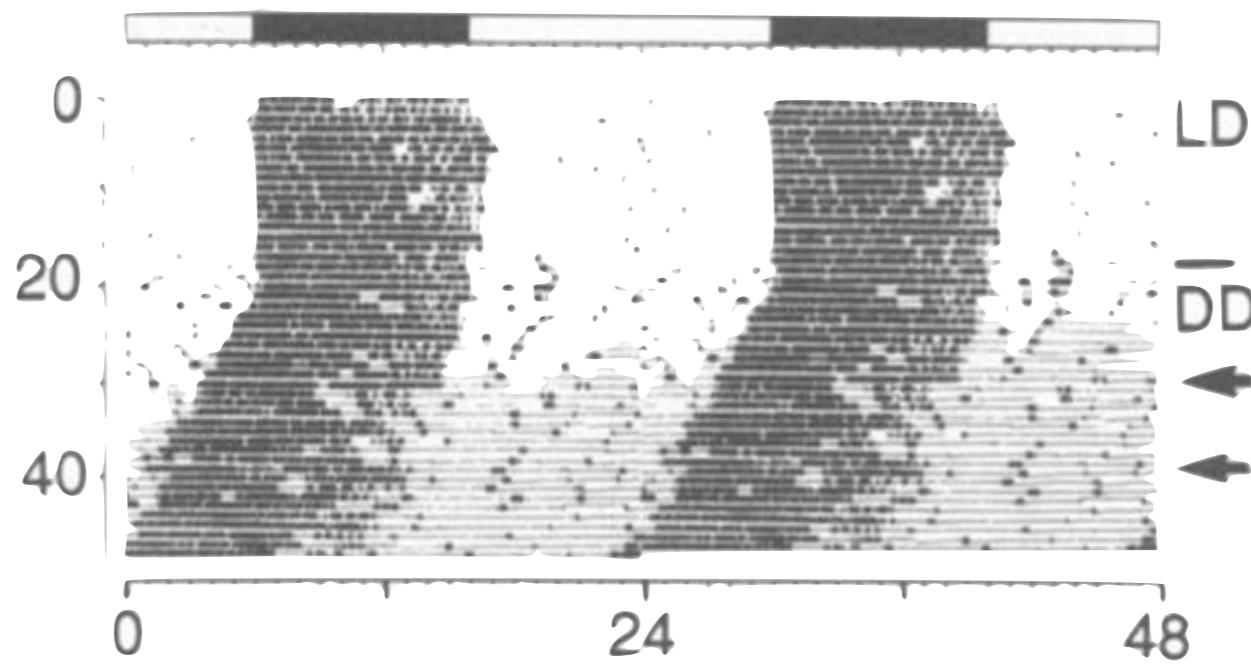
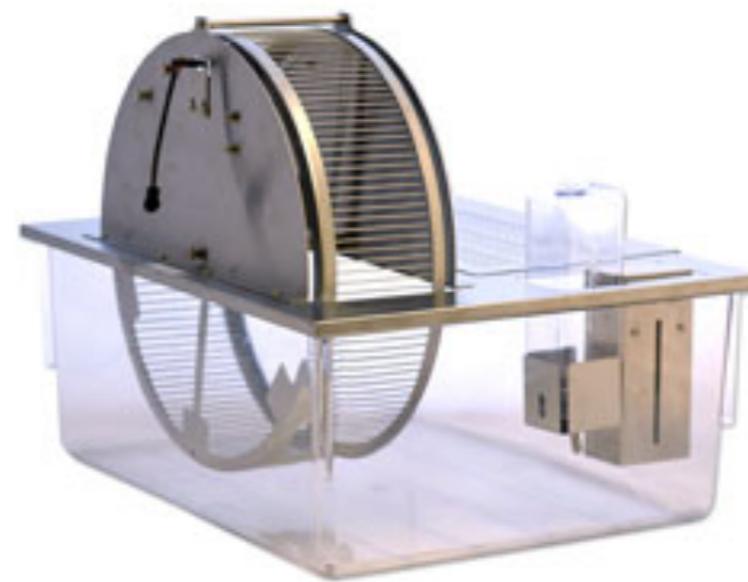
