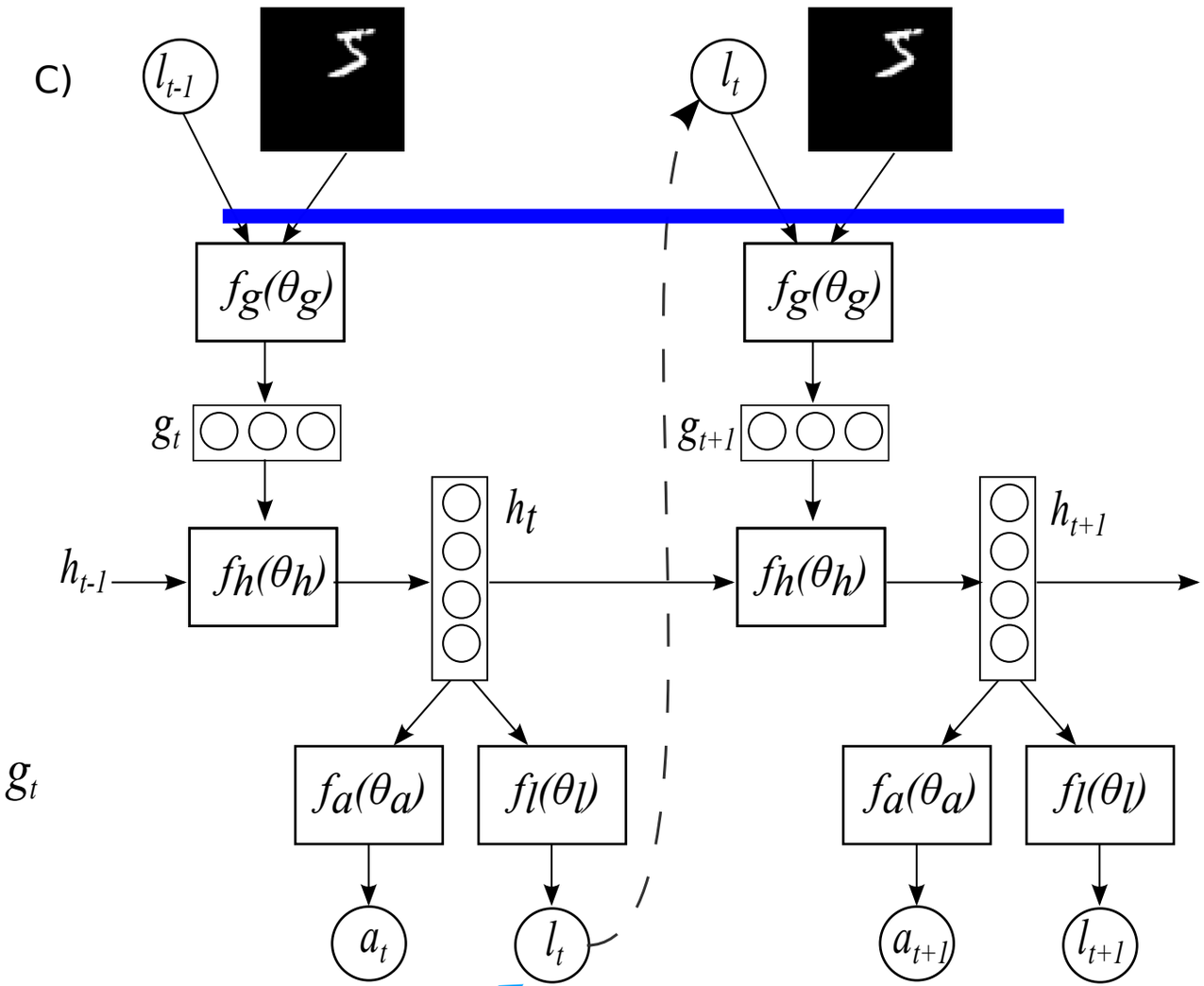


This network produces a probability distribution over all gaze locations l_t.

