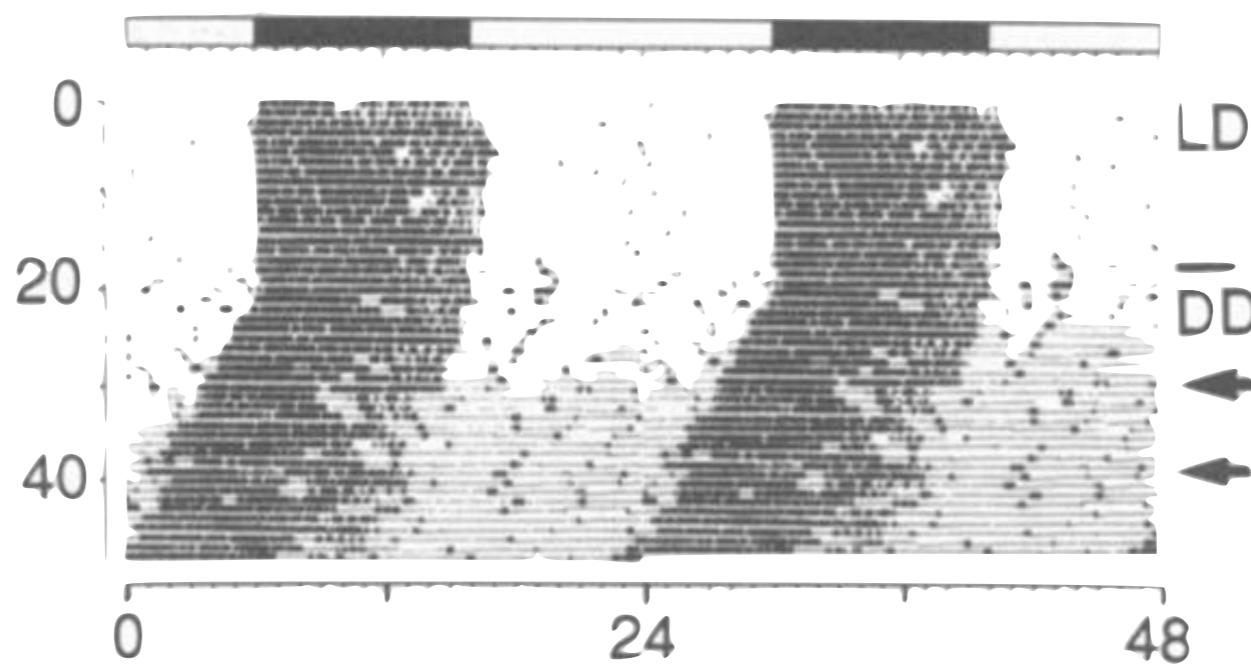
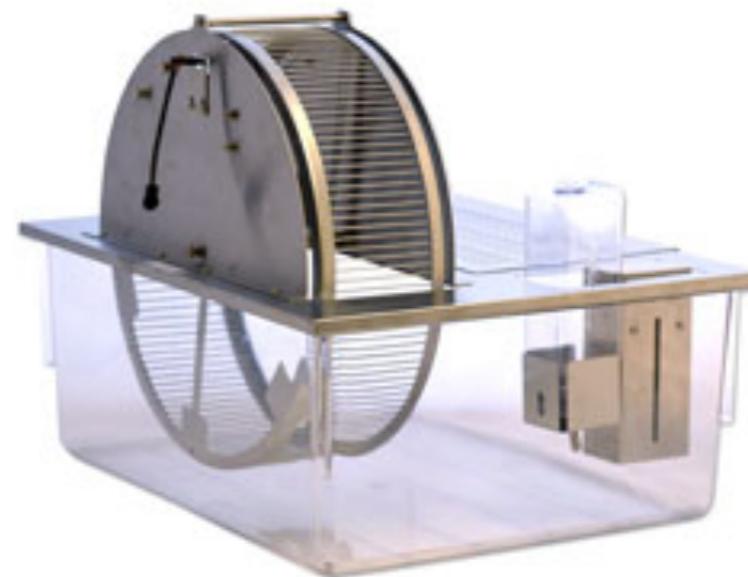
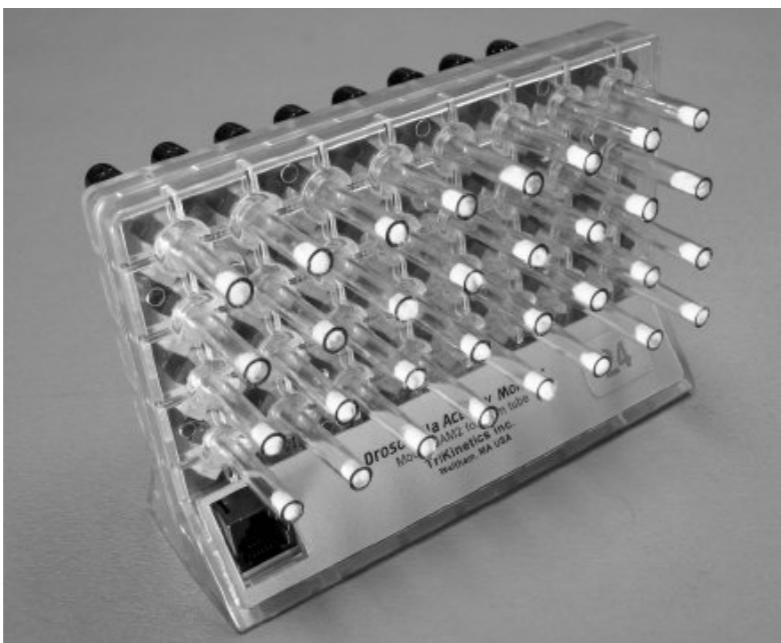
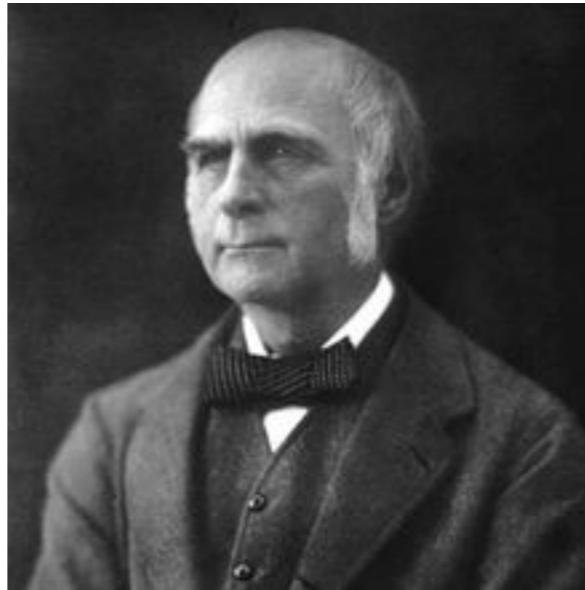


# Bio393: Genetic Analysis

## Behavioral genetics



# **Behavioral genetics is the study of the genes that determine and/or control behavior**

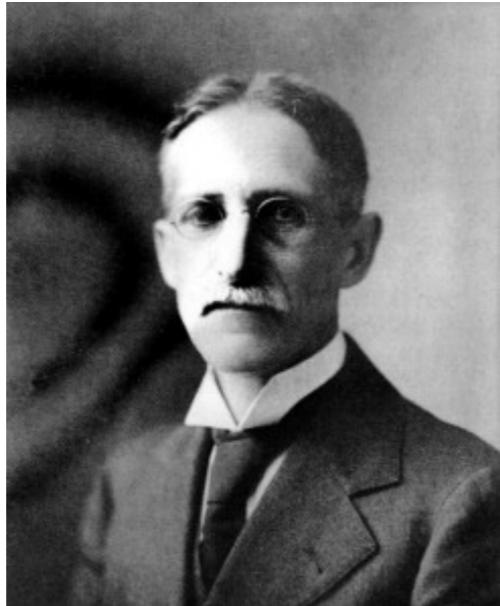


Francis Galton

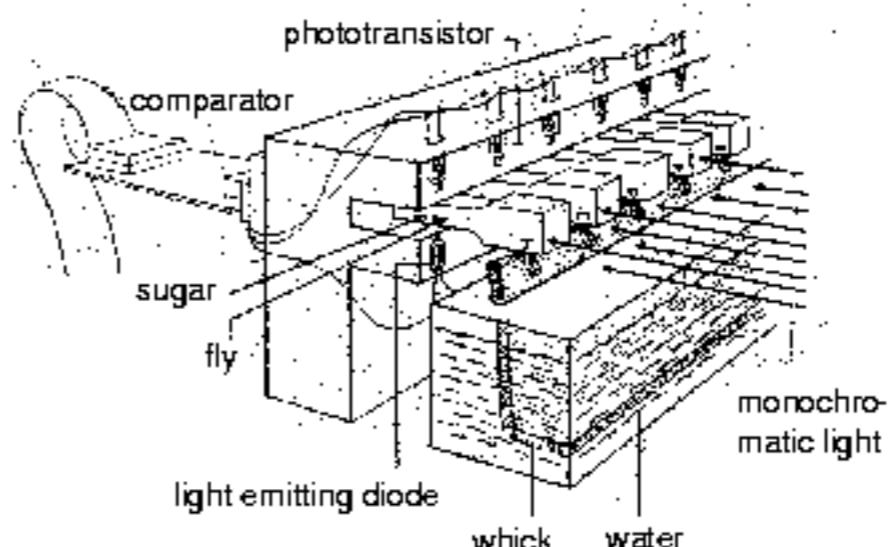
Intellectual abilities have a heritable component  
(in the English upper-class)