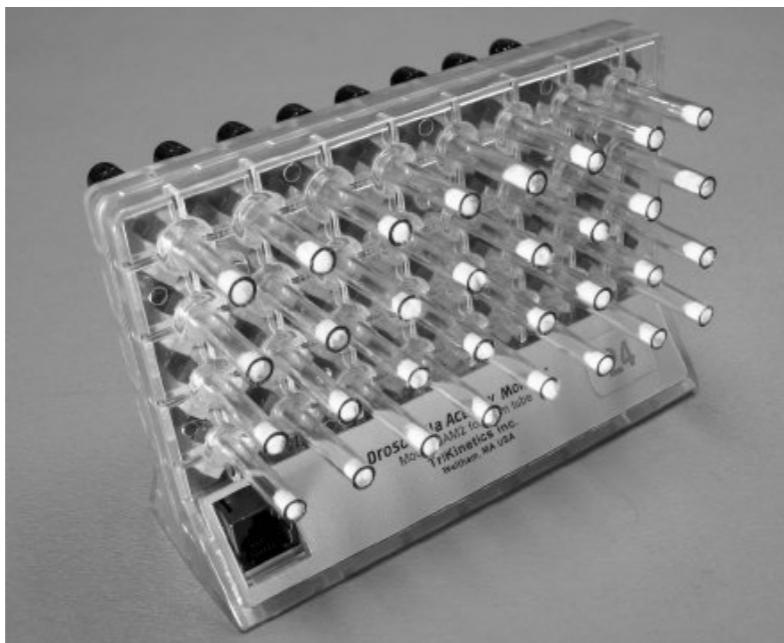
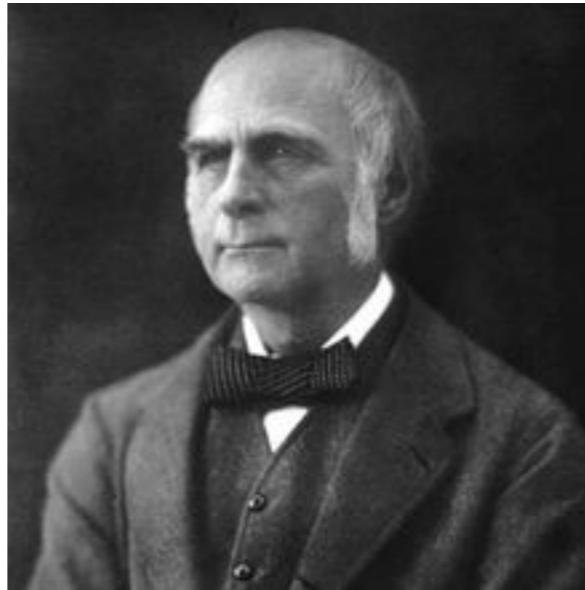


