RP2: Analysis of Drugs, Doses, and Biodistribution

Analysis of Lysergic Acid Diethylamide (LSD)

Group 6

Faris Abuain, Fireese Berg, Kristen Falik, Chichi Ohaka, Daniela Reyes Ladino

November 30, 2023

ISCI 1A24

Table of Contents

Alcohol Background

Approximately 86% of people above the age of 18 have consumed alcohol in some form (Adamson, Brace and Kennedy 2017). Alcohol's main components consist of water (H_2O) and ethanol (C_2H_5OH), a small, water-soluble molecule, more accurately called ethyl-alcohol (Paton 2005; IARC 1988). Ethanol is created through the fermentation of carbohydrates, usually fruits or vegetables, with yeast (IARC 1988). Anhydrous ethanol is a clear liquid that is used across various industries as fuel, within lotions and perfumes, and as a solvent for fats and oils (IARC 1988). As the human body is vastly comprised of water, alcohol is distributed to all parts of the body through the bloodstream. Ethanol is not a chiral molecule, meaning it has no mirror-like isomer (Texas University n.d.). At its core, it is a central nervous system (CNS) depressant drug, with a wide breadth of effects (Hironaka et al 2022). Alcohol (ethanol) has no one mode of action, as it acts on several different neurotransmitters in different ways. It is a glutamate N-methyl-D-aspartate (NMDA) antagonist as well as a gamma-aminobutyric acid (GABA) agonist (Hironaka et al 2022). GABA agonists generally produce anxiolytic and sedative effects (de Leon, Anthony 2023). Alcohol is no different, providing relief from anxiety and disinhibition at different blood concentrations (0.05–0.08%) (Hironaka et al 2022). In social drinkers, the laxity of neural signaling to the amygdala, the part of the brain that governs negative feelings, causes the desired psychological effect of reducing anxiety. Additionally, NMDA antagonists can cause vomiting, confusion, dizziness, and syncope, which correlates to several of alcohol's effects (cite). Furthermore, alcohol activates the pleasure centres of brain, causing physiological effects of sweating, tachycardia, and reddening of the face (Paton 2005). For alcohol to act on any neurotransmitter, the molecules must pass through the blood-brain barrier (BBB). The BBB is an important barrier that shields the CNS from disruption in the body. This allows the CNS to remain in contact with other organ systems while remaining unaffected by whatever may afflict the body. Formed of adherens and tight junctions, the BBB is a physical barrier that denies entrance to large, charged, or hydrophilic molecules (Vore and Deak 2022). Small, lipophilic molecules can enter through tight junctions, allowing passage to substances like ethanol. High concentrations of alcohol in the bloodstream, and thus the brain, later lead to deleterious effects, ranging from general anesthesia, coma, and eventually death (Hironaka et al 2022).

Works Cited

Adamson, Stuart S., Lear E. Brace, and Brian K. Kennedy. 2017. “Alcohol and Aging: From Epidemiology to Mechanism.” *Translational Medicine of Aging* 1 (October): 18–23. https://doi.org/10.1016/j.tma.2017.09.001.

Hironaka, Naoyuki. 2022. “Pharmacology of Alcohol and Alcohol Use Disorder.” In *NeuroPsychopharmacotherapy*, edited by Peter Riederer, Gerd Laux, Toshiharu Nagatsu, Weidong Le, and Christian Riederer, 2505–24. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-62059-2_340.

IARC, Working Group on the Evaluation of Carcinogenic Risks to. 1988. “Chemical Composition of Alcoholic Beverages, Additives and Contaminants.” In *Alcohol Drinking*. International Agency for Research on Cancer. https://www.ncbi.nlm.nih.gov/books/NBK531662/.

Jamero, Dana, Amne Borghol, Nino Vo, and Fadi Hawawini. 2011. “The Emerging Role of NMDA Antagonists in Pain Management.” https://www.uspharmacist.com/article/the-emerging-role-of-nmda-antagonists-in-pain-management.

Leon, Anthony S. de, and Prasanna Tadi. 2023. “Biochemistry, Gamma Aminobutyric Acid.” In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK551683/.

Paton, Alex. 2005. “Alcohol in the Body.” *BMJ : British Medical Journal* 330 (7482): 85–87.

Texas University. n.d. “CH610A/618A Achiral Picture.” Accessed November 30, 2023. https://iverson.cm.utexas.edu/courses/310M/Handouts/Handoutsfl05/Sterohandpics1.html

Vore, Andrew S., and Terrence Deak. 2022. “Alcohol, Inflammation, and Blood-Brain Barrier Function in Health and Disease Across Development.” *International Review of Neurobiology* 161: 209–49. https://doi.org/10.1016/bs.irn.2021.06.009.

Caffeine Background

Caffeine is widely consumed on a global scale, with a consumption of approximately 210-238 mg/person/day in the United States and Canada (Rodak, Kokot and Kratz 2021). Caffeine is most commonly found in coffee, tea leaves, and cacao beans (Rodak, Kokot and Kratz 2021). Caffeine, with the chemical name 1,3,7-trimethylpurine-2,6-dione, is composed of eight carbon atoms, ten hydrogen atoms, four nitrogen atoms, and two oxygen atoms (PubChem 2023). Caffeine is a nonchiral molecule because it lacks a chiral center with tetrahedral substituents and non-symmetrical elements (Libre text 2015). Caffeine is most known to reduce fatigue, but it has other uses such as pain relief, treating specific respiratory conditions in premature newborns, and athletic enhancement products. (PubChem 2023). Physiological effects of caffeine include the lowering of the risk of liver cancer, fibrosis, cirrhosis, and gallstones (Harvard 2020). Furthermore, there are also psychological effects that arise from different doses of caffeine. When taken in low or normal amounts, caffeine can provide a boost of alertness, energy, and elevation in mood which provide benefits in high-alert situations (Winston, Hardwick and Jaberi 2005). On the other hand, caffeine taken in excessive amounts can induce symptoms of caffeinism including intoxication, caffeine-induced anxiety, sleep disorders, migraines, and epilepsy. When caffeine dose is reduced, it can cause withdrawal symptoms like heart palpitations and nausea (Winston, Hardwick and Jaberi 2005). The root cause of these psychological effects mainly stems from the drug's three main modes of action on the nervous system (Nehlig 2004). Caffeine's first mode of action is as a competitive inhibitor preventing adenosine from binding to its receptor (Fiani et al. 2021.). This causes the release of neurotransmitters like norepinephrine, serotonin, and dopamine which alters psychological functions like alertness and cognition (Fiani et al. 2021). The second mode of action is the promotion of the movement of calcium through the plasma membrane. This allows for the calcium to be released by synaptic transmission. In turn, this influx affects the release of those neurotransmitters that have stimulating effects (Fiani et al. 2021). The final mode of action is the competitive inhibition that prevents methylxanthine from binding to phosphodiesterase. This leads to the promotion and accumulation of cAMP, which stimulates the influx of neurotransmitters which can alter mood and alertness (Fiani et al. 2021).

Works Cited

Harvard. 2020. “Caffeine.” https://www.hsph.harvard.edu/nutritionsource/caffeine/

Chemistry LibreTexts. 2015. “5.1: Chiral Molecules.” https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Map%3A_Organic_Chemistry_(Vollhardt_and_Schore)/05._Stereoisomers/5.1%3A_Chiral__Molecules.

Nehlig, Astrid. 2004. *Coffee, Tea, Chocolate, and the Brain*. CRC Press.

PubChem. n.d. “Caffeine.” Accessed November 20, 2023. https://pubchem.ncbi.nlm.nih.gov/compound/2519.

Fiani, Brian, Lawrence Zhu, Brian L Musch, Sean Briceno, Ross Andel, Nasreen Sadeq, and Ali Z Ansari. 2021. “The Neurophysiology of Caffeine as a Central Nervous System Stimulant and the Resultant Effects on Cognitive Function.” *Cureus* 13 (5): e15032. https://doi.org/10.7759/cureus.15032.

Quadra, Gabrielle R., José R. Paranaíba, Jéssica Vilas-Boas, Fábio Roland, André M. Amado, Nathan Barros, Roberto Júnio P. Dias, and Simone J. Cardoso. 2020. “A Global Trend of Caffeine Consumption over Time and Related-Environmental Impacts.” *Environmental Pollution* 256 (January): 113343. https://doi.org/10.1016/j.envpol.2019.113343

Rodak, Kamil, Izabela Kokot, and Ewa Maria Kratz. 2021. “Caffeine as a Factor Influencing the Functioning of the Human Body—Friend or Foe?” *Nutrients* 13 (9): 3088. https://doi.org/10.3390/nu13093088.

Winston, Anthony P., Elizabeth Hardwick, and Neema Jaberi. 2005. “Neuropsychiatric Effects of Caffeine.” *Advances in Psychiatric Treatment* 11 (6): 432–39. https://doi.org/10.1192/apt.11.6.432.

LSD Background

Lysergic acid diethylamide ($C_{20}H_{25}N_3O$), also known as LSD, is a potent hallucinogen that alters the consciousness of its user (CAMH n.d.). It is derived from the fungus ergot, found in rye or other grains. The chemical reaction of ergot, lysergic acid and diethylamine is one way LSD is synthesized, but there are numerous other possible reactions (Liu and Jia 2017). It was first intentionally consumed by Swiss chemist Albert Hoffman in 1943, with a dosage of 250 µg (Carhart-Harris et al. 2016). His detailed observations reported symptoms of altered perception, fear, paranoia, loss of reality and a fear of going insane (Hofmann 1980). Sandoz pharmaceuticals first commercially distributed LSD in 1948 for two main applications: analytical psychotherapy and experimental studies on psychosis (Carhart-Harris et al. 2016). However, commercial distribution promptly stopped in Canada in 1962 due to its widespread recreational use (CAMH n.d.). Currently, it has limited uses in Canada, but a select few patients in Switzerland are offered authorized LSD-assisted psychotherapy (Liechti 2017). Pure LSD looks like white, crystalline powder which is water soluble. The minimum effective dose is 20 to 80 µg, almost impossible to see. Hence, it is sold in LSD-soaked paper called “blotters,” often illustrated with colourful drawings, that are swallowed or absorbed sublingually (CAMH n.d.). More rarely, it can be injected or inhaled. The effects of LSD depend on a range of things such as age, drug sensitivity, history with drugs, and the environment. Some commonly reported physical symptoms are numbness, rapid heartbeat and reduced coordination (CAMH n.d.). It can also be unpredictable, as even a person who takes LSD multiple times may have both positive and negative experiences, otherwise known as “trips.” Some psychological effects include changes in mood, senses and thoughts, distortion of surroundings, and hallucinations (Government of Canada 2012). LSD has a complex mode of action. It interacts with the serotonin system, specifically the 5-HT_{2A} receptor, localized in areas of the brain that mediate cognitive functions and social interaction (EMCDDA n.d.; Raote, Bhattacharya, and Panicker 2007). This agonist interaction may be what causes the psychological disturbances described above (López-Giménez and González-Maeso 2018). Additionally, LSD is a chiral molecule, allowing for four stereoisomers (Jastrzębski, Kaczor, and Wróbel 2022). Certain chiral structures of LSD prefer specific serotonin receptors (Nichols et al. 1995). LSD can have environmental impacts, specifically on sewage-treatment plants. However only low concentrations have been found, possibly due to low-dosage use (Postigo, Lopez de Alda, and Barceló 2008).

Works Cited

CAMH. n.d. “LSD.” Accessed November 28, 2023. https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/lsd.

Carhart-Harris, R. L., M. Kaelen, M. Bolstridge, T. M. Williams, L. T. Williams, R. Underwood, A. Feilding, and D. J. Nutt. 2016. “The Paradoxical Psychological Effects of Lysergic Acid Diethylamide (LSD).” Psychological Medicine 46 (7): 1379–90. https://doi.org/10.1017/S0033291715002901.

EMCDDA. n.d. Accessed November 28, 2023. https://www.emcdda.europa.eu/publications/drug-profiles/lsd_en.

Government of Canada. 2012. “LSD.” Education and awareness. January 12, 2012. https://www.canada.ca/en/health-canada/services/substance-use/controlled-illegal-drugs/lsd.html.

Hofmann, Albert. 1980. LSD, My Problem Child. New York: McGraw-Hill.

Jastrzębski, Michał K., Agnieszka A. Kaczor, and Tomasz M. Wróbel. 2022. “Methods of Lysergic Acid Synthesis—The Key Ergot Alkaloid.” Molecules 27 (21): 7322. https://doi.org/10.3390/molecules27217322.

Liechti, Matthias E. 2017. “Modern Clinical Research on LSD.” Neuropsychopharmacology 42 (11): 2114–27. https://doi.org/10.1038/npp.2017.86.

Liu, Haichao, and Yanxing Jia. 2017. “Ergot Alkaloids: Synthetic Approaches to Lysergic Acid and Clavine Alkaloids.” *Natural Product Reports* 34 (4): 411–32. https://doi.org/10.1039/C6NP00110F.

López-Giménez, Juan F., and Javier González-Maeso. 2018. “Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways.” *Current Topics in Behavioral Neurosciences* 36: 45–73. https://doi.org/10.1007/7854_2017_478.

Nichols, David E., A. Monte, X. Huang, and D. Marona-Lewicka. 1995. “Stereoselective Pharmacological Effects of Lysergic Acid Amides Possessing Chirality in the Amide Substituent.” Behavioural Brain Research, Serotonin, 73 (1): 117–19. https://doi.org/10.1016/0166-4328(96)00080-0.

