Doctoral thesis proposal

Orexin and uncertainty effects on food-seeking behavior

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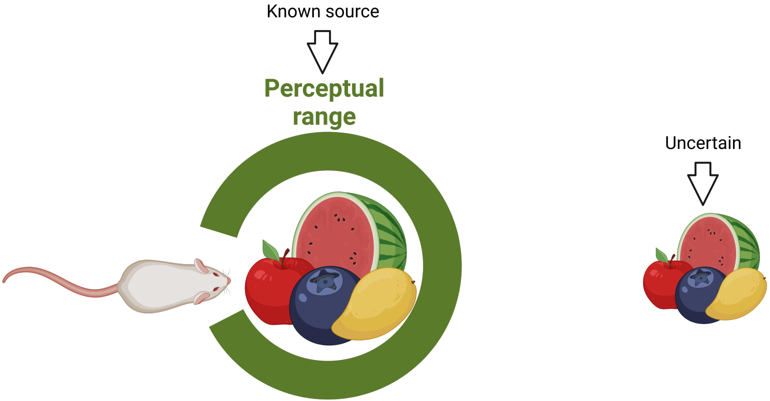
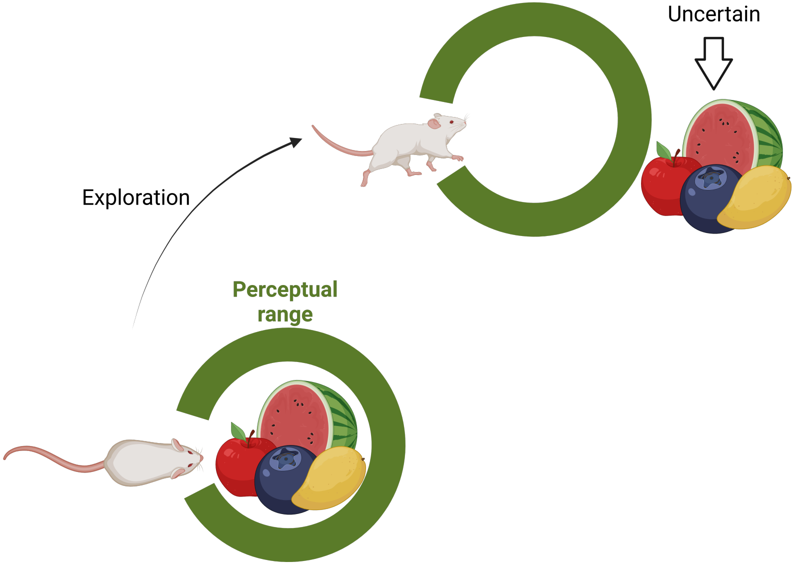
Food-seeking and uncertainty

Food-seeking behavior is the coordination of locomotor activity with internal and external cues to procure food

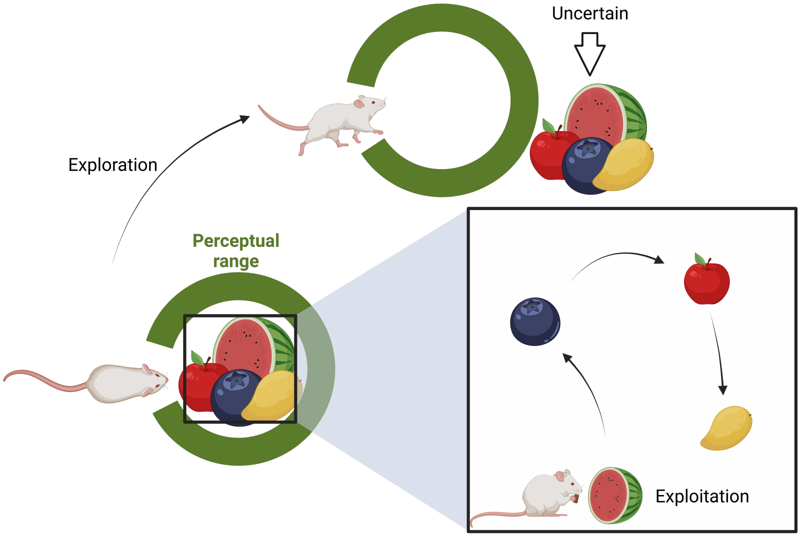
Food-seeking behavior implies a state of partial knowledge



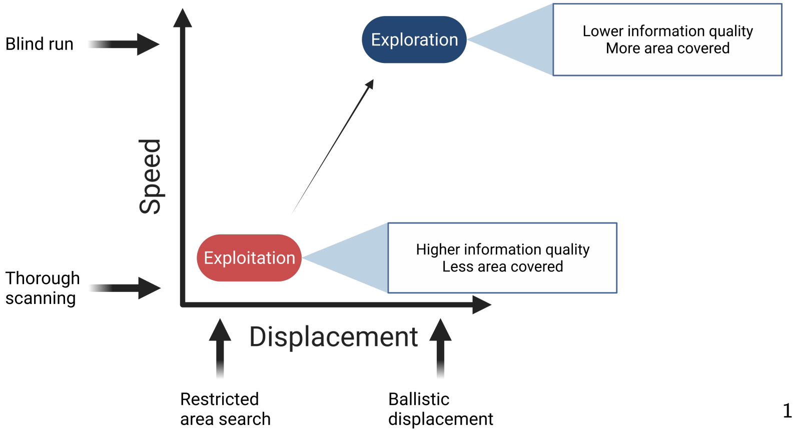
Partial knowledge forces animals to explore for new food sources



At some point animals need to stop exploring and start exploiting



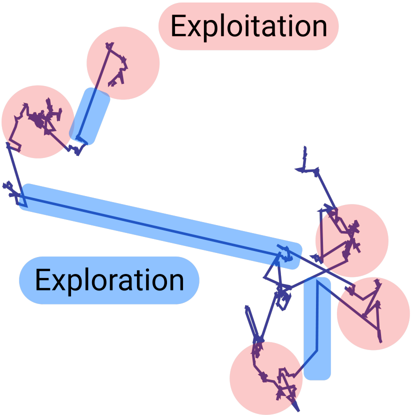
Uncertainty is inherent to food-seeking behavior



[1]

[1] Bartumeus et al. (2014)

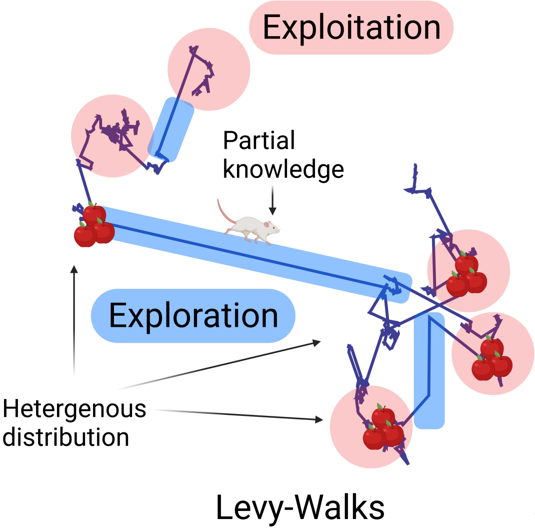
Food-seeking behavior evolved to deal with uncertainty, balancing between exploration and exploitation