Early motivation for eugenics

# Behavioral genetics didn't get well formulated until *Drosophila*



William Castle



Fly geotropism

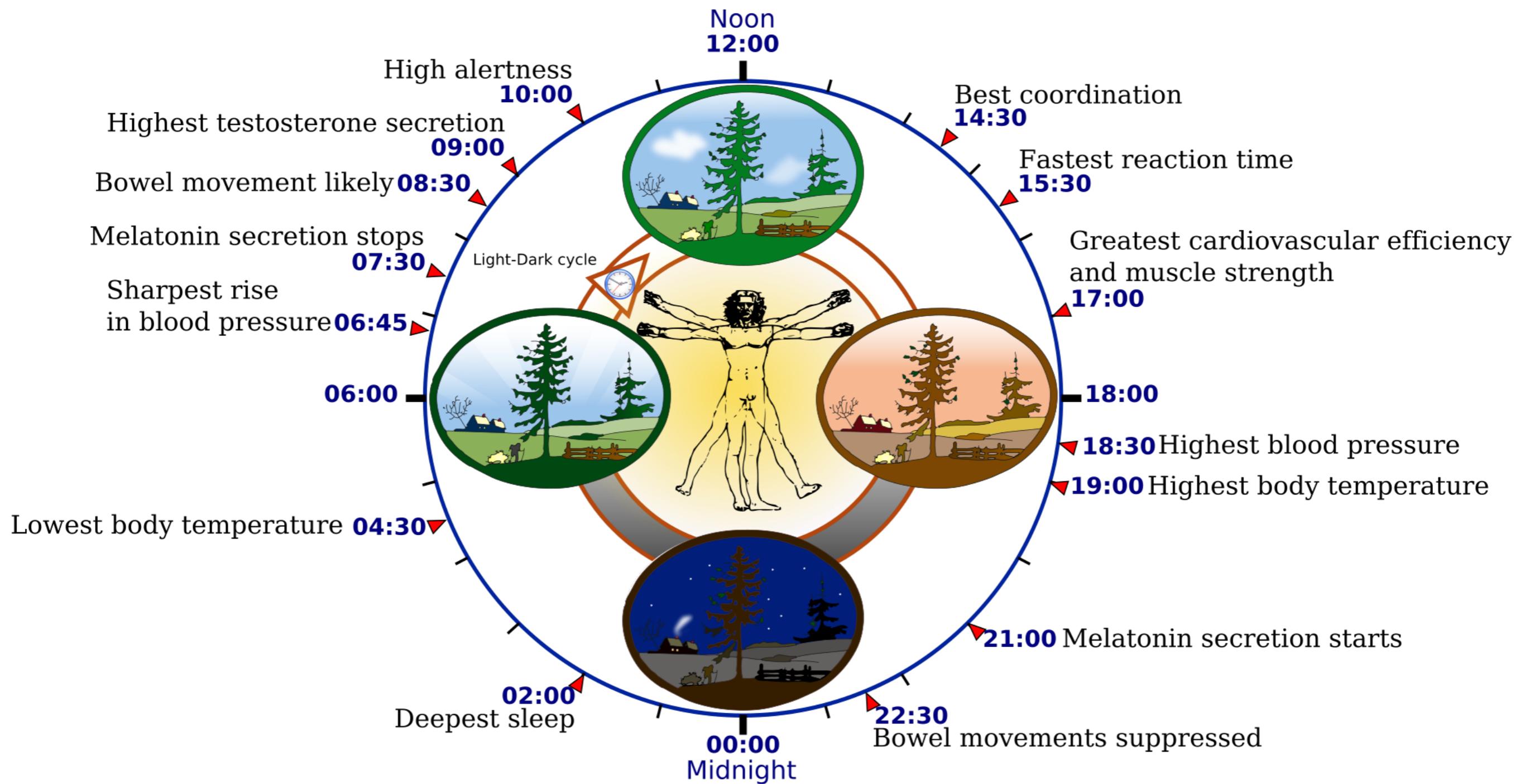


Theodore Dobzhansky

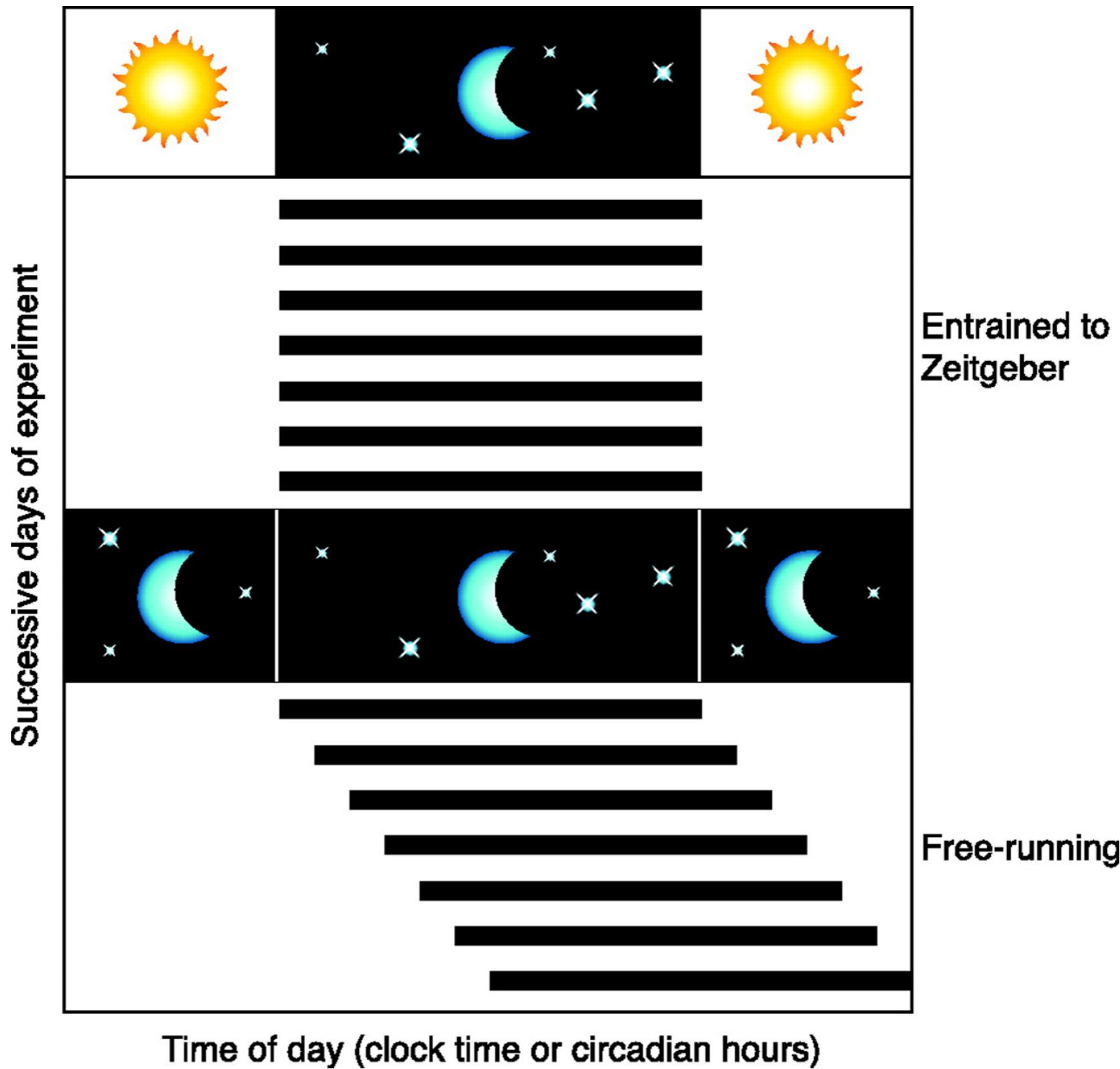


Fly mating

# Nearly all organisms have a natural cycle of activity



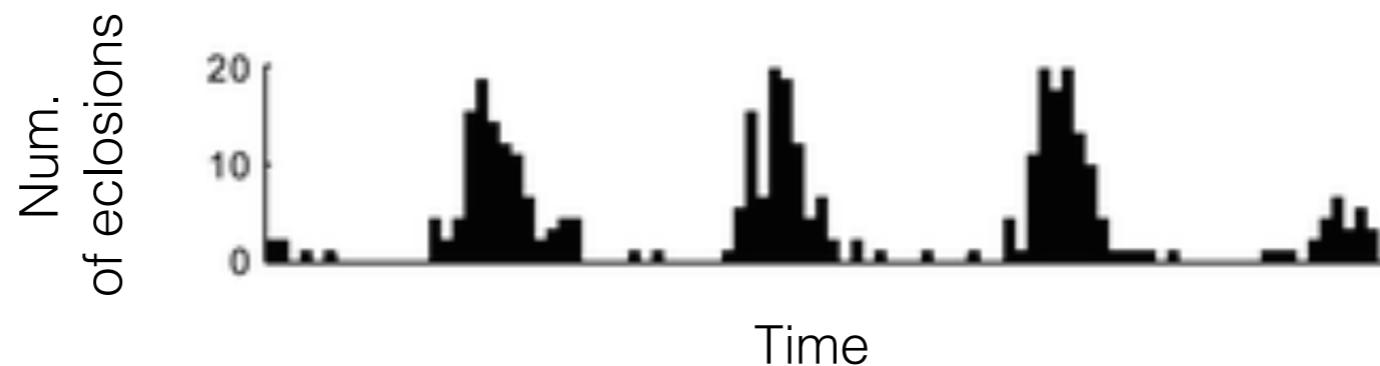
# Light and/or temperature can entrain the cycle





# Seymour Benzer

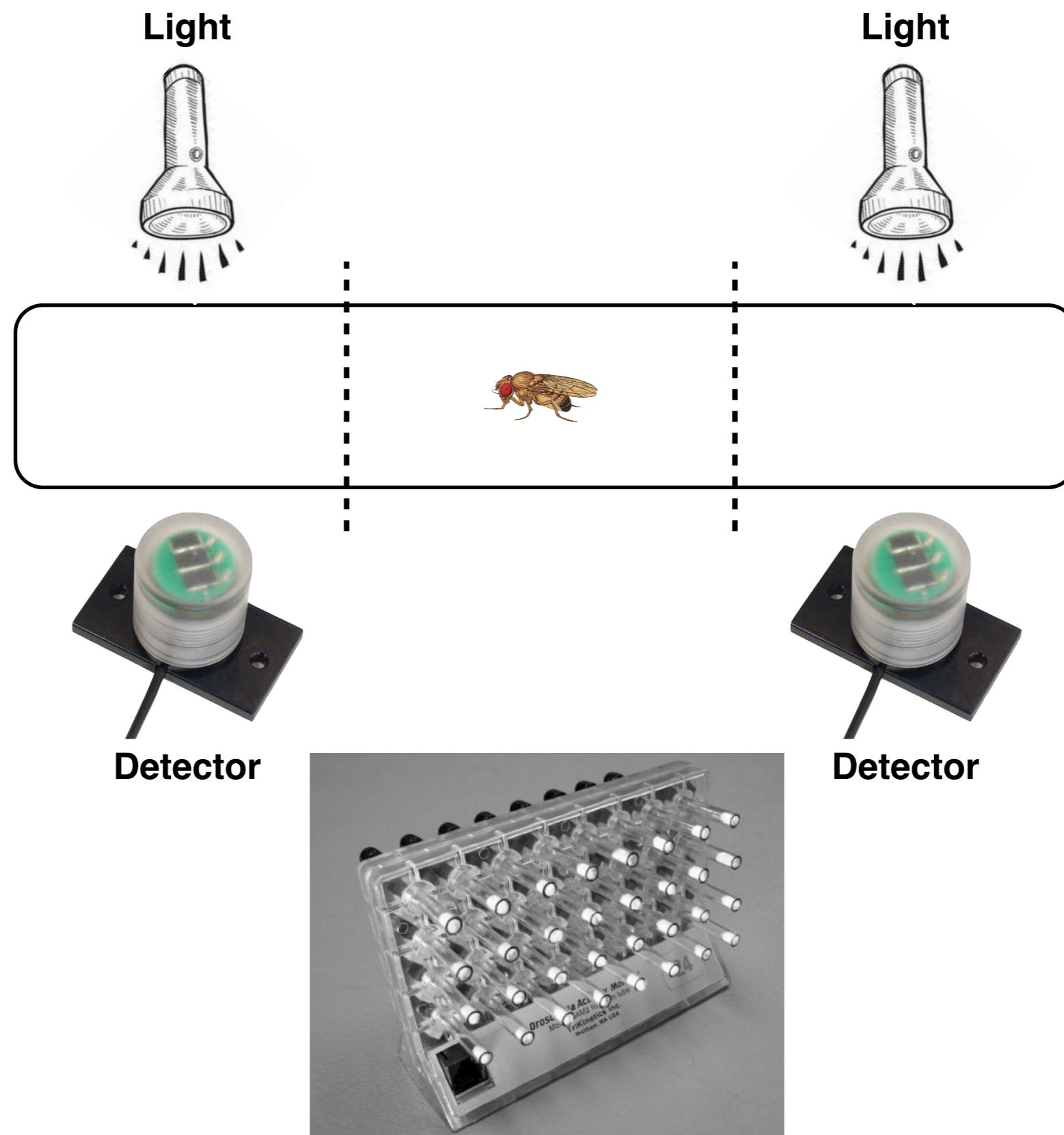
# *Drosophila* eclose from the pupal case with a reproducible cycle



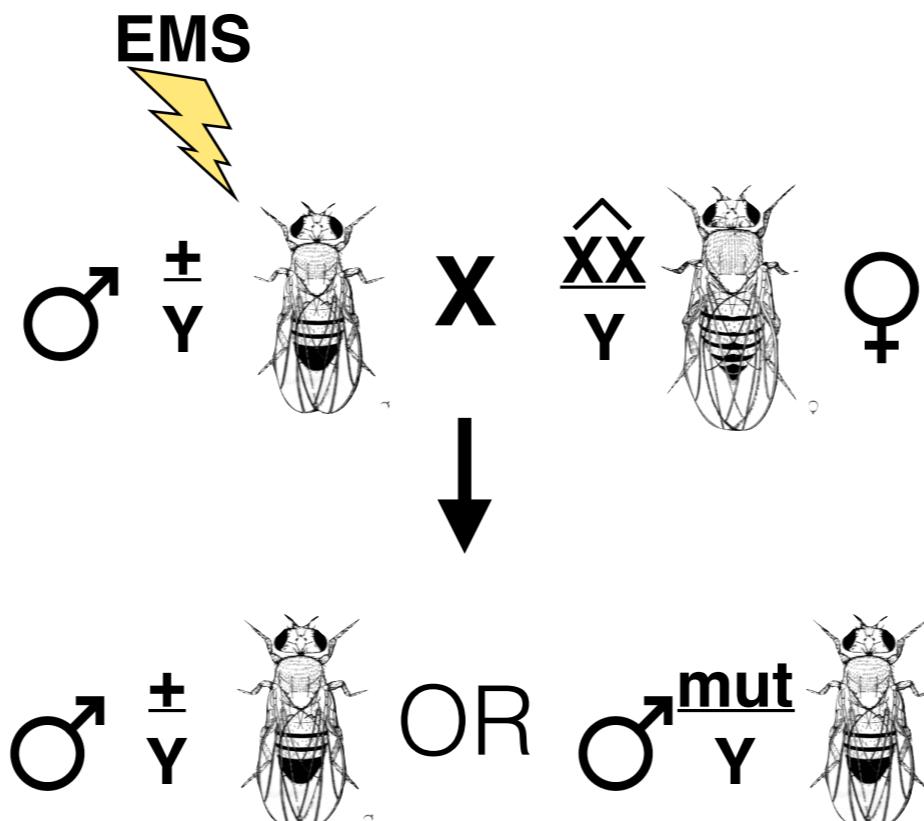
Difficult assay  
You need to watch the flies a lot of the time



# *Drosophila* movement cycles and is much easier to score



# The first genetic screen for behavioral mutants

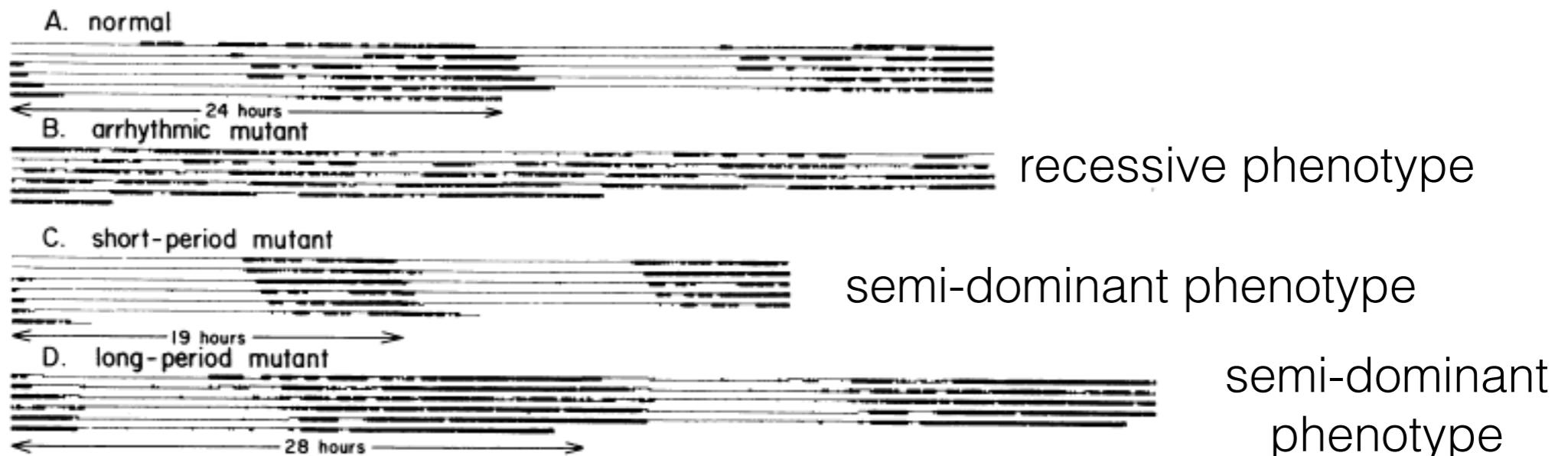


	$\frac{\hat{X}X}{Y}$	Y
X	$\frac{\hat{X}XX}{Y}$ dead	$\frac{XY}{Y}$ ♂
Y	$\frac{\hat{X}XY}{Y}$ ♀	$\frac{YY}{Y}$ dead

Screened 2,000 males

got three mutants  
that affected all cyclic behaviors

# *period* mutants



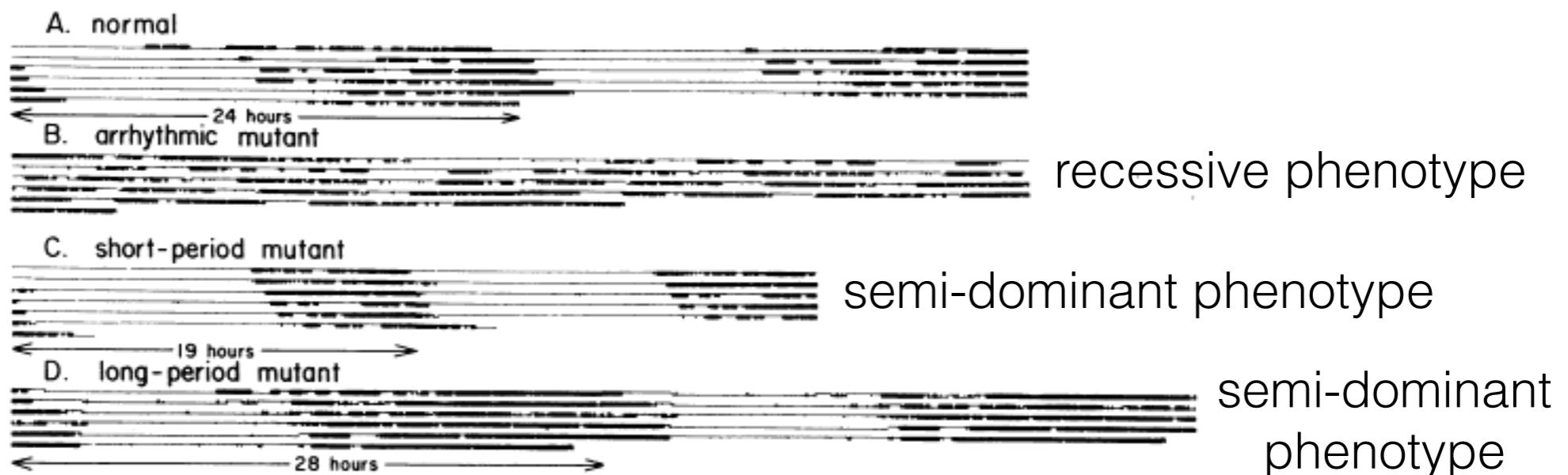
All three mutations mapped to the same place  
on the X chromosome

arrhythmic       $\triangleright$       arrhythmic  
arrhythmic    +

short       $\triangleright$        $\pm$   
+    +

long       $\triangleright$        $\pm$   
+    +

# *period* mutants

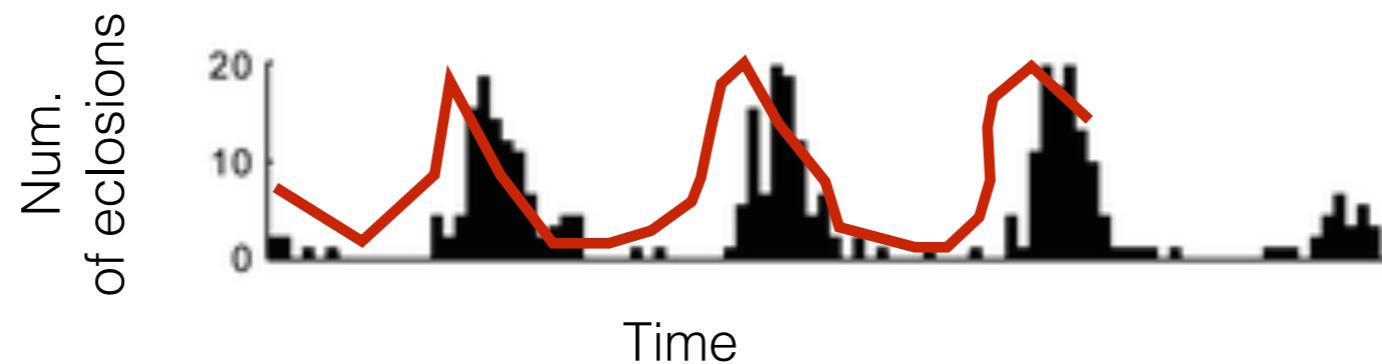


arrhythmic = arrhythmic  
arrhythmic      deficiency

**short phenotype**    short = short = short > short > ±  
                      short      deficiency      arrhythmic      +      +