Recurrent models of visual attention

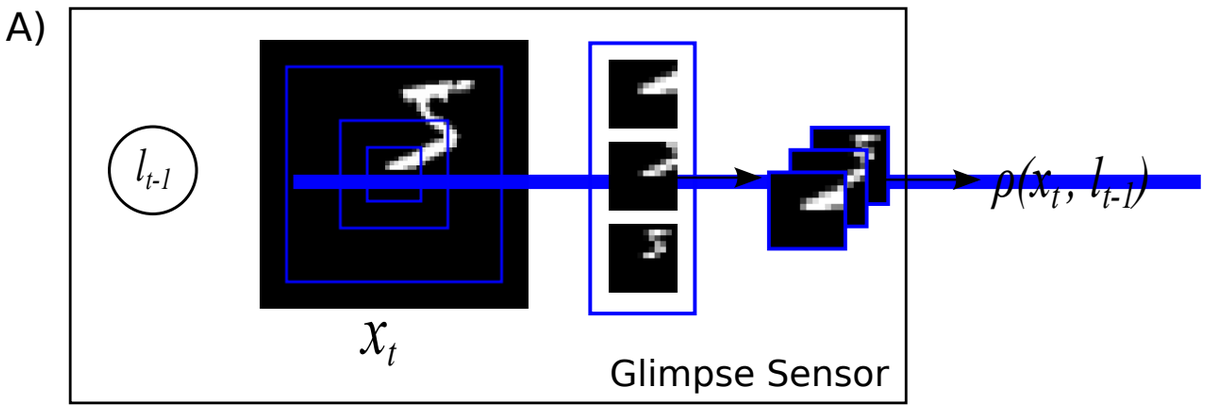


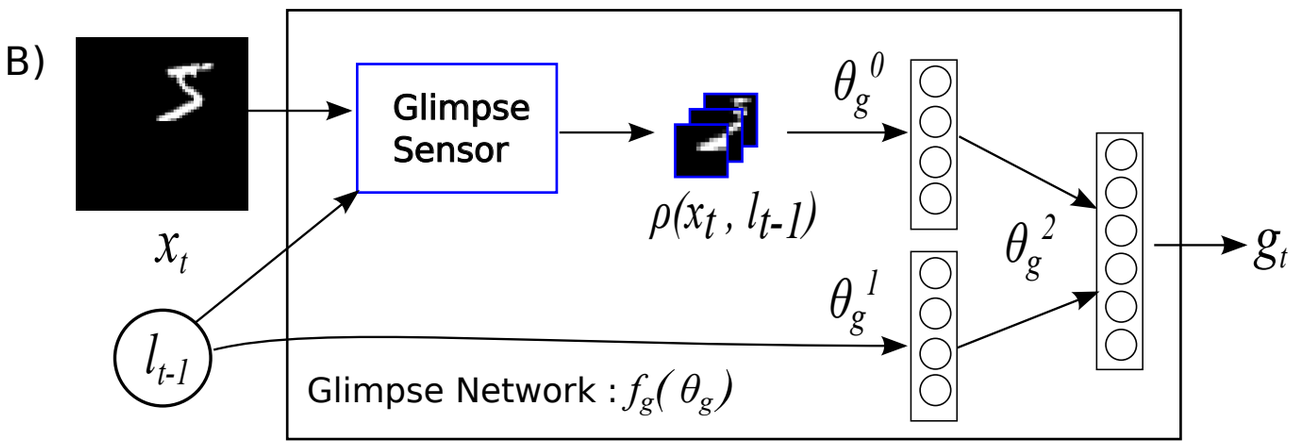


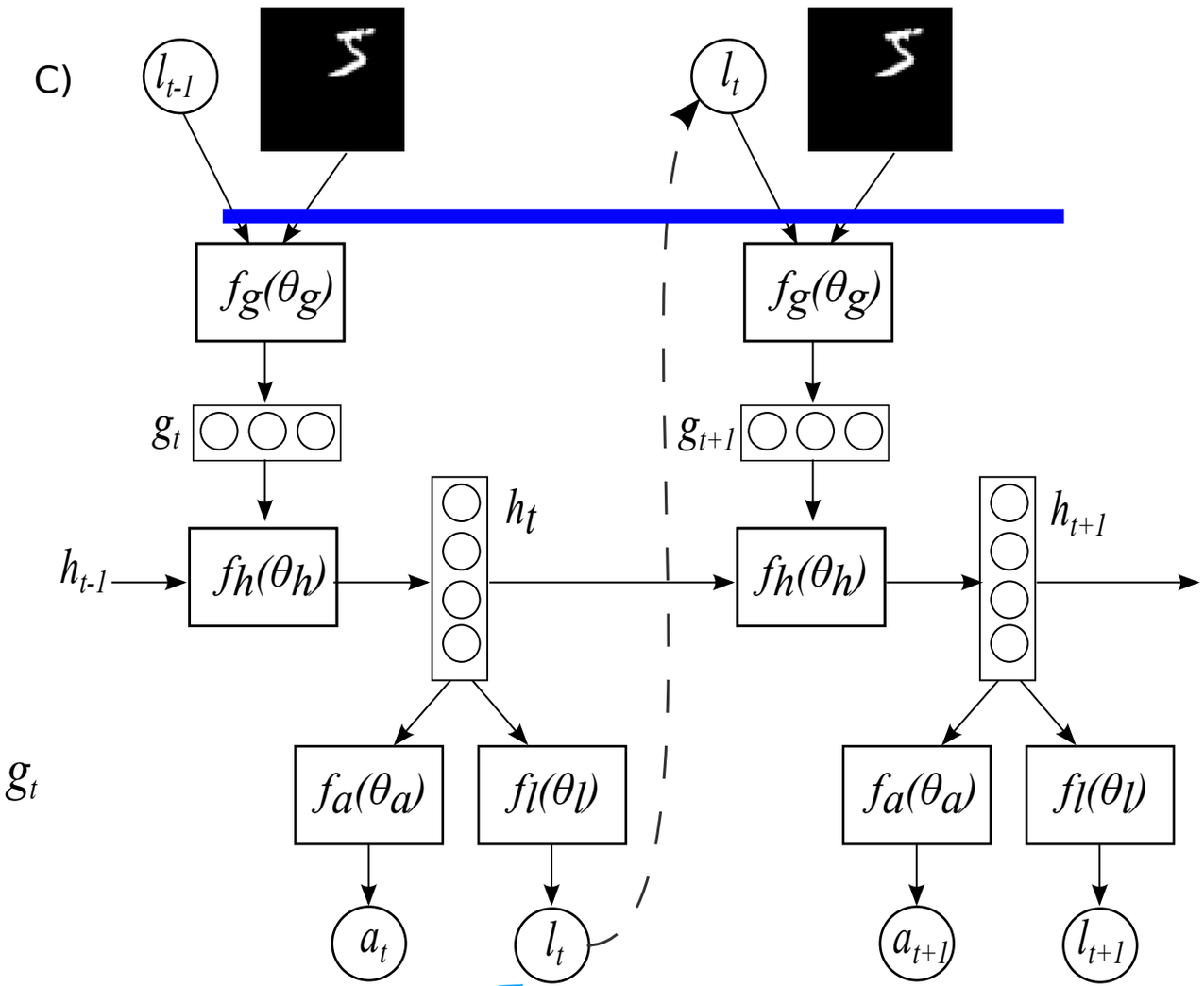


A sample from this probability distribution is then drawn to decide the actual (discrete) target l_t.

Recurrent models of visual attention







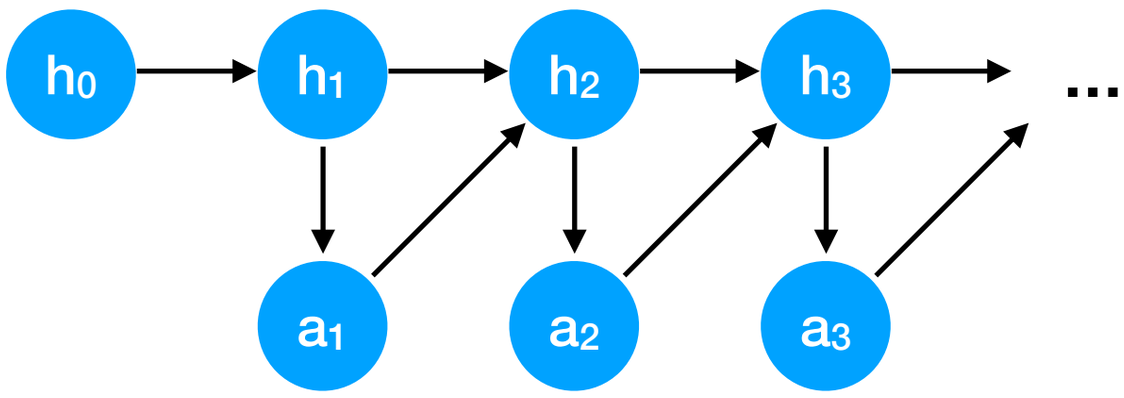
Sampling is non-differentiable, and thus we have broken back-propagation :-(.

REINFORCE

- Fortunately, Williams 1992 devised an algorithm called REINFORCE that offers a way to conduct gradient descent to optimize the RNN’s parameters despite the non-differentiability.

REINFORCE

- Premise:
  - We have a policy network $\boldsymbol{\pi}_\theta(h_t) = P(a_t \mid h_t, \theta)$ that computes the probability distribution over actions a_t, given h_t and θ, at each timestep t.
- We can represent the relationship between the actions and hidden states using a graphical model:



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  - $P(\tau \mid \theta)$ is the probability distribution over trajectories, given the policy network's parameters θ. It factorizes:

$$P(\tau \mid \theta) = P(a_1, \ldots, a_T, h_0, h_1, \ldots, h_T \mid \theta) = P(h_0) \prod_{t=1}^{T} P(a_t \mid h_t, \theta) P(h_t \mid h_{t-1}, a_{t-1})$$

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Action probability: we usually know this.

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System dynamics: we often do not know this.

REINFORCE

- Premise:
  - The prob. dist. of the initial state is called $P(h_0)$.
  - We have a return function R over trajectories τ.
  - We want to maximize the **expected return** over all possible trajectories τ:

$$J(\theta) = \mathbb{E}_{\tau \sim P(\tau \mid \theta)}[R(\tau)] = \int_{\tau} P(\tau \mid \theta) R(\tau) d\tau$$

Maximizing expected return

- We might want to conduct SGD on J w.r.t. θ.