Levy-Walks [2]

[2] Sims et al. (2014); Raichlen et al. (2014); Wosniack et al. (2017)

Food-seeking behavior evolved to deal with uncertainty, balancing between exploration and exploitation



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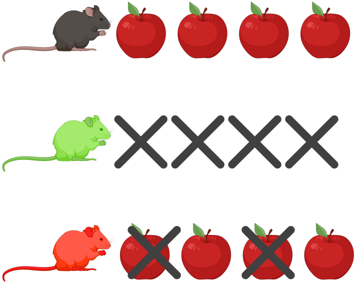
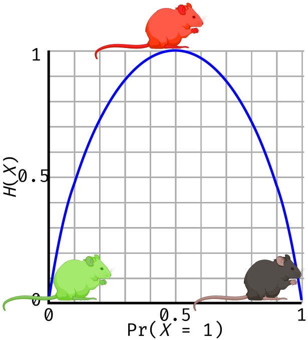
[3] Sims et al. (2014); Raichlen et al. (2014); Wosniack et al. (2017)

Key points

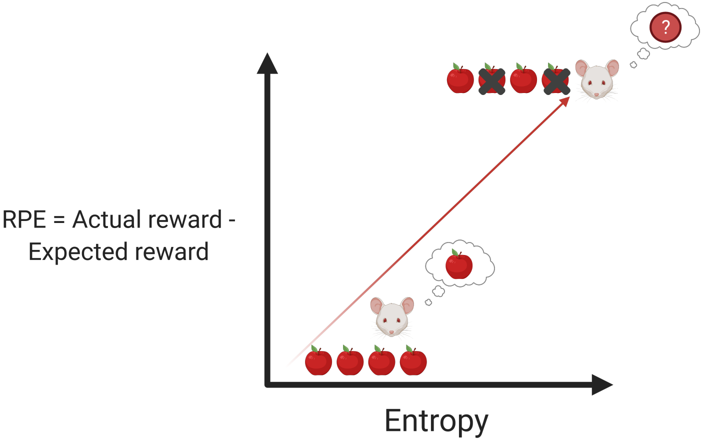
1. Due to limited perceptual ranges, animals must balance between exploration and exploitation
2. Exploratory behavior is trigered to reduce uncertainty of unknown food-sources
3. Food-seeking behavior adapted to deal with uncertainty by balancing between exploration and exploitation

Uncertainty and behavior: entropy relates the probability of obtaining food with uncertainty

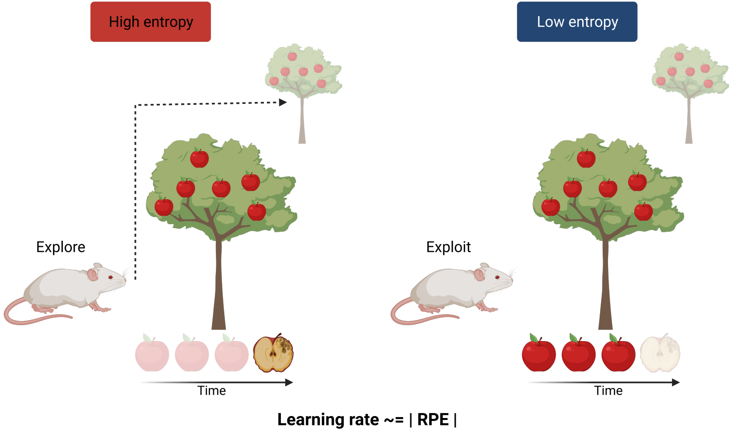




Increasing entropy makes prediction harder, leading to larger reward prediction errors



Reward prediction error changes the learning rate, adapting behavior to environment uncertainty



[4]Pearce and Hall (1980)

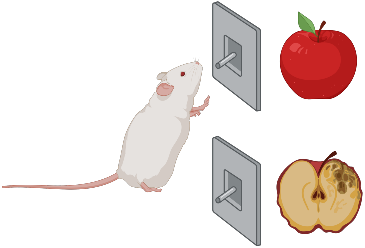
Key points

1. Entropy allows us to link food-access probability with uncertainty
2. The reward prediction error offers an inderect measure of environment uncertainty
3. The reward prediction error bias exploration/exploitation through the learning rate

Modeling food-seeking behavior in uncertain environments

Food-seeking behavior modeling starts by expected value computation

Expected value ~= Past value + (RPE * Learning rate)



Expected value ~= Action | State

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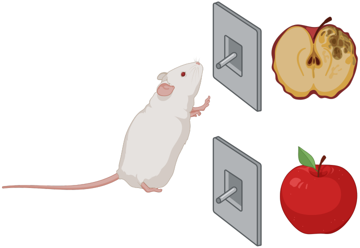
[5] Sutton and Barto (2018)

Food-seeking behavior modeling starts by expected value computation

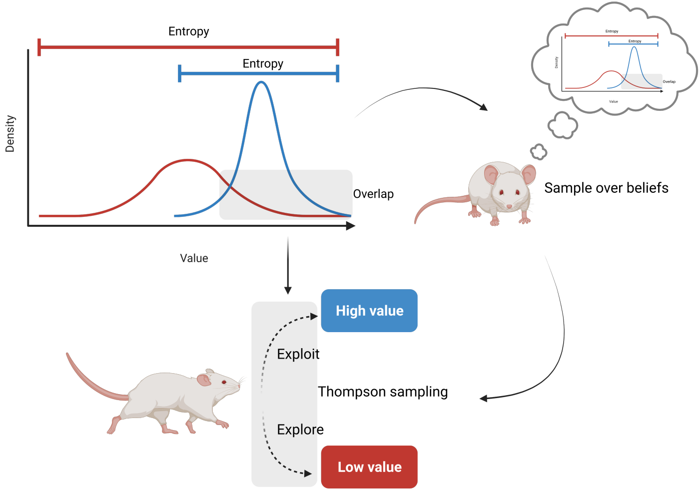
Expected value ~= Past value + (RPE * Learning rate)



Expected value ~= Action | State

[6] Sutton and Barto (2018)

Food-seeking behavior modeling starts by expected value computation



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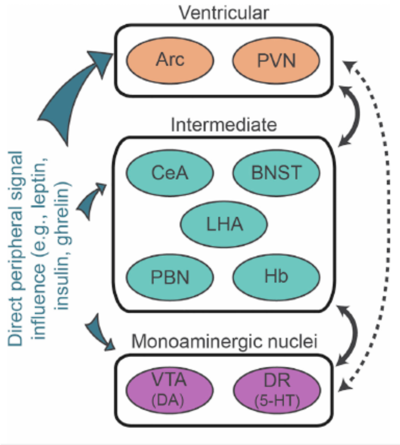
[7] Thompson (1933); Wang et al. (2017)

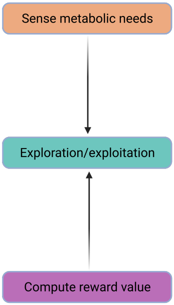
Key points

1. Uncertainty is inherent to food-seeking behavior and forces the animal to balance between exploration and exploitation
2. Uncertainty can be sensed inderectly through direct experience
3. The main aspects of food-seeking behavior can be modeled with RPE, learning rate and thompson sampling

