SC/BIOL 4310 3.0 DEPARTMENT OF BIOLOGY
WINTER TERM 2013/14 YORK UNIVERSITY

PHYSIOLOGY OF CIRCADIAN TIMING

(Formerly "Biological Timekeeping")

Calendar Description:
This course examines the mechanism by which cells generate 24h (circadian) rhythms, how the numerous sites of these cells are coordinated by nerves and hormones and the critical roles of human circadian clocks in health and diseases. Three lecture hours per week. One term. Three credits. Prerequisites: SC/BIOL 2020 4.00 or SC/BIOL 2020 3.0; SC/BIOL 2021 4.00 or SC/BIOL 2021 3.0; SC/BIOL 3060 4.0.

Course Director:

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Scheduling:

Lectures : M, W, F, 12:30 - 13:30.
Room S201, Ross Building

Text:
No required text. Reading will be assigned from books and recent review articles, all of which will be available on line as e-journals (which I will email to the class) or kept on Reserve for this course in Steacie.

Suggested Grading and Dates:

Mid Term Test, February 14th (on basic concepts, subcellular mechanisms, key model systems)	=	30%
Student in-class presentation of recent research paper, c. March 7-14th (details will be given as soon as known)	=	20%
Final Exam (3 hours), in exam period, April 8-24 (on whole course)	=	50%
TOTAL	=	100%

EXPANDED COURSE DESCRIPTION:

Life evolved in a cyclical environment alternating between the freezing darkness of night and the searing radiation of day. Early nucleated cells evolved the ability to time their various activities to occur in the most appropriate portion of daily and seasonal cycles. These cellular biological "clocks" are retained in modern organisms where they coordinate both cellular and physiological activities which are expressed in the whole organism as overt rhythms ranging from hormone secretion rhythms to sleep-wake (activity) rhythms. Interactions between the component "clocks" of an organism, mediated primarily by nerves and hormones, lead to internal temporal organisation of events within it. The fundamental cellular and physiological mechanisms of biological clocks were developed in key animal model systems such as bacteria, molluscs and insects and later applied to mammals and humans. Molecular clocks are now known in nearly all human tissues; new research reveals their importance in synchronizing the functions of various tissues with each other, to produce coordinated functioning of the various body parts. Clocks are master coordinators of physiology.

The analysis of human biological clocks has made extraordinarily rapid advances in recent years at the levels of physiology and cell and molecular biology. Human clocks are critical factors in the development of cancers, heart attacks, diabetes and a host of other diseases. This knowledge is creating profound changes in numerous medical practices. The subject has acquired a prominence in public awareness (rhythms in human performance, shift-work, jet-lag, etc.). In medicine, treatment of many diseases has been revolutionised by precise timing of administration of medications. Numerous disorders are now recognised as due to malfunctions of human biological "clocks" and are treated by the new techniques of "chronotherapy". Others are simply natural variants of timekeeping genes in humans (eg ‘larks’ and ‘owls’). We will discuss the need for education of society in general regarding the serious dangers to human health of requiring people to adopt work schedules or lifestyles that defy their biological clockwork.

The course will emphasise the physiological mechanisms underlying biological clocks but will also discuss the subject at the level of its cellular and molecular mechanisms and its human and medical implications. Therefore, the course crosses a number of the conventional disciplinary boundaries within biology.

Short Course Lecture Outline

Central concepts and properties of circadian clocks
How a cell keeps time; subcellular mechanisms of generation of circadian rhythm
Model systems that showed circadian clocks control all physiology by nerves and hormones
Mid Term Test
The ‘master clock’ in the brain of mammals, including humans
Clocks outside the brain and their interactions with it
Student presentations of recent research articles
Human and medical implications

Students are reminded that the University policies on academic honesty, ethics, conduct, disabilities and religious observance are always in force. For details see:
http://www.yorku.ca/secretariat/senate_cte_main_pages/ccas.htm

LECTURE SCHEDULE

I. Basic Concepts and Properties of Circadian Clocks

Origin and nature of periodicities in the environment.
The solar day cycle as a formative factor in the origin of life.
Evolutionary origin and adaptive significance of circadian clocks.