Postigo, Cristina, Maria J. Lopez de Alda, and Damià Barceló. 2008. “Analysis of Drugs of Abuse and Their Human Metabolites in Water by LC-MS2: A Non-Intrusive Tool for

Drug Abuse Estimation at the Community Level." TrAC Trends in Analytical Chemistry, Advanced MS Analysis of Metabolites and Degradation Products - II, 27 (11): 1053–69. https://doi.org/10.1016/j.trac.2008.10.002.

Raote, Ishier, Aditi Bhattacharya, and Mitradas M. Panicker. 2007. "Serotonin 2A (5-HT2A) Receptor Function: Ligand-Dependent Mechanisms and Pathways." In *Serotonin Receptors in Neurobiology*, edited by Amitabha Chattopadhyay. Frontiers in Neuroscience. Boca Raton (FL): CRC Press/Taylor & Francis. http://www.ncbi.nlm.nih.gov/books/NBK1853/.

Applied Mathematics: Question 1

Alcohol is eliminated from the body by the enzyme alcohol dehydrogenase (ADH), which is saturated with alcohol at relatively modest blood alcohol concentrations (BAC). Thus, the elimination of alcohol by ADH is linear. However, the concentration-dependent rate of alcohol metabolism by enzymes such as CYP2E1 and ADH4, means that the rate at which alcohol is eliminated from the body is overall concentration-dependent, with higher rates of elimination at higher BACs. This is confirmed by most observational studies, and therefore we should describe the elimination rate, $r(a_t)$, as a function of the amount of alcohol present, a_t (Cederbaum 2012). The equation:

$$\beta 60 = 0.15g/kg + 0.05g/kg \times BAC \qquad \text{Equation 1.1}$$

models the rate of elimination, which is measured in grams of alcohol per kilogram of blood (Simic and Tasic 2006). BAC, in g/kg, is equivalent to the expression a_t/kg of blood. To design a reasonable function, $r(a_t)$, we will assume administration to a 70kg adult, where the volume of blood is 5.5L (Vander et al. 2001, 375). The density of blood is approximately 1060kg/m^3, or 1.060kg/L, so there will be 5.83kg of blood in the 70kg subject (Cutnell and Johnson 1998, 308). Thus, we will define the rate of elimination as:

$$r(a_t) = (0.15g/kg/h) + \left(0.05g/kg/h \times \frac{a_t}{5.83kg}\right) \qquad \text{Equation 1.2}$$

where $r(a_t)$ is in terms of grams per kilogram per hour (g/kg/h) (Figure 1.1).

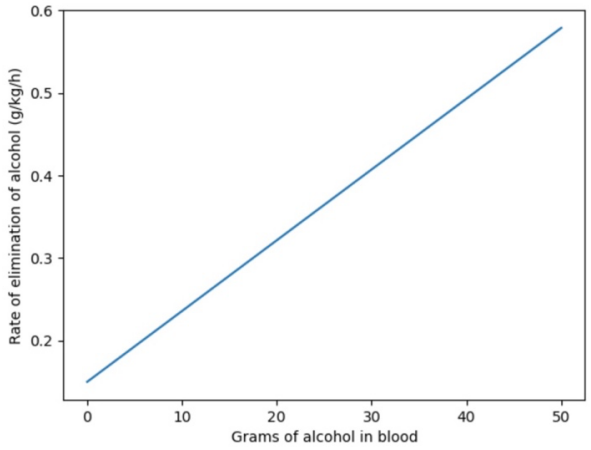

Figure 1.1: The graph in the figure above represents the rate at which alcohol is eliminated from the blood (g/kg/h) with respect to the amount of alcohol in the blood (in grams).

Based on Equation 1.2, we can determine $r(a_t)$ at a_t=10g, a_t=20g and a_t=40g to be 0.2358g/kg/h, 0.3215g/kg/h and 0.4931g/kg/h, respectively. To determine the alcohol eliminated per hour, we multiply these rates by the mass of blood (kg) that we determined earlier (5.83kg) as described by:

$$\text{Mass of alcohol eliminated} = (0.15g/kg/h \times 5.83kg) + (0.05g/kg/h \times 5.83kg)\left(\frac{a_t}{5.83kg}\right)$$

Equation 1.4

which simplifies to:

$$\text{Mass of alcohol eliminated} = 0.8745+(0.2915 \times \frac{a_t}{5.83})$$

Equation 1.5

Thus, within an hour of consuming 10, 20, or 40 grams of alcohol, 1.3745 grams, 1.8745 grams and 2.8745 grams will have been eliminated from the body. This function provides us with realistic rates of elimination for values of $a_t > 0$, however values below 0 result in a negative BAC, which is impossible.

The discrete-time dynamical system (DTDS) for alcohol elimination and consumption is described by the equation:

$$a_{t+1} = a_t - r(a_t)a_t + d$$

Equation 1.6

Here, a_t represents the amount of alcohol in grams at time *t*, $r(a_t)$ is the rate of elimination, and *d* is the amount of alcohol ingested in grams at time t+1. Thus, based on Equation 1.2, we can describe the DTDS as:

$$a_{t+1} = a_t - (0.15 + \left(\frac{0.05a_t}{5.83}\right))a_t + d$$

Equation 1.7

The equilibrium points for the DTDS occur where the updating function, $f(a_t)$, is equal to y = x. To find these points, we solve algebraically for:

$$f(a_t) = x$$

Equation 1.8

where,

$$f(a_t) = x - (0.15 + 0.05x5.83)x + d.$$

Equation 1.9

Solving algebraically (Appendix B), we find that the equilibria for this DTDS are found at the solutions to the equation:

$$\text{Equilibrium} = \frac{-0.15 \pm \sqrt{0.15^2 + 0.034305d}}{0.01715} \qquad \text{Equation 1.10}$$

Since we cannot have a negative amount of alcohol in the body, the equilibrium will only be plausible if ≥ 0. This occurs at values of d where $0.15 \leq \sqrt{0.15^2 + 0.034305d}$ (Appendix B). Thus, there exist biologically plausible equilibria so long as d, the amount of alcohol consumed at time t+1, is ≥ 0 (Appendix B). Based on these calculations, we chose a biologically plausible value, $d = 10$, to generate a cobweb plot which investigates how the amount of alcohol in the body changes over time (Figure 1.2).

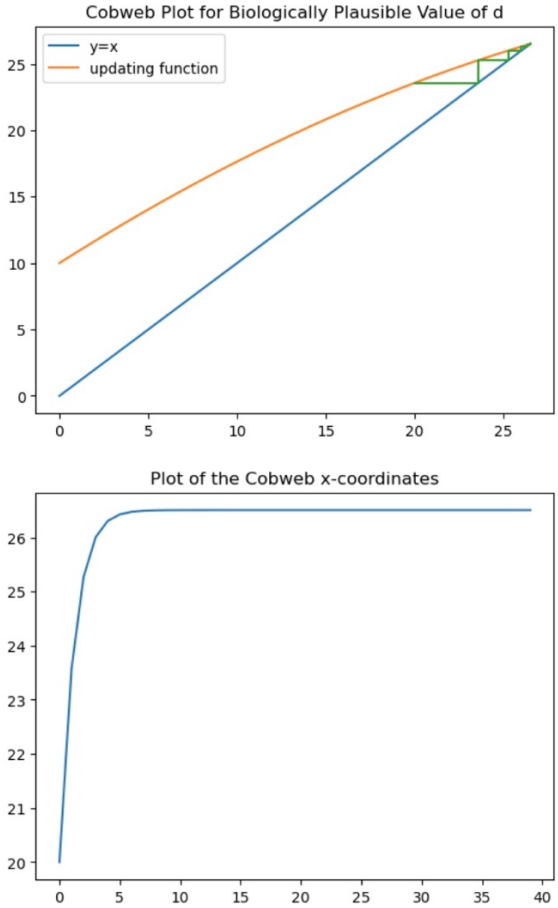

Figure 1.2: The cobweb plot of the updating function of our DTDS for alcohol elimination, for a biologically plausible value d = 10 (top). A graph of the x-coordinates of the cobweb plot, approximating the amount of alcohol, on the y-axis, as a function of time, on the x-axis (bottom). (Appendix A)

We can observe that, when a biologically plausible value of d is chosen, the amount of alcohol increases at a slowing rate, eventually reaching a stable equilibrium (Figure 1.2). Conversely, cobwebbing for the biologically implausible case (d<0) has no stable equilibrium. Instead, the amount of alcohol in the body decreases indefinitely, as can be seen with the growing size of steps on the cobweb between y = x and the updating function (Figure 1.3).

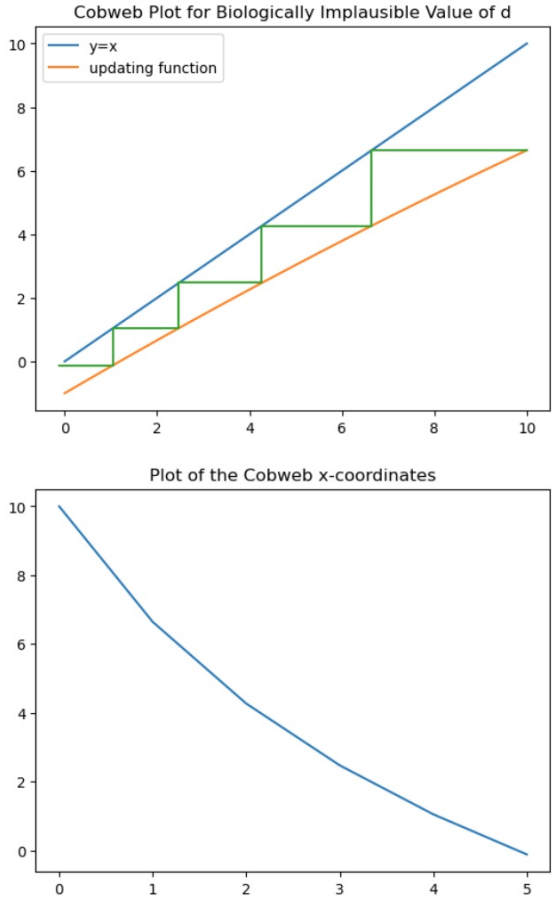

Figure 1.3: The cobweb plot of the updating function of our DTDS for alcohol elimination, for a biologically implausible value d = -1 (top). A graph of the x-coordinates of the cobweb plot, approximating the amount of alcohol, on the y-axis, as a function of time, on the x-axis (bottom). (Appendix A)

We can also use Python to generate and plot the possible solutions to our alcohol elimination DTDS for these two cases (Appendix A). To find the possible solutions to case (i), in which d=10, we generate a set of solutions, assuming an initial dose of 20g of alcohol (Figure 1.4).

```
values of t (h): [0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]
values of a (g): [20, 23.569468267581474, 25.269726977559777, 26.00277477894972, 26.303522402546513, 26.4242436924109
65, 26.47226533138019, 26.491298329486256, 26.49883096272334, 26.501810414447043, 26.502988635785186, 26.503454520275
394, 26.503638730670566, 26.503711566302393, 26.503740364892614, 26.503751751585497, 26.503756253773304, 26.503758033
894037, 26.50375873773615, 26.50375901602834, 26.50375912606231]
```

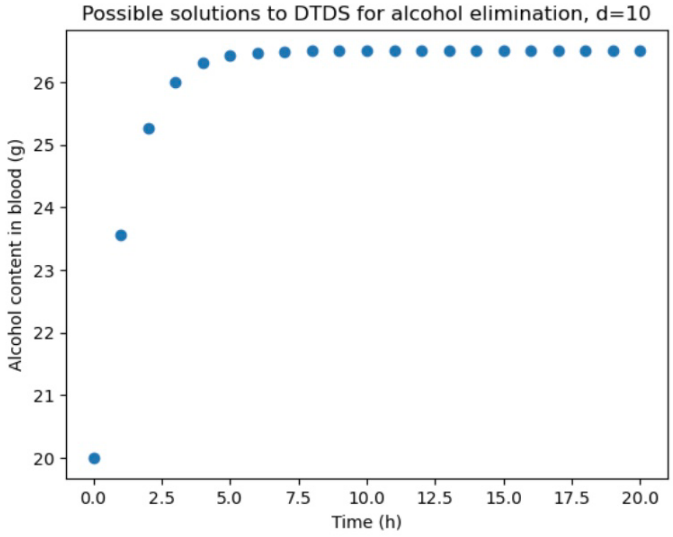

Figure 1.4: A graph of the possible solutions to our DTDS for alcohol elimination, in which we assume an initial amount of 20g of alcohol in the blood, and a d-value of 10. The time (t) and alcohol (a) solutions to our DTDS are printed above the graph. (Appendix A)

Here, the amount of alcohol in the body initially increases rapidly, with the rate of increase slowing down (Figure 1.4). The BAC eventually stabilizes once the rate of elimination and amount of alcohol consumed reach equilibrium. In case (ii), however, we start with an initial amount of 40g of alcohol and d = -1 (Figure 1.5). This is biologically implausible, as it would require the direct removal of a fixed amount of alcohol from the blood each hour, in addition to elimination by the body.

```
values of t (h): [0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]
values of a (g): [40, 19.2778730703259, 12.198916036744453, 8.09280459631391, 5.317190199884666, 3.2771372992180083,
1.6934601101849993, 0.4148458351256217, -0.6488570012660438, -1.5551392178693788, -2.342609827358401, -3.038283711772
9613, -3.661710691141021, -4.227446584773611, -4.746599791115152, -5.227836319677849, -5.678054290125338, -6.10284958
1611776, -6.506845583613397, -6.89393229194608, -7.267443669817435]
```

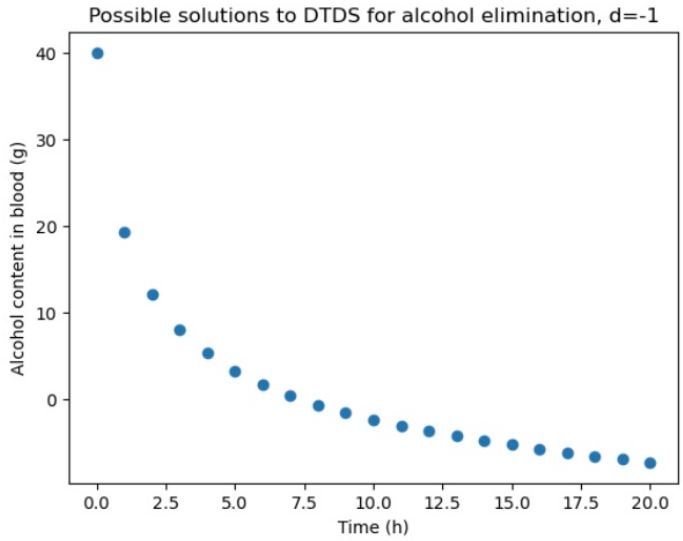

Figure 1.5: A graph of the possible solutions to our DTDS for alcohol elimination, in which we assume an initial amount of 40g of alcohol in the blood, and a d-value of -1. The time (t) and alcohol (a) solutions to our DTDS are printed above the graph. We can observe that the solutions to a, the amount of alcohol in grams, eventually reach values less than 0. (Appendix A)

The implausibility is further exemplified by the solutions in the figure above, which eventually reaches a negative BAC. This constant decrease shows that there is no equilibrium point as time increases, which supports what we observed in the cobwebbing in Figure 1.3. In case (i), the equilibrium is stable, as demonstrated by its own cobweb plot (Figure 1.2). As we can see on the graph in Figure 1.2, the x-coordinates of the first cobweb plot stabilize, converging on the equilibrium value. In case (ii), no equilibrium is reached. Instead, Figure 1.5 suggests that the amount of alcohol in the body will decrease until it reaches negative value, which does not reflect reality. Realistically, we should instead expect the amount of alcohol in the body to reach 0 and decrease no further.