Behavioral genetics



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

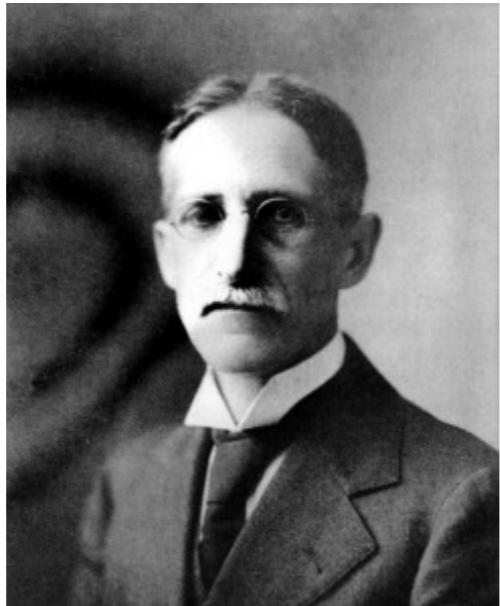


Francis Galton

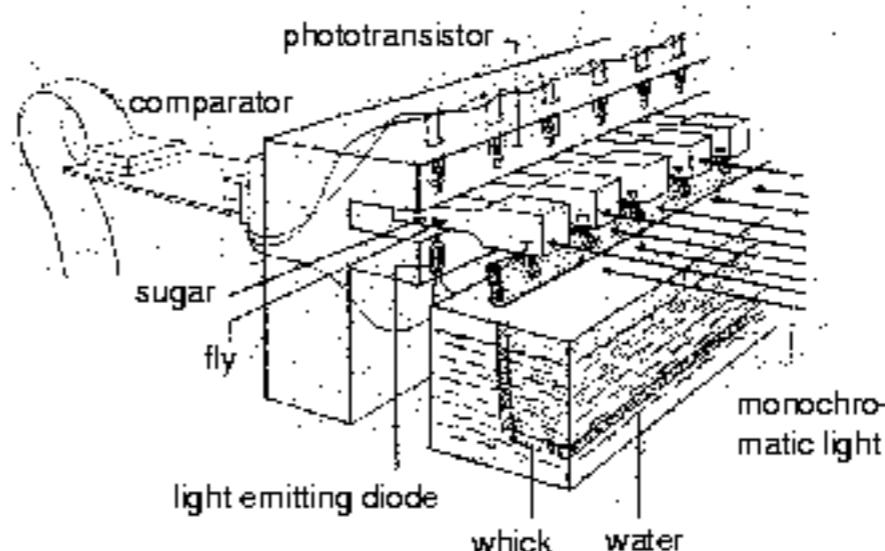
Intellectual abilities have a heritable component
(in the English upper-class)