Circadian rhythms in whole organisms.
Properties and evidence of endogenous nature.
Definitions: 'circadian clock' and related terminology.

Circadian rhythms in populations. Circadian gating: *Drosophila* eclosion rhythm.

Mechanism of synchronisation of clocks with environmental signals ie Entrainment.
The phase response curve. Pacemakers and slaves.
Importance of both 'dawn' and 'dusk': use of 'skeleton' photoperiods.
Entrainment to temperature cycles.
Conflict between Zeitgebers.

Reading for the above topics:
1) Chapters 1, 2 and 3 in **Saunders, D.S. (1977) "An Introduction to biological rhythms"** (3 copies on Steacie Reserves). Basic concepts have not changed despite the age of this book.
2) Slightly more detailed version of the above is in Chapters 1, 2, and 3 of **"Insect Clocks" (2002)** by D.S. Saunders, C.G.H. Steel, X. Vafopoulou, R.D. Lewis (also on Reserve). All the basic concepts were developed in insects, so this book covers all the same topics. Use it if you find the little book inadequate, otherwise not required reading.
3) Pages 1063-1071 of Golombek, D.A. and Rosenstein, R.E. (2010). Physiology of circadian entrainment, Physiol. Rev. 90, 1063-1102. The remaining pages of this review are not very well presented, do not read the rest!

From this point on, recent reviews will be used as reading material, available as e-journals I will email these to the class as they are needed. Some reviews may be published during the course, so I cannot specify ahead of time what these will be.

II. How Does a Cell Function as a Clock?

Circadian clocks of bacteria and their mechanism. *kai* genes. Antibiotic targets.
Circadian clocks in single celled eukaryotes: one or more clocks in a cell?
The molecular mechanism of circadian timing in *Drosophila* and mammals.
Clock gene products and transcription regulators: the transcription/translation oscillator (TTO).
A complete cellular clock needs many post-translational factors: circadian cycling of K^+, Ca^{++}, ATP, cAMP, phosphorylases, phosphatases.

III. Neurobiology and Endocrinology of Circadian Timing Systems.

Structure and function of clocks in the brain and other tissues. Multiple clocks are connected together into timekeeping systems. Concepts discovered in insects are applied to mammals.

Invertebrates:

Molluscan eye clock: the simple neuronal clock that foreshadowed the SCN.
Insect neuroendocrine clocks: a model multioscillator system of mammals.
Neuroarchitecture of the clockwork in the brain and how it controls rhythms in behaviour and rhythmic release of hormones.
Hormones as 'messengers of time'.
Discovery of oscillator cells in various tissues (peripheral oscillators) of insect models: evidence of hormones and nerves in driving these oscillators and their role in the broader circadian system.

Mid Term Test: Friday February 14th

Birds: Pineal gland as pacemaker and roles of melatonin.

Mammals (including humans):

The suprachiasmatic nucleus (SCN) in the brain of humans and other mammals.
Mechanisms of rhythm generation by SCN cells.
Circadian photoreceptors in the eye; melanopsin.
Melatonin and circadian timing.
Interaction of SCN with clocks in the retina and the pineal gland (melatonin).

Student Presentations of Recent Research Articles c.March 7th-14th

Peripheral oscillators in diverse mammalian tissues including:

Adrenal gland clock and corticosteroid rhythms as 'messengers of time'.
Clock in the heart (cardiomyocyte clock): relation to heart diseases.
Food entrainable oscillator: relation to diabetes, heart attacks etc.

Why clocks are everywhere and how they are coordinated together.
The emerging concept that networks of circadian clocks coordinate the timing of activities in diverse tissues by timing nervous activity and release of hormones.

IV. Human and Medical Implications.

Health problems resulting from ignoring your clocks.
Diseases related/caused by circadian defects: cancers, heart attacks, diabetes etc.
Jet-lag, shift-work.
Psychiatric disorders (depression etc), sleep disorders and 'SAD'.
'Night owls', 'larks' and natural clock mutations in humans.
City light pollution at night and cancers.
Self help techniques for surviving the 24/7 world: Use of melatonin and phototherapy.
Timing medications for effectiveness; 'Chronopharmacology'.
Circadian rhythms and cancer; roles in both cause and treatment.

Final exam in exam period April 8-24 (on whole course)