To further explore how we can use our DTDS to find solutions to the system of alcohol elimination, we will use Python and the DTDS to determine the time at which alcohol levels fall below 1g given one initial consumption of 50g.

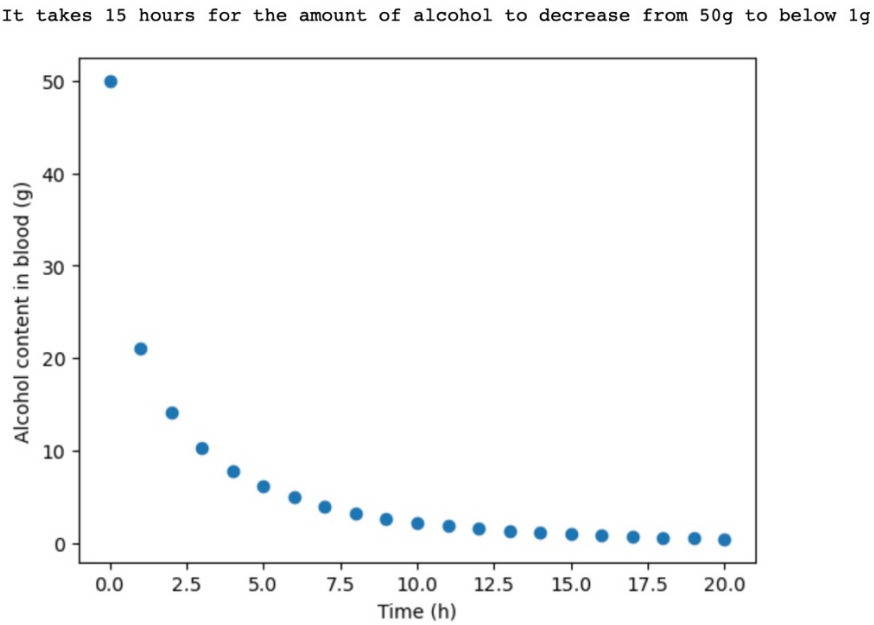

Figure 1.6: The graph above represents amount of alcohol in grams, on the y-axis, at specific values of time, on the x-axis, for the case in which the initial amount of alcohol in the body is 50g and no additional alcohol is consumed. The time at which the amount of alcohol in the body falls below 1g is printed above the graph (Appendix A).

Thus, we can determine that it will take 15 hours for the alcohol level to fall below 1g, if 50g of alcohol is consumed initially and no additional alcohol is ingested (Figure 1.6). In addition to using the DTDS to model elimination and consumption, we can use the inverse of the updating function, $f^{-1}(a(t))$, to find the point where blood alcohol levels no longer increase for a given value of d, the equilibrium. The inverse could be useful when determining the blood alcohol at a previous time based on current blood alcohol levels, since $f^{-1}(a(t))$ takes in blood alcohol and outputs time (Figure 1.7). This could be used in forensic cases, such as trying to determine BAC at the time of an accident or criminal incident, given the BAC as measured ex post facto. We can also observe where the equilibrium occurs, with those equilibrium points occurring at the vertical asymptote of the inverse function (Figure 1.8).

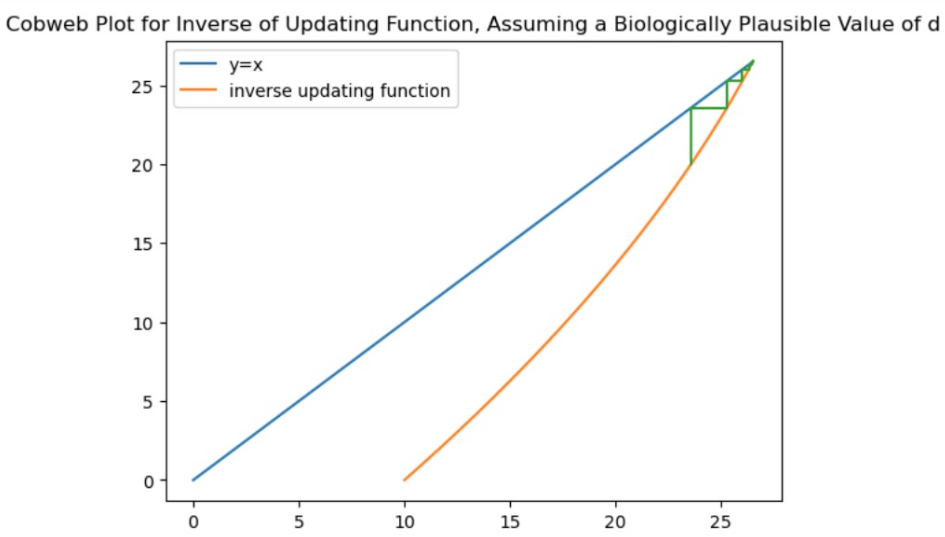

Figure 1.7: The figure above represents the cobweb plot for the inverse of our updating function for alcohol elimination (with a d-value of 10). The inverse updating function approximates time, on the y-axis, as a function the amount of alcohol in the blood, on the x-axis, a reverse of the updating function previously used for our DTDS. The inverse updating function approaches an asymptote at the equilibrium, as seen in Figure 1.8 (Appendix A).

```
values of t (h): [0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]
values of a (g): [20, 23.569468267581474, 25.269726977559777, 26.00277477894972, 26.303522402546513, 26.4242436924109
65, 26.47226533138019, 26.491298329486256, 26.49883096272334, 26.501810414447043, 26.502988635785186, 26.503454520275
394, 26.503638730670566, 26.503711566302393, 26.503740364892614, 26.503751751585497, 26.503756253773304, 26.503758033
894037, 26.50375873773615, 26.50375901602834, 26.50375912606231]
```

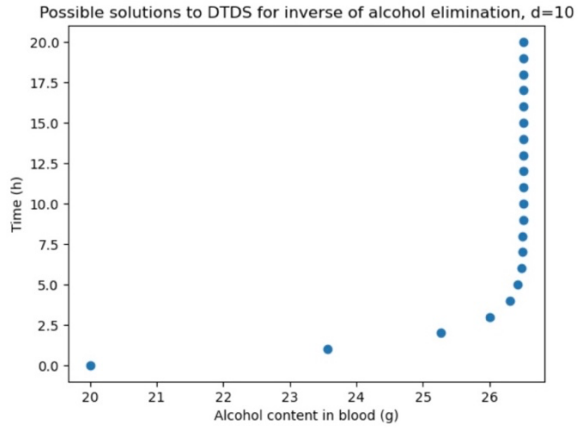

Figure 1.8: The graph above plots the set of possible solutions to the inverse of our DTDS for alcohol elimination, as graphed in the cobweb plot in Figure 1.7. We can observe that the alcohol content in blood reaches equilibrium, the point where it no longer increases, at a vertical asymptote. Based on the solutions printed above the graph, this asymptote occurs at an alcohol content of approximately 26.5 grams (Appendix A).

Works Cited

Cederbaum, Arthur I. "Alcohol Metabolism." *Clinics in Liver Disease* 16, no. 4 (November 1, 2012): 667–85. https://doi.org/10.1016/j.cld.2012.08.002.

Cutnell, John D., and Kenneth W. Johnson. *Physics*. New York, NY: Wiley, 1998.

Cousins, Gregory. *Discrete Time Dynamical Systems (1)*. iTeach. Jupyter Notebook. 2023.

Simic, M., and M. Tasic. "The Relationship between Alcohol Elimination Rate and Increasing Blood Alcohol Concentration—Calculated from Two Consecutive Blood Specimens." *Forensic Science International* 172, no. 1 (October 2, 2007): 28–32. https://doi.org/10.1016/j.forsciint.2006.11.008.

Vander, Arthur J., James H. Sherman, and Dorothy S. Luciano. *Human physiology: The mechanisms of body function*. Boston, MA: McGraw-Hill, 2001.

Appendix A

```
import numpy as np
import matplotlib.pyplot as plt
from collections import OrderedDict

def alcohol_elim_rate(x):
    return 0.15+(0.05*(x/5.83))

def alcohol_update(x, d=10):
    return (x-((alcohol_elim_rate(x))*x))+d

def plot_cobweb(f, m_0, steps): #function to cobweb

    cobwebs_x=[m_0] #starting x-value
    cobwebs_y=[f(m_0)] #starting y-value

    for i in range(1,steps):
        if i%2==1: #if the step i is odd
            cobwebs_x.append(cobwebs_y[i-1]) #append the same values along the diagonal y=x
            cobwebs_y.append(cobwebs_y[i-1])
        elif i%2==0: #if the step i is even
            cobwebs_x.append(cobwebs_y[i-1]) #append the same x-value, but "move up" to the updating curve.
            cobwebs_y.append(f(cobwebs_x[i]))


    xvalues=np.linspace(0,max(cobwebs_x), 500) #linspace for plotting
    plt.title("Cobweb Plot for Biologically Plausible Value of d")
    plt.plot(xvalues,xvalues, label="y=x") #plot the diagonal y=x
    plt.plot(xvalues, f(xvalues), label="updating function") #plot the updating function

    #plt.plot(cobwebs_x,cobwebs_y) #plot the cobwebs
    for x,y in zip(list(np.around(np.array(cobwebs_x),2)),list(np.around(np.array(cobwebs_y),2))): #add some labels
        label = f"({x},{y})"
        #uncomment the following code to see point labels. It gets too messy with a lot of steps
        #plt.annotate(label, # this is the text
                     #(x,y), # these are the coordinates to position the label
                     #textcoords="offset points", # how to position the text
                     #xytext=(0,10), # distance from text to points (x,y)
                     #ha='center') # horizontal alignment can be left, right or center
    plt.legend()
    plt.draw()

    plt.figure()



    distinct_solutions=list(OrderedDict.fromkeys(cobwebs_x))#get the x-components of the cobwebs to plot the solution.
    plt.title("Plot of the Cobweb x-coordinates")
    plt.plot(list(range(len(distinct_solutions))),distinct_solutions) #plots the solution set.
    plt.draw()

    plt.show()

plot_cobweb(alcohol_update,20,100)
```

Appendix A.1: Code for graphs shown in Figure 1.1 (Cousins 2023).

```
n = 20
t = [0]
a = [20]

d = 10

for i in range(1, n+1):
    at = a[i-1]-(0.15+(0.05*(a[i-1]/5.83)))*a[i-1]+d
    t.append(i)
    a.append(at)

print("values of t (h):", t)
print("values of a (g):", a)


plt.scatter(t,a)
plt.xlabel("Time (h)")
plt.ylabel("Alcohol content in blood (g)")
plt.title("Possible solutions to DTDS for alcohol elimination, d=10")
plt.show()
```

Appendix A.2: Code for graph of DTDS solutions for case (i), as seen in Figure 1.3.

In [29]:
```
import numpy as np
import matplotlib.pyplot as plt
from collections import OrderedDict

def alcohol_elim_rate(x):
    return 0.15+(0.05*(x/5.83))

def alcohol_update_2(x, d=-1):
    return (x-((alcohol_elim_rate(x))*x))+d

plot_cobweb(alcohol_update_2,10,10)
```

Appendix A.3: Code for graphs in Figure 1.2. The function known as plot_cobweb *is defined in a previous cell, as shown in Appendix A.1 (Cousins 2023).*

```
n = 20
t = [0]
a = [40]

d = -1

for i in range(1, n+1):
    at = a[i-1]-(0.15+(0.05*(a[i-1]/5.83)))*a[i-1]+d
    t.append(i)
    a.append(at)

print("values of t (h):", t)
print("values of a (g):", a)


plt.scatter(t,a)
plt.xlabel("Time (h)")
plt.ylabel("Alcohol content in blood (g)")
plt.title("Possible solutions to DTDS for alcohol elimination, d=-1")
plt.show()
```

Appendix A.4: Code for graph of DTDS solutions for case (ii), as seen in Figure 1.5.