Early motivation for eugenics

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



William Castle



Fly geotropism

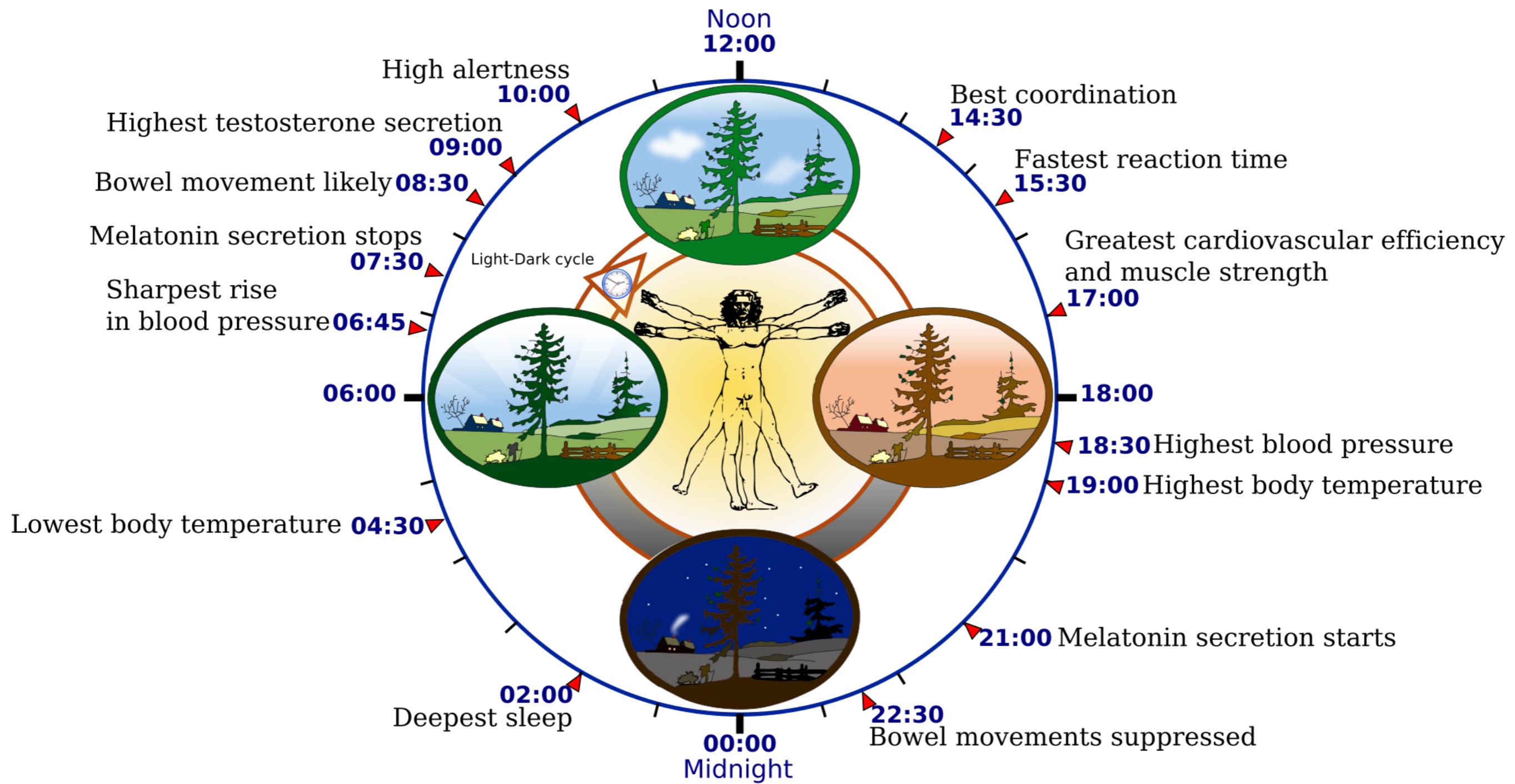


Theodore Dobzhansky

