HUMAN APPETITE REGULATION EMULATOR

Paul Frenger M.D.
A Working Hypothesis, Inc., P.O. Box 820506, Houston, TX 77282, USA
pfrenger@alumni.rice.edu

KEYWORDS

anorexia, appetite, cholecystokinin, corticotropin-releasing hormone, cytokines, diabetes mellitus, ghrelin, hypothalamus, leptin, nucleus accumbens, neuropeptide Y, obesity

INTRODUCTION

Neuroscientists are investigating the relative contribution of brain reward systems versus known homeostatic mechanisms in regulating appetite, food intake and weight control [1]. The outcome of this research will be important to healthy individuals and those suffering from various nutrition-related disease states. The author, as a practicing physician, has advised innumerable patients on dietary regimens and prescribed pharmacological remedies for their nutrition-related illnesses during his forty year medical career.

With this motivation, the author wished to create a computerized investigational tool to study appetite regulation, derived from his previous work in simulating other functions of the human nervous system. This human appetite regulation emulator (acronym: HARE) was intended to represent the control mechanisms for hunger, appetite and eating behavior in sufficient detail, based on known mechanisms, to allow worthwhile study of results based on thoughtful manipulation of these variables.

PHYSIOLOGICAL CONTROL MECHANISMS

Regulation of appetite, hunger and eating behavior is complex. It mainly resides within the hypothalamus adjacent to the brainstem, with direct neural connections to the limbic system, prefrontal cortex, pituitary gland, parasympathetic nervous system, adrenal gland and elsewhere [2]. Food palatability is appreciated in the so-called "pleasure center" within the nucleus accumbens [3]. Indirect appetite regulation is accomplished by hormones, neurotransmitters and other chemicals working in opposition. The stimulatory hormone ghrelin [4] and the neurotransmitter neuropeptide Y [5] are resisted by inhibitory hormones leptin [6], cholecystokinin (CCK) [7], corticotropin-releasing hormone (CRH) [8], and several cytokines: tumor necrosis factor-alpha (TNF-a), and interleukins IL-1 and -6 [9]. Hunger elicits high-level foraging behavior and feeding activities by the animal / human [10]. Lesser-known chemicals also can have a variable effect.

The metabolic control hormones thyroxin (increases the cellular metabolic rate), insulin (reduces glucose levels in the blood), glucagon, cortisol and growth hormone (all increase blood glucose) must be accounted for because of their direct and indirect effects on appetite regulation in health and diseased states (hypo- and hyperthyroidism, anorexia, malnutrition, obesity, diabetes and metabolic reactions to stress) [11].

Some functional overlaps are known to exist within this system. For example, endocannabinoids, synthesized in neurons of the lateral hypothalamus which disinhibit feeding activity, are down-regulated by leptin [12]. Pleasurable sensations associated with ingesting food mimic those generated by taking narcotics [13]. Nicotine, which serves as a defense mechanism against herbivore insects by plants such as tobacco, teas, eggplant, potatoes, tomatoes, peppers, and cauliflower, can inhibit appetite when ingested [14]. CCK can activate the fear mechanism to precipitate panic attacks [15].

Such effects do not appear to be beneficial for the animal but are important in a comprehensive computerized emulator.

Loss of control of the food intake system results in serious overfeeding, morbid obesity and death; or critical underfeeding, starvation and death.

HUMAN NERVOUS SYSTEM EMULATOR

System software

The author's human nervous system function emulator (acronym: HNSFE) is an artificial intelligence (AI) program, written in the Forth language, which simulates the brain's neural-cognitive operations [16]. It consists of two parts: a high-level component (the author calls this "BRAIN.FORTH") which imitates human intellectual processing, knowledge database, memory, emotions, personality and volition; and a lower-level component (the author calls it "ANDROID.FORTH") which provides machine vision, optical character recognition, speech synthesis and recognition, facial gestures, a dexterous hand, multimode sensory inputs and motor outputs for an anthropomorphic robot. The HNSFE features IEEE standard 1275-1994, a hardware-independent, byte-coded, network-compatible "plug-and-play" virtual machine which boots computers made by *Apple*, *IBM*, *Sun Microsystems* and the *One Laptop Per Child* (OLPC) project [17-18].

System hardware

These programs run on an *x86*-compatible *PC/104* bus multiprocessor network [19]. The author designed *PC/104* analog circuits with artificial neural networks for machine vision [20], synthetic emotions [21] and simulated neural cell membrane substrate-receptor binding using the *Microchip Technology TC9400* frequency-to-voltage converter (F/V) [22]. A *Parallax Propeller* 8-core 32-bit *P8X32A* CPU was added for improved brainstem, reticular activating system and thalamic functions [23]. Programs for the *P8X32A* are written in a multitasking Forth which supports up to 100 simultaneous tasks per core [24]. The highest-level AI mental processes (personality, volition and self awareness) were moved to a separate 1.0 by 1.3 inch *ARM7* 32-bit CPU coprocessor board also programmed in Forth [25].