Neural basis of uncertainty-driven food-seeking behavior

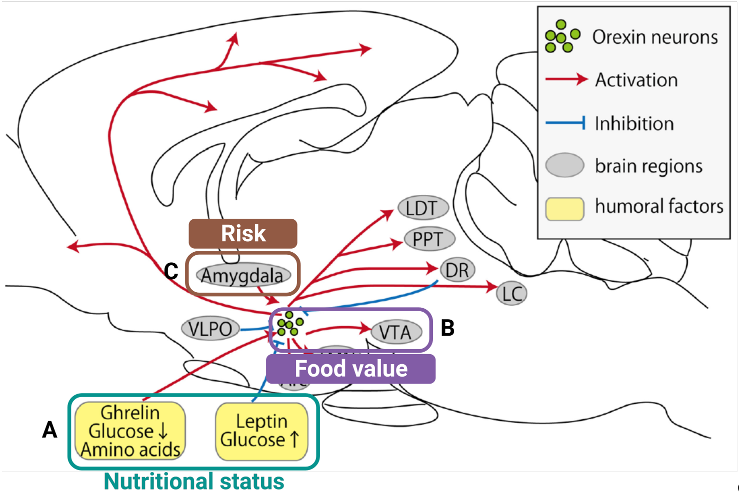
Reward and feeding centers connectivity permits procuring rewarding food to meet metabolic demands





[8] Rossi and Stuber (2018)

Reward and feeding centers connectivity permits procuring rewarding food to meet metabolic demands



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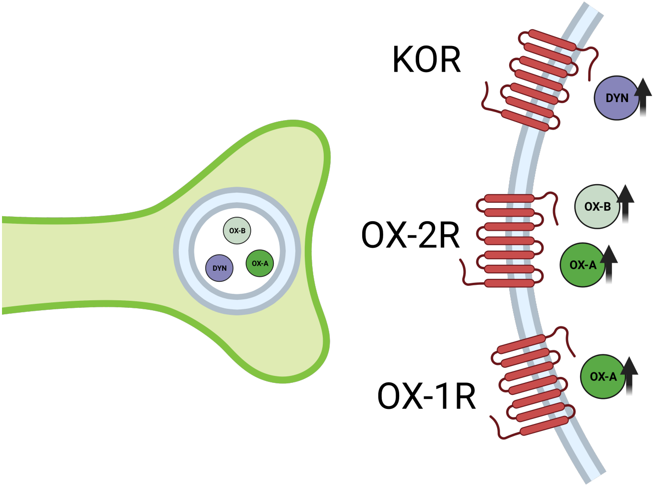
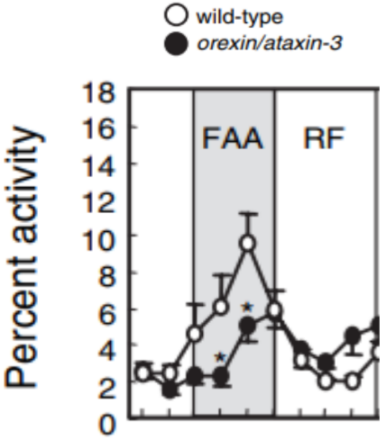
[9] Inutsuka and Yamanaka (2013)

Orexin could modulate exploration/exploitation through VTA DA activity



LHA orexin activity role in food-seeking behavior



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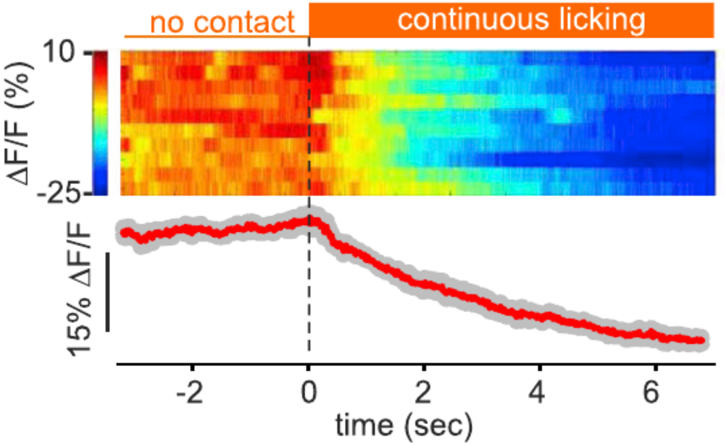
[10] Akiyama et al. (2004)

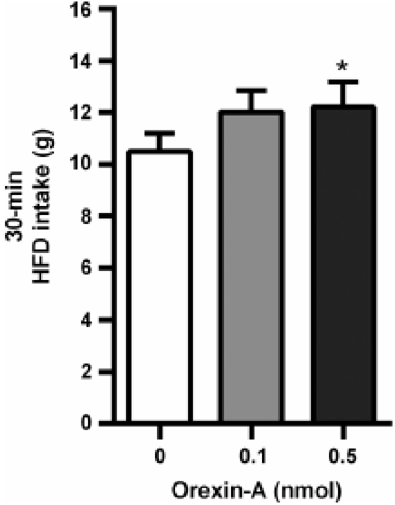
LHA orexin activity role in food-seeking behavior



[11]

[11] González et al. (2016)

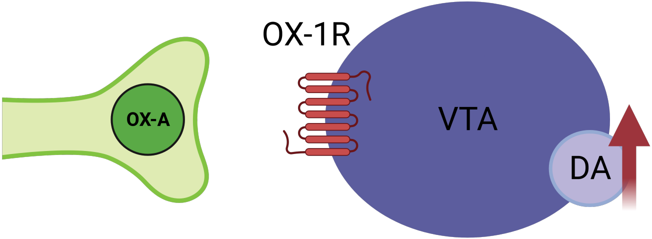
LHA orexin activity role in food-seeking behavior



[12]

[12] Terrill et al. (2016)

Orexin could modulate exploration/exploitation through VTA DA activity



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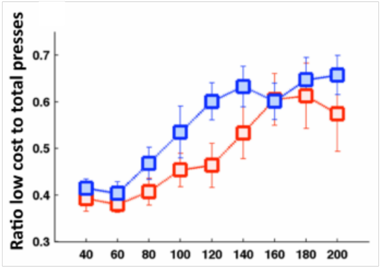
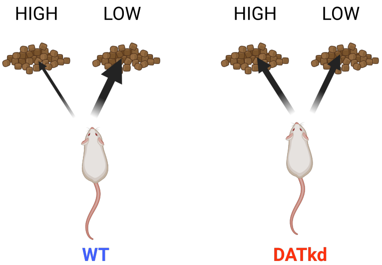
[13] Baimel et al. (2017)

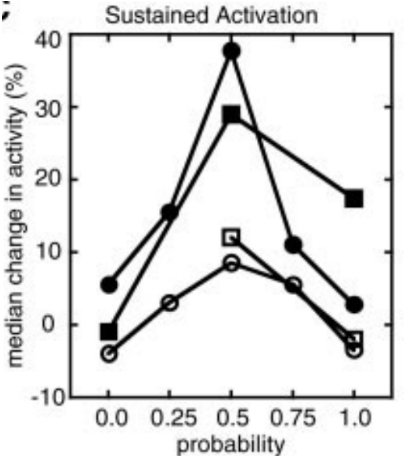
Orexin could modulate exploration/exploitation through VTA DA activity