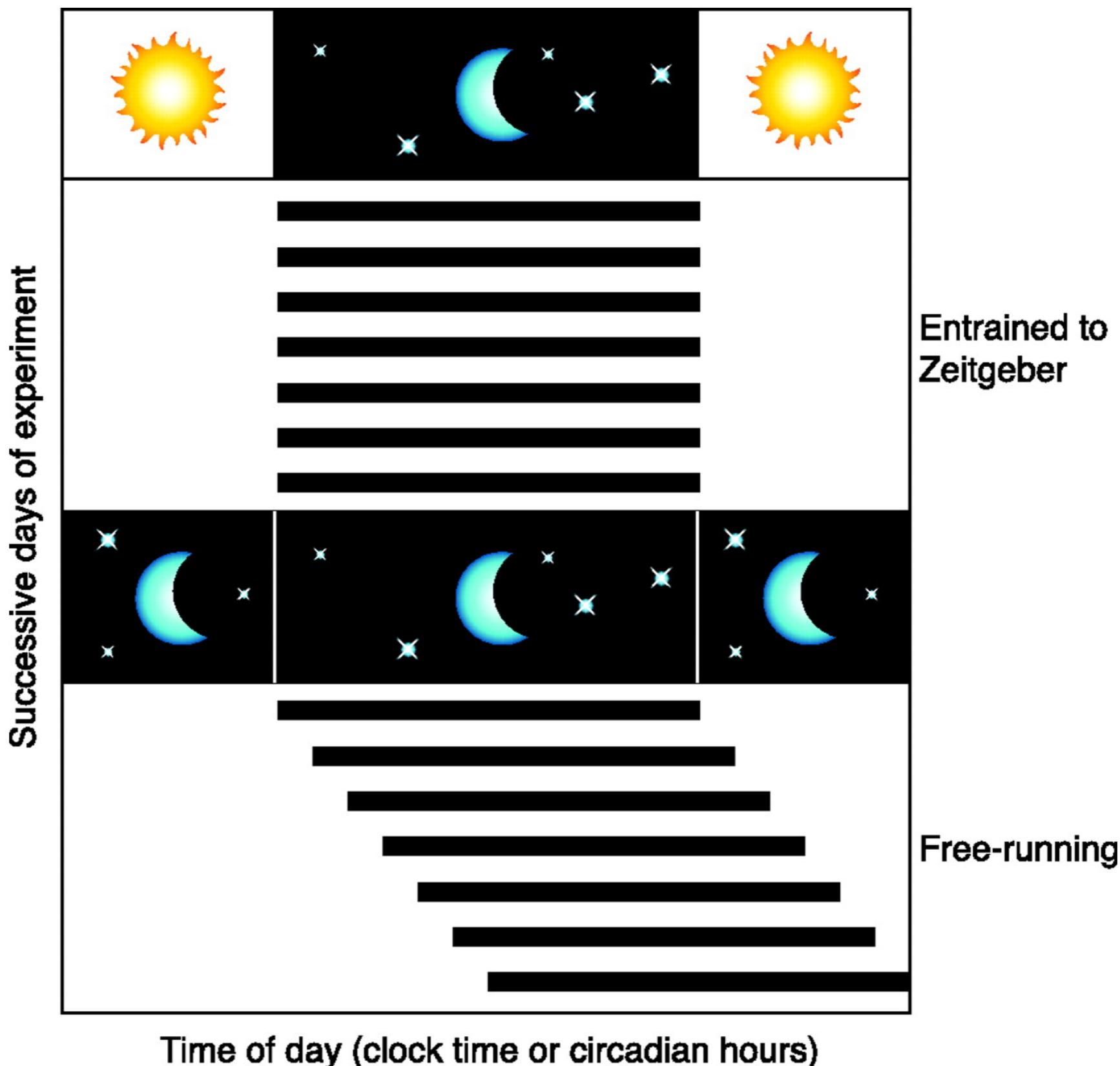


Fly mating

Nearly all organisms have a natural cycle of activity



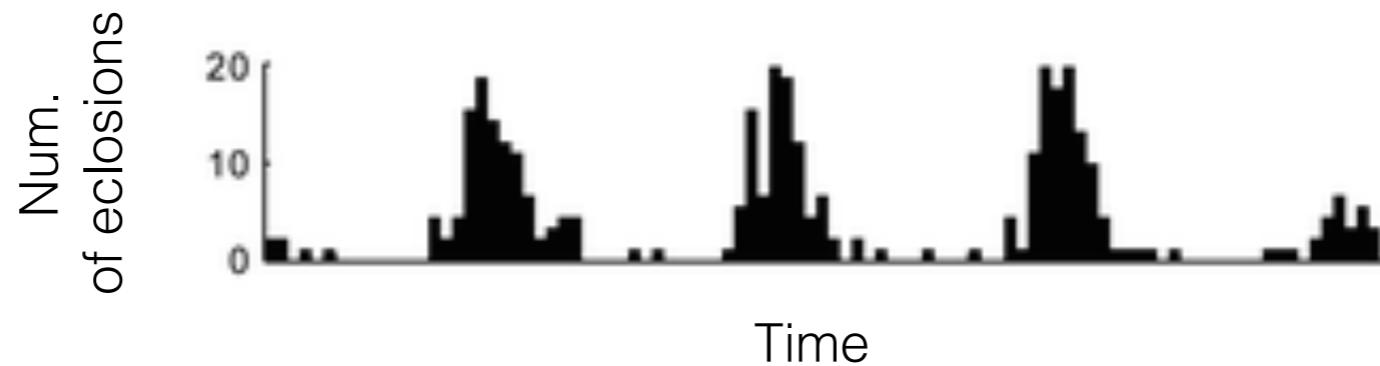
Light and/or temperature can entrain the cycle