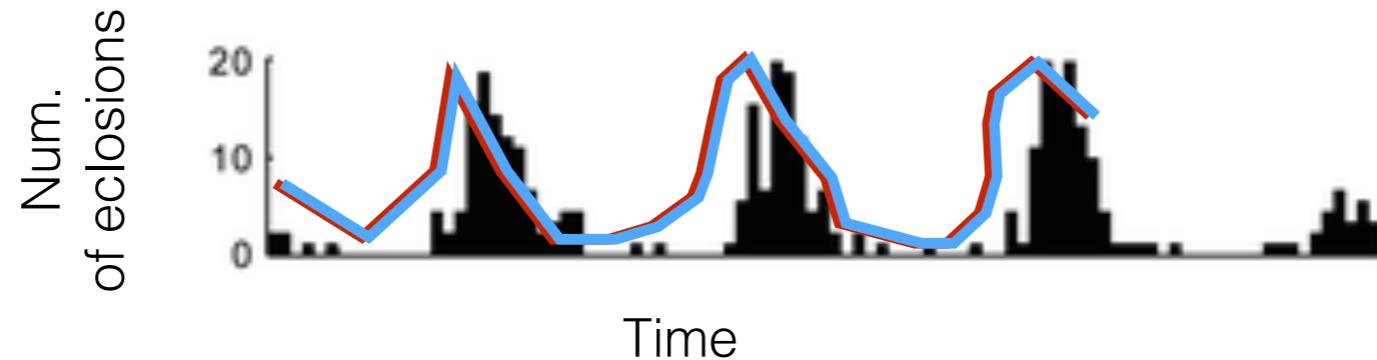
**long phenotype**    long = long = long > long > ±  
                      long      deficiency      arrhythmic      +      +

*period* encoded a novel protein at the time



*period* transcription and translation cycles

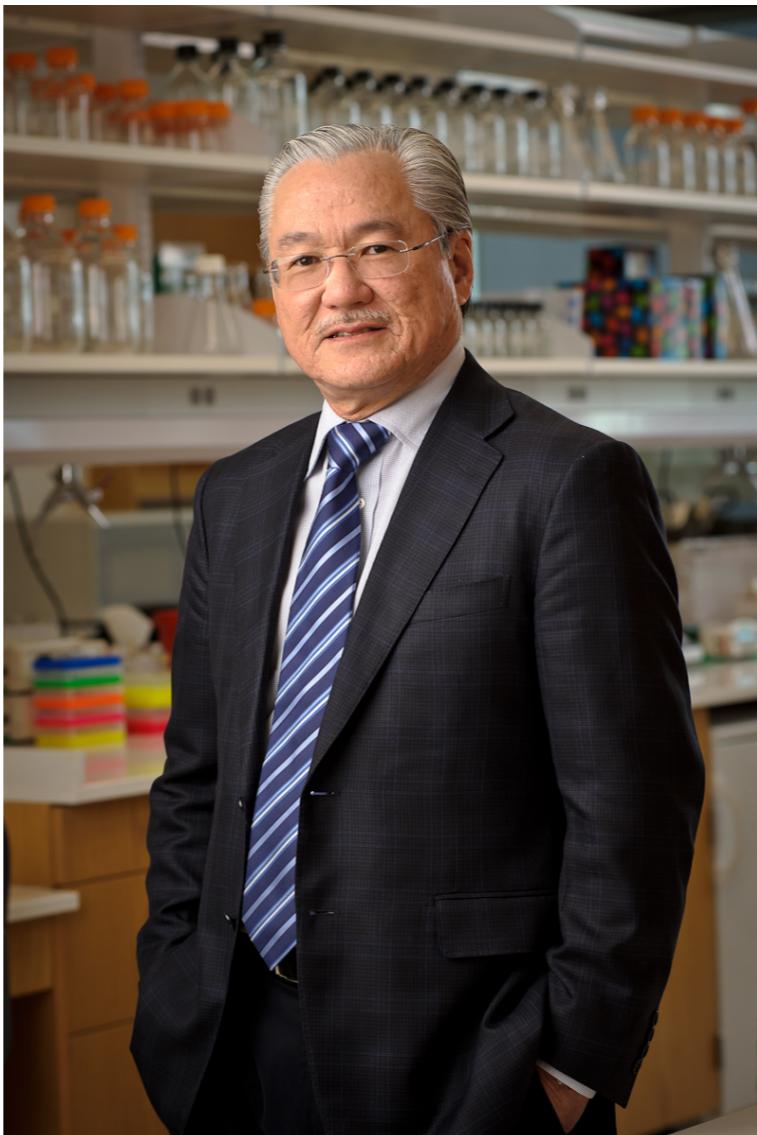
# Another genetic screen with a focus on chromosome 2 found the gene *timeless*



*period* transcription and translation cycles

*timeless* transcription and translation cycles

Period Timeless

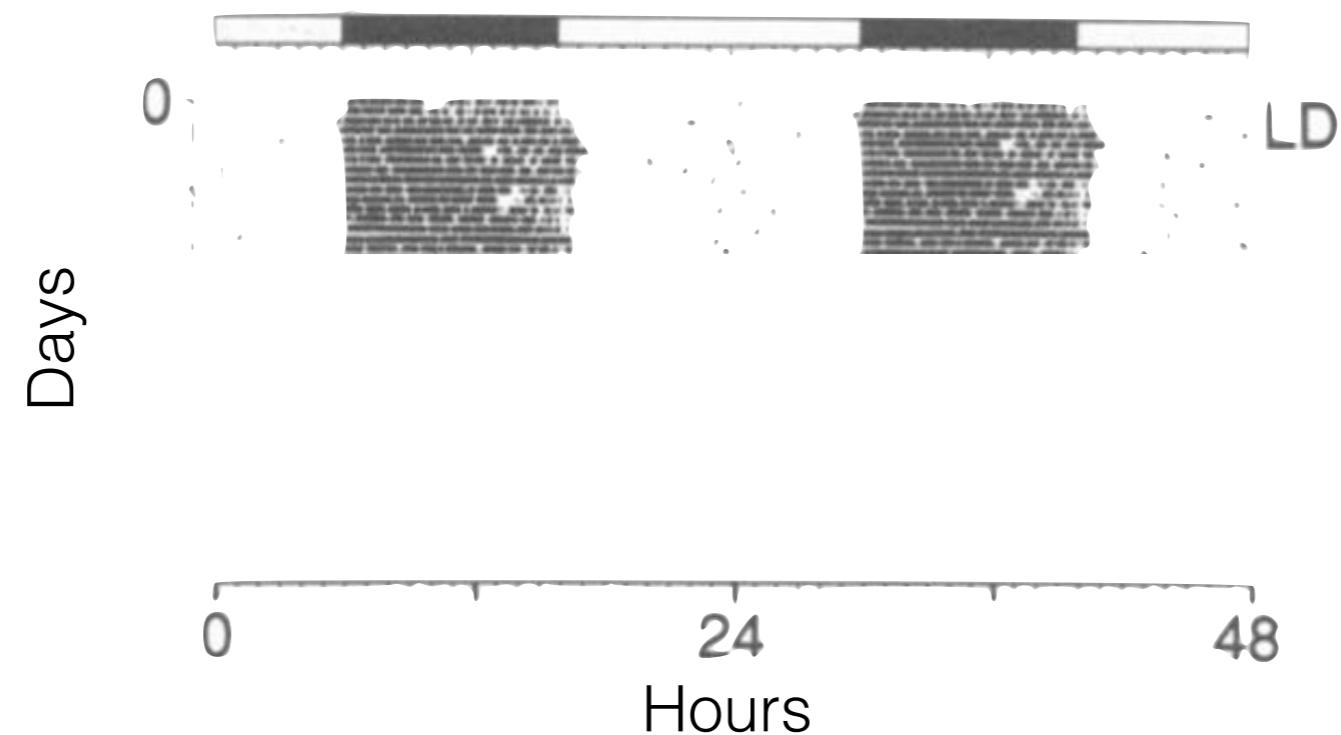


**Joe Takahashi**

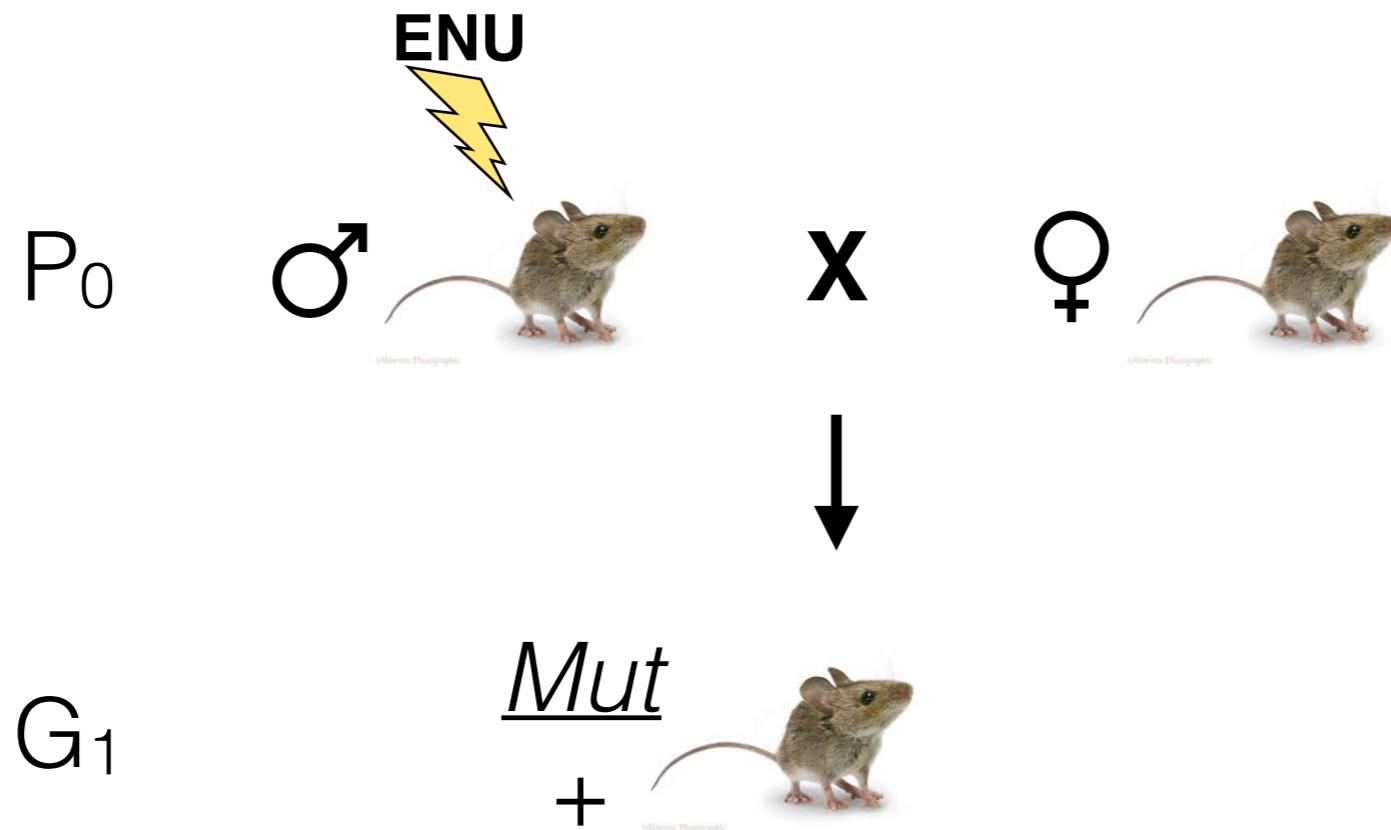
# Mice love to run at night



© Warren Photographic



# Circadian rhythm screen

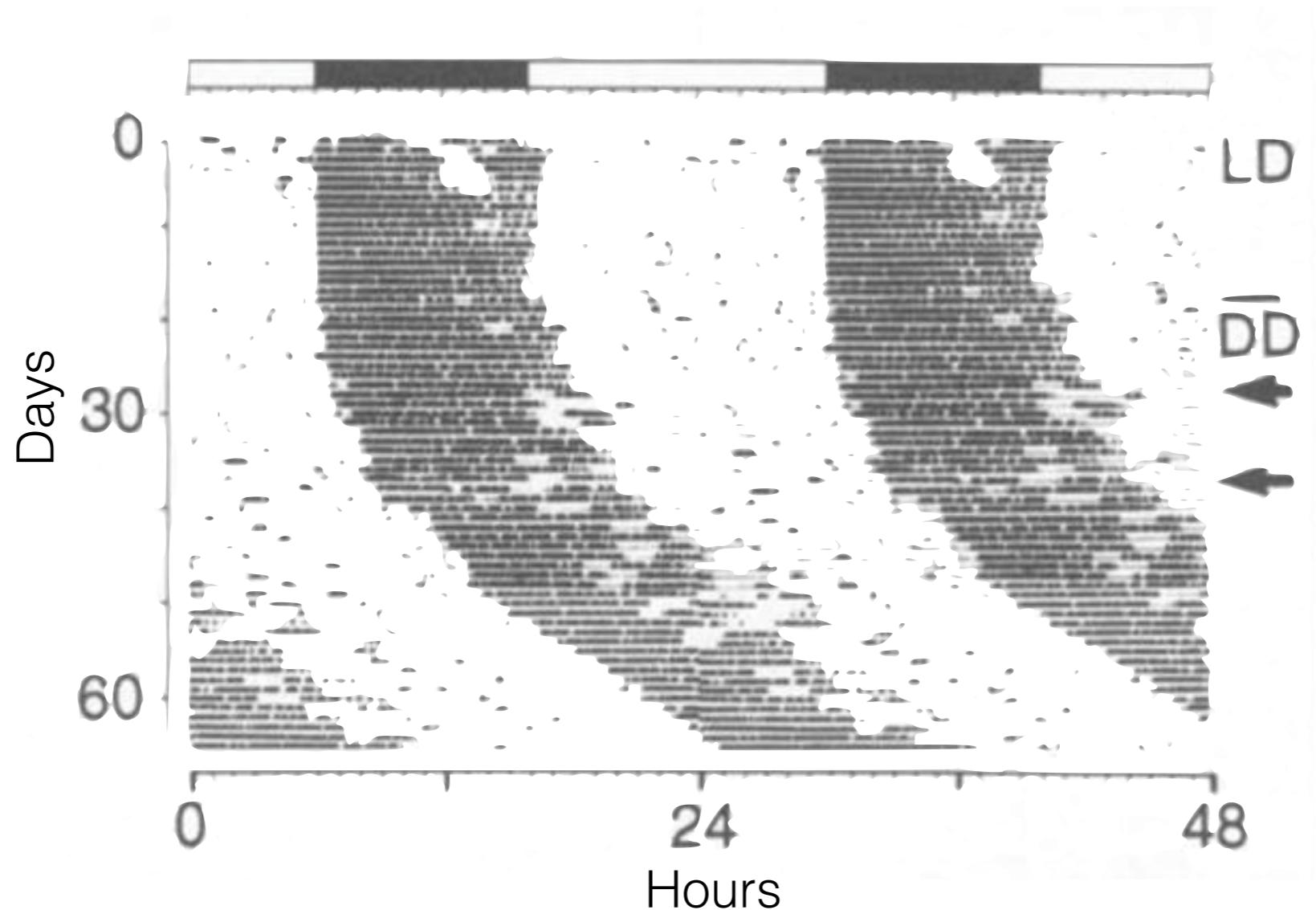


304 mutant mice screened

1 mutant with 24.7 hour clock  
(WT = 23.8 hour clock)