- Unfortunately, the integral is generally intractable.

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- Instead, we use the **log-likelihood ratio trick**…

$$\nabla_\theta P(\tau \mid \theta) = P(\tau \mid \theta) \nabla_\theta \log P(\tau \mid \theta)$$

Maximizing expected return

$$\nabla_\theta J(\theta) = \int \nabla_\theta P(\tau \mid \theta) R(\tau) d\tau$$

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$$= \mathbb{E}_{\tau \sim P(\tau \mid \theta)} \left[\nabla_\theta \log P(\tau \mid \theta) R(\tau) \right]$$

Maximizing expected return

$$\nabla_\theta J(\theta) = \int \nabla_\theta P(\tau \mid \theta) R(\tau) d\tau$$

$$= \int P(\tau \mid \theta) \nabla_\theta \log P(\tau \mid \theta) R(\tau) d\tau$$

$$= \mathbb{E}_{\tau \sim P(\tau \mid \theta)} \left[\nabla_\theta \log P(\tau \mid \theta) R(\tau) \right]$$

$$\approx \frac{1}{n} \sum_{i=1}^{n} \nabla_\theta \log P(\tau \mid \theta) R(\tau)$$

Maximizing expected return

$$\begin{aligned}
\nabla_\theta J(\theta) &= \int \nabla_\theta P(\tau \mid \theta) R(\tau) d\tau \\
&= \int P(\tau \mid \theta) \nabla_\theta \log P(\tau \mid \theta) R(\tau) d\tau \\
&= \mathbb{E}_{\tau \sim P(\tau \mid \theta)} \left[\nabla_\theta \log P(\tau \mid \theta) R(\tau) \right] \\
&\approx \frac{1}{n} \sum_{i=1}^{n} \nabla_\theta \log P(\tau \mid \theta) R(\tau)
\end{aligned}$$

- In other words, we can approximate the gradient of *J* by sampling many trajectories and averaging.

Maximizing expected return

$$P(\tau \mid \theta) = P(h_0) \prod_{t=1}^{T} P(h_t \mid h_{t-1}, a_{t-1}) P(a_t \mid h_t, \theta)$$

Maximizing expected return

$$P(\tau \mid \theta) = P(h_0) \prod_{t=1}^{T} P(h_t \mid h_{t-1}, a_{t-1}) P(a_t \mid h_t, \theta)$$

$$\Longrightarrow$$

$$\log P(\tau \mid \theta) = \log P(h_0) + \sum_{t=1}^{T} \log P(h_t \mid h_{t-1}, a_{t-1}) + \sum_{t=1}^{T} \log P(a_t \mid h_t, \theta)$$

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$$\Longrightarrow$$ **The first two terms do not depend on θ.**

$$\nabla_\theta \log P(\tau \mid \theta) = \sum_{t=1}^{T} \nabla_\theta \log P(a_t \mid h_t, \theta)$$

Maximizing expected return

$$P(\tau \mid \theta) = P(h_0) \prod_{t=1}^{T} P(h_t \mid h_{t-1}, a_{t-1}) P(a_t \mid h_t, \theta)$$

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$$\Longrightarrow$$

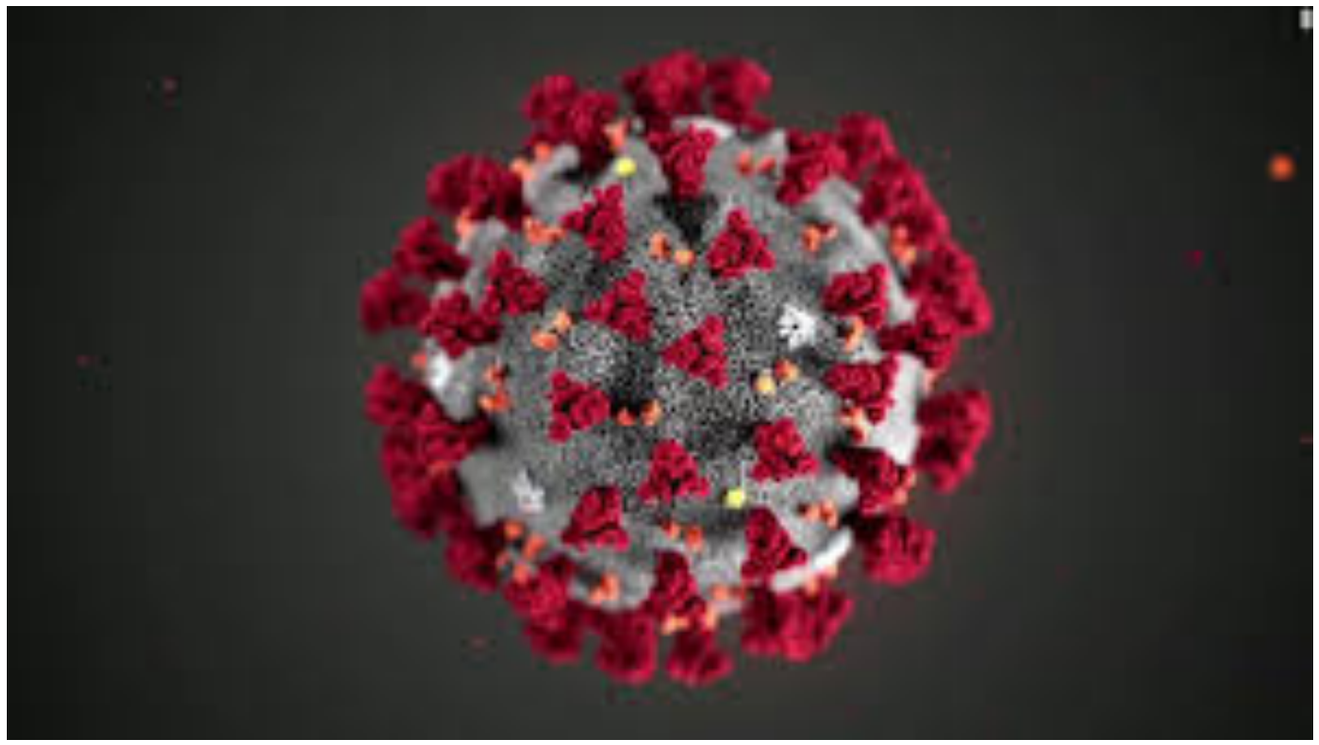
$$\nabla_\theta \log P(\tau \mid \theta) = \sum_{t=1}^{T} \nabla_\theta \log P(a_t \mid h_t, \theta)$$

$$= \sum_{t=1}^{T} \nabla_\theta \pi_\theta(h_t)$$

This is just the softmax output of our action prediction network.

REINFORCE: summary

- REINFORCE provides a tractable approximate method (based on sampling) to compute the gradient of a cost function that depends in a non-differentiable way on a variable that was sampled from a probability distribution produced by the neural network.