In [37]:
```
import numpy as np
import matplotlib.pyplot as plt
from collections import OrderedDict


n = 20
t = [0]
a = [50]
d = 0

stop = False

for i in range(1, n+1):
    at = a[i-1]-((0.15+(0.05*(a[i-1]/5.83)))*a[i-1])+d
    t.append(i)
    a.append(at)
    if at < 1 and stop == False:
        print(f"It takes {t[i]} hours for the amount of alcohol to decrease from 50g to below 1g")
        stop = True

plt.scatter(t,a)
plt.xlabel("Time (h)")
plt.ylabel("Alcohol content in blood (g)")
#plt.title("")
plt.show()
```

Appendix A.5: Code for graph of solutions to DTDS for alcohol elimination, in the case where 50g of alcohol is initially consumed. Code is also designed to find, and output, the time at which the amount of alcohol in the body falls below 1g.

In [7]:
```
import numpy as np
import matplotlib.pyplot as plt
from collections import OrderedDict

def alcohol_elim_rate(x):
    return 0.15+(0.05*(x/5.83))

def alcohol_update(x, d=10):
    return (x-((alcohol_elim_rate(x))*x))+d

def plot_cobweb(f, m_0, steps): #function to cobweb

    cobwebs_x=[m_0] #starting x-value
    cobwebs_y=[f(m_0)] #starting y-value

    for i in range(1,steps):
        if i%2==1: #if the step i is odd
            cobwebs_x.append(cobwebs_y[i-1]) #append the same values along the diagonal y=x
            cobwebs_y.append(cobwebs_y[i-1])
        elif i%2==0: #if the step i is even
            cobwebs_x.append(cobwebs_y[i-1]) #append the same x-value, but "move up" to the updating curve.
            cobwebs_y.append(f(cobwebs_x[i]))


    xvalues=np.linspace(0,max(cobwebs_x), 500) #linspace for plotting
    plt.title("Cobweb Plot for Inverse of Updating Function, Assuming a Biologically Plausible Value of d")
    plt.plot(xvalues,xvalues, label="y=x") #plot the diagonal y=x
    plt.plot(f(xvalues), xvalues, label="inverse updating function") #plot the updating function

    plt.plot(cobwebs_y, cobwebs_x) #plot the cobwebs
    for x,y in zip(list(np.around(np.array(cobwebs_x),2)),list(np.around(np.array(cobwebs_y),2))): #add some labels
        label = f"({x},{y})"
        #uncomment the following code to see point labels. It gets too messy with a lot of steps
        #plt.annotate(label, # this is the text
                     #(x,y), # these are the coordinates to position the label
                     #textcoords="offset points", # how to position the text
                     #xytext=(0,10), # distance from text to points (x,y)
                     #ha='center') # horizontal alignment can be left, right or center
    plt.legend()
    plt.draw()

    plt.figure()



    distinct_solutions=list(OrderedDict.fromkeys(cobwebs_x))#get the x-components of the cobwebs to plot the solution.
    plt.title("Plot of the Cobweb x-coordinates")
    plt.plot(list(range(len(distinct_solutions))),distinct_solutions) #plots the solution set.
    plt.draw()

    plt.show()

plot_cobweb(alcohol_update,20,100)
```

Appendix A.6: The code used to plot the graph of the inverse updating function and the diagonal. Created through minor modifications to the code in Appendix A.1 (Cousins 2023).

Appendix B

$$f(a_t) = x$$

$$f(a_t) = x - (0.15 + 0.05 \times \frac{x}{5.83})x + d$$

Thus,

$$x = x - (0.15 + 0.05 \times \frac{x}{5.83})x + d$$

Subtracting x from both sides, we get:

$$0 = -(0.15 + 0.05 \times \frac{x}{5.83})x + d$$

Expanding, we get:

$$0 = -0.15x - 0.00857633x^2 + d$$

We can rearrange this equation, so that the x^2 and x terms are both positive:

$$0 = 0.00857633x^2 + 0.15x - d$$

The equilibrium occurs at solutions to the equation above. To find the solutions, we use the quadratic formula:

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Plugging in our values of a, b and c:

$$x = \frac{-0.15 \pm \sqrt{0.15^2 - 4(0.00857633)(-d)}}{2(0.00857633)}$$

$$= \frac{-0.15 \pm \sqrt{0.15^2 + 0.034305d}}{0.01715}$$

Thus our equilibrium can be found by the following equation:

$$Equilibrium = \frac{-0.15 \pm \sqrt{0.15^2 + 0.034305d}}{0.01715}$$

Equilibrium must be ≥ 0 (as explained in the text). This only occurs for values of $d \geq 0$, as shown in the following calculations:

Equilibrium must be ≥ 0. Therefore numerator of the following expression must be ≥ 0:

$$Equilibrium = \frac{-0.15 \pm \sqrt{0.15^2 + 0.034305d}}{0.01715}$$

Thus we obtain the inequality

$$0 \leq -0.15 \pm \sqrt{0.15^2 + 0.034305d}$$

We assume that we will be adding the expression

$$\sqrt{0.15^2 + 0.034305d},$$

as otherwise the numerator will be negative. Thus, we simplify the inequality to:

$$0 \leq -0.15 + \sqrt{0.15^2 + 0.034305d}$$

We can add 0.15 to both side to obtain:

$$0.15 \leq \sqrt{0.15^2 + 0.034305d}$$

Squaring both sides, we get:

$$0.15^2 \leq 0.15^2 + 0.034305d$$

We can now simplify by subtracting the like-term, 0.15^2, on both sides:

$$0 \leq 0.034305d$$

Dividing both sides by 0.034305, we obtain the final equality

$$0 \leq d,$$

which can also be expressed as:

$$d \geq 0$$

Applied Life Sciences: Question B

Learning Model for Addiction

With the ongoing opioid crisis in Canada and the United States, addressing drug addiction has become a topical and relevant issue. To begin to investigate solutions to this epidemic, the mechanism of addiction needs to be understood. Drugs act as exogenous agonists or inverse agonists that change the brain, and therefore the body's, natural state. Since addiction is heavily dependent on the brain's ability to respond to stimuli, a learning model can be proposed for the study of addiction. The most deleterious setback in recovery is relapse (Melemis 2015). Relapse often occurs due to withdrawal, which can happen even while the drug is no longer in the body. A popular model for understanding learning is that of Ivan Pavlov. Pavlov conducted a study in which a tone was played every time a group of dogs were fed. The salivation levels of dogs were measured, and it was found that after the association was made, the dogs salivated at the sound of the tone, even in the absence of food. This study was the pioneer of the theory of classical conditioning. This theory states that when an unconditional stimulus (UCS) that elicits an unconditional biological response (UCR) is paired with a conditional stimulus (CS) the UCR will occur in response to the CS, even in the absence of the UCS (Siegel and Ramos 2002). In the case of Pavlov's dogs, the UCS is food, the UCR is salivation, and the CS is the bell tone.

The way the body responds to drugs and associated cues follows this same pattern. Subkov and Zilov (1937) ran a study in which dogs were routinely injected with adrenaline. It was measured that after multiple rounds of adrenaline injection, when the dogs were placed in the same laboratory set up and injected with saline instead, they showed a reduction in heart rate. This response is due to the body's natural homeostatic response, which reduces the effect of adrenaline by producing endogenous inverse agonists in response to an exogenous agonist. The dogs associated the environment with the administration of adrenaline, so the UCR was for the body to lower the heart rate in preparation.

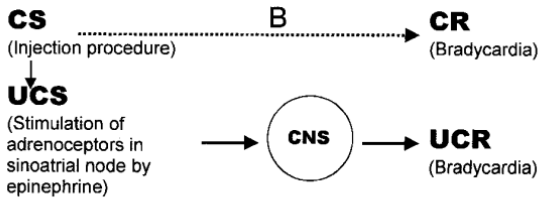

Figure 2.1: Conditional and unconditional stimulus flow chart for injection of dogs with adrenaline (Siegel and Ramos 2002).

This same effect can be seen in people who use drugs. When a person is in recovery from drug use, the first step is typically abstaining from the drug until it is no longer in their system. Many people do this through a rehabilitation center, where they are placed in an environment in which they do not have access to drugs until they are no longer exhibiting signs of withdrawal. These facilities are not typically effective, with a relapse rate of 40-75% in the first three weeks to six months after patients arrive home (Nagy et al. 2022). Patients' home environments are typically full of CS, which could include daily routines in which drug use occurred, spending time with those whom they used drugs with, or seeing drug paraphernalia. These CS could elicit a physiological response in the body, as it is preparing to receive a dose of the patient's drug of choice. This can lead to the patient experiencing symptoms of withdrawal, as the body is responding as if euphoric or pain-relieving drugs are in its system, and may react with an inverse response (Siegel and Ramos 2002).

When evaluating models for addiction, it's important to not fall into the "broken brain" model. Although drug use has an impact on the functions of the brain, it is still elastic and can grow, learn, and change associations. The behaviors associated with addiction are not entirely compulsive and involuntary; the use of substances alters the way one makes decisions and prioritizes (Wiers and Verschure 2021). A learning model would analyze addiction from a systems perspective that looks at different levels of organization: drug interactions in cells and endogenous responses to drugs, how the brain and the central nervous system react to CS and UCS in the environment, how the body can respond to these cues to influence a patient's physiology, and how the environment and connections with other people can influence behaviour are all important parts of a learning model of addiction.

Restructuring Detox Centers

An effective way to implement this model is to restructure detox centers to acknowledge these findings. Although relocation after treatment of drug use is an effective and ideal solution (Kirk 2019), this may not be accessible for all patients. Current detox centers focus on detoxifying the patient from the drug in their system, but a more effective way of reducing withdrawal would be detoxifying the patients from the CS they associate drug use with. One way this relearning can be done is by investigating controlled stimuli and creating new UCS to associate with current

CS. For example, if a patient uses drugs upon waking up and entering a recreational space, creating a structured morning routine could reduce the withdrawal associated with being in that space upon waking up. This routine could include showering, eating breakfast in the kitchen, and going for a walk before entering the recreational space.

Giving patients tools to distance themselves from people in their life who still use drugs that may act as a CS could also decrease likelihood of relapse due to social situations. Stress and emotional distress are often heavily associated with drug use and are a large factor in relapse (Sinha 2001). Therapies such as motivational enhancement therapy and cognitive behavioural therapy can help patients manage stress and associate stressful situations with safe coping strategies, rather than drug use (Buckner et al. 2023). This proposed detoxification could mirror sober living homes, where patients live with others recovering from drug use in a safe and supervised manner to build new habits, associations, and learning opportunities (Edwards et al. 2022). When analyzing addiction on multiple levels of biological organization using a learning model, it becomes clear that an ideal detox center would focus on changing association to conditional stimulus and modifying learned responses and behaviours.

Works Cited

Buckner, Julia D., Raymond P. Tucker, Paige E. Morris, Caroline R. Scherzer, Kathleen A. Crapanzano, and Sarah Pardue-Bougeois. 2023. “Substance Misuse among a Diverse Psychiatric Inpatient Sample: Suicidal Thoughts and Behaviors and Motivation to Change.” Behavioral Medicine 49 (3): 231–35. https://doi.org/10.1080/08964289.2022.2065240.

Edwards, Katie M., Laura Siller, Sarah E. Ullman, Katherine D. M. Lee, and Sharon B. Murphy. 2022. “Post-Traumatic Growth in Women With Histories of Addiction and Victimization Residing in a Sober Living Home.” Journal of Interpersonal Violence 37 (13–14): NP11180–97. https://doi.org/10.1177/0886260521991283.

Kirk, David S. 2019. “The Association between Residential Relocation and Re-Incarceration among Drug-Dependent Former Prisoners.” Addiction 114 (8): 1389–95. https://doi.org/10.1111/add.14617.

Melemis, Steven M. 2015. “Relapse Prevention and the Five Rules of Recovery.” The Yale Journal of Biology and Medicine 88 (3): 325–32.

Nagy, Nahla El Sayed, Eman Ibrahim Abo Ella, Eman Mohamed Shorab, Mohamed Hossam El-Din Abdel Moneam, and Arwa Ahmed Tohamy. 2022. “Assessment of Addiction Management Program and Predictors of Relapse among Inpatients of the Psychiatric Institute at Ain Shams University Hospital.” Middle East Current Psychiatry, Ain Shams University 29 (1): 80. https://doi.org/10.1186/s43045-022-00246-5.

Siegel, Shepard, and Barbara M. C. Ramos. 2002. “Applying Laboratory Research: Drug Anticipation and the Treatment of Drug Addiction.” Experimental and Clinical Psychopharmacology 10 (3): 162–83. https://doi.org/10.1037/1064-1297.10.3.162.

Sinha, Rajita. 2001. “How Does Stress Increase Risk of Drug Abuse and Relapse?” Psychopharmacology 158 (4): 343–59. https://doi.org/10.1007/s002130100917.

Wiers, Reinout W., and Paul Verschure. 2021. “Curing the Broken Brain Model of Addiction: Neurorehabilitation from a Systems Perspective - ClinicalKey.” January 1, 2021. https://www-clinicalkey-com.libaccess.lib.mcmaster.ca/#!/content/playContent/1-s2.0-S0306460320307322?scrollTo=%23hl0000306.