[14] Beeler et al. (2010)

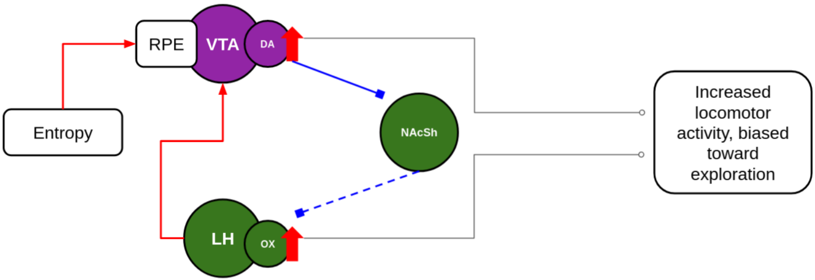
VTA DA tonic activity encodes entropy



[15]

[15] Fiorillo (2003)

Proposed connectivity

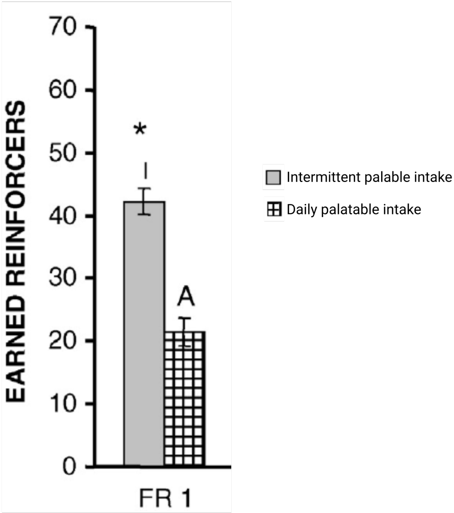


Key points

1. Orexin coordinates locomotor activity towards procuring food
2. VTA DA tonic activity encodes entropy
3. Orexin functional connectivity with VTA, allows modulation of exploration/exploitation in food-seeking behavior

Food-seeking in modern obesogenic environments

Uncertainty increases motivation to obtain food



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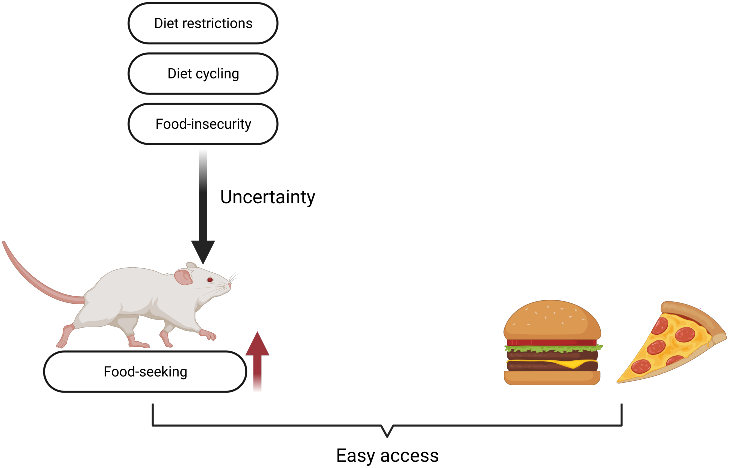
[16] Wojnicki et al. (2015)

Modern environments turn food-seeking behavior maladaptive



General overview

1. Uncertainty is inherent to food-seeking behavior
2. Animals sense uncertainty through RPE, and modulate its behavior through the learning rate
3. Orexin modulates uncertainty-drive VTA-DA activity
4. Easy-access to calorically dense foods turns food-seeking behavior maladaptive

Hypothesis and objectives

Main hypothesis and general objective

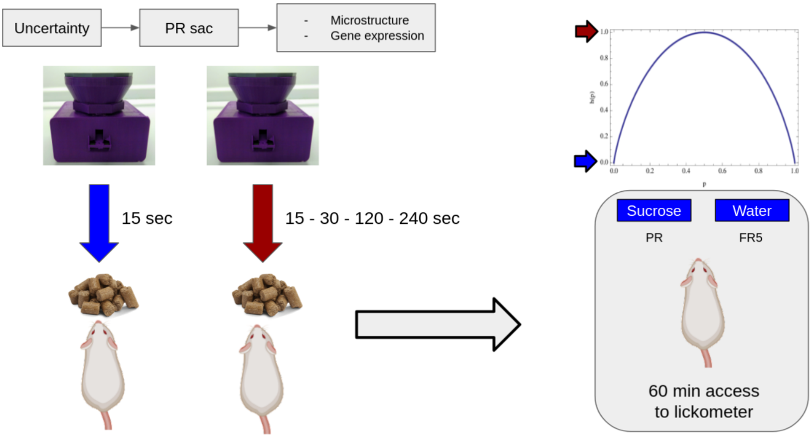
- Objective: Determine how uncertainty in food-access increases food-seeking behavior, and how orexin mediates uncertainty-driven increased food-seeking behavior
- Hypothesis: Food-access uncertainty increases food-seeking behavior, and this increase is modulated by orexin neurons activity

Specific objectives

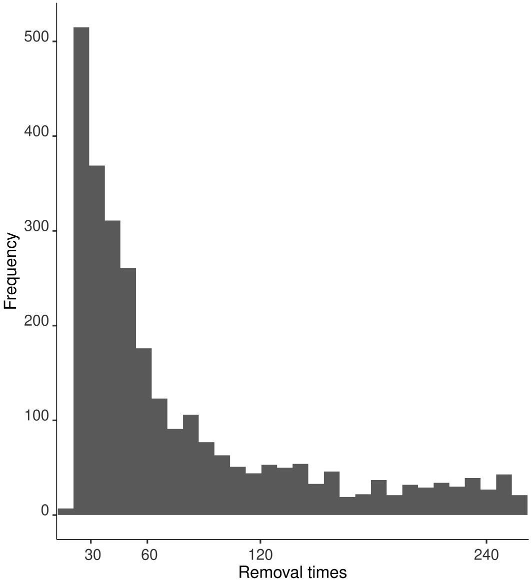
1. Determine whether uncertainty in food access required for subsistence increase motivation for palatable foods, and if this correlates with orexin gene expression
2. Determine whether uncertainty in obesogenic environments increases food-seeking behavior and assess if increased food-seeking behavior correlated with orexin gene expression
3. Determine if orexin/dynorphin neurons projecting to the VTA are active during sucrose intake
4. Determine whether orexin in VTA elicits increased food-seeking behavior towards uncertain options, and orexin agonists inhibits food-seeking behavior towards uncertain options