Accelerating drug discovery via computational chemistry & machine learning

https://cdn.cnn.com/cnnnext/dam/assets/200130165125-corona-virus-cdc-image-super-tease.jpg

Drug discovery

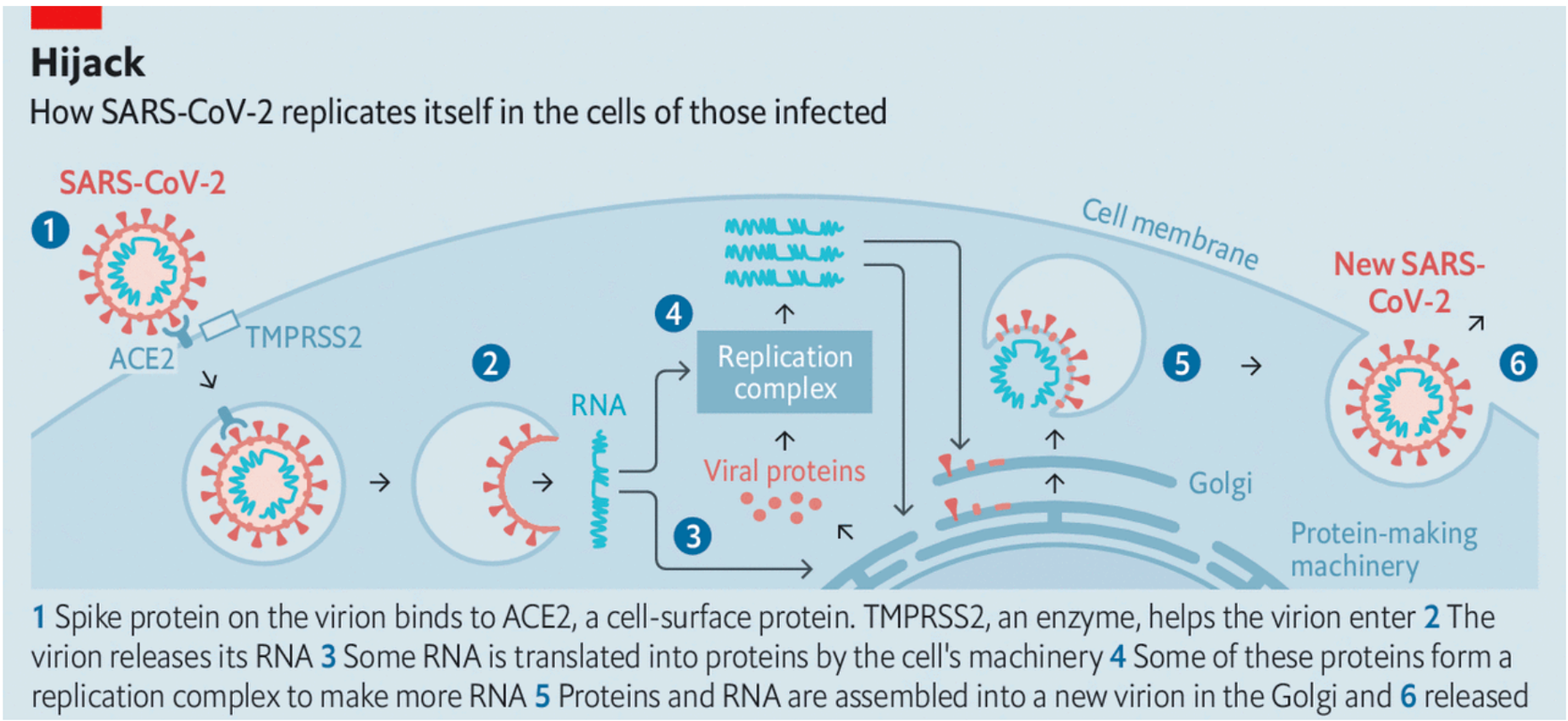
- For SARS-CoV-2 (coronavirus) and many other pathogens, scientists are searching intensely for:

- Vaccines to prevent infection.

- Therapeutic drugs to treat infection.

Drug discovery

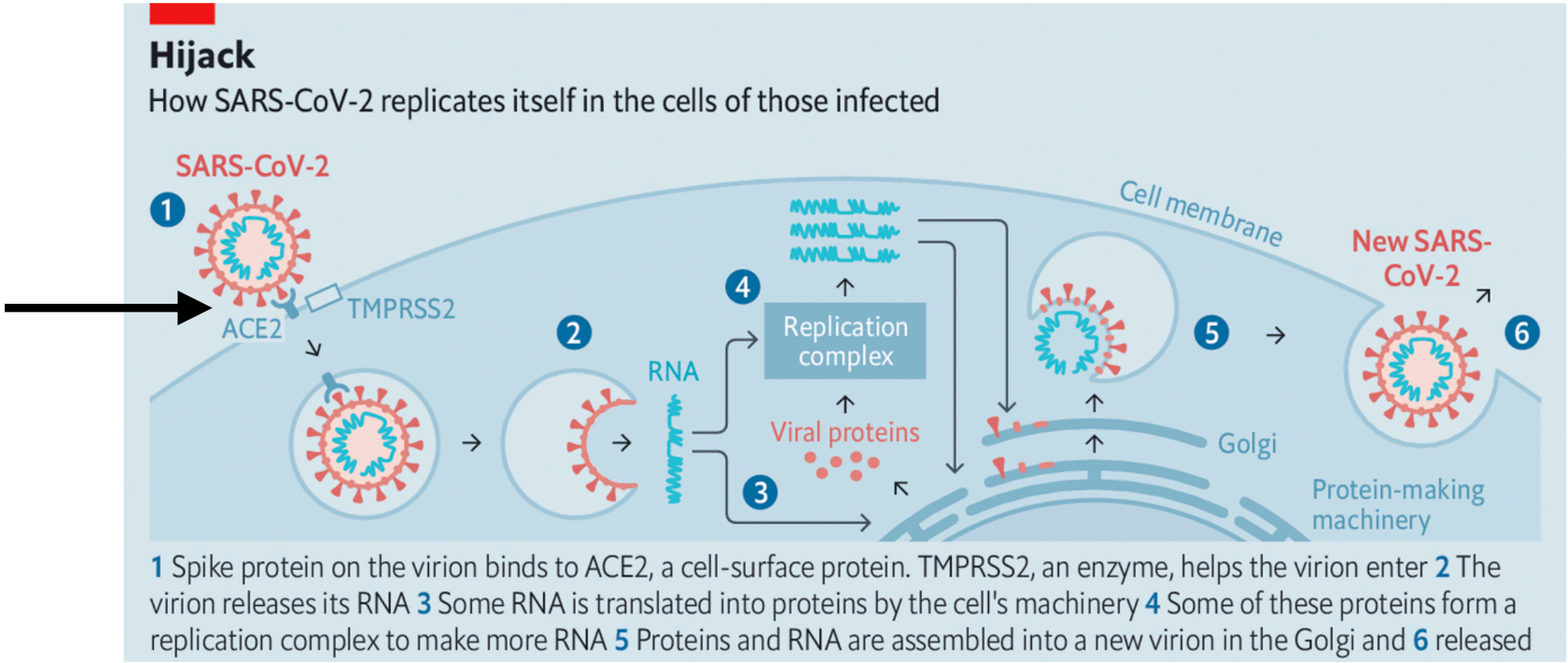
- For drugs against coronavirus, there are several possibilities:



https://www.economist.com/sites/default/files/images/print-edition/20200314_FBC902.png

Drug discovery

- For drugs against coronavirus, there are several possibilities:
  - Prevent the coronavirus from entering the cell.



