EDITORIAL:

FLIP FLOP MODEL IN BASIC MEDICAL SCIENCES

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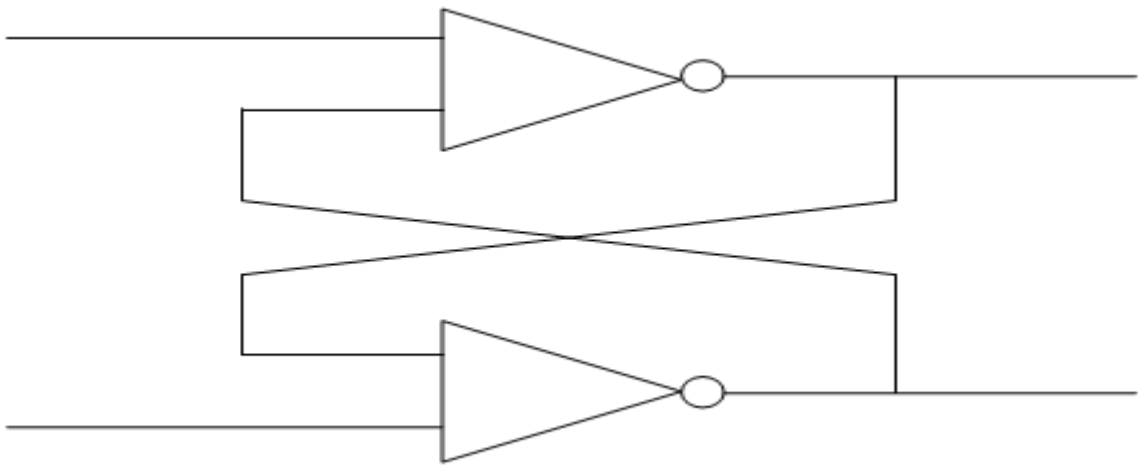
Only change is eternal. We have learned from homeostasis that internal environment must be kept constant whatever changes take place in external environment. To keep internal environment constant we know we have established models feedback mechanisms i.e. positive feedback and negative feedback mechanisms. But certain changes are so sudden i.e. from wakefulness to sleep or sleep to wakefulness; such changes are better explain by flip flop model. Flip flop circuit model is often used in computer and electronics and called bistable an electronic circuit that can assume either of two stable states by the application of a suitable pulse. So flip-flop circuit is a loops having two stable conditions, each one corresponding to one of two alternative input signals. This two component circuit model is, however, evocative of Walter Cannon's original formulation of the homeostasis concept which referred to the balance of two opposing factors .The flip flop circuit analogy is taken from electronic engineering and provide framework for functioning of two mutually influential circuits in brain i.e. awakening circuit and sleep inducing circuit. Though it appear to be a form of positive feedback loop but it has a switch like component which decide either of two bistable circuit. It can only exist in one of two states interdependent but quiet opposite to each other. It is found in nature where tight control is needed. The most important feature of this Positive feedback circuit is that they help to make the rapid switch from one state to another state. We have just began to identify these switches which can on and off, so that only the correct state of two state is assumed. Such switches in central nervous gramsystem are frequently a center or clusters of neurons secreting specific neurotransmitters which decides on-off states in either side.

Diagram showing analogy of flip flop circuit in electronics



In electronics memory i.e., a flip-flop or latch is a circuit that has two stable states and can be used to store state information. The circuit can be made to change state by signals applied to one or more control inputs and will have one or two outputs. It is the basic storage element in sequential logic. Flip-flops and latches are a fundamental building block of digital electronics systems used in computers, communications, and many other types of systems. The word *latch* is mainly used for storage elements, while clocked devices are described as *flip-flops*.

In reference to neuro physiology, during sleep and wake states, the most of the cortical columns are in their respective sleeplike and wake like states, suggesting synchrony of state between columns. Cortical columns are connected to subcortical sleep regulatory circuits. Von Economo and Moruzzi, work concluded that cortical arousal is regulated by sub cortical regions. Ascending reticular activating system [ARAS] originated from brain by two major branches of ARAS. [1] Cholinergic cell groups in the upper pons input into thalamus and densely innervate cortex. This system is responsible for either wakefulness and REM sleep. [2] The Other second branch originates from lower pons and locus coeruleus (norepinephrine), dorsal and medial raphe (serotonin), and tuberomammillary cells (histamine) to innervate lateral hypothalamic region, basal forebrain and cortex. End target neuron of this system is cholinergic or Gabaminobutyric acid (GABA) –mediated neurons. This branch fire maximally during wakefulness and slowing or absent during NREM sleep. Discovery of orexin (also called hypocretin) from the lateral hypothalamus through more light in understanding how sleep is initiated, maintained and terminated. It is postulated that there is Switch i.e. being in the ventrolateral preoptic area (VLPO) of hypothalamus. VLPO area maximally active during sleep and major out to mono aminegernic neurons of brain stem and basal region and neurotransmitters are inhibitory (ie, galanin and GABA). Saper and colleagues postulated VLPO function as an “off switch” to inhibit arousal. Lesion in this region reduced sleep. VLPO not only inhibits wakefulness but also inhibited by wakefulness. This reciprocal relationship between the VLPO and the ARAS is the functioning of a “flip flop circuit.” These studies suggest that mutually inhibitory wake and sleep promoting circuits (“flip-flop switches”) are an evolutionarily conserved mechanism to promote fast and complete state switching between wake and sleep. Similarly Hunger and fed states are also an example of a flip-flop circuit via a synaptic AMPK-dependent positive feedback circuit pathway for physiologic regulation. Here “set”: ghrelin and “reset”: leptin hormones or neurotransmitters separately maintain flip flop circuit. In this circuit, though, we add the provision that these signals operate as discrete Boolean logical operations due to an AMPK-dependent positive feedback loop. For physiological state constructed from bistable synapses that are flipped between sustained high and low activity states by transient exposure to hormones associated with energy deficit and surfeit, respectively.

Flip flop model is likely to be useful to explain some regulatory mechanisms i.e. circadian and diurnal rhythms, regulation of heart beat, cardiac arrhythmias i.e. circus phenomenon, neural and chemical regulation of respiration. The model already helped to explain moment of phospholipid particles on cell membrane and many intracellular and intra nuclear and movement genetic molecules [molecular switches] some biochemical mechanisms i.e. lipid signaling.

References:

1] Christopher J. Davis, PhD, James M. Krueger, PhD*, Sleep and Cytokines.
A book biology of sleep-sleep medicine clinics. sept 2012,vol.7 - no. 3 ,published by Elsevier publication

2] Michael Perlis, PhD[a]*, Wil Pigeon, PhD[b], Phil Gehrman, PhD[a], Jim Findley, PhD[a], Neurobiological Mechanisms in Chronic Insomnia, Sean Drummond, PhD[c], A book biology of sleep-sleep medicine

3] Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001; 24: 726-31.

4] Yunlei Yang, Deniz Atasoy, Helen H. Su, and Scott M. Sternson[*] Hunger states switch a flip-flop memory circuit via a synaptic AMPK-dependent positive feedback loop**,** CELL. 2011 September 16; 146(6): 992–1003. PMCID: PMC3209501