Methods

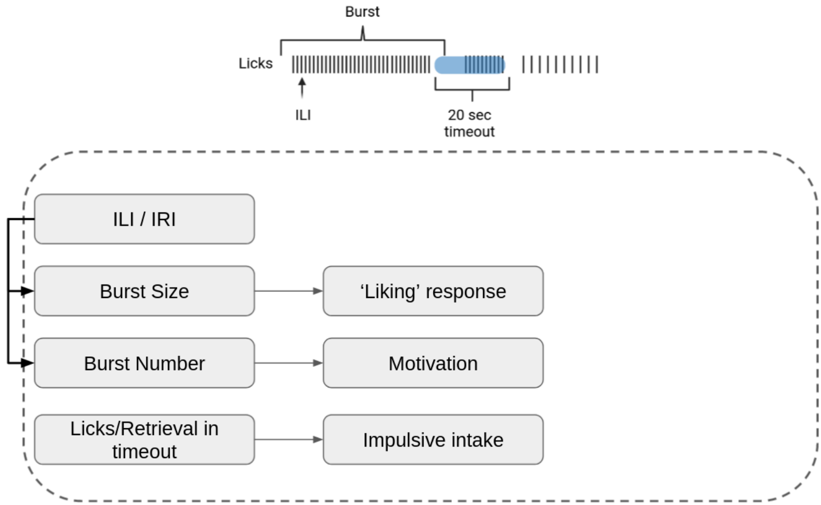
Specific objective 1: setting



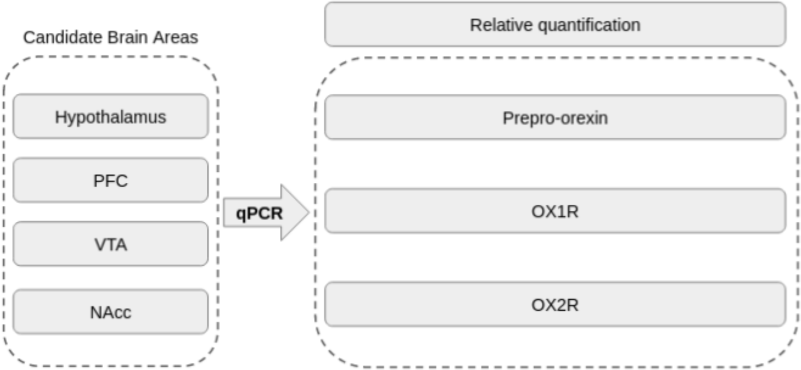
Inter removal intervals



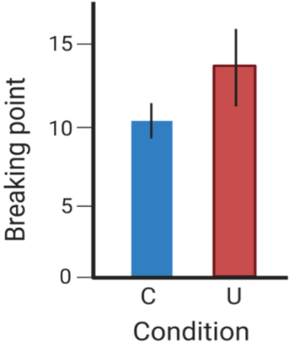
Specific objective 1: behavioral analysis

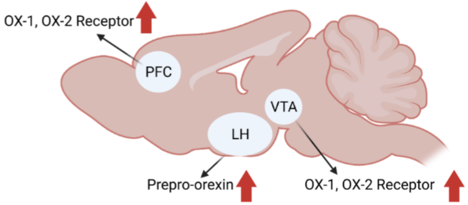


Specific objective 1: gene expression

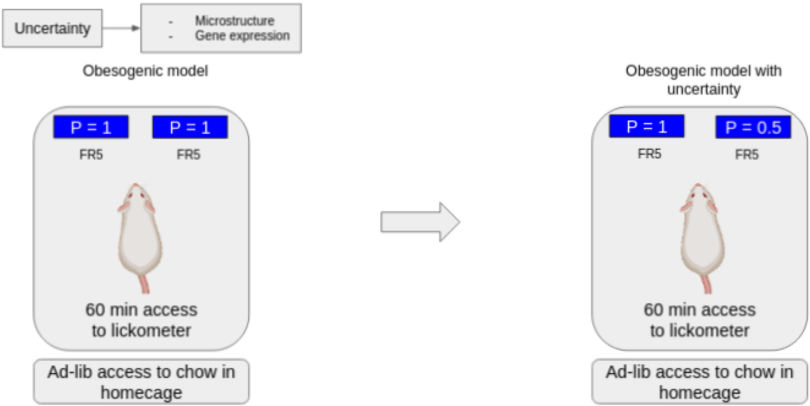


Specific objective 1: expected results

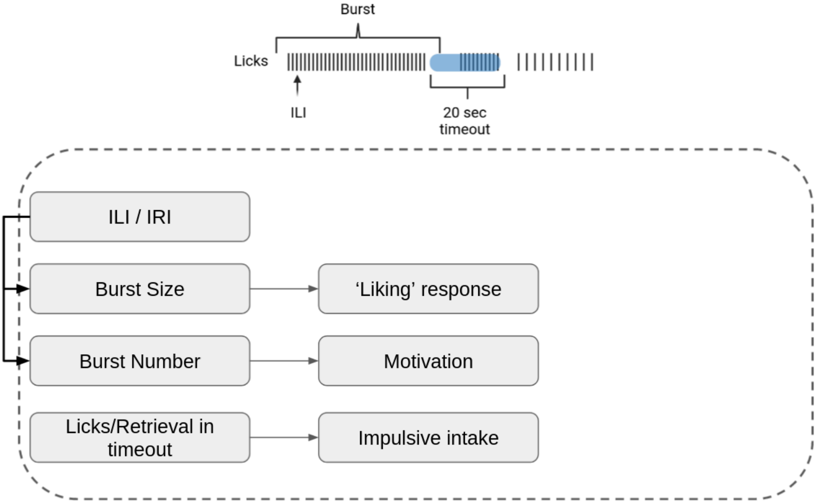




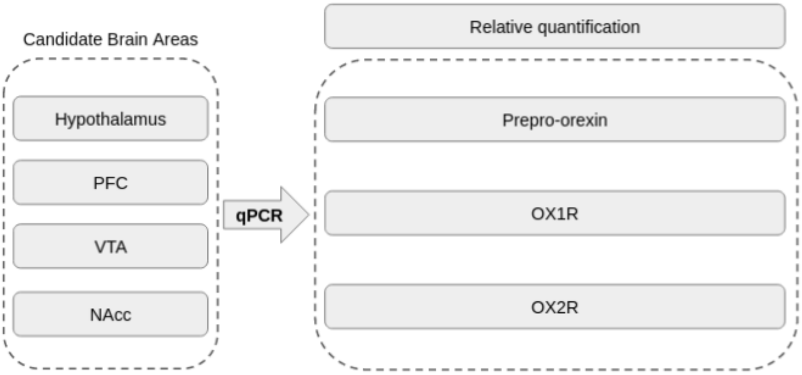
Specific objective 2: setting



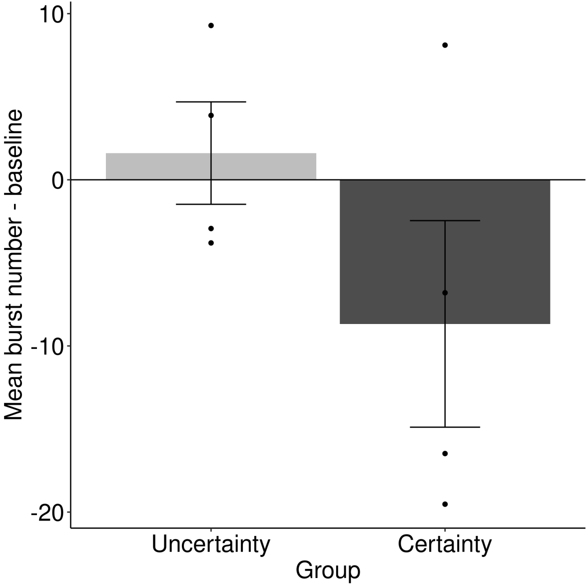
Specific objective 2: behavioral analysis