Autosomal dominant

# ***Clock* mutants have lengthened cycles and go arrhythmic without light entrainment**

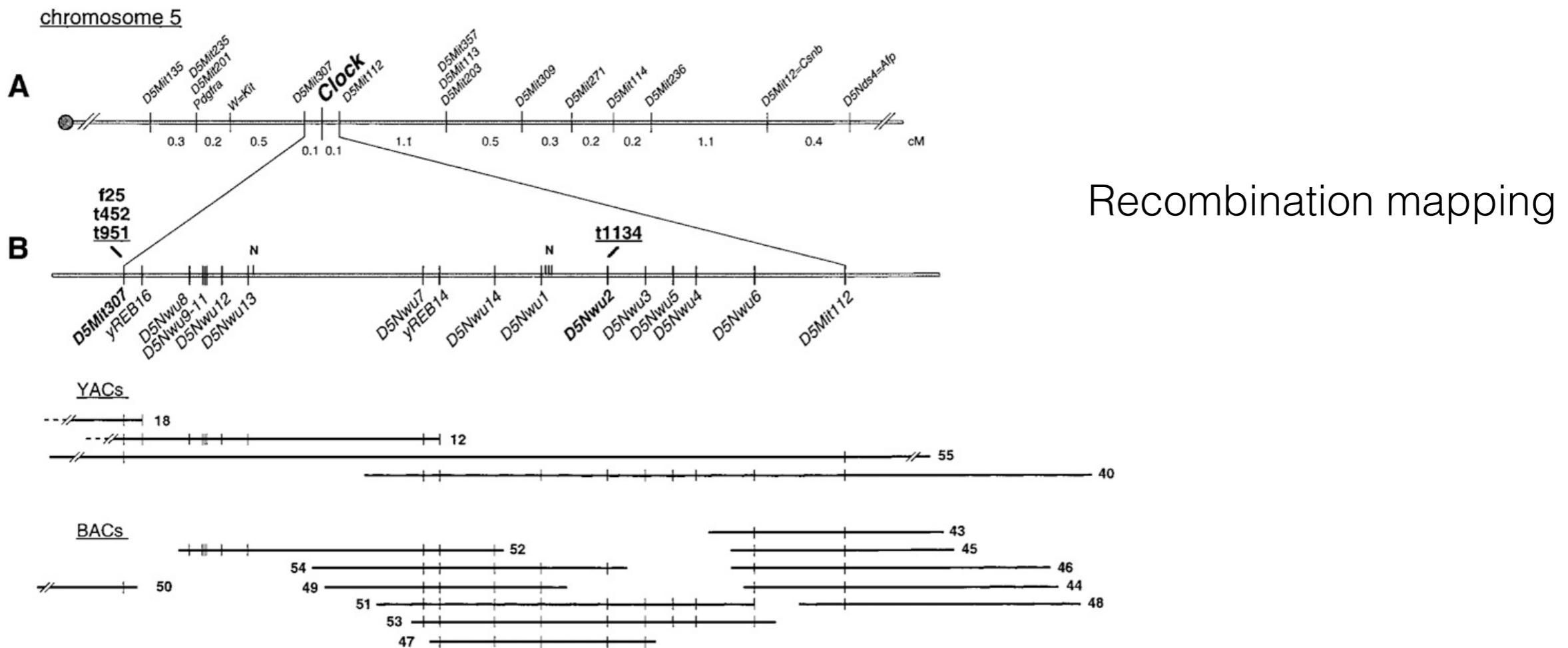


*Clock* = circadian locomotor output cycles kaput

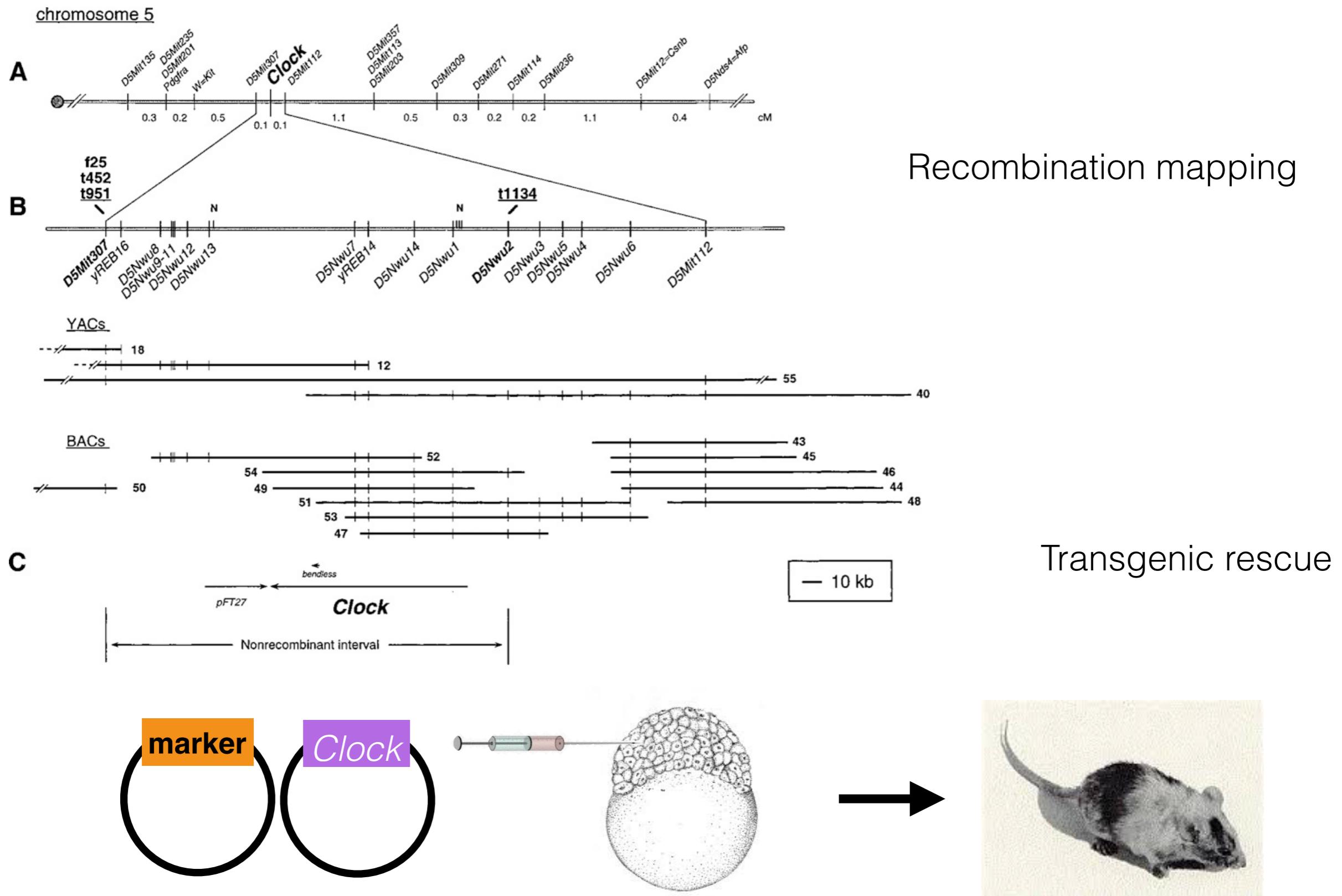
# ***Clock* mutants have a semi-dominant phenotype**

<u><i>Clock</i></u> <i>Clock</i>	<u><i>Clock</i></u> Deficiency	<u><i>Clock</i></u> +	$\frac{+}{+}$	$\frac{+}{+}$ Deficiency
27.3 hr	27.0 hr	24.7 hr	23.8 hr	23.8 hr

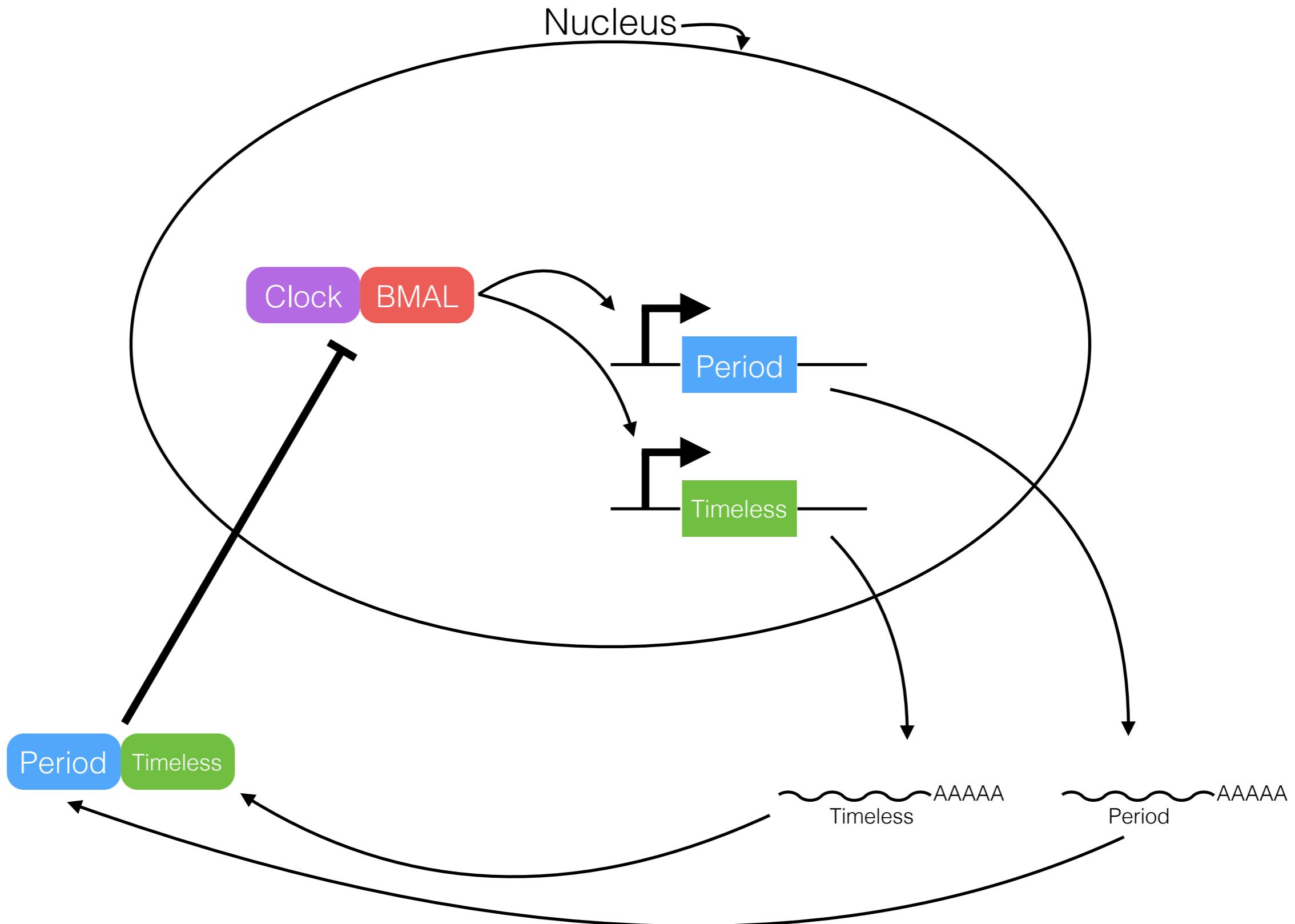
# ***Clock* was cloned and encodes a transcription factor**



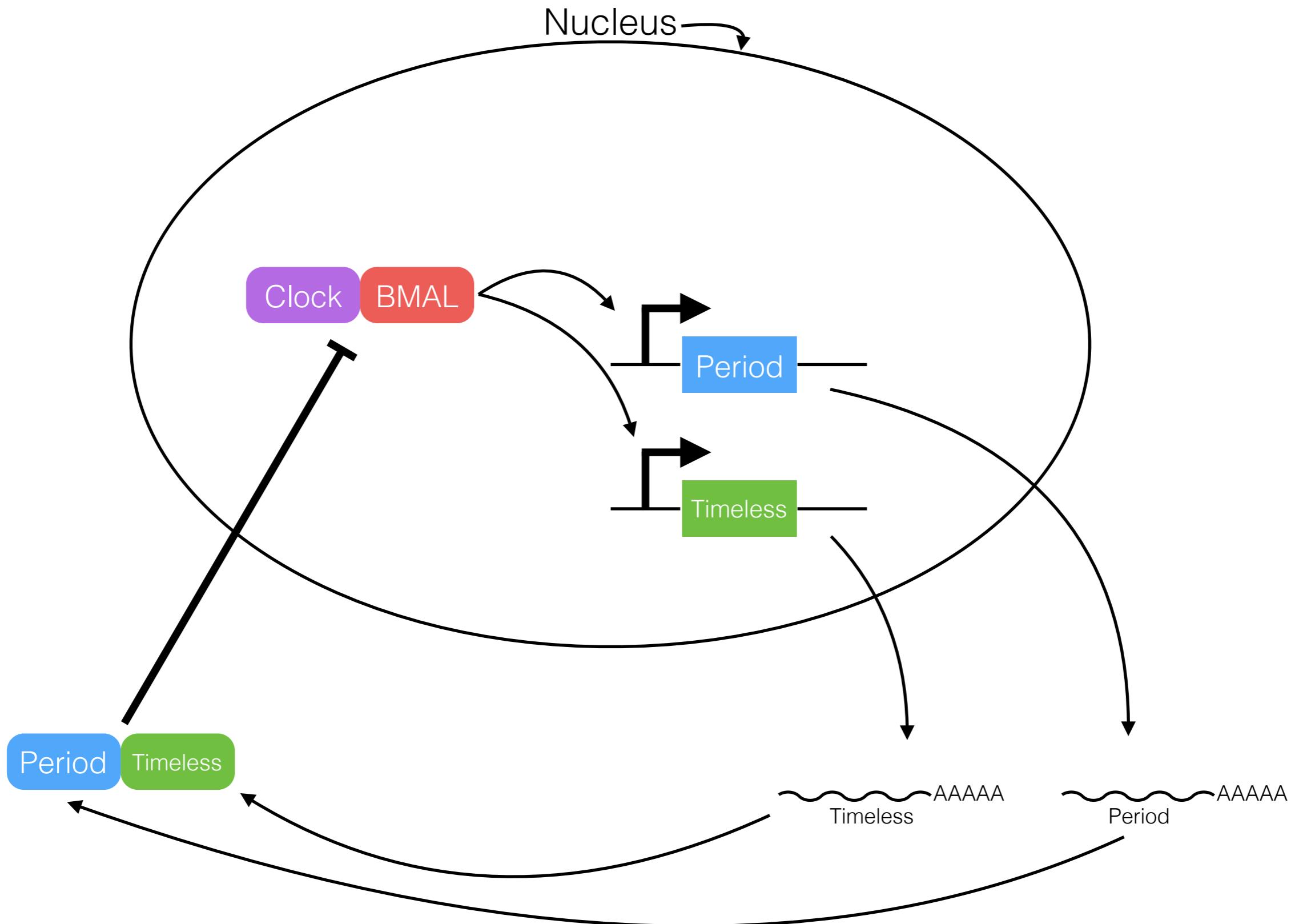
# *Clock* was cloned and encodes a transcription factor