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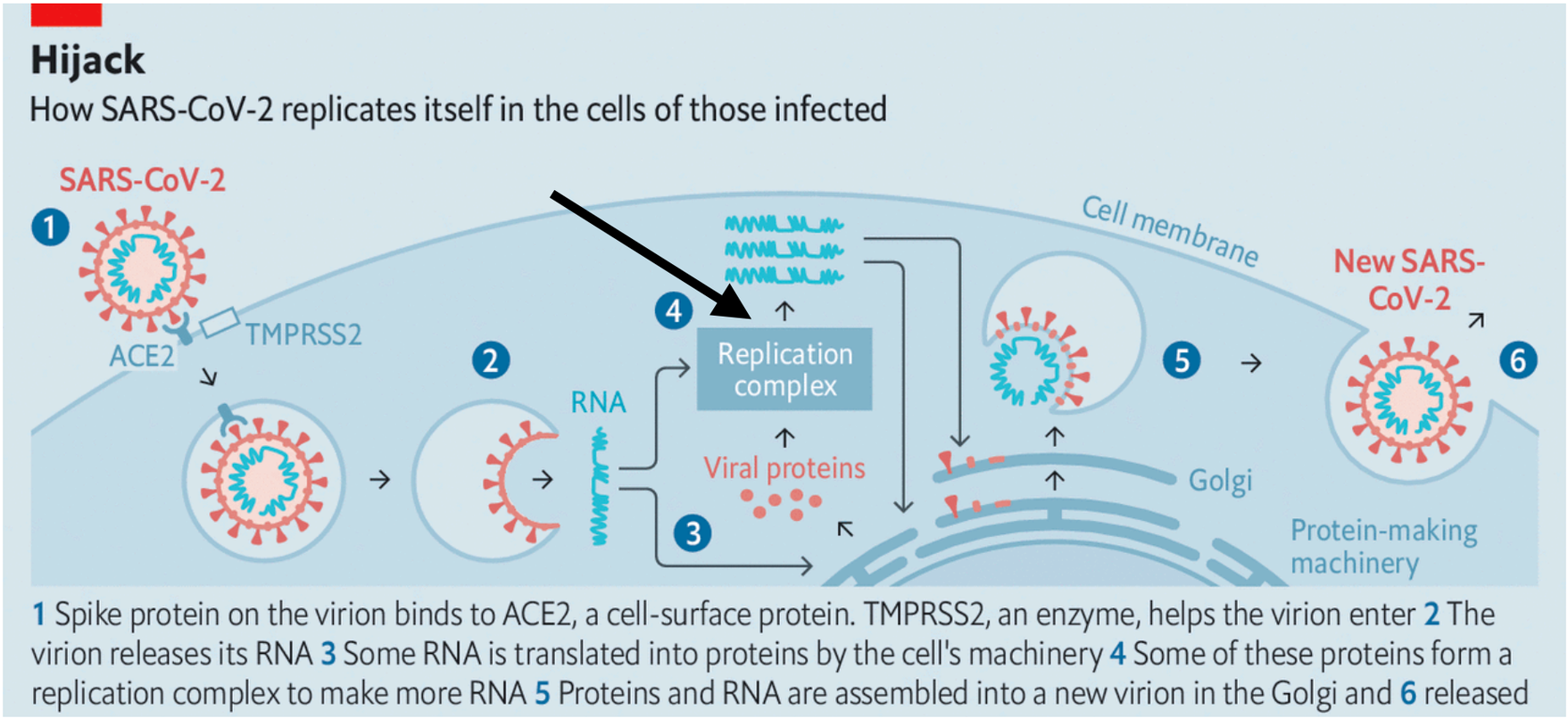
Drug discovery

- For drugs against coronavirus, there are several possibilities:
  - Prevent the coronavirus from entering the cell.
  - Disrupt the virus' ability to replicate its RNA.



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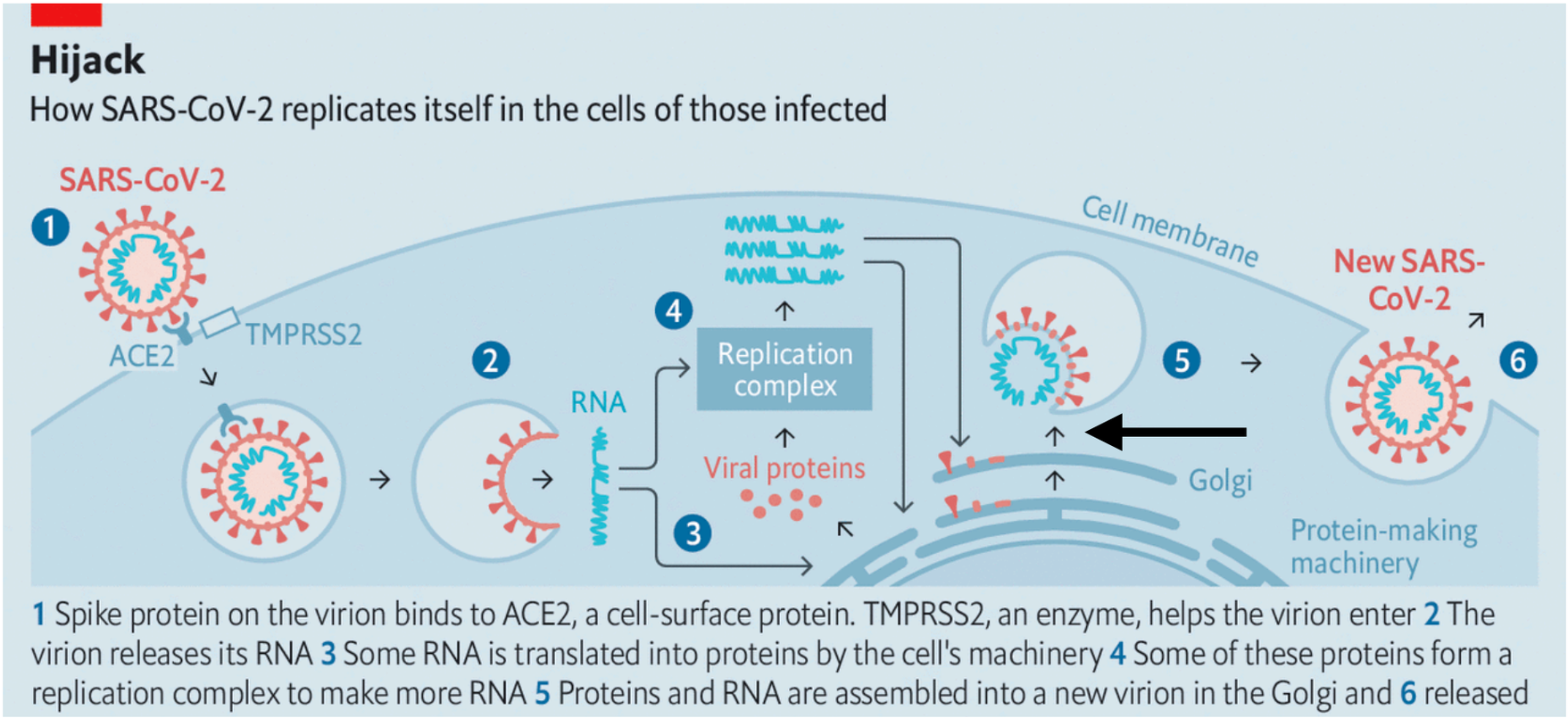
Drug discovery

- For drugs against coronavirus, there are several possibilities:
  - Prevent the coronavirus from entering the cell.
  - Disrupt the virus' ability to replicate its RNA.
  - Inhibit the virus' self-assembly process.