Android robot

The author's robot is named ANNIE, an acronym for "Android with Neural Network, Intellect and Emotions" [26]. ANNIE is a meter tall and has some resemblance to the *iCub* robot which it preceded by five years [27].

New complex functional emulators

Neglecting ANNIE's robotic underpinnings somewhat over the last few years, the author has concentrated on creating an array of emulators, featuring: the hormones epinephrine [28] and oxytocin [29]; the response to opioid drugs [30]; the endocannabinoid system [31]; the fear mechanism [32]; a genetic autism [33]; anti-viral and autoimmune system functions in fibromyalgia [34]; and male-female courtship and sexual responses [35]. The plasticity of "BRAIN.FORTH" software makes programming new emulators relatively easy.

Using a variety of coprocessors, the author has given the ANNIE robot realistic outputs for electrocardiogram (EKG), electroencephalogram (EEG) and neural action potentials (AP) [36].

APPETITE REGULATION EMULATOR

The human appetite regulation emulator (HARE) is a multilevel system which spans the range from cell membrane events to high level sensation and behavioral responses. At the cellular level, the oppositional (negative feedback) effect of the above-mentioned hormones, neurotransmitters and other chemicals can be processed by the main CPU under program control.

For example, to depict the result (**IN**) of indirect appetite regulation by ghrelin (**G**) and neuropeptide Y (**NY**) stimulation, as opposed by the inhibition of leptin (**L**), cholecystokinin (**CK**), corticotropin-releasing hormone (**CR**), tumor necrosis factor (**TN**), and the interleukins (**I1**) and (**I6**), one could solve Equation 1 for **IN** after loading values into the variables.

$$IN = G + NY - L - CK - CR - TN - I1 - I6 \quad (1)$$

(Scaling factors are not shown).

Similarly, the effects of direct hypothalamic neural stimulation on appetite (**DN**) may be added to Equation 1, as well as the additive effects of thyroxin, insulin, glucagon, cortisol and growth hormone (**HN** in Equation 2) as **XN**, which represents the *total appetite urge*.

$$XN = DN + IN + HN \quad (2)$$

Variable **XN** is an 8-bit unsigned number between 0 and 255. **XN** depicts how "hungry" ANNIE "feels"; it can be checked against a threshold value to determine if a robotic subroutine for food "foraging" for ANNIE should be triggered.

The author has a fondness for computations using analog circuits, so his alternate methods are given next. Figure 1 shows the *TC9400* used as an F/V converter to depict the effects of hippocampal and other brain APs on neurons responsible for appetite and hunger. Combined AP pulses enter into pin 11, are internally converted to a voltage, amplified, and then appear on output pin 12. The output voltage then enters the operational amplifier (op-amp) shown in Figure 2 below for further processing.

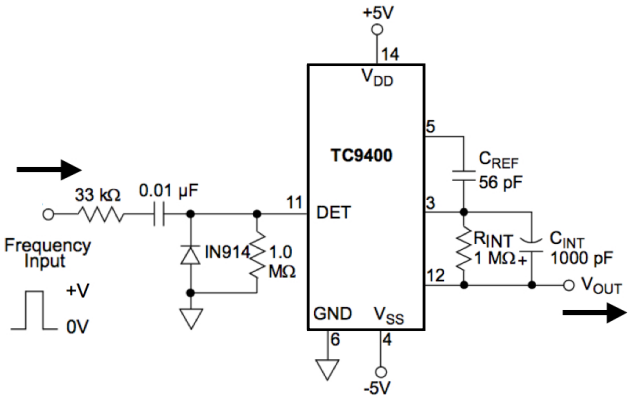

Figure 1: *TC9400* F/V simulates neural AP effects.

DC voltages from the *TC9400* and all other sources are applied to an op-amp used as a summing amplifier (Figure 2).

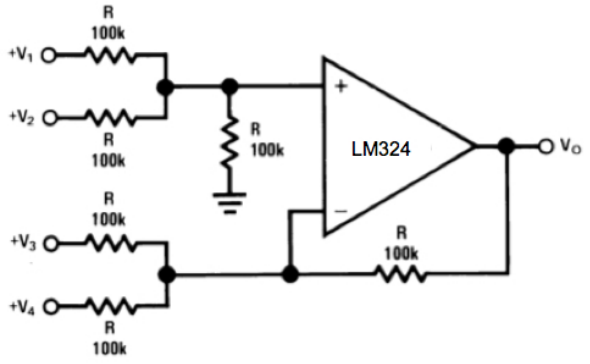

Figure 2: Summing amplifier using *LM324* op-amp to accommodate stimulatory and inhibitory inputs.