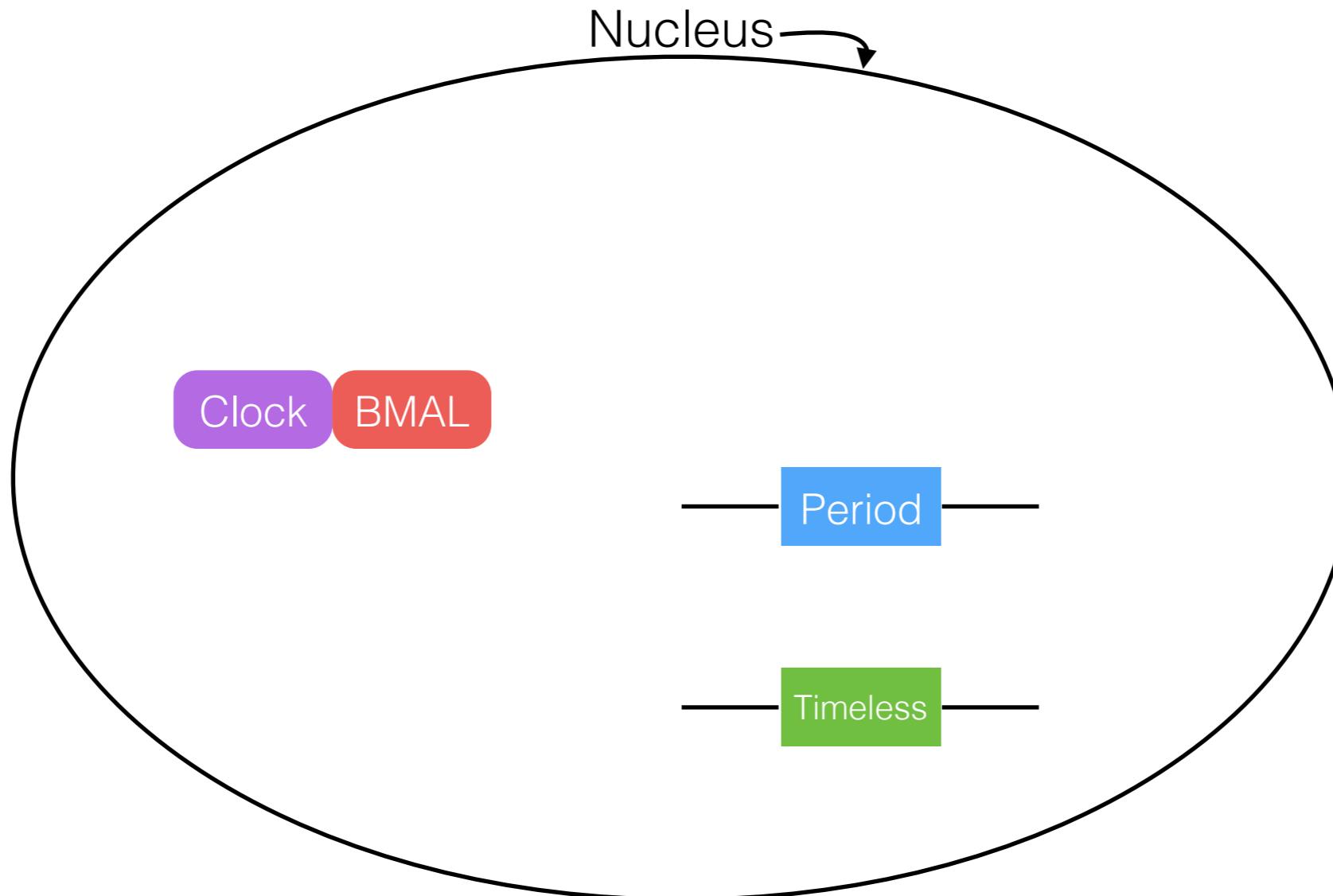
# A simplified model of the circadian clock



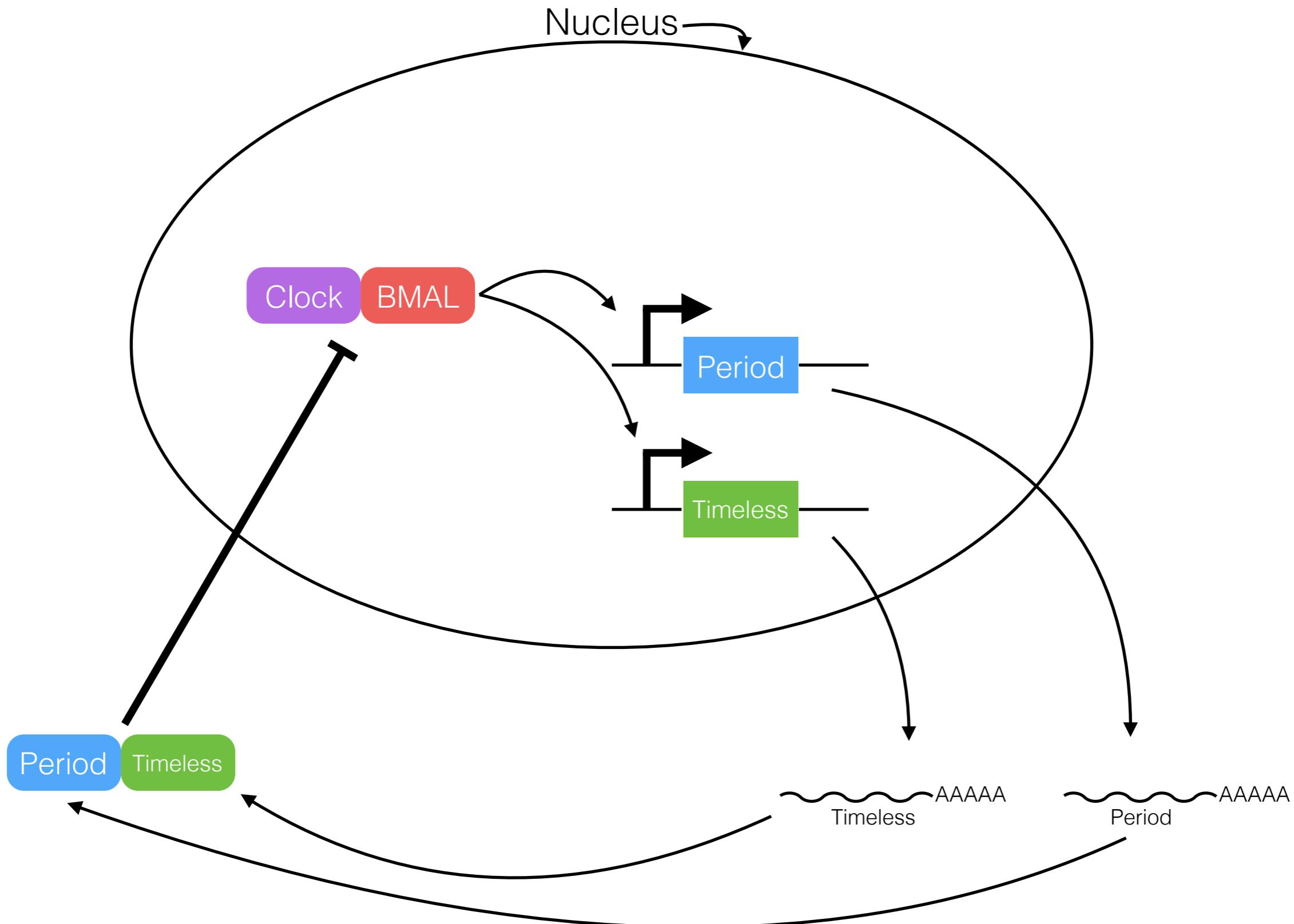
# A simplified model of the circadian clock



# A simplified model of the circadian clock

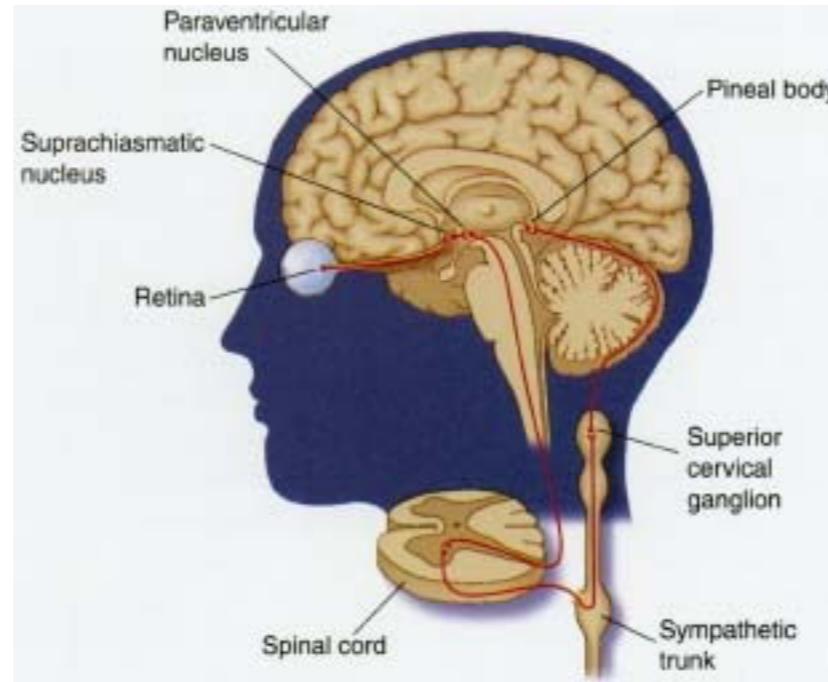


# A simplified model of the circadian clock



How do you think light entrains the system?

# In humans, the suprachiasmatic nucleus regulates sleep and wakefulness



Do blind people have circadian cycles?

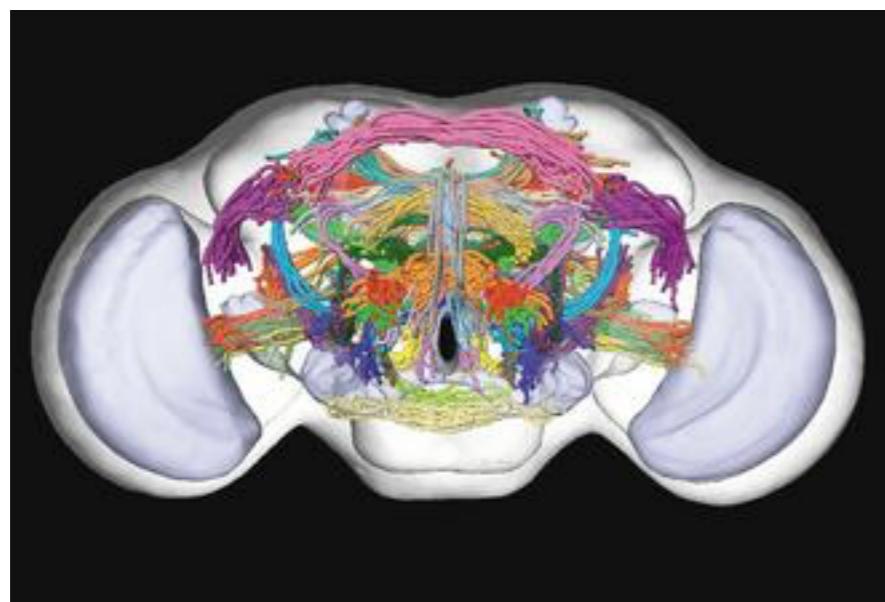
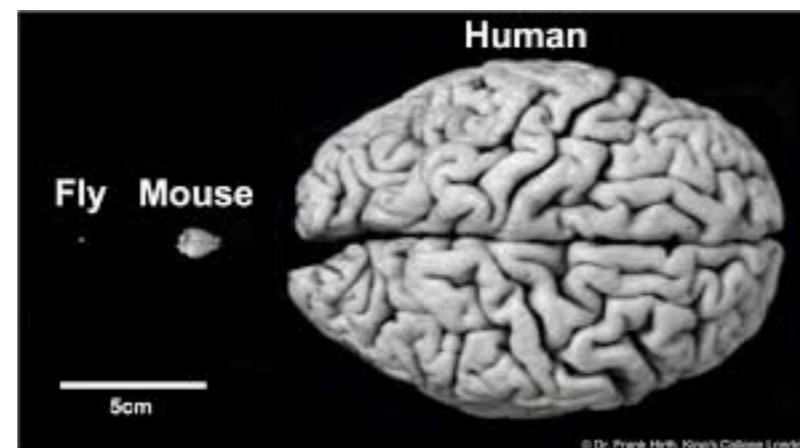
# Using narcoleptic dogs, researchers found the gene underlying narcolepsy



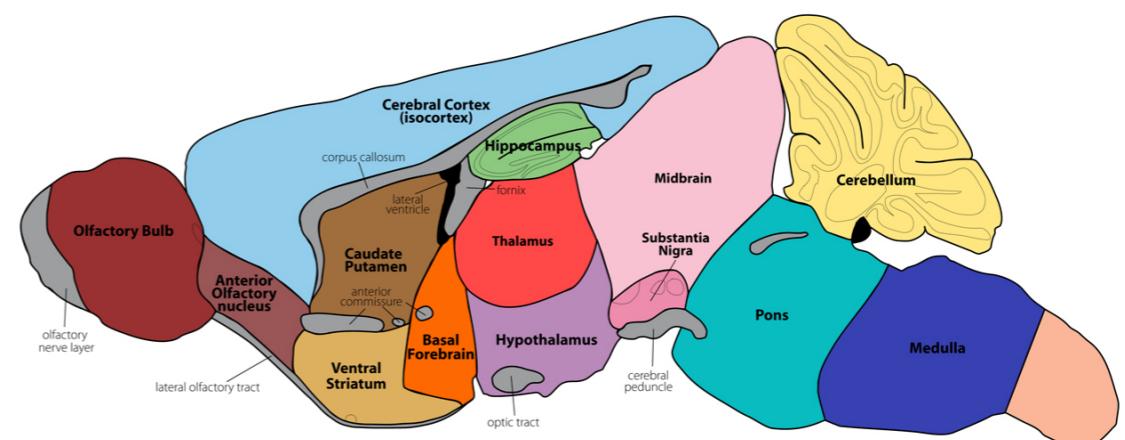
How?

No genetic screens,  
no balancers,  
small numbers of offspring

# Gene products act in neurons and neuronal circuits

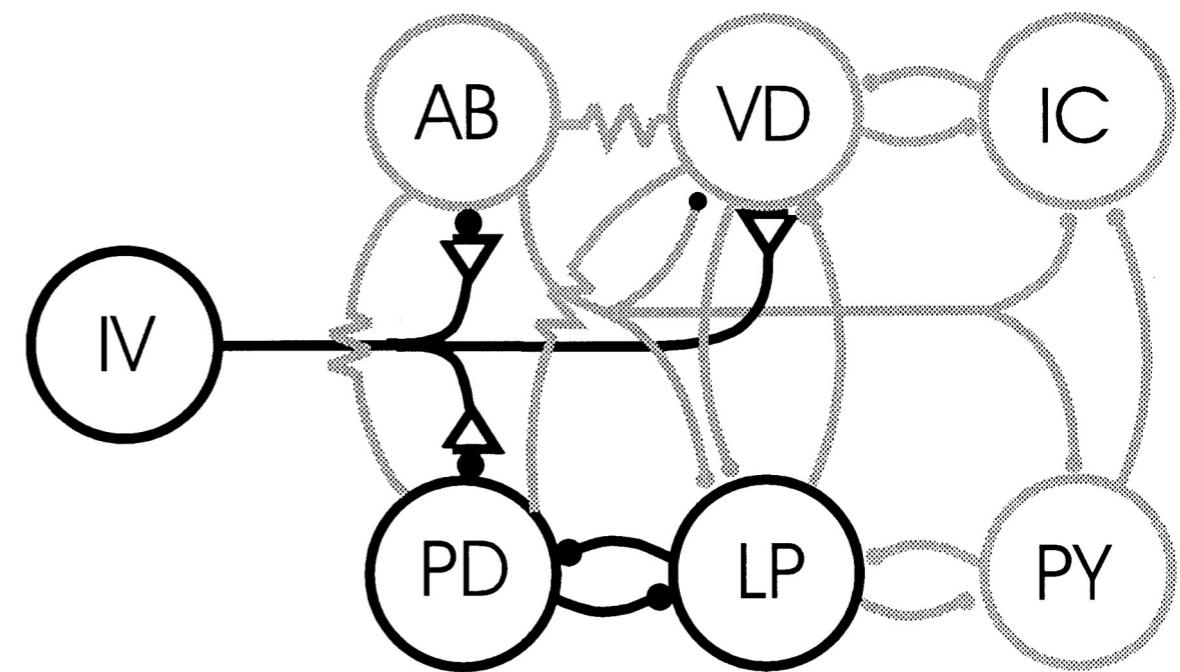
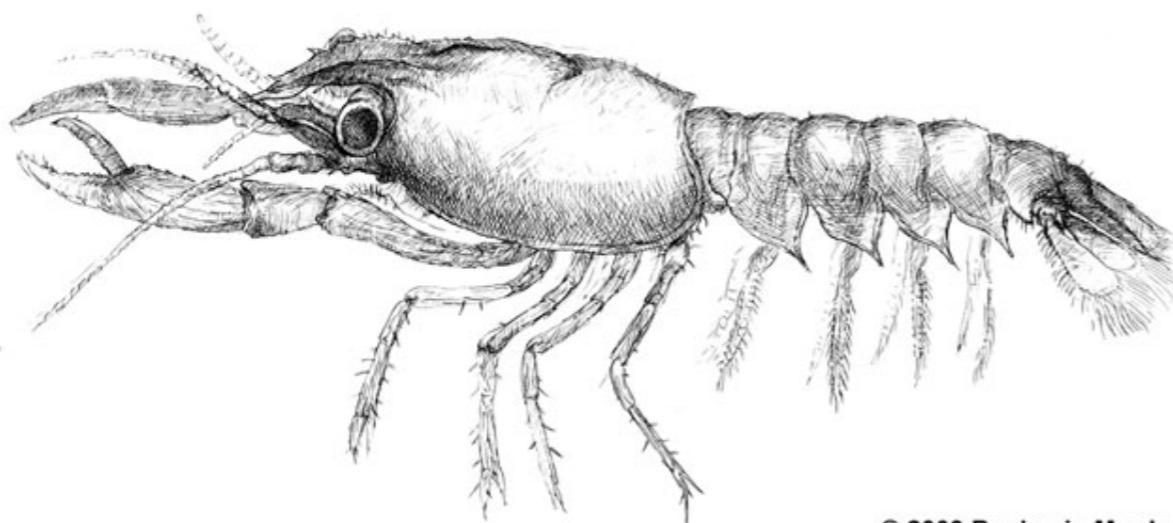