Applied Chemistry: Question 3

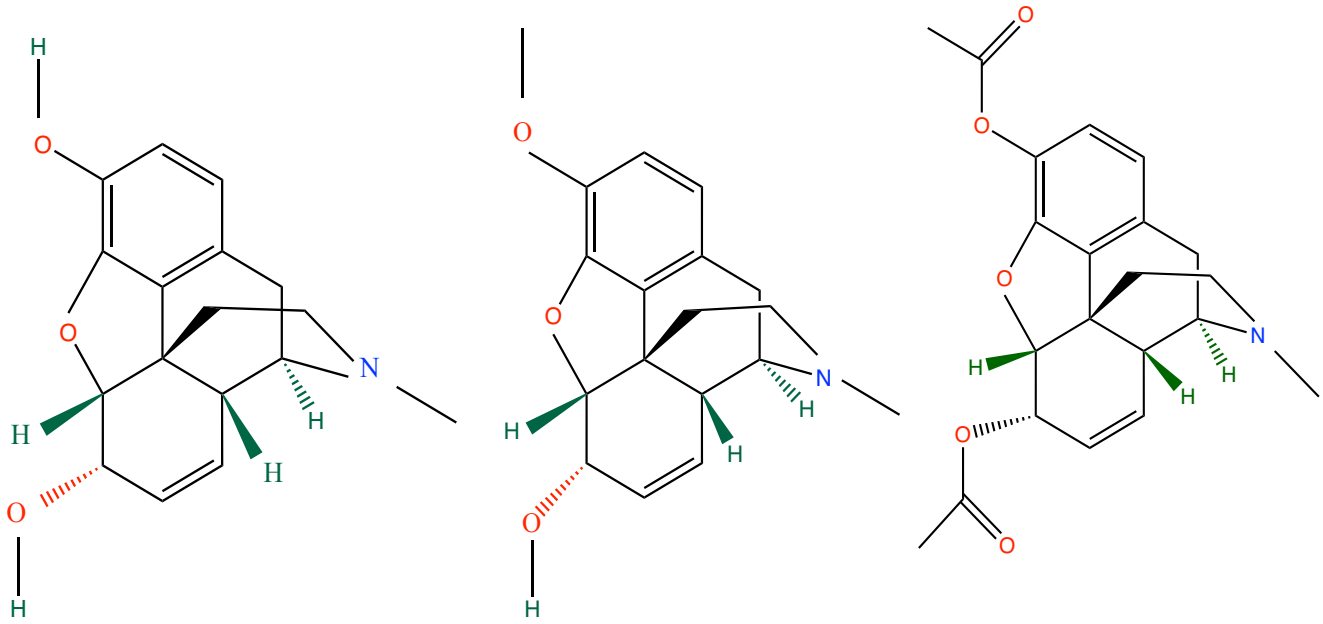

Figure 3.1: (from left to right) Chemical structures of morphine *(PubChem n.d. d), codeine (PubChem n.d, a), and diacetylmorphine (heroin) (PubChem n.d. b).*

Morphine ($C_{17}H_{19}NO_{3)}$, codeine ($C_{18}H_{21}NO_3$) and diacetylmorphine ($C_{21}H_{23}NO_5$) are structurally related opiates. They all have hydrocarbon chains accompanied by nitrogen and oxygen atoms. Their main differences lie in the number of atoms each has, which causes differences in their physical properties such as lipophilicity, which influences solubility and has a great impact in how each drug acts on organisms.

The values of pK_a are correlated to the acid dissociation constant, K_a. As an equilibrium constant, K_a indicates the strength of an acid by quantitatively determining if a compound is able to completely dissociate in water. In other words, the products of an acid-base reaction would be favoured in the reaction. The structure of the chemical formula for K_a is as follows:

$$HA_{(aq)} + H_2O \leftrightarrow H_3O^+ + A^-_{(aq)}$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Therefore, the pK_a value of a reaction is found by:

$$pK_a = -\log(K_a)$$

This formula would indicate that the lower the value of pK_a, the more acidic a compound is. Codeine, morphine, and heroin, as seen in *Figure 3.*1 have phenols and amine functional groups in their chemical structure. With the following chemical reactions, the phenolic and amine pK_a values of the phenol and amine groups found on morphine can be calculated.

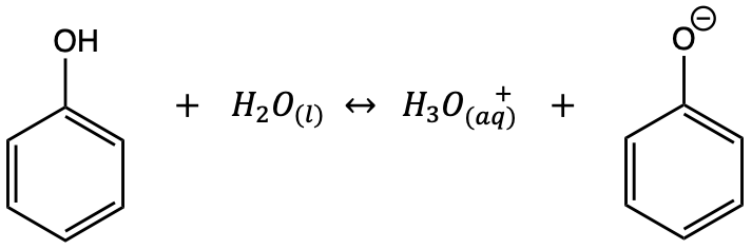

Figure 3.2: Chemical reaction that shows how phenolic pKa can be determined. In terms of morphine, the rest of the molecule is not affected by the acid reaction of the phenol group, hence why only the phenolic group reaction is shown. The hydroxyl group attached to the hydrocarbon in the phenol group will give up its hydrogen and become negatively charged, also known as a phenoxide ion. This is an example of a weak acid (Clark 2013).

The pKa of the phenolic reaction for morphine is 9.26 (Avdeef et al. 1996). This is on the higher end of the pKa scale, indicating this phenolic reaction is more basic than acidic.

$$NHR_3{}^+ + H_2O_{(l)} \rightarrow H_3O^+{}_{(aq)} + NR_3$$

Equation 3.1: Chemical reaction that shows how amine pKa can be determined. Similarly to Figure 3.2*, the rest of the morphine molecule is not affected by the acid reaction of the amine group, hence why only the amine group reaction is shown. For this reaction, the protonated amine group is losing a proton, becoming a neutral NR_3 molecule.*

The amine pKa of this reaction is 8.18 (Avdeef et al. 1996). This is a slightly more acidic reaction compared to *Figure 3.2*.

At different pH levels, the hydroxyl group bonded to the phenol group, and the tertiary amine groups, which occur when the nitrogen is bonded to three carbon atoms, found in the morphine molecule will behave differently and have a different charge, as Avdeef et al. (1996) found on *Figure 3.3*.

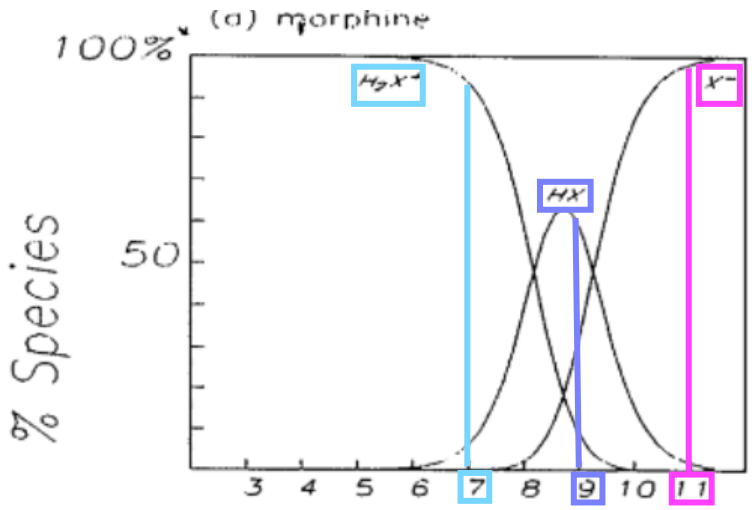

Figure 3.3: Graph of morphine at different pH levels and how its charge is affected (Avdeef et al. 1996).

This plot of % species vs pH of morphine is described as ampholytes. This is when a cation converts into an anion as the pH increases via a neutral species (see HX curve on *Figure 3.3*), as long as the concentration of HX is not greater than about 65-70% of the drug (Avdeef et al. 1996). In other words, morphine can act as both an acid and a base. Using this graph, the chemical structures of morphine at pH levels 7, 9 and 11 can be drawn.

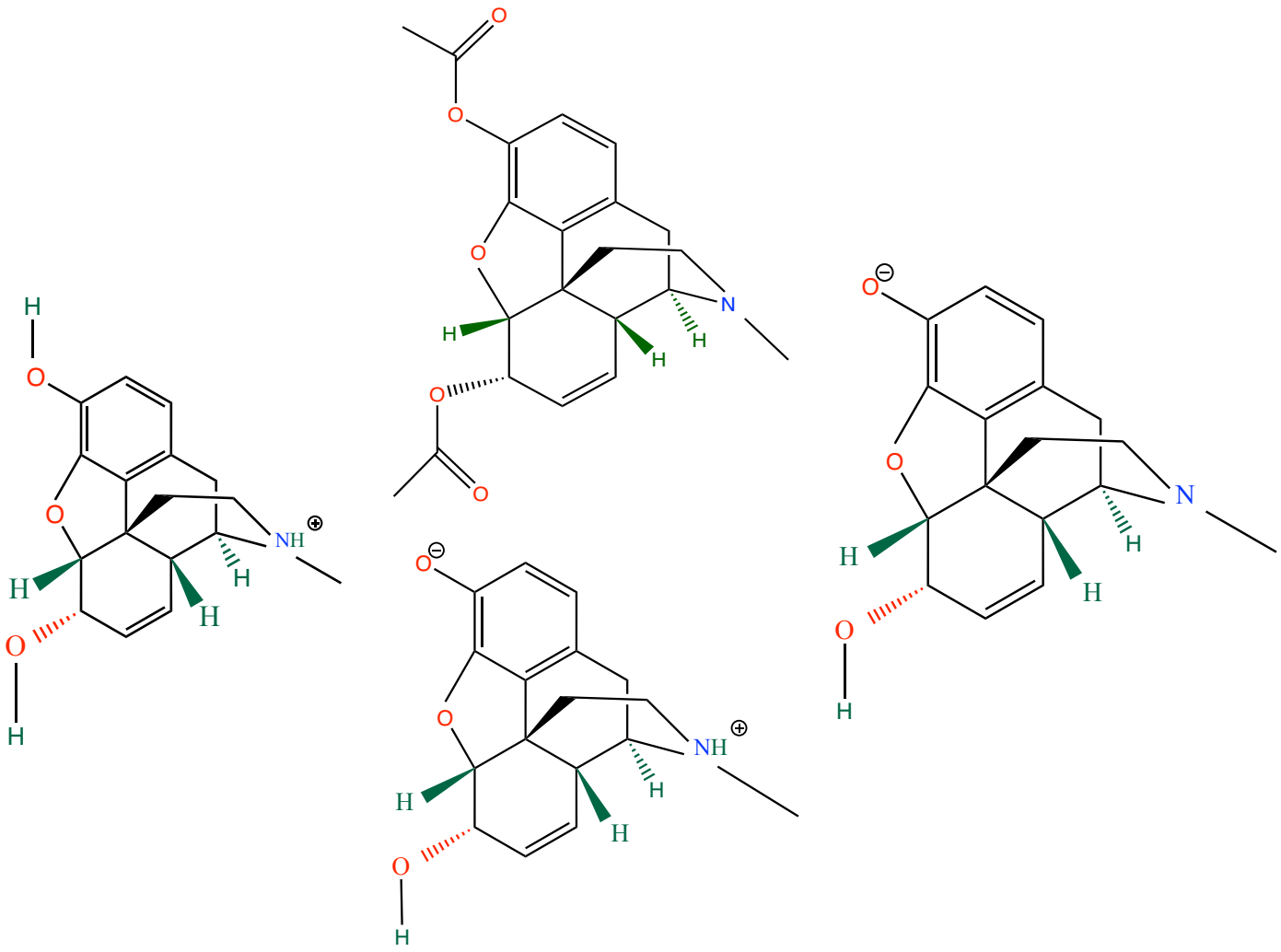

Figure 3.4: Four different structures of morphine at different pH levels. On the far left is morphine with a pH of 7. As was seen in Figure 3.3*, the tertiary amine group has been protonated, giving it a positive charge. When the pH of morphine is 9, the molecule can be found at its neutral state, as seen in the structure diagram on the top. However, morphine is also a zwitterion, which means a molecule can have positively and negatively charged groups, as seen in the bottom diagram in the middle. This molecule has a positive charge in the amine group, and a negative charge in the oxygen. Lastly, at pH 11, morphine (Avdeef et al. 1996).*

Based on the data from Avdeef et al. (1996), heroin has a pKa value of 7.95. Compared to morphine's 8.18 and codeine's 8.22, heroin has the least basic amine. As mentioned previously, the lower the pKa value, the more acidic a substance is. Therefore, heroin has the most acidic amine group out of the three.

Partition coefficients are used widely in drug discovery to understand the solubility of a drug, and how the drug is distributed between two immiscible solvents, such as water and octanol for example (Bannan et al. 2016). These values are found through this equation:

$$P = \frac{[species]_{lipid}}{[species]_{water}}$$

Therefore, logP refers to the log of this partition coefficient (Avdeef at al. 1996). The higher a logP value is, the more lipophilic a drug is. Conversely, the lower a logP value is, the more hydrophilic a drug is. A similar measurement is $logD_{7.4}$, which also measures lipophilicity but at a pH of 7.4. This is an essential physical property of a drug because it affects its behaviours, such as solubility, permeability, metabolism, distribution, protein-binding and toxicity (Wang et al. 2023). LogD is specific to the pH 7.4 because that is the pH of blood, so measuring the lipophilicity of a drug at this pH allows for more realistic models for how drugs will act on the human body. Furthermore, the pKa values are also vital in pharmaceutical development due to how different drugs are affected in different pH conditions (Manallack et al. 2013). Similarly, to lipophilicity, pKa values affect physical properties such as aqueous solubility, metabolism, excretion, and toxicity. These values can also be used to improve the efficiency of drug discovery. The main difference between logP and $logD_{7.4}$ against $logK_{ow}$ is that $logK_{ow}$ is a constant value for a molecule in its neutral form, as opposed to $logD_{7.4}$, which considers both neutral and charged forms of the molecule (Hodges et al. 2019).