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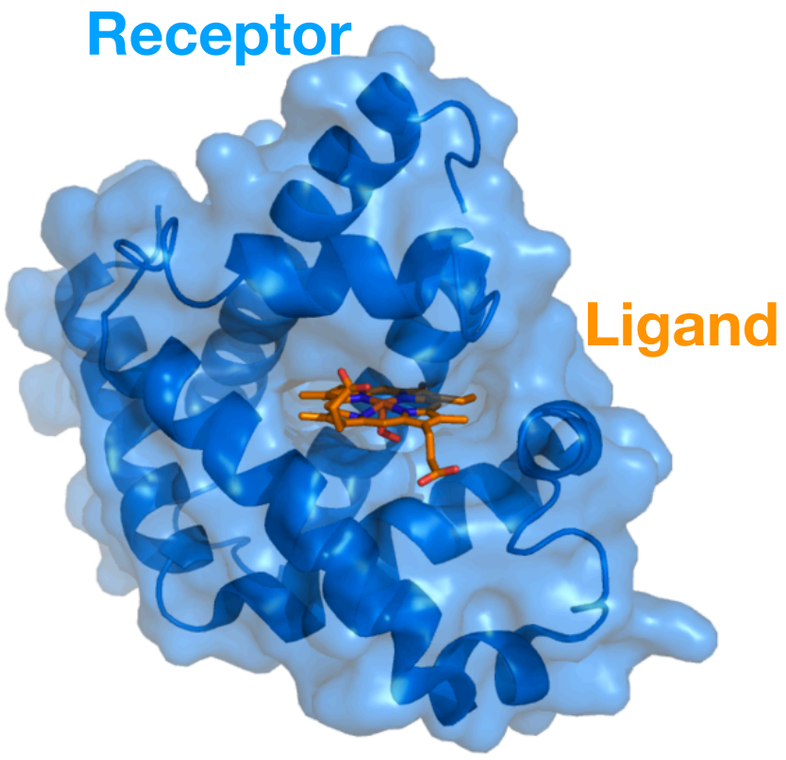
Ligand-receptor binding

- Drugs are molecules (**ligands**) that bind to a protein receptor, which can belong to either the human host or the virus itself.

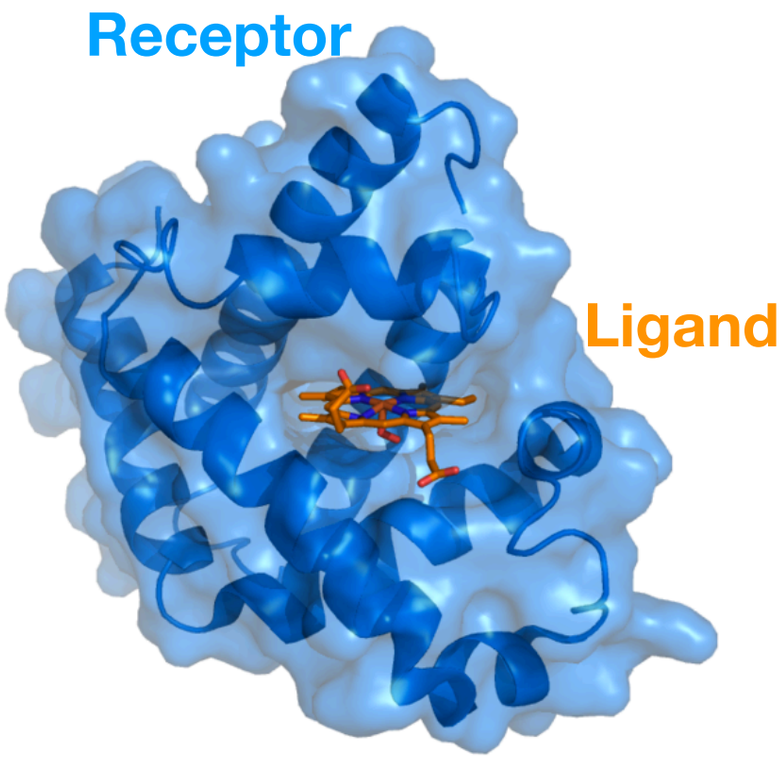


Ligand-receptor binding

- Drugs are molecules (**ligands**) that bind to a protein receptor, which can belong to either the human host or the virus itself.

- Once bound to the receptor, the protein's behavior may change; this can be harnessed to create a drug.

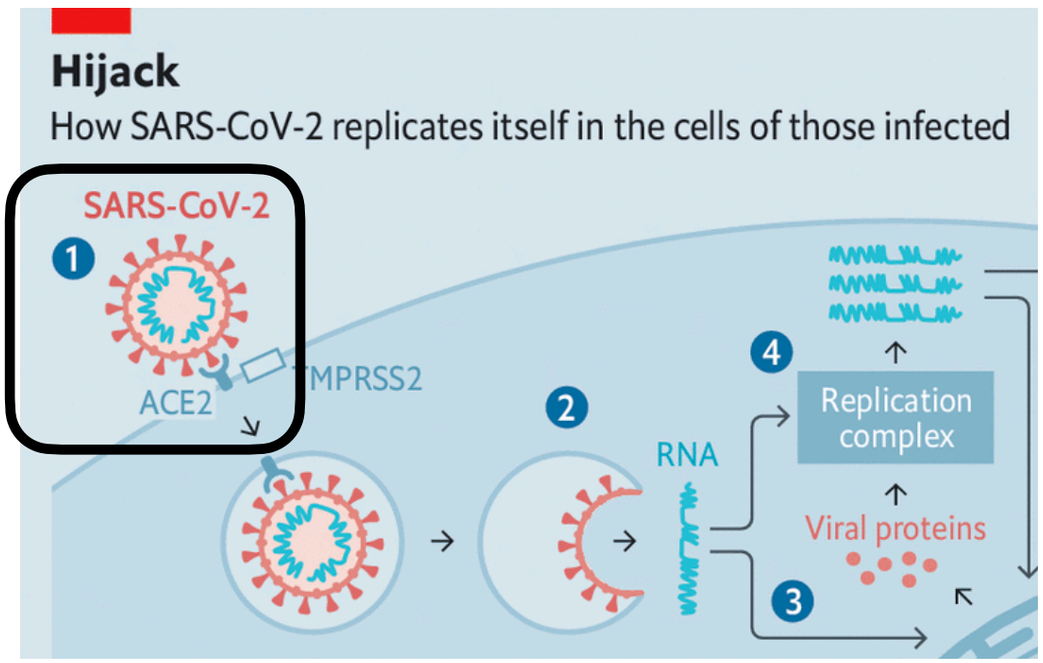
- A useful receptor constitutes a **target** in the drug discovery process.