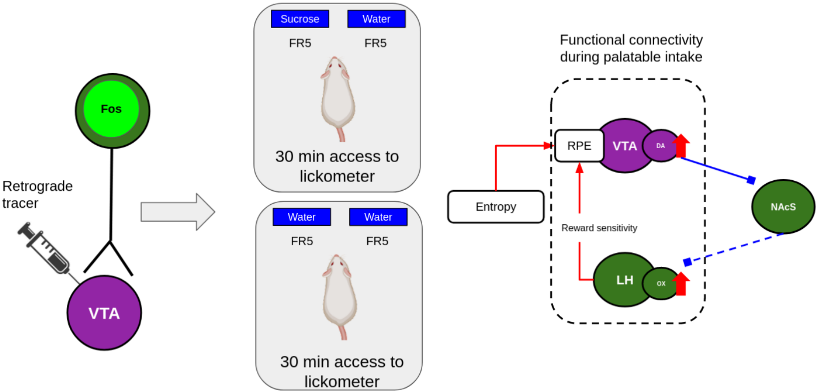
Specific objective 2: gene expression



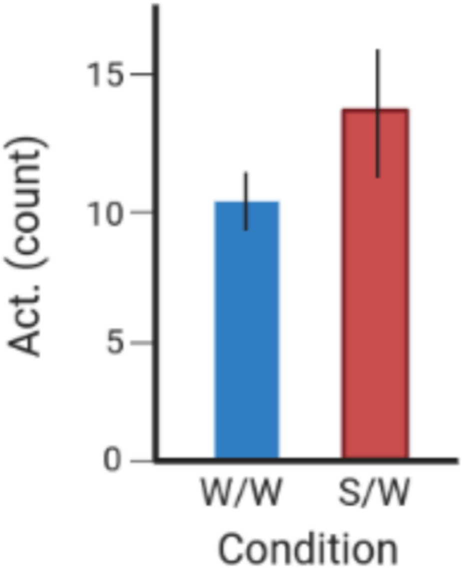
Specific objective 2: pilot study



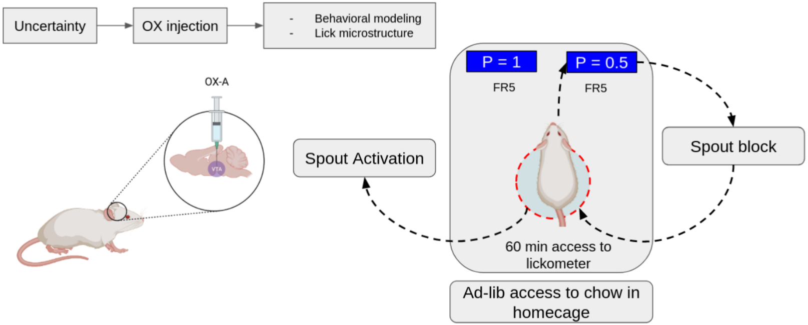
Specific objective 3: setting



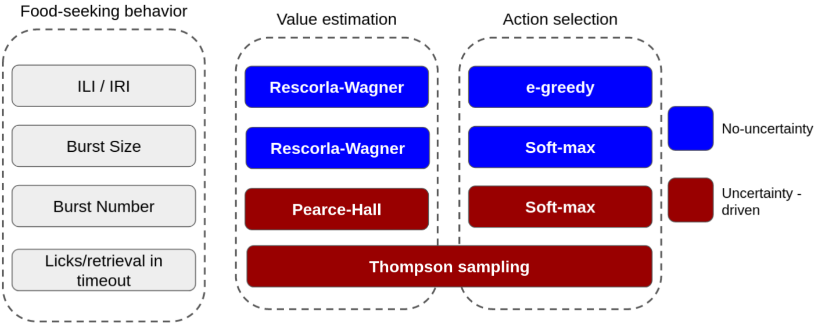
Specific objective 3: expected results



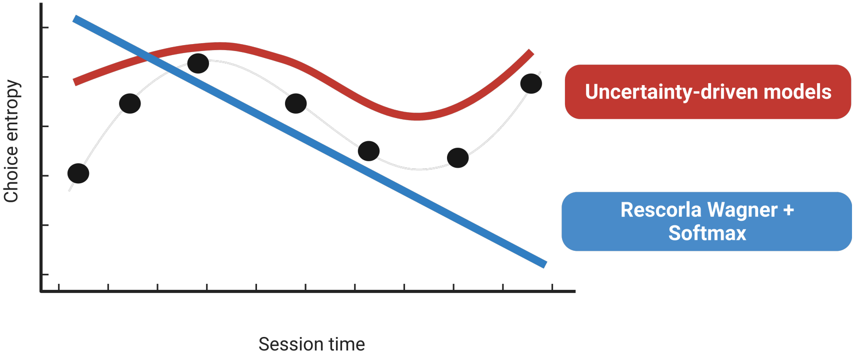
Specific objective 4: setting



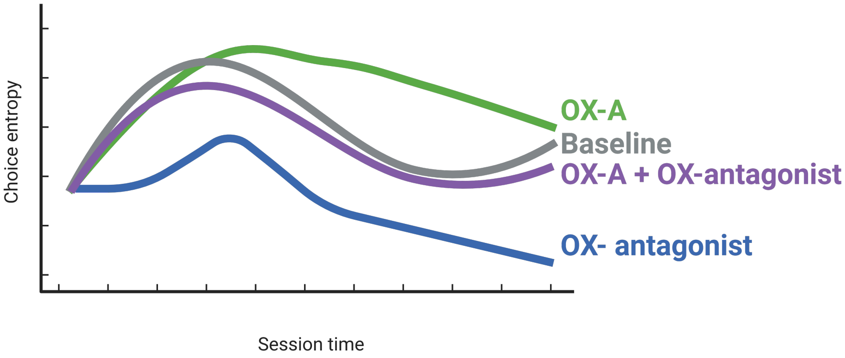
Specific objective 4: behavioral analysis