At a pH of 7.4, heroin ($logD_{7.4}$ = +0.85) is more lipophilic than morphine ($logD_{7.4}$ = -0.07). If heroin is converted into morphine in the brain, this means that heroin must have passed through the blood-brain barrier (BBB). The BBB is a term coined for the blood vessels in the central nervous system (CNS) in charge of monitoring and regulating the movement of ions, molecules, and cells between the blood and the brain (Daneman and Prat 2015). The endothelial cells, which line the blood vessels of the CNS, limit the flux of hydrophilic molecules across the BBB (Ballabh, Braun, and Nedergaard 2004). This means that lipophilic substances have an easier time crossing the BBB than hydrophilic substances, resulting in heroin having a more addictive effect on the body than morphine. A similar pattern can be seen with logP values of both heroin

and morphine. Heroin has a higher logP (+1.58±0.01) compared to morphine (+0.89 ± 0.01). In this case, both have positive log values, yet heroin still has a greater lipophilicity than morphine. Methadone ($C_{21}H_{27}NO$) has many differences when compared to heroin ($C_{21}H_{23}NO_5$), as can be seen in *Figure 3.5*.

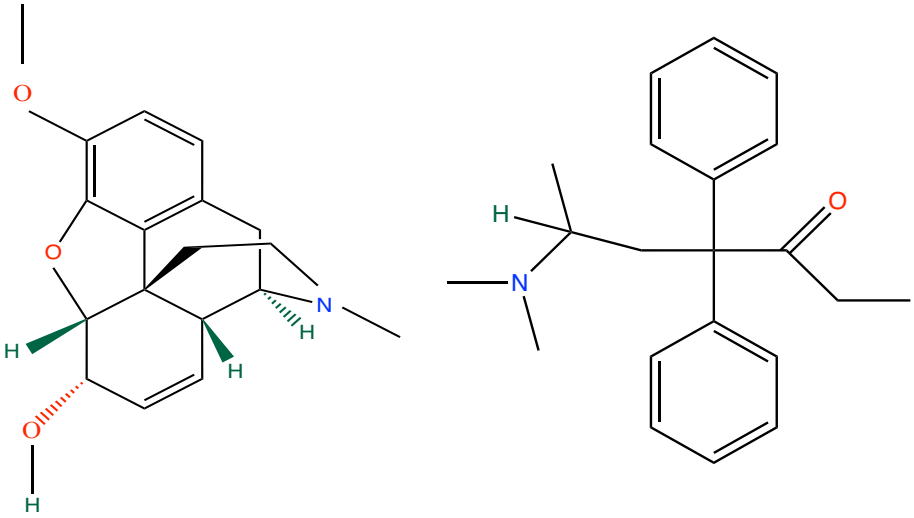

Figure 3.5: Chemical structure of heroin (PubChem n.d. b) on the left versus methadone (PubChem n.d. c) on the right.

Methadone is used as a detoxification treatment for heroin or other morphine-like drugs instead of treating substance abuse with complete abstinence, which can be fatal for people struggling with opioid addiction (PubChem, n.d.; NIDA 2021). Using methadone allows for a safer recovery by reducing the negative effects of withdrawal and cravings, without having the same euphoric effects that heroin causes. Methadone is an opioid agonist, therefore it mimics the action of heroin, but in a safer and more controlled way by activating opioid receptors more slowly. The morphine rule is a key aspect in determining why methadone works as a treatment method, as it describes the homologous structures different opiates and opioids share, such as codeine and heroin (Chambers et al. 2018). The four similarities shared are: a tertiary nitrogen with a small alkyl substituent, a quaternary carbon, a phenyl ring (or its equivalent) attached to quaternary carbon, and an ethyl linkage between the quaternary carbon and tertiary nitrogen. As seen in *Figure 3.5*, methadone has these properties, which is what allows it to act as a morphine-like drug without the addictive side-effects.

Works Cited

Abuse, National Institute on Drug. --. "How Do Medications to Treat Opioid Use Disorder Work? | National Institute on Drug Abuse (NIDA)." --. https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/how-do-medications-to-treat-opioid-addiction-work.

Avdeef, Alex, David A. Barrett, P. Nicholas Shaw, Roger D. Knaggs, and Stanley S. Davis. 1996. "Octanol−, Chloroform−, and Propylene Glycol Dipelargonat−Water Partitioning of Morphine-6-Glucuronide and Other Related Opiates." *Journal of Medicinal Chemistry* 39 (22): 4377–81. https://doi.org/10.1021/jm960073m.

Ballabh, Praveen, Alex Braun, and Maiken Nedergaard. 2004. "The Blood–Brain Barrier: An Overview: Structure, Regulation, and Clinical Implications." *Neurobiology of Disease* 16 (1): 1–13. https://doi.org/10.1016/j.nbd.2003.12.016.

Bannan, Caitlin C., Gaetano Calabró, Daisy Y. Kyu, and David L. Mobley. 2016. "Calculating Partition Coefficients of Small Molecules in Octanol/Water and Cyclohexane/Water." *Journal of Chemical Theory and Computation* 12 (8): 4015–24. https://doi.org/10.1021/acs.jctc.6b00449.

Chambers, Schuyler A., Jenna M. DeSousa, Eric D. Huseman, and Steven D. Townsend. 2018. "The DARK Side of Total Synthesis: Strategies and Tactics in Psychoactive Drug Production." *ACS Chemical Neuroscience* 9 (10): 2307–30. https://doi.org/10.1021/acschemneuro.7b00528.

Clarke, Jim. 2013. Chemistry LibreTexts. October 2, 2013. https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Phenols/Properties_of_Phenols/Acidity_of_Phenols.

Daneman, Richard, and Alexandre Prat. 2015. "The Blood–Brain Barrier." *Cold Spring Harbor Perspectives in Biology* 7 (1): a020412. https://doi.org/10.1101/cshperspect.a020412.

Hodges, Geoff, Charles Eadsforth, Bart Bossuyt, Alain Bouvy, Marie-Helene Enrici, Marc Geurts, Matthias Kotthoff, et al. 2019. "A Comparison of Log Kow (n-Octanol–Water Partition Coefficient) Values for Non-Ionic, Anionic, Cationic and Amphoteric Surfactants Determined Using Predictions and Experimental Methods." *Environmental Sciences Europe* 31 (1): 1. https://doi.org/10.1186/s12302-018-0176-7.

Manallack, David T., Richard J. Prankerd, Elizabeth Yuriev, Tudor I. Oprea, and David K. Chalmers. 2013. “The Significance of Acid/Base Properties in Drug Discovery.” *Chemical Society Reviews* 42 (2): 485–96. https://doi.org/10.1039/c2cs35348b.

PerkinElmer. *ChemDraw*. V. 22.2.0.3348. PerkinElmer. Mac OS. 2023.

PubChem. n.da. “Codeine.” Accessed November 27, 2023. https://pubchem.ncbi.nlm.nih.gov/compound/5284371.

———. n.db. “Heroin.” Accessed November 27, 2023. https://pubchem.ncbi.nlm.nih.gov/compound/5462328.

———. n.dc. “Methadone.” Accessed November 28, 2023. https://pubchem.ncbi.nlm.nih.gov/compound/4095.

———. n.dd. “Morphine.” Accessed November 27, 2023. https://pubchem.ncbi.nlm.nih.gov/compound/5288826.

Wang, Yitian, Jiacheng Xiong, Fu Xiao, Wei Zhang, Kaiyang Cheng, Jingxin Rao, Buying Niu, et al. 2023. “LogD7.4 Prediction Enhanced by Transferring Knowledge from Chromatographic Retention Time, Microscopic pKa and logP.” *Journal of Cheminformatics* 15 (1): 76. https://doi.org/10.1186/s13321-023-00754-4.

Applied Earth Science: Question D

Retrieving accurate information on illicit drug use is a difficult task. Beyond there being risks in coming forward for testing, people must overcome unpleasant social treatment due to the stigma around drug use (Harrison 1997). As such, there are benefits and downfalls particular to both urine drug tests and monitoring sewage when it comes to navigating these barriers and detecting illicit drug use.

Urine drug testing is a well-researched technique that identifies the presence of a substance within the metabolites in a sample (McNeil et al. 2023). There are many advantages when using it to find the rates of LSD consumption, be it for a single person, a small community, or a society. One positive is that urine drug tests are relatively inexpensive, or entirely free of charge from harm reduction programs (Hadland and Levy 2016; CCSA 2023). Additionally, while usually done in clinical settings, there are at-home urine drug tests available to individuals, which is essential when taking a health geographical approach. A person's health and well-being are intricately connected to place, geography, and location (Drummer 2008). Important services like hospitals, pharmacies, or gyms might be too far away to be accessible, and this includes centers that provide urine drug testing. By being portable, urine drug tests become practical for anyone who may need or want to self-report, regardless of location. Even still, urine drug testing comes with a few disadvantages.

Detection Windows by Drug Test Type	
Substance	Urine
Alcohol	10-12 hours EtG -- Up to 48 hours
Amphetamines	2 to 4 days
Methamphetamine	2 to 5 days
Barbiturates	Up to 7 days
Benzodiazepines	Up to 7 days
Cannabis (Marijuana)	1-30 days
Cocaine	1 to 3 days
Codeine (Opiate)	2 to 4 days
Morphine (Opiate)	2 to 5 days
Heroin (Opiate)	2 to 3 days
PCP (Phencyclidine)	5 to 6 days

Figure 4.1: Window of detection for various substances in urine. PCP stands for Phencyclidine (NCSACW, 2023).

Once a drug is taken, the body attempts to eliminate it in various ways. Urination is one such way used to flush out substances. Trace elements can be detected in urine for a certain amount of time, depending on the type of drug. Figure 4.1 shows the optimal period to identify the presence of a drug in the body using a urine test. As shown, the detection windows are too small for testing to be error-free. In comparison to the main substances tested in Figure 4.1, LSD can be detected only up to 24 hours. That leaves very little time for a test to be taken, making it hard to determine LSD use within a society. Moreover, LSD cannot be detected through normal urine testing (Hadland and Levy 2016). Figure 4.1 displays the drugs that are caught in a typical urine test. For LSD to be detected, a specific urine test must be administered. This may leave another barrier in retrieving accurate numbers of LSD use in a community. Other disadvantages include people viewing the test as an invasion of privacy (Hadland and Levy 2016; Mcneil, Richard and Cogburn 2023). Besides self-reporting, urine drug tests are often used in settings where

supervision is required to ensure that the sample remains untampered. Some circumstances include job clearances, verifying that athletes are dope-free, and questioning from the police. Beyond purposeful sabotage, however, there remains a chance of false positives and negatives due to mistakes or lab errors.

Detecting illicit drug use through sewage, a technique better known as wastewater-based epidemiology (WBE), is one way to circumvent the disadvantages of urine drug testing. WBE is the process by which chemical or biological signals are used to indicate the presence of a substance in a sewage sample (O'Keefe 2021). Such information can give a clearer view of public health, particularly when it comes to illicit drug use. Wastewater epidemiologists assess the concentrations of biological and chemical substances, allowing them to determine drug use patterns (O'Keefe 2021).

WBE's capability to connect drug consumption to spatial and temporal patterns is one of its biggest advantages (O'Keefe 2021). It adds an informational layer that is not easily observed through surveilling over-the-counter sales or self-reporting. Intangible influences on drug use, such as geographical differences between cities, may be detected when location is factored, especially if approached from a health geography perspective. WBE indicates numbers that are often above the ones conventionally retrieved through surveys, self-reports (urine tests included), and emergency care. Psychoactive drugs, including LSD, are primarily monitored through forensic and toxicological data, individual questionnaires, and drug seizures. Due to the nature of these kinds of monitoring, cases are largely underreported. In rural areas or places where drug use is highly stigmatized, drug consumption might not be well tracked at all (Bishop, et al 2020; Brandeburová et al. 2020). WBE has been an active method to overcome these barriers, as it did for the geographically isolated communities in the intermountain region of the United States (Brandeburová et al. 2020). Analyzing the sewage that passes through wastewater treatment plants acts as one drug test for the entire society, providing evidence-based data that can be used towards better policymaking, prevention measures, and public heath procedures (Bishop et al. 2020). A few more positives of WBE include its anonymity and its non-invasive execution (O'Keefe 2021). Nevertheless, wastewater-based epidemiology comes with its drawbacks.

Wastewater-based trends typically take a year to determine, which is significantly slower than a urine drug test. While the process can be accelerated for an ongoing drug crisis, analysts and wastewater epidemiologists must account for fluctuations (StatsCan 2023). For example, the consumption of alcohol and psychoactive substances is heightened in Slovakia during musical festivals (Brandeburová et al. 2020). Extrapolating any final estimates without accounting for the unusual rise in drug use will give a false perspective of the community. Furthermore, WBE programs involve many steps where issues can occur, some of which are sample preparation, data processing, interpretation, and analysis (O'Keefe 2021). Above all, WBE fails to retain the precision achieved by individual testing, as each sewage sample represents thousands of people (O'Keefe 2021).

Urine drug tests and WBE are optimal for finding drug consumption when utilizing their strengths. Perhaps in the case of a smaller community, urine drug testing may be considered, as the time spent collecting surveys and conducting analyses may be less than finding the wastewater-based trend. However, if the need to account for temporal and spatial aspects of a society arises, WBE takes precedence, as the evidence-based information provided will be far more practical than a series of urine drug tests. Therefore, neither technique is considerably better, just more apt in certain circumstances.

Works Cited

Bishop, Nicholas, Tammy Jones-Lepp, Miranda Margetts, Jordan Sykes, David Alvarez, and Deborah E. Keil. 2020. "Wastewater-Based Epidemiology Pilot Study to Examine Drug Use in the Western United States." *The Science of the Total Environment* 745 (November): 140697. https://doi.org/10.1016/j.scitotenv.2020.140697.