Ligand-receptor binding

- For SARS-CoV-2, one particular target is its spike protein that binds to the ACE2 on the human cells' membranes.

- If we can find a molecule that binds with enough affinity (attraction between ligand and receptor), then we might inhibit the virus from entering the cell.



SARS-CoV-2 and ACE2

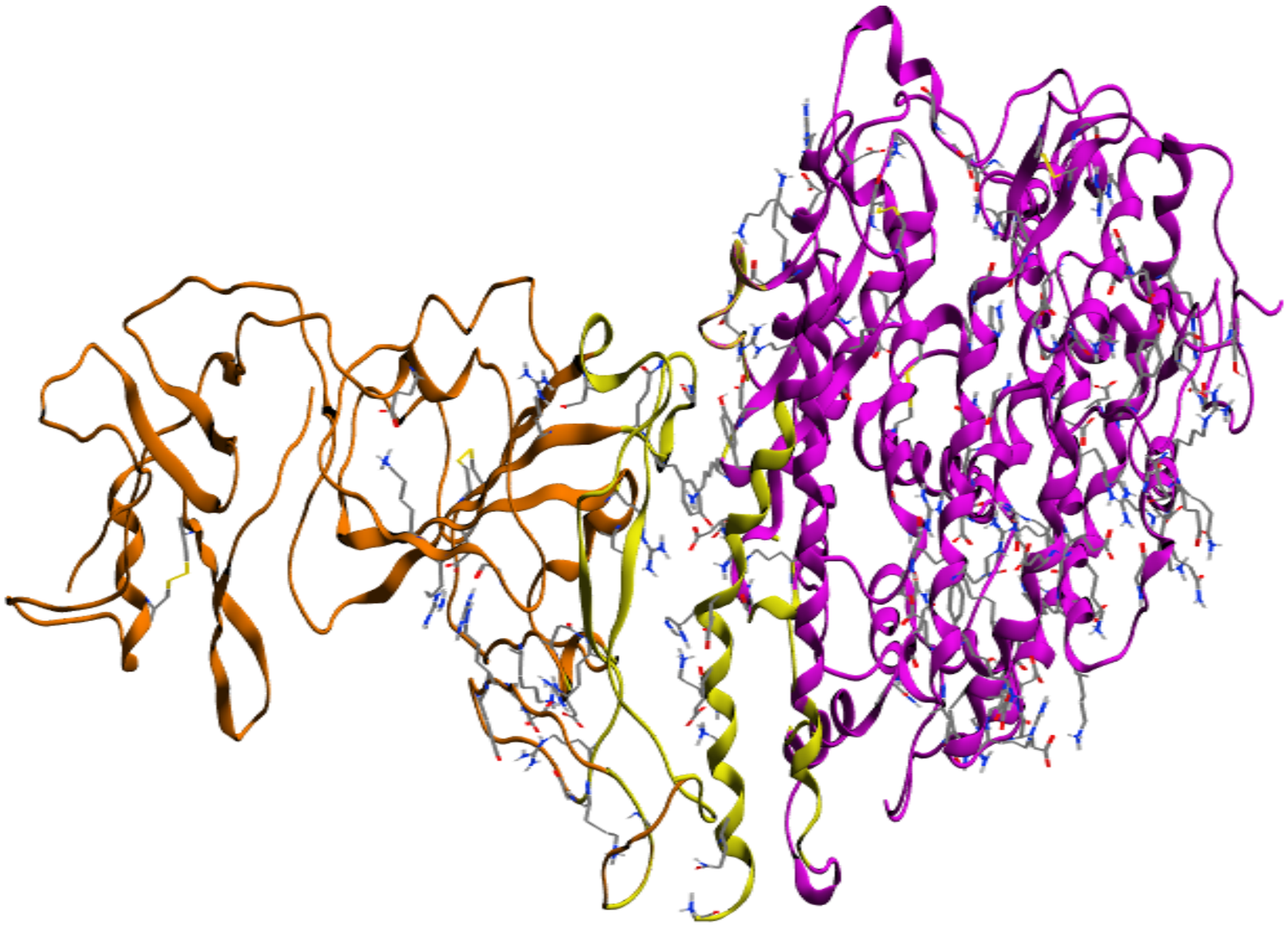


Figure 1) Rendering of nCoV-2019 S-protein and ACE2 receptor complex. Orange ribbons represent the S-protein, purple corresponds to ACE2, and yellow is a highlight of the interface targeted for docking.

Smith and Smith 2020

Drug discovery

- Drug discovery is extremely expensive and slow (often 5-10 years):
  1. Identify a target in either the host cells or the virus.
  2. Search for a compound that can bind to the target.
     a. Rational design based on the structure of the target.
     b. High-throughput screening of existing compound libraries.
  3. Perform in-vivo studies on animals to measure efficacy and safety.
  4. Perform clinical trials on humans to measure efficacy and safety.

Drug discovery

- Drug discovery is extremely expensive and slow (often 5-10 years):
  1. Identify a target in either the host cells or the virus.
  2. Search for a compound that can bind to the target.
     a. Rational design based on the structure of the target.
     b. High-throughput screening of existing compound libraries.
     c. Computational techniques to identify a promising “starting point” for a drug.
  3. Perform in-vivo studies on animals to measure efficacy and safety.
  4. Perform clinical trials on humans to measure efficacy and safety.

Drug discovery

- One technique for automatically identify potential drug compounds is to simulate the **molecular dynamics** (MD) of how the compound interacts with the receptor.

https://www.youtube.com/watch?v=meEX8jDF9-k

Mollica et al. 2015

Drug discovery

- Researchers at the Oak Ridge National Laboratory recently explored how MD simulations conducted on a supercomputer could identify potentially useful compounds from a set of already approved drugs.