*Drosophila* brain



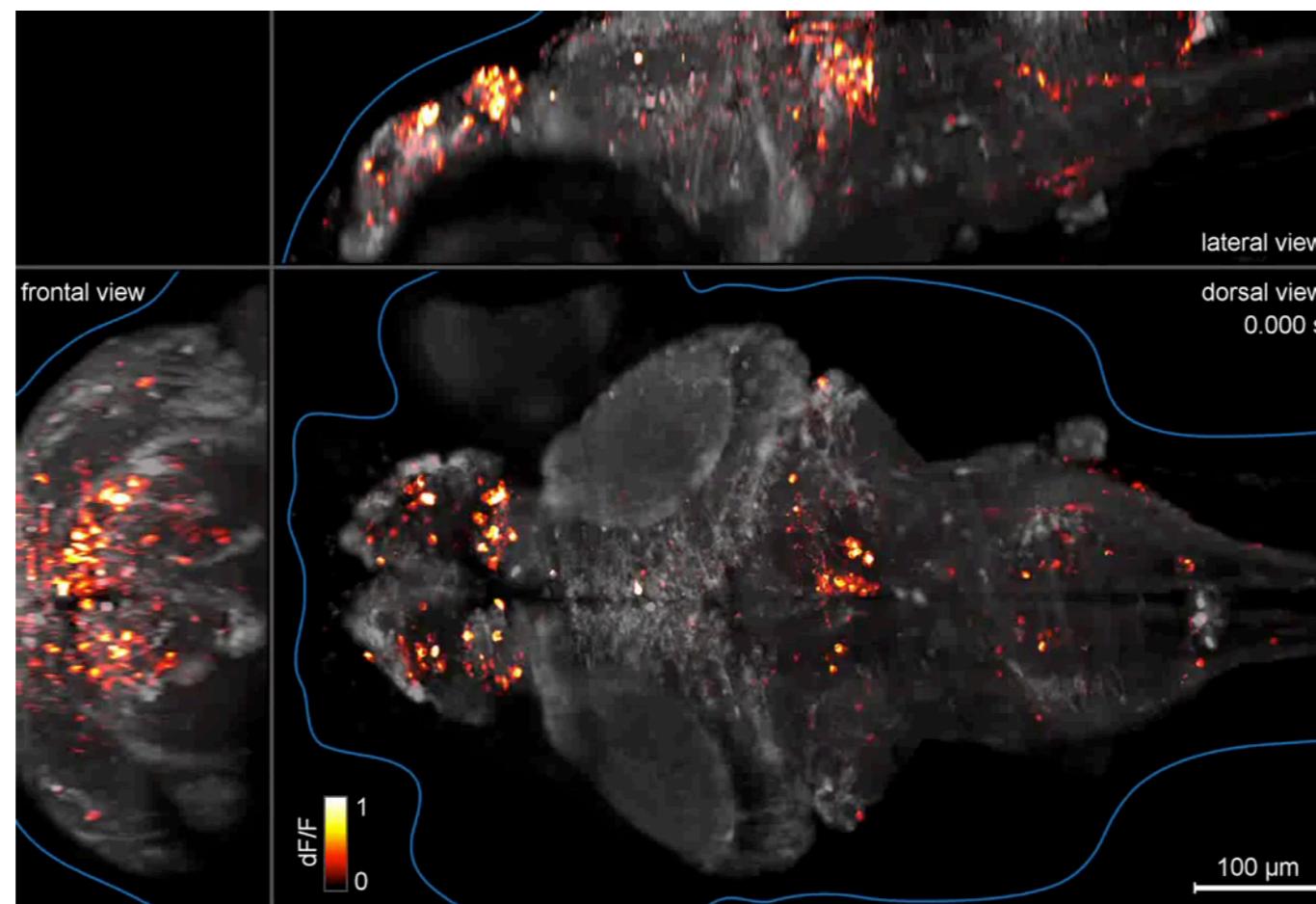
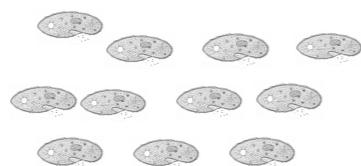
Mouse brain

# The activities of neurons AND their connections regulate behavior

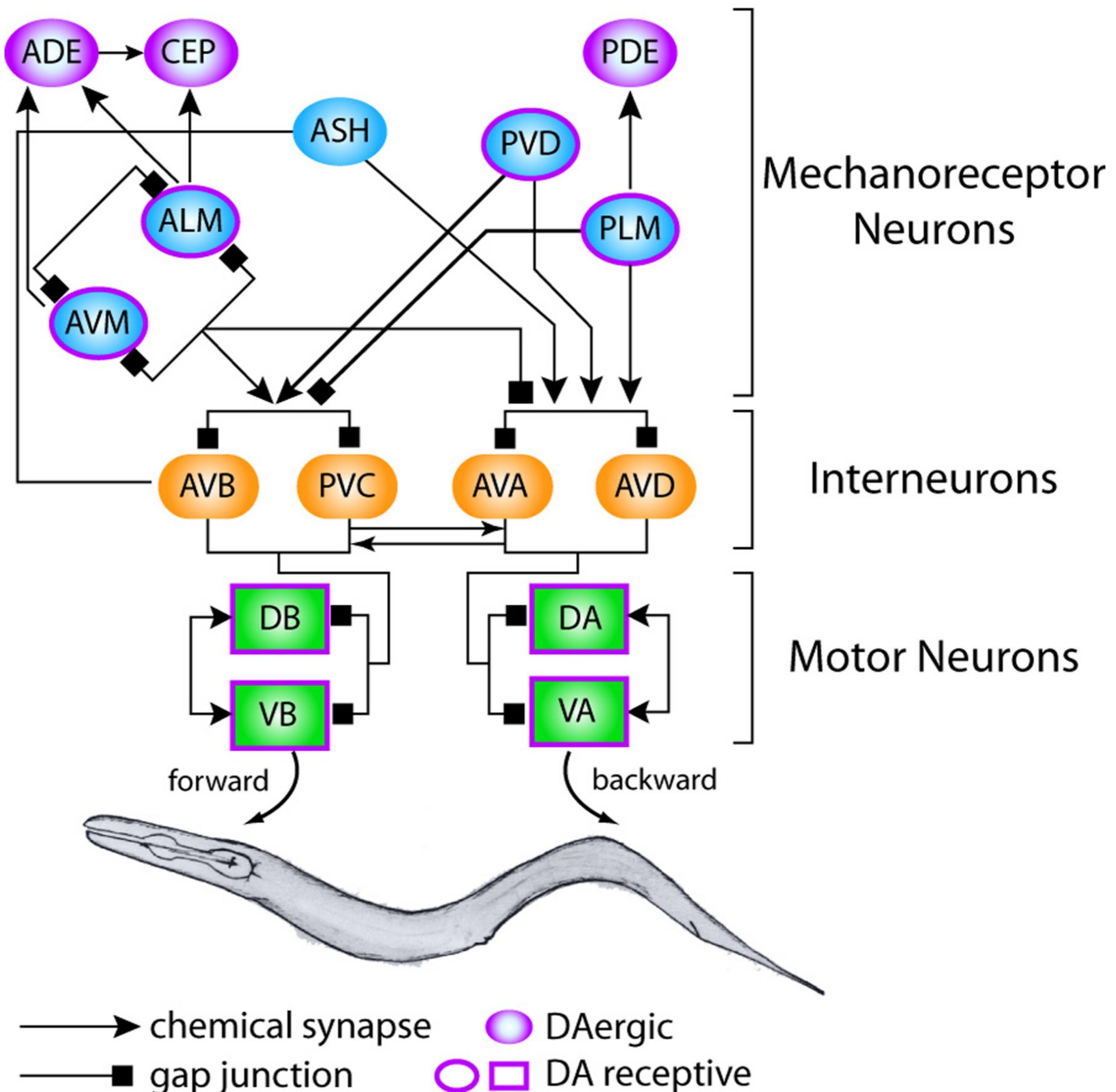


When neurons are active,  
intracellular calcium concentration increases

# Genetically encoded calcium indicators show neuronal activity



# Using cell lineage, genetics, and calcium indicators, we can build neuronal circuits for behavior



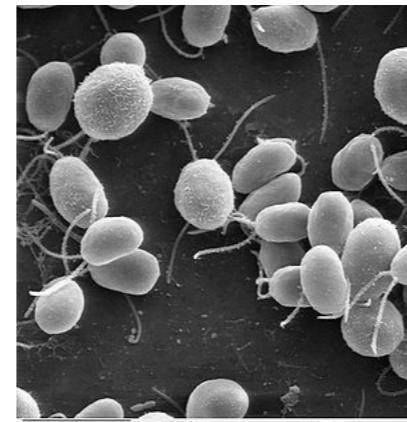
# What if you want to turn neurons ON or OFF at will?



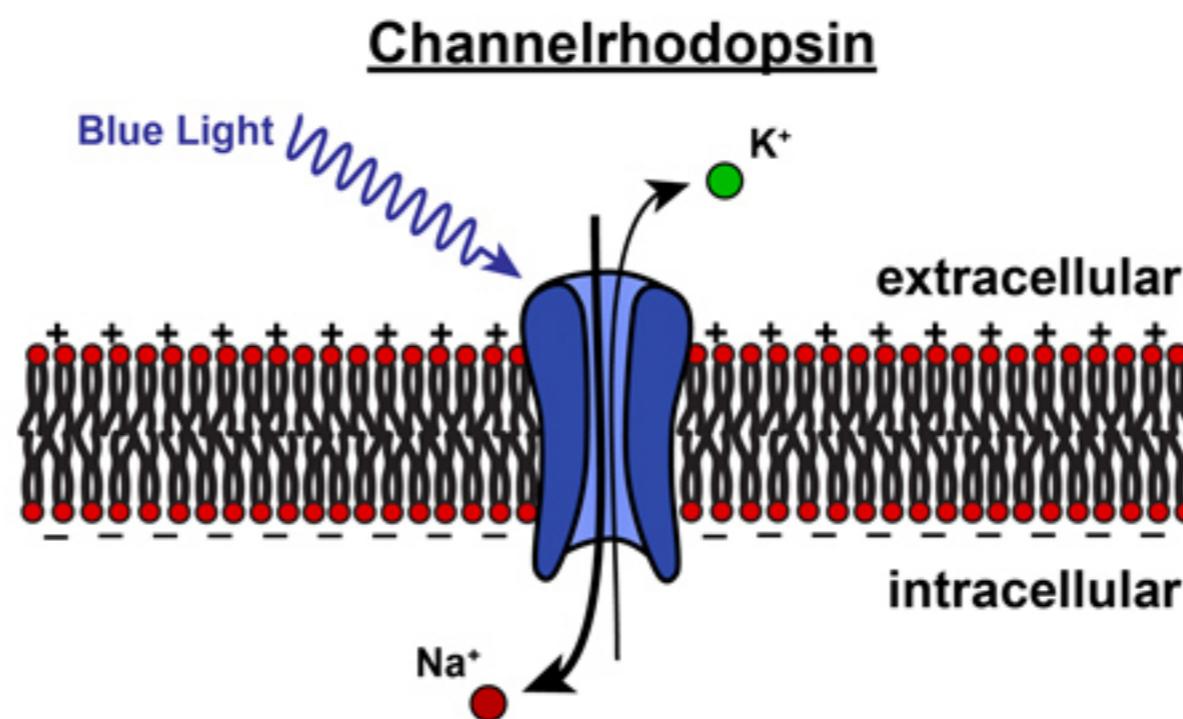
Karl Deisseroth

# What if you want to turn neurons ON or OFF at will?

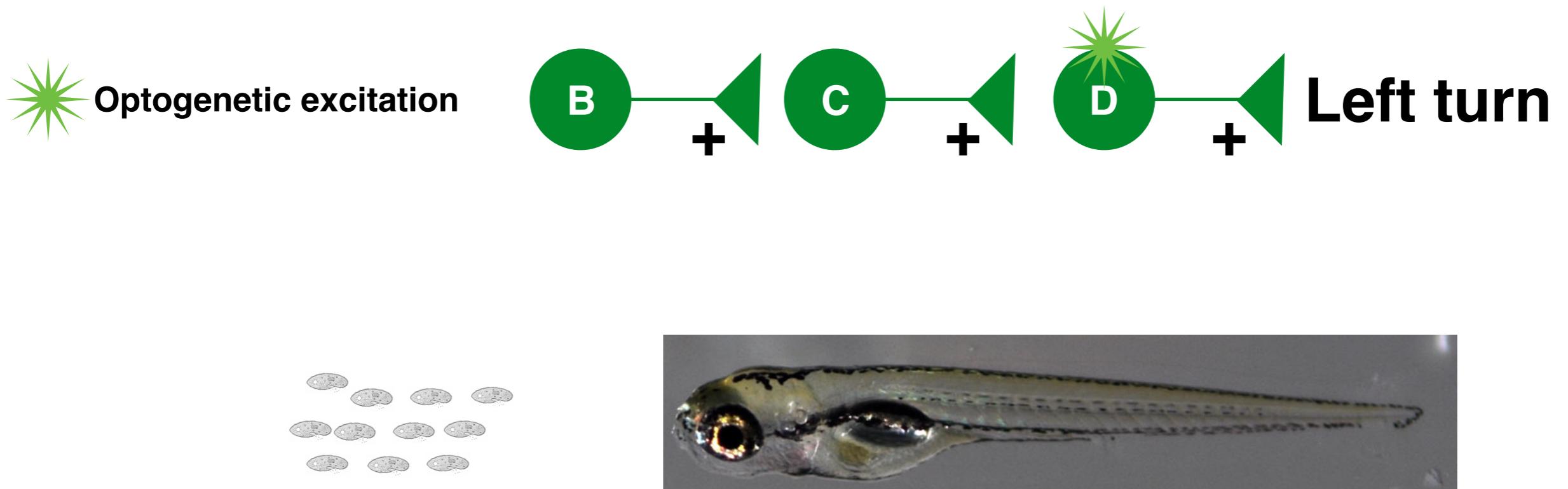
Channelrhodopsin for turning cells ON



*Chlamydomonas reinhardtii*



# Ontogenetic control of neuronal activity



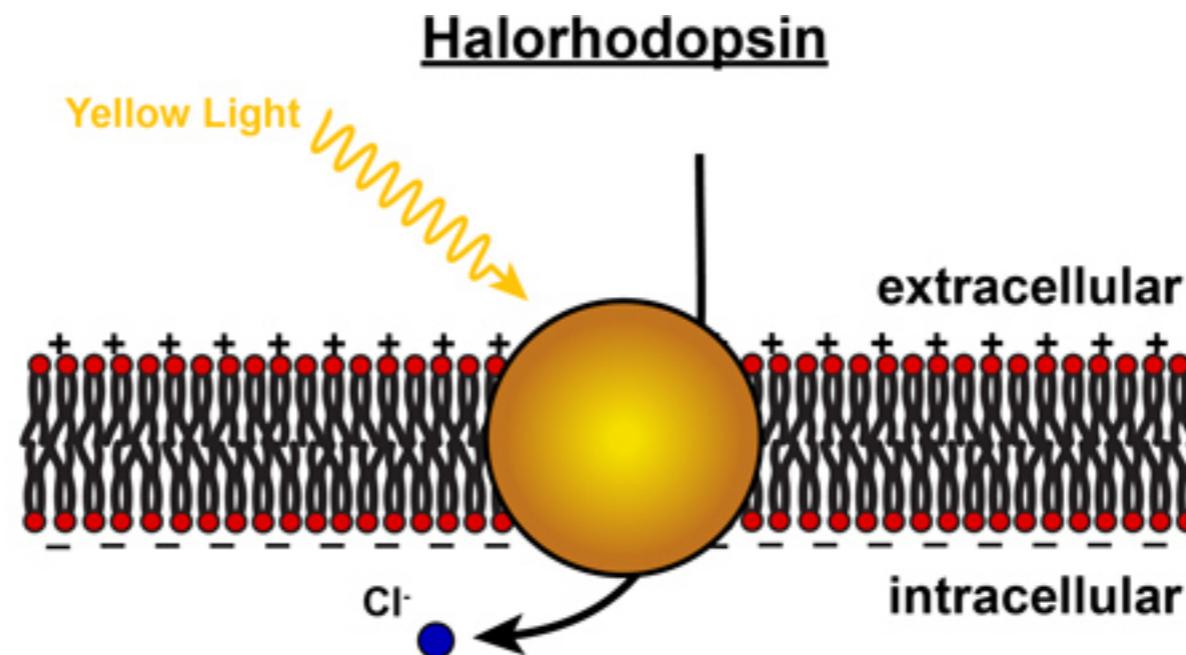
Sodium ions polarize neurons and activate them