The noninverting (+) input of the op-amp [37] is used to apply stimulatory voltages representing ghrelin and neuropeptide Y, for example. The inverting (-) input applies voltages representing inhibitory factors (leptin, cholecystokinin, corticotropin-releasing hormone, tumor necrosis factor, and interleukins). Figure 2 (taken from the manufacturer's data sheet) does not show all of the inputs required.

As mentioned previously, the **DN** voltage is produced by the *TC9400*. The stimulatory and inhibitory voltage inputs to the op-amp represented by **IN** and **HN** variables may be generated by an 8-bit digital-to-analog converter (D/A) loaded by the CPU under program control. The author uses an octal D/A converter [38] because it has multiple outputs.

The output voltage (**Vo**) of the op-amp represents the *total appetite urge* as rendered in Equation 2, which can be read by an analog-to-digital converter (A/D) and scaled to 8-bits, unsigned (which will then be identical to digital variable **XN**). Alternatively, this voltage may be input to a linear threshold detector (comparator) to give a binary "yes / no" output based on a user-selected reference voltage.

Some functional interactions in this system are included in the emulator. For example, a background subroutine updates and monitors the serum glucose variable, adjusting it based on simulated eating, exercise, and secretion of epinephrine, glucagon, cortisol, thyroxin, insulin and growth hormone. The glucose variable's value is output to a window comparator which has upper and lower trip points that bracket the allowable "normal range". Low serum glucose produces a simulated hypoglycemic episode, while high glucose produces coma. The former is "treated" very realistically with a glucose injection, the latter with insulin and IV fluids.

DISCUSSION

Body function emulation techniques allow the AI / robot designer to give their creations many of the intrinsic properties of the living creatures which are being imitated. The ANNIE robot has sleep and waking cycles; shows a variety of emotional responses and the ability to make facial expressions appropriate to the emotional content she is expressing; under-

stands the spoken word and responds in kind with a pleasant female voice; reads a CRT screen or a book; uses a fully functional dexterous hand; senses touch, pain, temperature, humidity, excess CO_2 levels and even sexual stimulation. ANNIE has a personality with likes, dislikes and fears; is curious; has an extensible fund of knowledge; can speak more than one language; has friends and a pet. ANNIE now can get hungry and look for palatable food.

CONCLUSION

Emulation has given a *sense of appetite* to the android robot ANNIE. The HARE AI simulation allows the many factors involved in appetite, hunger and eating behavior to be manipulated for educational purposes.

REFERENCES

[1] G. Finlayson, N. King and J.E. Blundell, "Liking vs. wanting food: importance for human appetite control and weight regulation," *Neurosci & Biobehavioral Rev*, vol. 31, no. 7, pp.987-1002, 2007.

[2] N.M. Neary, A.P. Goldstone and S.R. Bloom, "Appetite regulation: from the gut to the hypothalamus," *Clin Endocrinol*, vol. 60, no. 2, pp.153-160, 2004.

[3] E.R. Kandel, J.H. Schwartz and T.M. Jessell, *Principles of Neural Science*, 4th ed., McGraw-Hill, New York, 2000.

[4] E. Egecioglu, *Ghrelin in the regulation of feeding and energy balance*, Vasastaden, Göteborg, Sweden, 2007. http://gupea.ub.gu.se/bitstream/2077/17061/1/gupea_2077_17061_1.pdf.

[5] E. Rohner-Jeanrenaud and B. Jeanrenaud, "Central nervous system and body weight regulation". *Ann Endocrinol* (Paris), vol. 58, no. 2, pp.137–142, 1997.

[6] A.M. Brennan and C.S. Mantzoros, "Drug Insight: the role of leptin in human physiology and pathophysiology -- emerging clinical applications," *Nat Clin Pract Endocrinol Metab*, vol. 2, no. 6, pp.318–27, June 2006.

[7] H. Fink, A. Rex, M. Voits and J.P. Voigt, "Major biological actions of CCK--a critical evaluation of research findings," *Exp Brain Res,* vol. 123, no. 1-2, pp.77–83, 1998.

[8] E. Valassi, M. Scacchi and F. Cavagnini, "Neuroendocrine control of food intake," *Nutr Metab Cardiovasc Dis*, vol. 18, no. 2, pp.158-168, Feb. 2008.