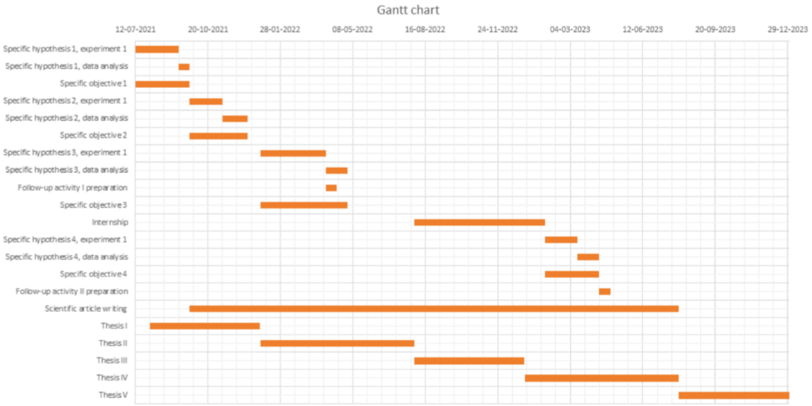
Specific objective 4: expected results



Specific objective 4: expected results

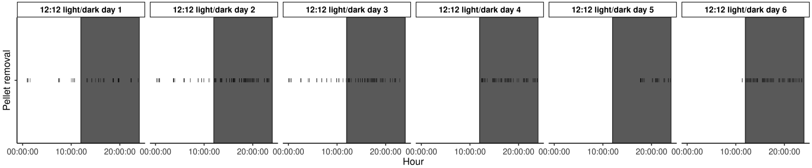


Workplan

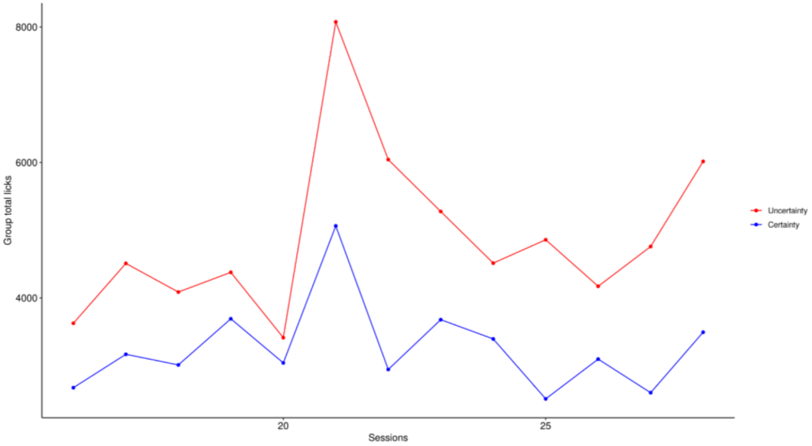


Gantt chart
12-07-2021
20-10-2021
28-01-2022
08-05-2022
16-08-2022
24-11-2022
04-03-2023
12-06-2023
20-09-2023
29-12-2023
Specific hypothesis 1, experiment 1
Specific hypothesis 1, data analysis
Specific objective 1
Specific hypothesis 2, experiment 1
Specific hypothesis 2, data analysis
Specific objective 2
Specific hypothesis 3, experiment 1
Specific hypothesis 3, data analysis
Follow-up activity I preparation
Specific objective 3
Internship
Specific hypothesis 4, experiment 1
Specific hypothesis 4, data analysis
Specific objective 4
Follow-up activity II preparation
Scientific article writing
Thesis I
Thesis II
Thesis III
Thesis IV
Thesis V

Circadian pellet intake



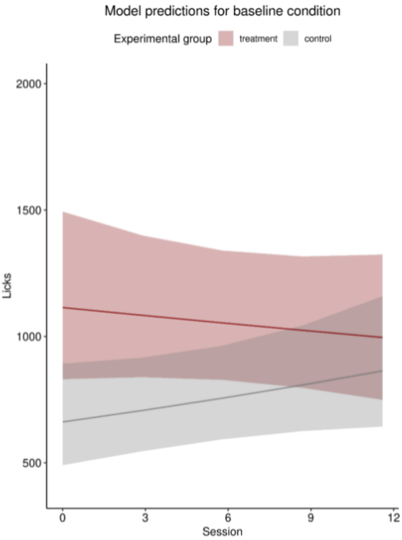
Sucrose intake reward value decreases over time

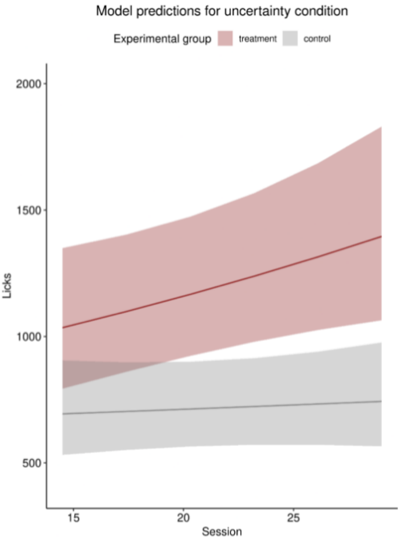


LMM parameters

Random effects intercepts	Fixed effects	Interactions	AIC
Animal	-	-	2859
Animal	(pre/post)	-	2861
Animal	(pre/post) + (control/treatment)	(pre/post):(control/treatment)	2860
Animal	(pre/post) + (control/treatment) + (sessions)	• (pre/post):(control/treatment) • (pre/post):(sesiones) • (pre/post):(control/treatment):(sessions)	2861
Animal	**(pre/post) + (control/treatment) + (sessions) + (baseline licks)**	• **(pre/post):(control/treatment)** • **(pre/post):(sesiones)** • **(pre/post):(control/treatment):(sessions)**	**2842**

LMM model results





LMM model results

Comparison	Ratio	p-value	CI-lower	CI-uperr
Treatment post / control post	1.511	0.0272*	1.048	2.18
Treatment pre / control pre	1.022	0.932	0.615	1.7
Treatment pre / treatment post	0.914	0.5730	0.667	1.25
Control pre / control post	1.350	0.0744(.)	0.971	1.88

Reinforcement learning main formulas

$$V_{t+1}(c_t) = V_t(c_t) + \alpha_V \cdot \delta_t,$$

Value update

$$\delta_t = abs(r_t) - V_t(c_t).$$

Prediction error

$$p(X \mid \Theta) = \prod_{i=1}^{N} p(x_i \mid \Theta)$$

Likelihood function

$$V_{t+1}(-c_t) = V_t(-c_t) + \alpha_V(0 - V_t(-c_t)).$$

Value update to non-selected option

$$P(c_t = 1) = \frac{\exp(\beta \cdot V_t(1))}{\exp(\beta \cdot V_t(1)) + \exp(\beta \cdot V_t(-1))}$$

Softmax

$$= \sigma\left(\beta\left[V_t(1) - V_t(-1)\right]\right)$$

logistic function over the difference in estimated value is similar to logistic regression

$$(R - L)/R$$

Pseudo r2 statistic: R is negative log likelihood of the data under random chance, L negative log likelihood of the data under the model

Reinforcement learning main formulas

The expected return (value) at the current state s is:

The expected reward for taking action a at state s...