# What if you want to turn neurons ON or OFF at will?

Halorhodopsin for turning cells OFF



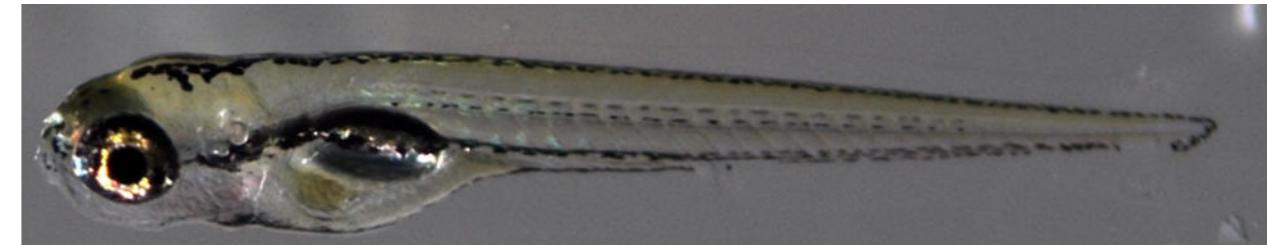
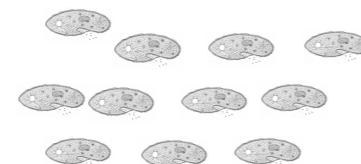
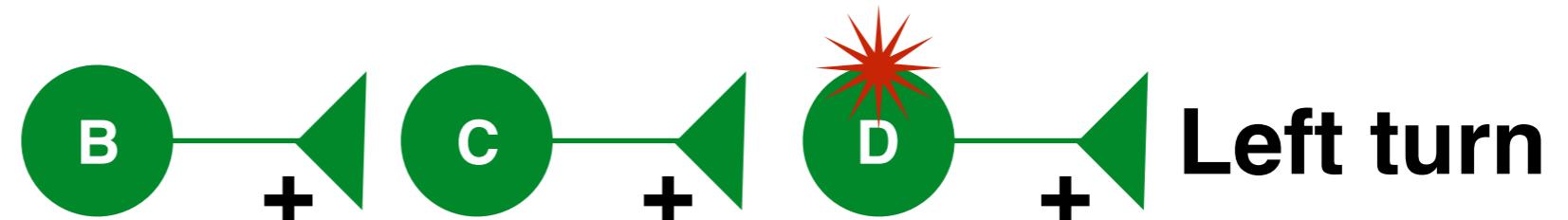
*Halobacterium salinarum*



# Ontogenetic control of neuronal activity

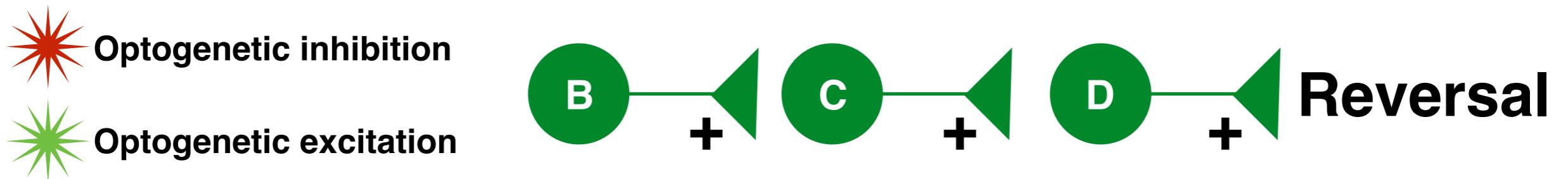


Optogenetic inhibition



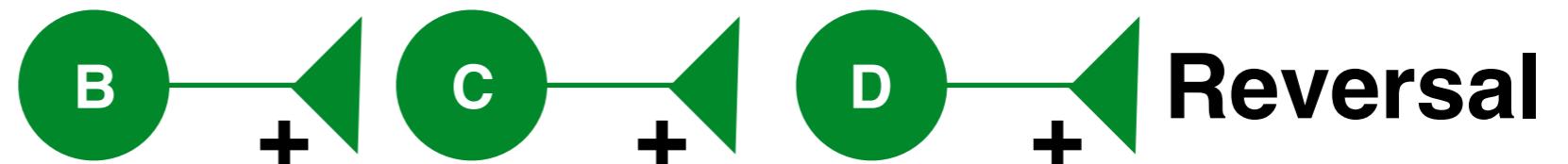
Chloride ions depolarize neurons and inhibit them

# Ontogenetic control of neuronal activity



# Ontogenetic control of neuronal activity

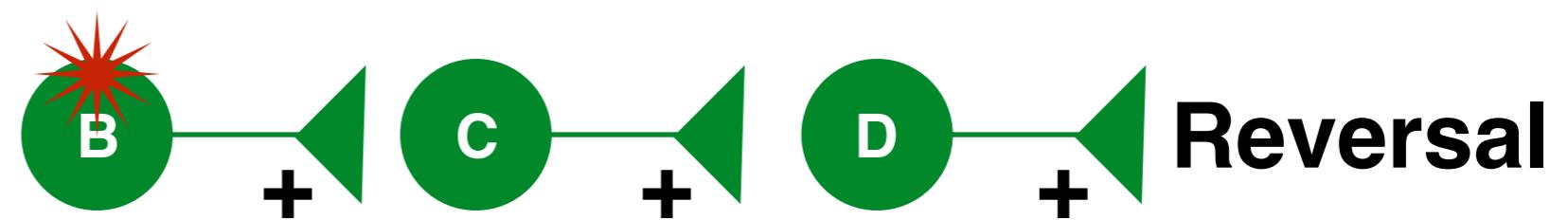
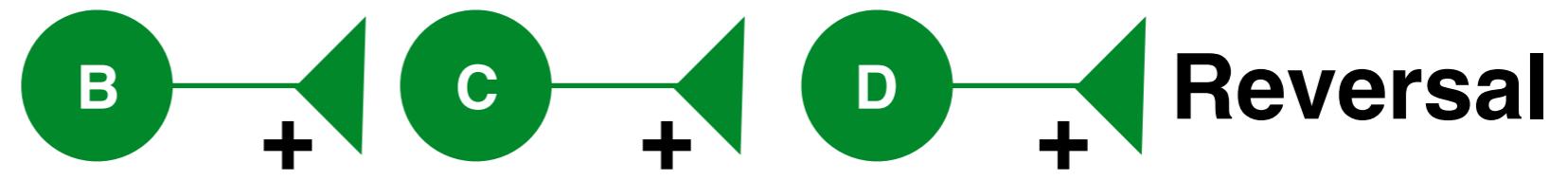
-  Optogenetic inhibition
-  Optogenetic excitation



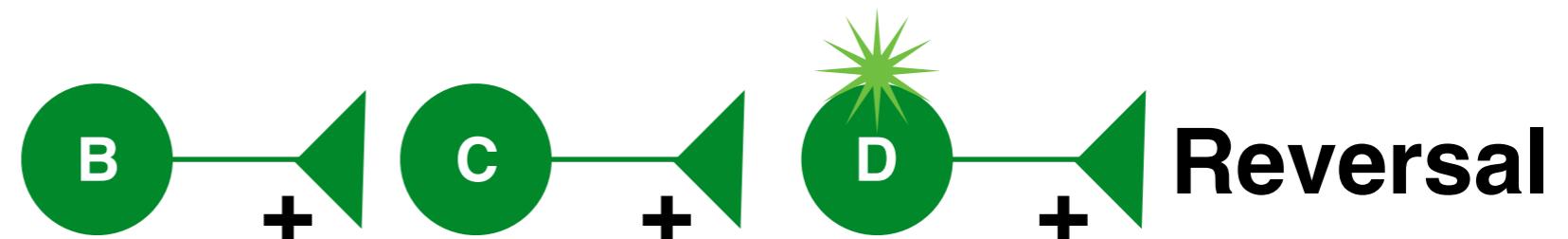
Animal crawls straight

# Ontogenetic control of neuronal activity

-  Optogenetic inhibition
-  Optogenetic excitation



Animal crawls straight



Animal reverses

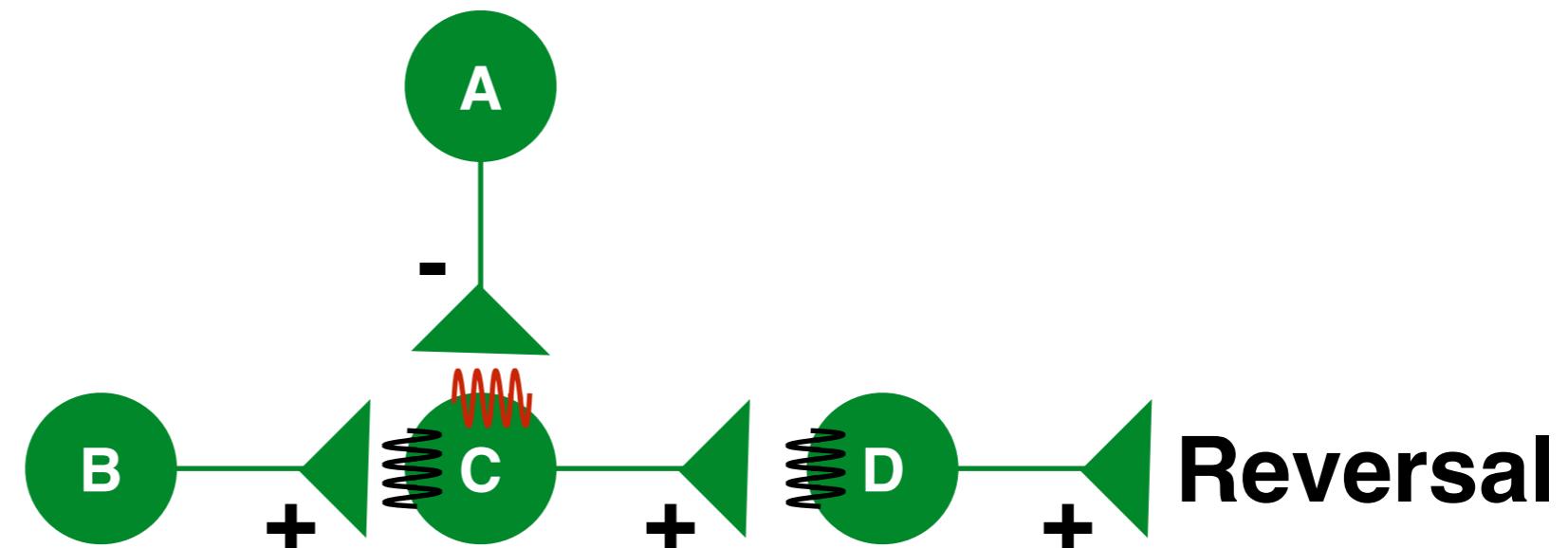
# Using optogenetics to probe gene and neuronal functions

 Inhibitory receptor

 Excitatory receptor

 Optogenetic inhibition

 Optogenetic excitation



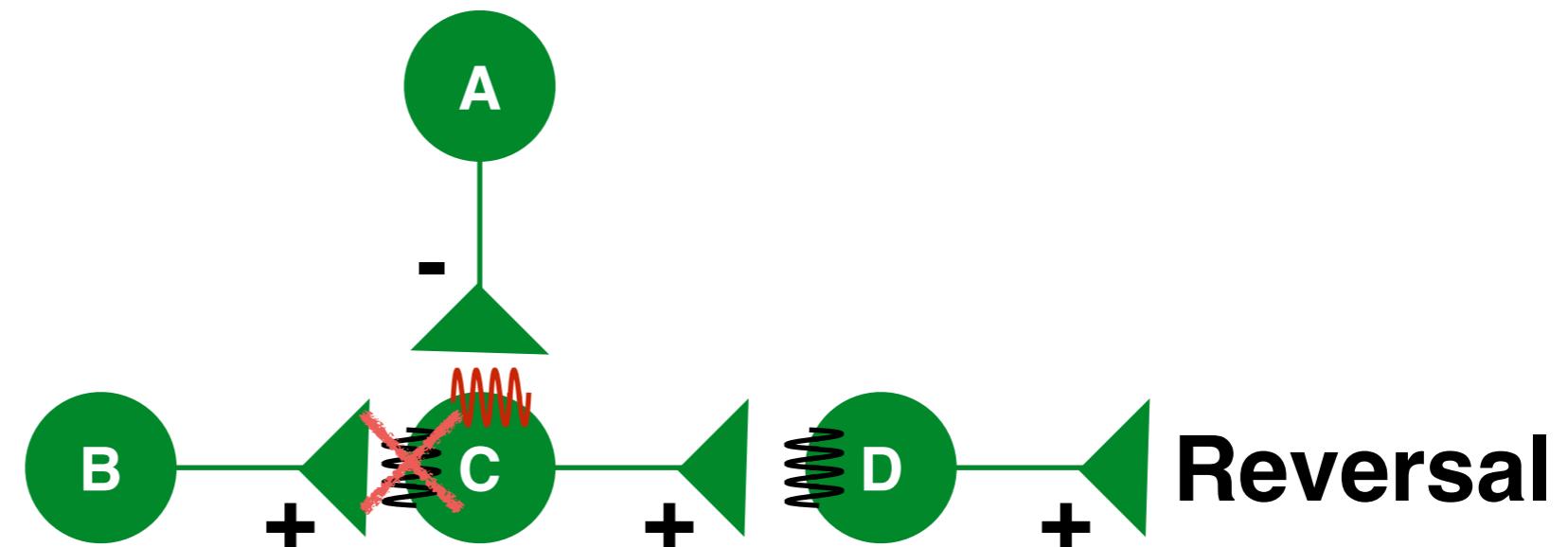
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Mutant in excitatory receptor = Animal fails to reverse