[9] L. Gautron and S. Layé, "Neurobiology of inflammation-associated anorexia," *Frontiers in Neurosci*, vol. 3, art. 59, online doi: 10.3389/neuro.23.003.2009, 8 Jan. 2010.

[10] A.J. Carlson, "Hunger," *The Scientific Monthly*, vol. 33, pp.77-79, 1931.

[11] S.K. Powers and E.T. Howley, chap. 5, "Hormonal response to exercise," *Exercise Physiology*, 7th ed., McGraw-Hill, New York, 2009.

[12] Young-Hwan Jo, Ying-Jiun J. Chen, C.C. Streamson Jr., D.A. Talmadge and L.W. Role, "Integration of endocannabinoid and leptin signaling in an appetite-related neural circuit," *Neuron*, vol. 48, no. 6, pp.1055-1066, 22 Dec. 2005.

[13] J. Hamilton, "Overeating, like drug use, rewards and alters brain," *National Public Radio*, 1 Dec. 2010. http://www.npr.org/2010/12/01/131698228/overeating-like-drug-use-rewards-and-alters-brain.

[14] E.F. Domino, E. Hornbach and T. Demana, "The nicotine content of common vegetables," Correspondence, *N Engl J Med*, vol. 329, no. 6, pp.437, 5 Aug. 1993.

[15] J. Bradwejn, "Neurobiological investigations into the role of cholecystokinin in panic disorder," *J Psych and Neurosci*, vol. 18, no. 4, pp.178–188, Jul. 1993.

[16] P. Frenger, "Human nervous system function emulator," *Biomed Sci Instrum*, vol. 36, pp.289-294, 2000.

[17] Welcome to the Open Firmware Home Page. http://playground.sun.com/1275/home.html.

[18] One Laptop Per Child: Open Firmware. http://wiki.laptop.org/go/Open_Firmware.

[19] Welcome to the PC/104 Consortium Website. http://www.pc104.org.

[20] P. Frenger, "Forth and artificial vision," *EuroFORTH*, Oxford Univ., England, pp.87-96, Sept 26-28, 1997. *Best paper award.*

[21] P. Frenger, "Thirty-five years of artificial emotions: an extended case history", *Can Med Biol Engr Conf*, Calgary, Alberta, Canada, 2009.

[22] P. Frenger, "Human narcotic use emulator", *Biomed Sci Instrum*, vol. 43, pp.278-283, 2007.

[23] P. Frenger, "Human brainstem emulator using an extensible multicore processor network", *Workshop on Automation and Robotics*, NASA / JSC, pp.5, 2008.

[24] PropellerForth Interpreter/Compiler. http://www.cliff.biffle.org.

[25] P. Frenger, "Emulating i," *Biomed Sci Instrum*, vol. 46, pp.26-32, 2010.

[26] P. Frenger, "Meet ANNIE: an open systems android robot," *Smart Engineering Systems Design Conf.*, pp.33-38, 2000. *Best paper nomination.*

[27] Welcome to the RobotCub Website, home of iCub. http://www.robotcub.org.

[28] P. Frenger, "Human Hormone Function Emulator," *Biomed Sci Instrum*, vol. 42, pp.513-517, 2006.

[29] P. Frenger, "Human Trust-Love Mechanism Emulator," *Houston Conf Biomed Engr Res*, pp.42, 2008.

[30] P. Frenger, "Human Narcotic Use Emulator," *Biomed Sci Instrum*, vol.43, pp.278-283, 2007.

[31] P. Frenger, "Human Endocannabinoid System Emulator," *Can Med Biol Engr Conf*, SA-7.5, pp.1-3, 2008.

[32] P. Frenger, "Human Fear Mechanism Emulator," *Biomed Sci Instrum*, vol. 44: pp.322-328, 2008.

[33] P. Frenger, "Oxytocin Receptor-Based Autism Emulator," *Houston Conf Biomed Engr Res*, pp.110, 2009.

[34] P. Frenger, "Multi-System Fibromyalgia Syndrome Emulator," *Biomed Sci Instrum*, vol. 45, pp.292-298, 2009.

[35] P. Frenger, "Human Sexual Function Emulator," *accepted to Biomed Sci Instrum*, vol. 47, 2011.

[36] P. Frenger, "The ANNIE robot ten years later," *Smart Engineering Systems Design Conf.*, pp.637-644, 2010.

[37] National Semiconductor LM324 quad op-amp. http://www.national.com/mpf/LM/LM324.html.

[38] Maxim Semiconductor MX7228 octal D/A converter. http:// www.maxim-ic.com/parts.cfm/q/other.