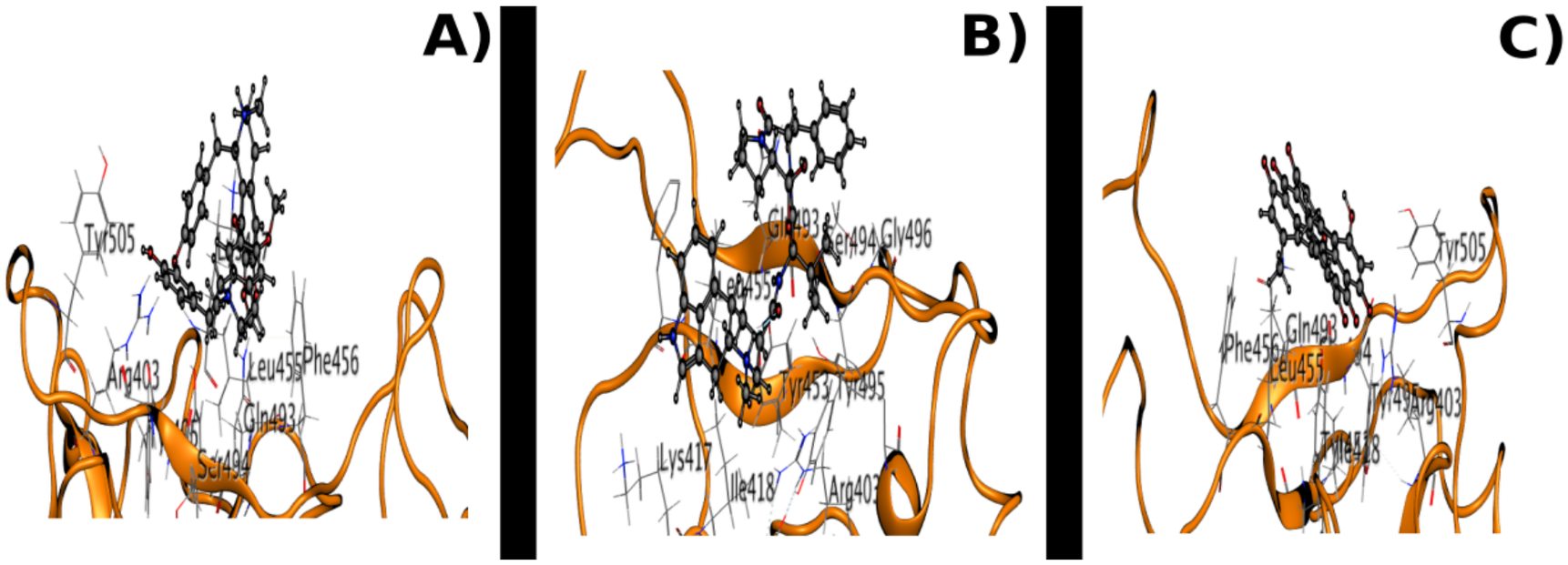


Figure 7) Renderings of three of the top scoring previously regulator approved small-molecules binding with the S-protein receptor recognition region. A) Cepharanthine (ZincID: 30726863). B) Ergoloid (ZincID: 3995616). C) Hypericin (Zinc ID: 3780340). Orange ribbons represent the S-protein.

Smith and Smith 2020

Drug discovery

- However, MD simulations are computationally extremely intensive.

- Smith and Smith's 2020 study was conducted on one of the world's largest supercomputers.

- Is there a way to identify candidate compounds more quickly, i.e., without MD simulations?

- Machine learning may be a useful tool.

Machine learning for drug discovery

- We can formulate the problem as follows:

  - Let **x** represent the components and structure of a candidate ligand (e.g., chemical formula, amino acid sequence, 3-D molecular structure) as well as the target, e.g.:

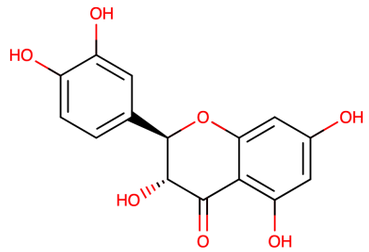
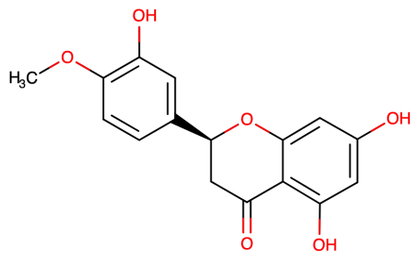
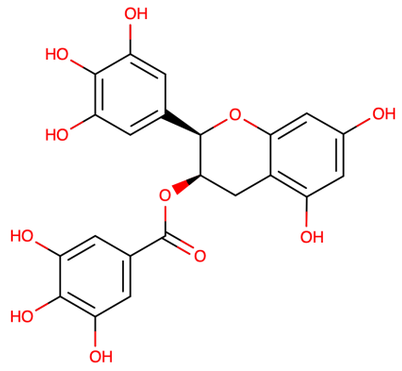
    `x = "OC1=C(C([C@H](O)… mssssw lllslvavtaaqstieeq… ]"`

  - Let *y* represent the affinity between the compound and the target receptor, e.g.:

    $y = 2.4\ \mu M$

  - We want to compute a function *f* that maps **x** to its associated *y*.

Machine learning for drug discovery

x (chemical structure)	*y* (affinity)*
 **Taxifolin**	**2.4 *μM***
 **Hesperitin**	**2.2 *μM***
 **Epigallocatechin gallate**	**0.8 *μM***

*These numbers are fictitious.

Machine learning for drug discovery

- A key requirement is that *f* is more accurate and/or faster to compute than other techniques to determine the binding affinity (e.g., MD simulations).

- Once we have *f*, we can:

  - Estimate the binding affinity for a novel compound+target combination.

  - Search for the best compound from a large set.

Machine learning for drug discovery

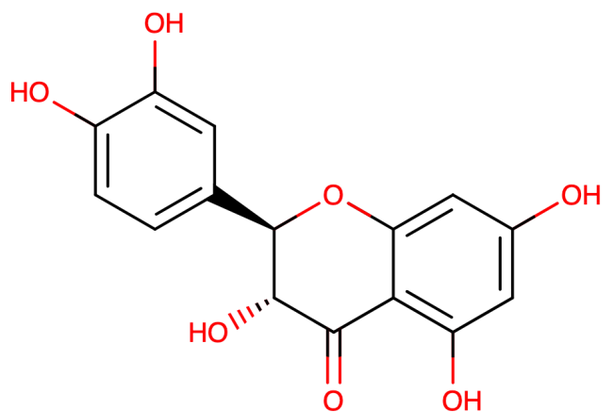
- Using a similar process, we could potentially compute a (different) function *g* that estimates the toxicity *y* of a given compound based on its chemical structure **x**.

Modeling molecules and their interactions

- We can represent the structure and attributes of a chemical molecule as a **graph**:

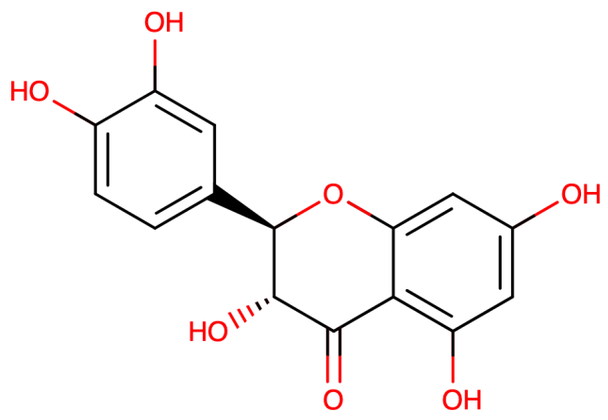
  - Each atom is a node with associated features.

- Each bond is an edge with associated features.



Modeling molecules and their interactions

- We want to extract high-level features from sub-graphs, irrespective of their locations in the whole graph.
- This is akin to a convolution kernel that operates on 2D sub-images in the same way, irrespective of location.



Modeling molecules and their interactions

- Starting next lecture, we will examine Graph Convolutional Networks (GCNs).
- Example application to drug discovery.