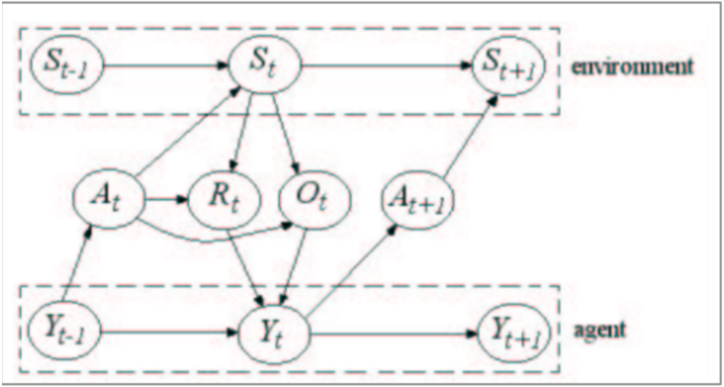
$$\boxed{V(s)} = \boxed{\max_a}(\boxed{R(s,a)} + \boxed{\gamma V(s')})$$

The maximum value of any possible action a for:

...plus the discount factor (gamma) multiplied by the value of the next state

Bellman equation for MDP's

Reinforcement learning main formulas

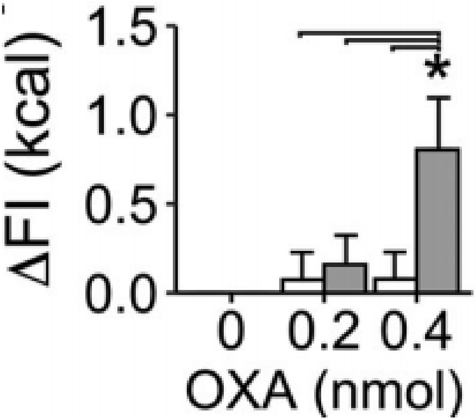


Partially observable markov decision process

$$\boxed{P[S_{t+1} \mid S_t] = P[S_{t+1} \mid S_1, \ldots, S_t]}$$

Markov property

Orexin-A in VTA increases paltable food intake



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[17] Mattar et al. (2020)

Thanks!

References I

Akiyama, Masashi, Tomoyo Yuasa, Naomi Hayasaka, Kazumasa Horikawa, Takeshi Sakurai, and Shigenobu Shibata. 2004. "Reduced Food Anticipatory Activity in Genetically Orexin (Hypocretin) Neuron-Ablated Mice: Food Anticipatory Activity of Orexin/Ataxin-3 Mice." *European Journal of Neuroscience* 20 (11): 3054–62. https://doi.org/10.1111/j.1460-9568.2004.03749.x.

Baimel, Corey, Benjamin K. Lau, Min Qiao, and Stephanie L. Borgland. 2017. "Projection-Target-Defined Effects of Orexin and Dynorphin on VTA Dopamine Neurons." *Cell Reports* 18 (6): 1346–55. https://doi.org/10.1016/j.celrep.2017.01.030.

References II

Bartumeus, Frederic, Ernesto P. Raposo, Gandhimohan M. Viswanathan, and Marcos G. E. da Luz. 2014. "Stochastic Optimal Foraging: Tuning Intensive and Extensive Dynamics in Random Searches." Edited by Mark D. McDonnell. *PLoS ONE* 9 (9): e106373. https://doi.org/10.1371/journal.pone.0106373.

Beeler, Jeff A., Nathaniel D. Daw, Cristianne R. M. Frazier, and Xiaoxi Zhuang. 2010. "Tonic Dopamine Modulates Exploitation of Reward Learning." *Frontiers in Behavioral Neuroscience* 4. https://doi.org/10.3389/fnbeh.2010.00170.

Fiorillo, C. D. 2003. "Discrete Coding of Reward Probability and Uncertainty by Dopamine Neurons." *Science* 299 (5614): 1898–1902. https://doi.org/10.1126/science.1077349.

References III

González, J. Antonio, Lise T. Jensen, Panagiota Iordanidou, Molly Strom, Lars Fugger, and Denis Burdakov. 2016. “Inhibitory Interplay Between Orexin Neurons and Eating.” *Current Biology* 26 (18): 2486–91. https://doi.org/10.1016/j.cub.2016.07.013.

Inutsuka, Ayumu, and Akihiro Yamanaka. 2013. “The Physiological Role of Orexin/Hypocretin Neurons in the Regulation of Sleep/Wakefulness and Neuroendocrine Functions.” *Frontiers in Endocrinology* 4. https://doi.org/10.3389/fendo.2013.00018.

Mattar, P., S. Uribe-Cerda, C. Pezoa, T. Guarnieri, C. M. Kotz, J. A. Teske, E. Morselli, and C. Perez-Leighton. 2020. “Brain Site-Specific Regulation of Hedonic Intake by Orexin and DYN Peptides: Role of the PVN and Obesity.” *Nutritional Neuroscience*, November, 1–10. https://doi.org/10.1080/1028415X.2020.1840049.

References IV

Pearce, John M., and Geoffrey Hall. 1980. "A Model for Pavlovian Learning: Variations in the Effectiveness of Conditioned but Not of Unconditioned Stimuli." *Psychological Review* 87 (6): 532–52. https://doi.org/10.1037/0033-295X.87.6.532.

Raichlen, D. A., B. M. Wood, A. D. Gordon, A. Z. P. Mabulla, F. W. Marlowe, and H. Pontzer. 2014. "Evidence of Levy Walk Foraging Patterns in Human Hunter-Gatherers." *Proceedings of the National Academy of Sciences* 111 (2): 728–33. https://doi.org/10.1073/pnas.1318616111.

Rossi, Mark A., and Garret D. Stuber. 2018. "Overlapping Brain Circuits for Homeostatic and Hedonic Feeding." *Cell Metabolism* 27 (1): 42–56. https://doi.org/10.1016/j.cmet.2017.09.021.

References V

Sims, D. W., A. M. Reynolds, N. E. Humphries, E. J. Southall, V. J. Wearmouth, B. Metcalfe, and R. J. Twitchett. 2014. "Hierarchical Random Walks in Trace Fossils and the Origin of Optimal Search Behavior." *Proceedings of the National Academy of Sciences* 111 (30): 11073–78. https://doi.org/10.1073/pnas.1405966111.

Sutton, Richard S., and Andrew G. Barto. 2018. *Reinforcement Learning: An Introduction*. Second edition. Adaptive Computation and Machine Learning Series. Cambridge, Massachusetts: The MIT Press.

References VI

Terrill, Sarah J., Kellie M. Hyde, Kristen E. Kay, Hayden E. Greene, Calyn B. Maske, Amanda E. Knierim, Jon F. Davis, and Diana L. Williams. 2016. "Ventral Tegmental Area Orexin 1 Receptors Promote Palatable Food Intake and Oppose Postingestive Negative Feedback." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 311 (3): R592–99. https://doi.org/10.1152/ajpregu.00097.2016.

Thompson, William R. 1933. "On the Likelihood That One Unknown Probability Exceeds Another in View of the Evidence of Two Samples." *Biometrika* 25 (3/4): 285. https://doi.org/10.2307/2332286.

References VII

Wang, Haifeng, Baohong Wen, Jingliang Cheng, and Hongpeng Li. 2017. "Brain Structural Differences Between Normal and Obese Adults and Their Links with Lack of Perseverance, Negative Urgency, and Sensation Seeking." *Scientific Reports* 7 (1): 40595. https://doi.org/10.1038/srep40595.

Wojnicki, F. H. E., D. S. Johnson, G. Charny, and R. L. W. Corwin. 2015. "Development of Bingeing in Rats Altered by a Small Operant Requirement." *Physiology & Behavior* 152 (December): 112–18. https://doi.org/10.1016/j.physbeh.2015.09.009.

Wosniack, Marina E., Marcos C. Santos, Ernesto P. Raposo, Gandhi M. Viswanathan, and Marcos G. E. da Luz. 2017. "The Evolutionary Origins of Lévy Walk Foraging." Edited by Frederic Bartumeus. *PLOS Computational Biology* 13 (10): e1005774. https://doi.org/10.1371/journal.pcbi.1005774.