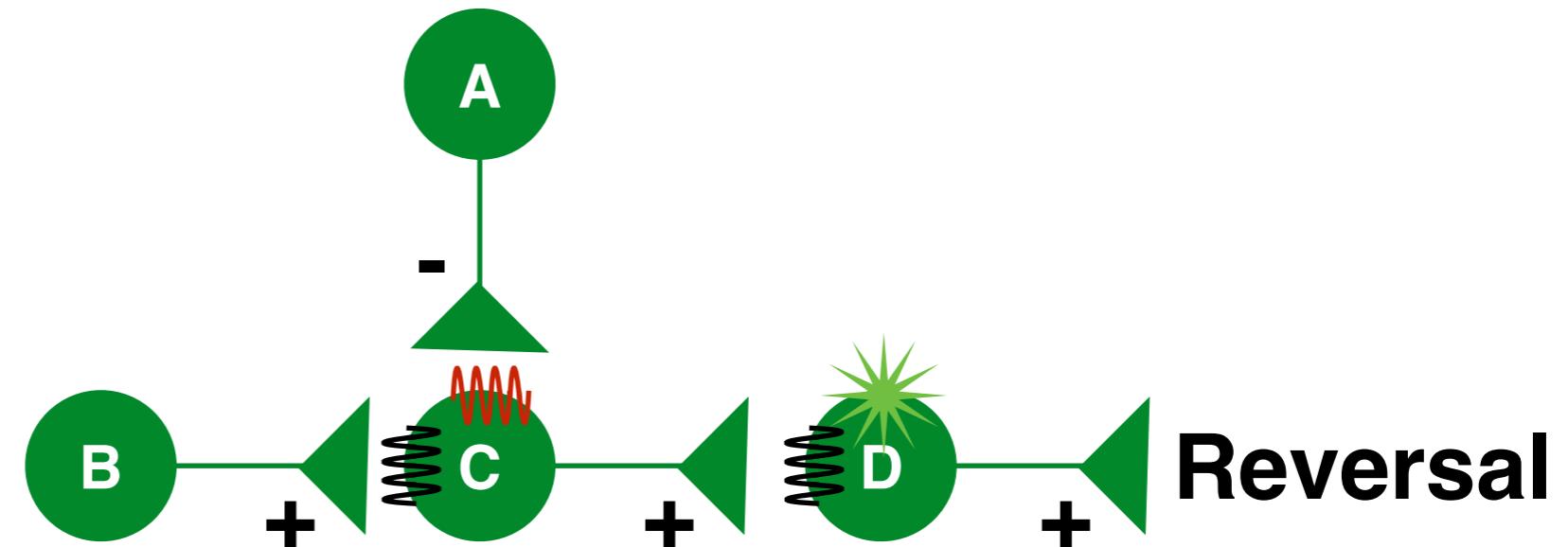
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Optogenetic excitation of D = Animal reverses

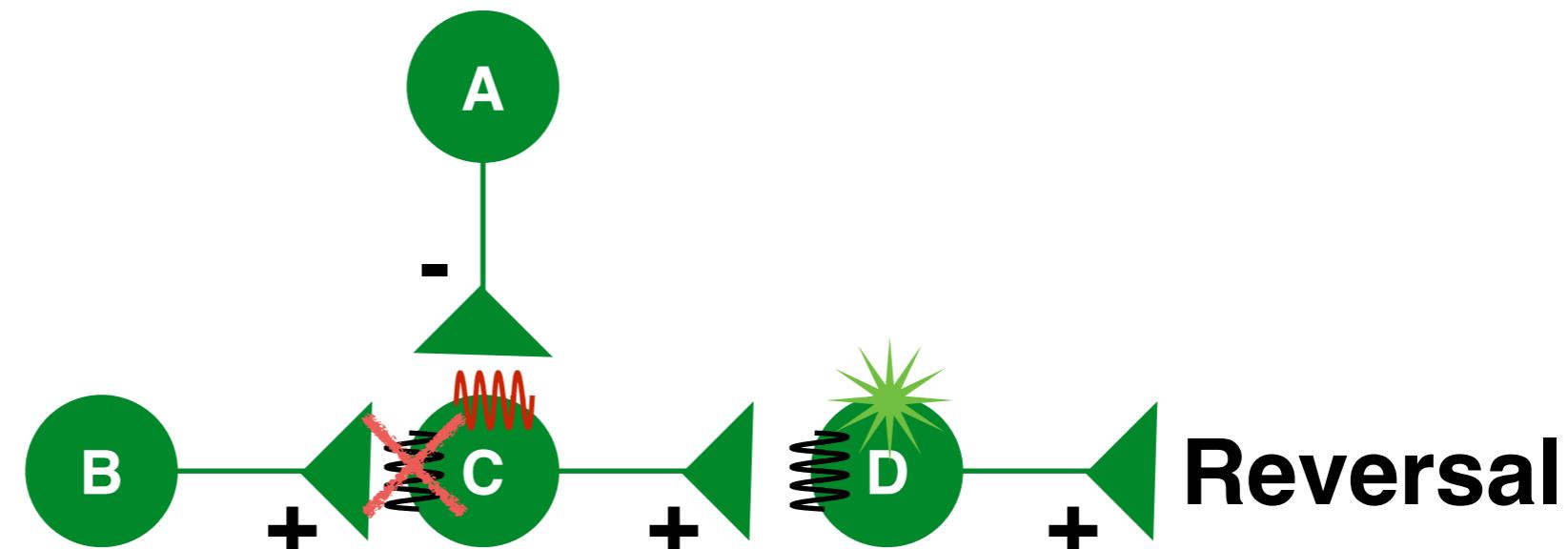
# Using optogenetics to probe gene and neuronal functions

 Inhibitory receptor

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 Optogenetic inhibition

 Optogenetic excitation



Mutant in excitatory receptor = Animal fails to reverse

Optogenetic excitation of D = Animal reverses

D activation is epistatic to loss of receptor in C

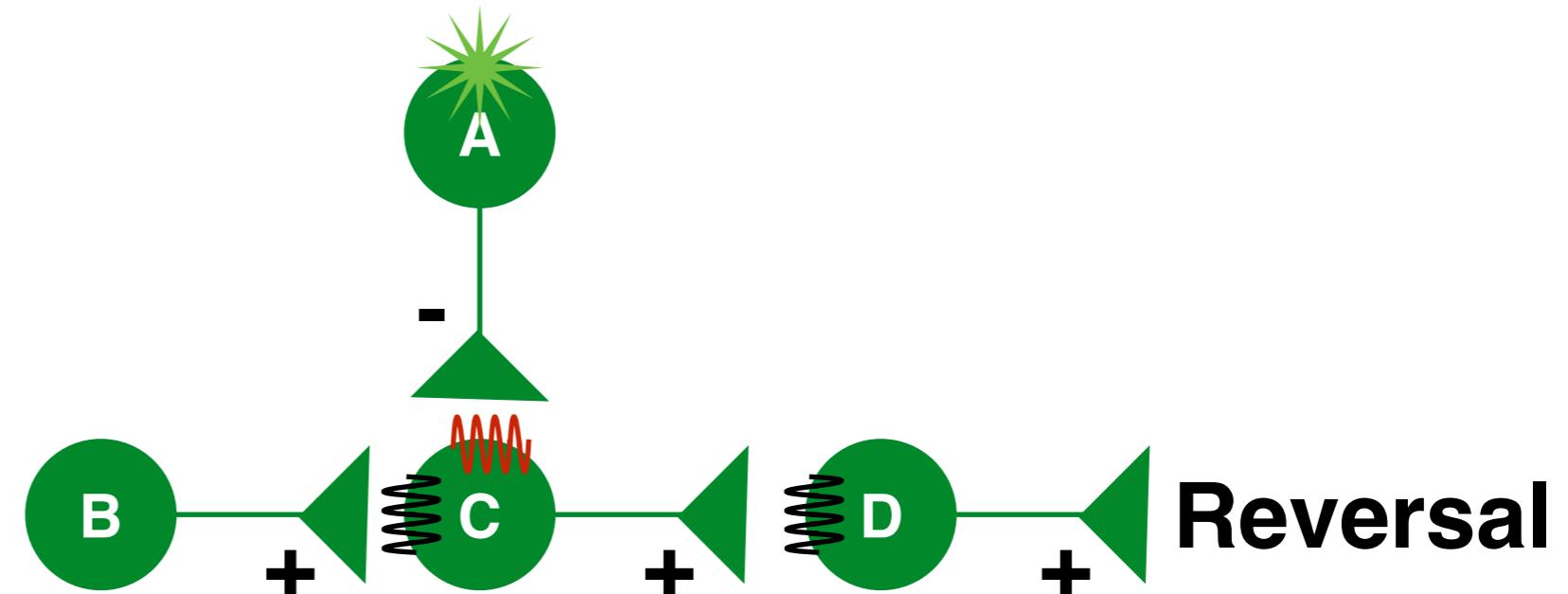
# Using optogenetics to probe gene and neuronal functions

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Excitation of A = animal fails to reverse

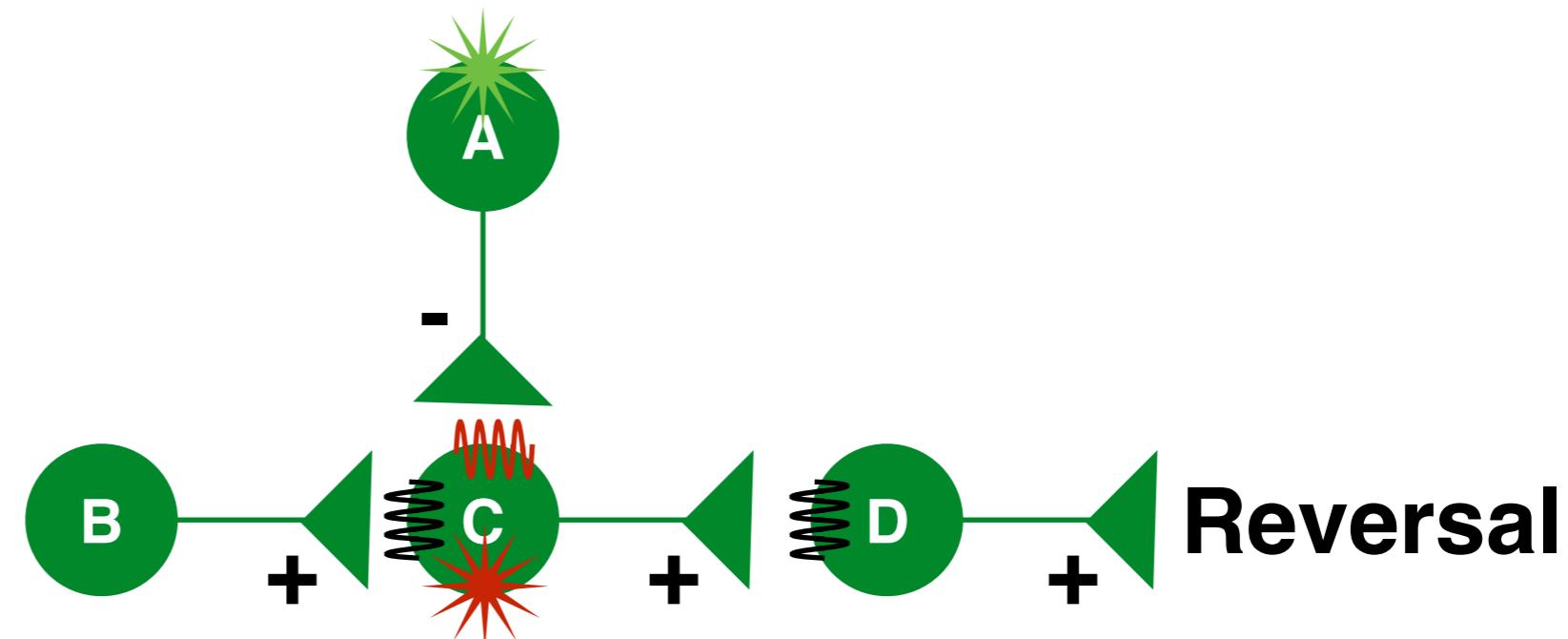
# Using optogenetics to probe gene and neuronal functions

 Inhibitory receptor

 Excitatory receptor

 Optogenetic inhibition

 Optogenetic excitation



Excitation of A = animal fails to reverse

Inhibition of C = animal fails to reverse

**Also can be combined with ablation and/or autonomy experiments**

These tools allow researchers to make remote control animals

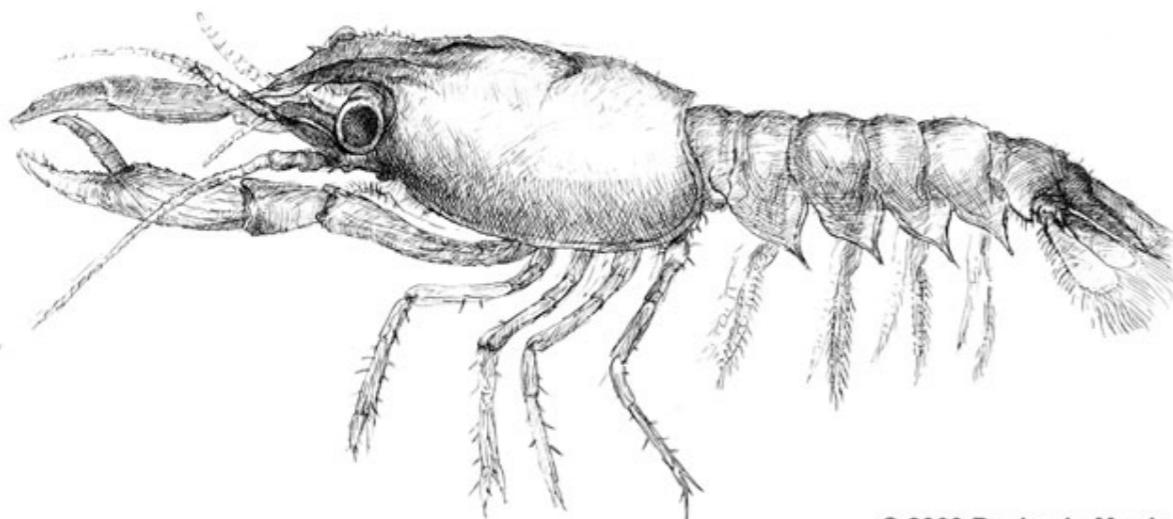


These tools allow researchers to make remote control animals

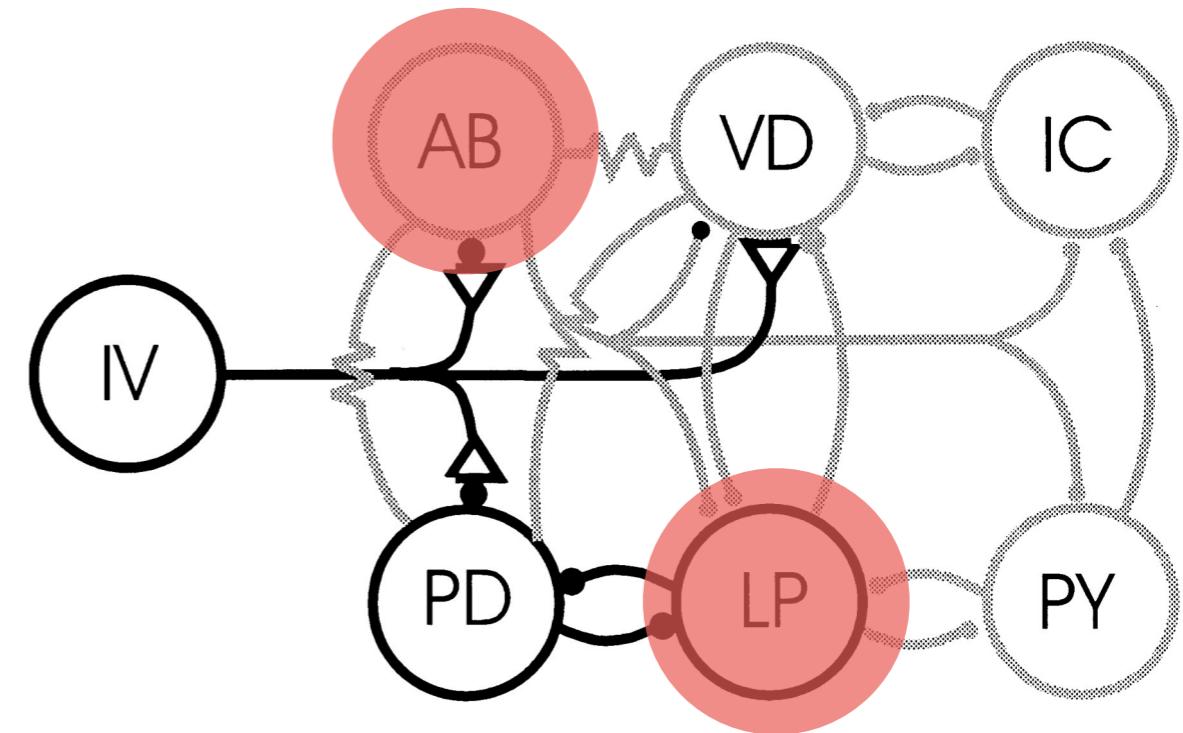
Why useful?

Build a model of how nervous systems work

# The activities of neurons AND their connections regulate behavior



© 2003 Benjamin Marder



Context of neurons (not just connections) matters!

# The BRAIN Initiative

Brain Research through Advancing Innovative Neurotechnologies