Brandeburová, Paula, Igor Bodík, Ivana Horáková, Dušan Žabka, Sara Castiglioni, Noelia Salgueiro-González, Ettore Zuccato, Viera Špalková, and Tomáš Mackuľak. 2020. "Wastewater-Based Epidemiology to Assess the Occurrence of New Psychoactive Substances and Alcohol Consumption in Slovakia." *Ecotoxicology and Environmental Safety* 200 (September): 110762. https://doi.org/10.1016/j.ecoenv.2020.110762.

CCSA. 2023. "Urinalysis and Self-Reporting | Canadian Centre on Substance Use and Addiction." https://www.ccsa.ca/urinalysis-and-self-reporting.

Dummer, Trevor J.B. 2008. "Health Geography: Supporting Public Health Policy and Planning." *CMAJ : Canadian Medical Association Journal* 178 (9): 1177–80. https://doi.org/10.1503/cmaj.071783.

Hadland, Scott E., and Sharon Levy. 2016. "Objective Testing: Urine and Other Drug Tests." *Child and Adolescent Psychiatric Clinics of North America*, Substance Use Disorders, Part I, 25 (3): 549–65. https://doi.org/10.1016/j.chc.2016.02.005.

Harrison, L. 1997. "The Validity of Self-Reported Drug Use in Survey Research: An Overview and Critique of Research Methods." *NIDA Research Monograph* 167: 17–36.

McNeil, Shawn E., Richard J. Chen, and Mark Cogburn. 2023. "Drug Testing." In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK459334/.

National Center on Substance Abuse and Child Welfare (NCSACW). 2011. "Drug testing practice guidelines, substance abuse and mental health services administration." https://ncsacw.samhsa.gov/files/IA_Drug_Testing_Bench_Card_508.pdf

O'Keeffe, Juliette. 2021. "Wastewater-Based Epidemiology: Current Uses and Future Opportunities as a Public Health Surveillance Tool." *Environmental Health Review* 64 (3): 44–52. https://doi.org/10.5864/d2021-015.

StatsCan, Statistics Canada. 2023. “The Daily — Stimulants in the Wastewater of Canadian Cities: Provisional Results, January 2022 to May 2023.” November 1, 2023. https://www150.statcan.gc.ca/n1/daily-quotidien/231101/dq231101b-eng.htm.

Applied Physics: Question 5

There are different pressures associated with different parts of the body as seen in Figure xx. Each body system has a different pressure specific to the function it serves. However, they must all maintain certain pressures for internal processes to occur.

Body system	Gauge pressure in mm Hg
Blood pressures in large arteries (resting)	
Maximum (systolic)	100–140
Minimum (diastolic)	60–90
Blood pressure in large veins	4–15
Eye	12–24
Brain and spinal fluid (lying down)	5–12
Bladder	
While filling	0–25
When full	100–150
Chest cavity between lungs and ribs	−8 to −4
Inside lungs	−2 to +3
Digestive tract	
Esophagus	−2
Stomach	0–20
Intestines	10–20
Middle ear	<1

Figure 5.1: List of some of the most common pressures in the body and their normal gauge pressure range in mmHg (Urone and Hinrichs, 2022). The esophagus, chest cavity, and inside lungs can have negative pressure as the pressure in this enclosed volume is less than the outside pressure from the rest of the body. This is useful in the esophagus for example as the negative pressure helps to pull the food downwards. On the other hand, if you compare it to body systems that have positive pressures these values are essential. For example, in the stomach the pressure must be positive, or else the stomach would collapse on itself and cause the stomach contents to flow back up into the esophagus.

Blood pressure

Blood pressure is associated with the arteries in the body but can also be measured in the veins, lungs, and heart chambers. The two types of blood pressure are systolic pressure (SP) and diastolic pressures (DP). SP is the amount of pressure on the arteries while the heart is beating. DP measures the amount of pressure in the arteries in between heartbeats. This value is representative of how balanced fluids are when passing into the circulatory system from the

arteries. Normal ranges for blood pressure are 90-120 mmHg for SP and 60-80 mmHg for DP (Urone and Hinrichs 2022, 474-478). Blood pressure values lower than this range can cause complications, and any drop in pressure of 20 mmHg is considered dangerous (Mayo Clinic 2023).

Top number (systolic) in mm Hg	And/or	Bottom number (diastolic) in mm Hg	Blood pressure category*
Below 120	and	Below 80	Normal blood pressure
120-129	and	Below 80	Elevated blood pressure
130-139	or	80-89	Stage 1 high blood pressure (hypertension)

Figure 5.2: Summary of the different blood pressure ranges for normal and high BPs. Pressure of SP above 120 mm Hg and DP above 80 mm Hg is considered high, and a reading of 180/120 or greater is considered a hypertensive emergency, which can be fatal (Mayo Clinic, 2023).

Caffeine

The European Food Safety Authority (EFSA) reported that in studies of single doses of 80 to 300 mg of caffeine, there was an increase in SP of 3-8 mmHg and 4-6 mmHg for DP (De Giuseppe et al. 2019, 170). Overall, blood pressure increases after 30 minutes of consuming caffeine, peaks at 60-90 minutes, and returns to normal levels after 2-4 hours (De Giuseppe et al. 2019, 170). The exact cause is unknown, but researchers believe caffeine affects a gene that restricts the arteries from widening (De Giuseppe et al 2019, 170).

Alcohol

A research study found that after the consumption of 14 g of alcohol or less, there was no effect on blood pressure over six hours (Tasnim et al. 2020). Doses of 14 to 28 g showed a decrease of 5.6 mmHg in SP and 4 mmHg in DP once 6 hours passed (Tasnim et al. 2020). Additionally, after the consumption of 30 g or more, there was a decrease of 3.5 mmHg for SP and 1.9 mmHg in DP at the 6-hour mark and then there was an increase after 13 hours of 3.7 mmHg for SP and 2.3 mmHg for DP (Tasnim et al. 2020). Alcohol releases substances like nitric oxide which causes blood vessels to widen thus decreasing blood pressure for a short term. (Husain, Ansari, and Ferder 2014) Then, once these substances leave the body the blood pressure can increase due to its effects on the release of hormones that raise blood pressure or on other body systems long term.

LSD

In a study done with a placebo and various amounts of LSD, blood pressure was measured hourly. All three doses of 50, 100, and 200 µg of LSD revealed to increase both SP and DP the most for the first 3 hours after receiving the dose (Holze et al. 2021). The 200-µg dose increased both SP and DP the most out of the three doses, approximately 10 mmHg (Holze et al. 2021). LSD increases blood pressure by restricting blood flow in the blood vessels (Holze et al. 2021).

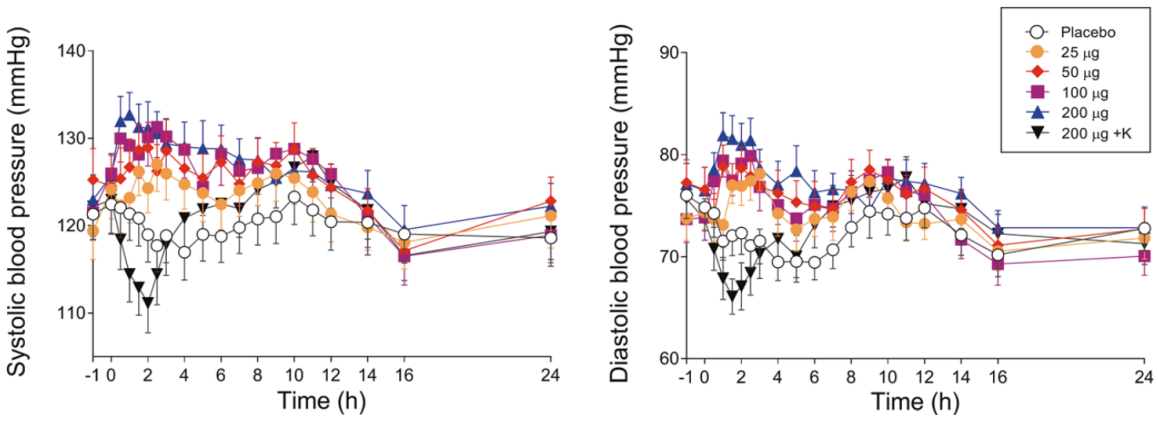

Figure 5.3: Shows the graph of changes in blood pressure of different doses of LSD. As seen on the graph there was an increase of both SP and DP for around the first 3 hours. Then after four hours both pressures started decreasing, and after 16 hours, the pressures were back to normal levels, the same as the placebo (Holze et al. 2021).

Eye pressure:

Intraocular pressure refers to the pressure of fluid inside of the eyes and it helps to maintain the general shape of the eye (Urone and Hinrichs 2022). Any increase in pressure happens when the circulation of fluid is blocked or disrupted (Urone and Hinrichs 2022). The normal pressure ranges are between 10-21 mmHg (Machiele, Motlagh and Patel 2023). Values above 21 mmHg are dangerously high, which is called ocular hypertension. Ocular hypertension puts the individual at risk of having glaucoma, a disease that damages the optic nerve (Loeffler and Bashour 2013). Pressure below 6 mmHg can cause serious problems with vision (Loeffler and Bashour 2013).

Caffeine

Caffeine intake elevates eye pressure by increasing the fluid that is made and stored in the eye (Beck 2018). A greater amount of fluid means greater intraocular pressure (Beck 2018). In general, research has shown that there is no effect of high caffeine intake on eye pressure except for individuals who are genetically susceptible to elevated eye pressure. Particularly, those who consume more than 480 mg of caffeine are seen to have an increase of 0.35 mm Hg of eye pressure (Mount Sinai Health System 2021). In addition, those who are genetically predisposed to high eye pressure when drinking more than 321 mmHg of caffeine a day are more susceptible to glaucoma than individuals who are not genetically predisposed (Mount Sinai Health System 2021).

Alcohol

Alcohol raises the blood sugar level, which can cause the eyes to swell and increases the pressure. However, of 34 studies, 10 showed eye pressure of over 21 mmHg from regular alcohol consumption. Therefore, alcohol's effect was very minimal and would not cause glaucoma (Seminara 2022).

LSD

There are no known effects of LSD on eye pressure in increasing or decreasing the fluid in the eye, although one effect of LSD is dilation of pupils. When pupils dilate, this causes a drop in the flow of liquid which can increase the pressure of the eye (Novak 2022).

Bladder Pressure:

Bladder pressure starts from 0 mmHg when the bladder is empty and increases to 25 mmHg as the bladder fills to full capacity (Urone and Hinrichs 2022). This pressure is important because it stimulates the brain which creates the urge to urinate (Urone and Hinrichs 2022). Consistent pressures above and below12 mmHg are indications of underlying health conditions (Clausen, W. Tvedt and Glott 2018).

Caffeine

Prolonged high bladder pressure is linked to increased urination frequency. Caffeine increases blood pressure, causing more blood to flow into the kidneys and thus reducing the amount of water and sodium absorbed (Lohsiriwat, Hirunsai and Chaiyaprasithi 2011). Researchers have found that caffeine is shown to have this diuretic effect at doses of 4.5 mg/kg (Lohsiriwat, Hirunsai and Chaiyaprasithi 2011).

Alcohol

A 2017 study's overall outcome shows that the stronger the alcohol content in a drink, the higher the frequency of urination (Polhuis et al. 2017). Although, researchers have found that for someone who drinks alcohol on a regular basis, the diuretic effect of alcohol is lesser than someone who doesn't drink often (Polhuis et al. 2017). This diuretic effect is created by the imbalance of the body's water content, causing increased pressure as the bladder gets full faster.

LSD

LSD is not known to influence bladder pressure, rather it gets excreted through the urine normally and is a good test for the presence in the body (Passie et al. 2008).

Applied Physics: Question F

Orthostatic hypotension is a sudden decrease in blood pressure when moving from a horizontal position to an upright position as is demonstrated in *Figure 6.1*. This occurs because when a person is horizontal, their blood doesn't have to travel a very large height to reach all important organs (Wieling et al. 2022). To find pressure in a fluid dynamical system, Bernoulli's equation can be used:

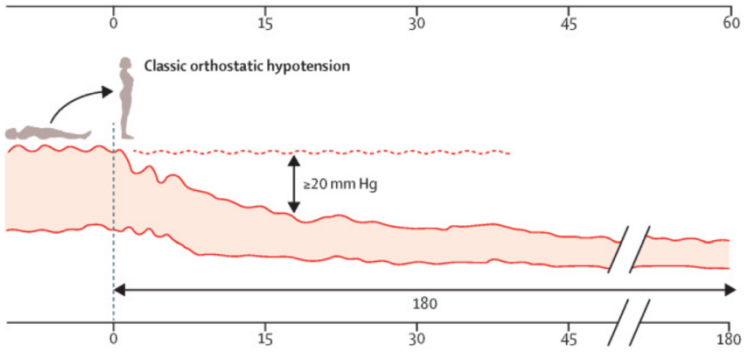

Figure 6.1: Blood pressure ranges in mmHg vs time (s) in a patient with classic orthostatic hypotension (Wieling et al. 2022).

$$\frac{1}{2}\rho v^2 + \rho g\, h_1 + P_1 = \frac{1}{2}\rho v^2 + \rho g\, h_1 + P_2$$ Equation 2.1

We can say that h_1 is the height of the brain laying down, and h_2 is the height of the brain standing. If we assume constant velocity, we can rearrange (see Appendix F.1) to get:

$$P_1 - P_2 = 2\rho g(h_1 - h_1)$$ Equation 2.2

This means that the difference in pressure between standing and laying down can be modeled as density of blood (approximately 1060kg/m^3) (Vitello et al. 2015), times gravity (9.8m/s^2), times the height difference between laying down and standing up. The average height of a young adult in Canada is 1.7m (Statistics Canada 2013). Using these numbers, we find that the pressure change would be 35,319.2 Pa, which when converted to mmHg is 264.9 mmHg (See appendix x). This rapid change in pressure can lead to light-headedness and loss of consciousness.

To test the accuracy of this equation, we can test against numbers from the literature. A study done by Voors et al. (1982) showed a 5 mmHg increase for a height increase of 15 cm. Plugging this height change into our equation yields 23.37 mmHg. This means that, although the numbers are not orders of magnitude apart, there's a large enough difference to conclude that this equation is likely an oversimplification. Regardless, it can still show correlation between height change and pressure, just not to an ideal degree of accuracy.

When astronauts are placed in near-zero gravity environments, the difference in pressure throughout the body will also be near zero regardless of height, as per Equation 2.2 (See appendix x). For the astronaut, this is equivalent to staying in a horizontal position the whole time they are in a zero-G environment. If there is very little change in pressure throughout the body, the heart muscles do not have to work as hard to get blood to the brain, as the fluid is not as affected by the force of gravity. This can cause heart muscles to atrophy, similar to the atrophy caused by the disuse of a muscle from wearing a cast for a long time (Fu et al. 2019). When astronauts return to environments with higher gravity, the pressure needed to pump blood throughout the body increases, and the heart may struggle to keep up.

One drug used to treat orthostatic hypotension in astronauts is midodrine, which is a selective alpha-1 adrenergic agonist. It works as a vasoconstrictor which causes blood vessels to constrict (Platts et al. n.d.). This reduces the area in the blood vessel, which increases the velocity of the blood, as per the equation:

$$A_1 v_1 = A_2 v_2$$ Equation 2.3

Looking again at Equation 2.1, if we assume that the height is constant, but velocity changes, we get that an increase in velocity results in an increase in pressure (see Appendix x). This increase in pressure reduces the stress on the heart, as it does not need to generate as much of a change in pressure to pump the blood to the brain.

A non-pharmaceutical approach that has been investigated as a means of decreasing orthostatic hypotension is hydration to increase blood volume (Fu et al. 2019). The greater the volume of blood, the greater the pressure the blood can exert on the walls of blood vessels, as per the equation:

$$P = \rho g V$$ Equation 2.4

Since acceleration perpendicular to a blood vessel is zero, the sum of forces is also zero. This means that the walls of blood vessels exert more force on the blood as well, which increases the flow to the brain. A contributing factor to orthostatic hypotension is the reduction of plasma volume, so the ingestion of an isotonic saline solution was studied to mitigate this source

(Convertino 1991). The results showed improvement in the symptoms of orthostatic hypotension, but not enough to reduce symptoms past an effective threshold. However, the results of the study additionally showed that a state of hypovolemia (lower than typical volume) was correlated with a 16% plasma volume loss as compared to a state of normovolemia (typical blood pressure) (Convertino 1991). From this information it can be gathered that, although hydration is not enough to eliminate negative effects of orthostatic hypotension, it is important for reducing sensitivity to gravitational changes.

An increase in gravity is also an issue that impacts astronauts, especially upon re-entry. During the landing phase of a mission, astronauts can be subjected to three to five times the force of gravity on earth (Jordan, Limper, and Tank 2022). When gravity increases, it becomes much harder for blood to get to the brain, as the pressure of the blood at any given height increases by the same margin. This makes it more difficult for the heart to pump blood toward the brain, thus resulting in vision darkening or loss of consciousness. One strategy to prevent this is the implementation of anti-G suits. These suits provide external circumferential pressure on the lower limbs to increase blood flow to the brain (Jordan, Limper, and Tank 2022). This method works similarly to midodrine, as it prevents blood pooling by squeezing blood vessels, therefore decreasing their area. Other targeted garments that add external pressure to the calves, thighs, and abdominal area have also shown to be effective in preventing syncope and presyncope upon re-entry (Jordan, Limper, and Tank 2022).

The difference between those who can and cannot sustain high G-forces is the ability to handle high pressure in the blood vessels in the leg. Physiologically, this manifests as more rigid blood vessels. This rigidity can be acquired through multiple exposures to high G-forces over a period of time (Eiken et al. 2022). A method to achieve this resistance is the use of human centrifuges, which can safely expose those with less tolerance to high G-forces. These machines work by rotating astronauts rapidly around an axis with a metal arm, which mimics the high G-force conditions that astronauts would need to withstand upon re-entry into the atmosphere (Winter et al. 2019). To investigate this potential, Eiken et al. (2022) measured heart rate and blood pressure in astronauts in a G-training regimen, where participants were put into a human centrifuge until 0.2-0.4 G below the point at which peripheral vision is lost. After five weeks of

three 40-minute sessions a week, the subjects showed a 13% increase in rapid onset G-force tolerance. Human centrifuges can therefore be used to prepare astronauts for higher G-forces by training their cardiovascular tolerance.

Works Cited A

Mount Sinai Health System. 2021. “High Caffeine Consumption May Be Associated with Increased Risk of Blinding Eye Disease” | Mount Sinai - New York.” Accessed November 18, 2023. https://www.mountsinai.org/about/newsroom/2021/high-caffeine-consumption-may-be-associated-with-increased-risk-of-blinding-eye-disease.

Beck, Kate. 2018. “Healthfully.” n.d. Healthfully. Accessed November 18, 2023. https://healthfully.com/caffeine-eye-pressure-6703740.html.

Clausen, Ingelin, Lars Geir W. Tvedt, and Thomas Glott. 2018. “Measurement of Urinary Bladder Pressure: A Comparison of Methods.” *Sensors (Basel, Switzerland)* 18 (7): 2128. https://doi.org/10.3390/s18072128.

De Giuseppe, Rachele, Ilaria Di Napoli, Francesca Granata, Antonia Mottolese, and Hellas Cena. 2019. “Caffeine and Blood Pressure: A Critical Review Perspective.” *Nutrition Research Reviews* 32 (2): 169–75. https://doi.org/10.1017/S0954422419000015.

Holze, Friederike, Patrick Vizeli, Laura Ley, Felix Müller, Patrick Dolder, Melanie Stocker, Urs Duthaler, et al. 2021. “Acute Dose-Dependent Effects of Lysergic Acid Diethylamide in a Double-Blind Placebo-Controlled Study in Healthy Subjects.” *Neuropsychopharmacology* 46 (3): 537–44. https://doi.org/10.1038/s41386-020-00883-6.

Husain, Kazim, Rais A Ansari, and Leon Ferder. 2014. “Alcohol-Induced Hypertension: Mechanism and Prevention.” World Journal of Cardiology 6 (5): 245–52. https://doi.org/10.4330/wjc.v6.i5.245

Keil, Ulrich, Angela Liese, Birgit Filipiak, John D. Swales, and Diederick E. Grobbee. n.d. “Alcohol, Blood Pressure and Hypertension.” In *Novartis Foundation Symposium 216 - Alcohol and Cardiovascular Diseases*, 125–58. John Wiley & Sons, Ltd. Accessed November 26, 2023. https://doi.org/10.1002/9780470515549.ch9.

Lohsiriwat, Supatra, Muthita Hirunsai, and Bansithi Chaiyaprasithi. 2011. “Effect of Caffeine on Bladder Function in Patients with Overactive Bladder Symptoms.” *Urology Annals* 3 (1): 14–18. https://doi.org/10.4103/0974-7796.75862.

Machiele, Ryan, Mahsaw Motlagh, and Bhupendra C. Patel. 2023. “Intraocular Pressure.” In *StatPearls*. Treasure Island (FL): StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK532237/.

Mayo Clinic. n.d.“Blood Pressure Chart: What Your Reading Means.” Accessed November 17, 2023. https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/blood-pressure/art-20050982.

Mayo Clinic. n.d. “Low Blood Pressure (Hypotension) - Symptoms and Causes.” Accessed November 17, 2023. https://www.mayoclinic.org/diseases-conditions/low-blood-pressure/symptoms-causes/syc-20355465.

Novak, Giordano. 2023. “LSD Effects on Eyes and Pupils.” *Prisms LSD* (blog). January 24, 2023. https://prismslsd.co/lsd-effects-on-eyes-and-pupils/.

Passie, Torsten, John H. Halpern, Dirk O. Stichtenoth, Hinderk M. Emrich, and Annelie Hintzen. 2008. “The Pharmacology of Lysergic Acid Diethylamide: A Review.” *CNS Neuroscience & Therapeutics* 14 (4): 295–314. https://doi.org/10.1111/j.1755-5949.2008.00059.x.

Polhuis, Kristel C. M. M., Annemarthe H. C. Wijnen, Aafje Sierksma, Wim Calame, and Michael Tieland. 2017. “The Diuretic Action of Weak and Strong Alcoholic Beverages in Elderly Men: A Randomized Diet-Controlled Crossover Trial.” *Nutrients* 9 (7): 660. https://doi.org/10.3390/nu9070660.

Seminara, Lynda. 2022. “Effects of Alcohol on IOP and Glaucoma.”American Academy of Ophthalmology. https://www.aao.org/eyenet/article/effects-of-alcohol-on-iop-and-glaucoma.

Tasnim, Sara, Chantel Tang, Vijaya M Musini, and James M Wright. 2020. “Effect of Alcohol on Blood Pressure.” *The Cochrane Database of Systematic Reviews* 2020 (7): CD012787. https://doi.org/10.1002/14651858.CD012787.pub2.

Urone, Paul P. “11.9 Pressures in the Body - College Physics 2e | OpenStax.” n.d. Accessed November 17, 2023. https://openstax.org/books/college-physics-2e/pages/11-9-pressures-in-the-body.

Appendix F

$$\frac{1}{2}\rho v^2 + \rho g h_1 + P_1 = \frac{1}{2}\rho v^2 + \rho g h_2 + P_2$$

$$\rho g h_1 + P_1 = \rho g h_2 + P_2$$

$$P_1 - P_2 = \rho g h_2 - (\rho g h_1)$$

$$P_1 - P_2 = \rho g (h_2 - h_1)$$

Appendix F.1: Rearranging Bernoulli's equation to isolate for change in pressure. The variable ρ represents density of the fluid, v represents velocity, g represents gravity, h represents height, and P represents pressure.

Works Cited B

Convertino, Victor A. 1991. “Carotid-Cardiac Baroreflex: Relation with Orthostatic Hypotension Following Simulated Microgravity and Implications for Development of Countermeasures.” Acta Astronautica 23 (January): 9–17. https://doi.org/10.1016/0094-5765(91)90093-K.

Eiken, Ola, Michail E. Keramidas, Håkan Sköldefors, and Roger Kölegård. 2022. “Human Cardiovascular Adaptation to Hypergravity.” American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 322 (6): R597–608. https://doi.org/10.1152/ajpregu.00043.2022.

Fu, Qi, Shigeki Shibata, Jeffrey L. Hastings, Steven H. Platts, Douglas M. Hamilton, Michael W. Bungo, Michael B. Stenger, Christine Ribeiro, Beverley Adams-Huet, and Benjamin D. Levine. 2019. “Impact of Prolonged Spaceflight on Orthostatic Tolerance During Ambulation and Blood Pressure Profiles in Astronauts.” Circulation 140 (9): 729–38. https://doi.org/10.1161/CIRCULATIONAHA.119.041050.

Jordan, Jens, Ulrich Limper, and Jens Tank. 2022. “Cardiovascular Autonomic Nervous System Responses and Orthostatic Intolerance in Astronauts and Their Relevance in Daily Medicine.” Neurological Sciences 43 (5): 3039–51. https://doi.org/10.1007/s10072-022-05963-7.

Platts, Steven H, Michael B Stenger, L Christine Ribeiro, and Stuart M C Lee. n.d. “Midodrine as a Countermeasure to Orthostatic Hypotension.”

Statistics Canada. 2013. “Canadian Health Measures Survey: Cycle 2 Data Tables: Table 22 — Measured Standing Height, by Age and Sex, Household Population, Canada, 2009 to 2011.” Accessed November 30, 2023. https://www150.statcan.gc.ca/n1/pub/82-626-x/2012001/t023-eng.htm.

Vitello, Dominic J., Richard M. Ripper, Michael R. Fettiplace, Guy L. Weinberg, and Joseph M. Vitello. 2015. “Blood Density Is Nearly Equal to Water Density: A Validation Study of the Gravimetric Method of Measuring Intraoperative Blood Loss.” Journal of Veterinary Medicine 2015: 152730. https://doi.org/10.1155/2015/152730.

Voors, A W., D. W. Harsha, L. S. Webber, and G. S. Berenson. 1982. “RELATION OF BLOOD PRESSURE TO STATURE IN HEALTHY YOUNG ADULTS1 | American Journal of Epidemiology | Oxford Academic.” June 1982. https://academic-oup-com.libaccess.lib.mcmaster.ca/aje/article/115/6/833/113741.

Wieling, Wouter, Horacio Kaufmann, Victoria E Claydon, Veera K van Wijnen, Mark P M Harms, Stephen P Juraschek, and Roland D Thijs. 2022. “Diagnosis and Treatment of Orthostatic Hypotension.” The Lancet Neurology 21 (8): 735–46. https://doi.org/10.1016/S1474-4422(22)00169-7.

Winter, Julia, Charles Laing, Bernd Johannes, Edwin Mulder, Bianca Brix, Andreas Roessler, Johannes Reichmuth, Joern Rittweger, and Nandu Goswami. 2019. “Galanin and Adrenomedullin Plasma Responses During Artificial Gravity on a Human Short-Arm Centrifuge.” Frontiers in Physiology 9 (February): 1956. https://doi.org/10.3389/fphys.2018.01956.