Seymour Benzer

Drosophila eclose from the pupal case with a reproducible cycle

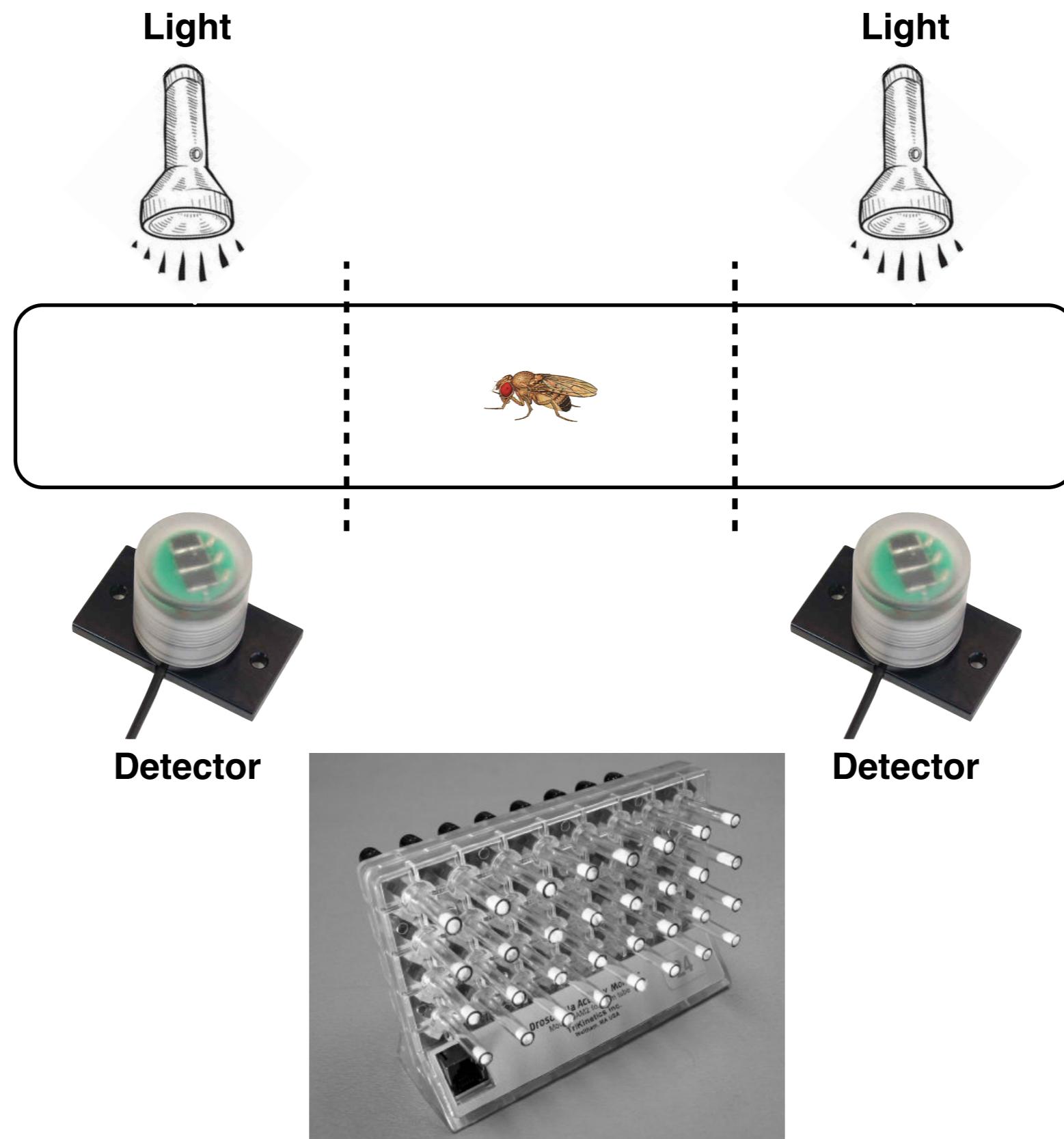


Difficult assay

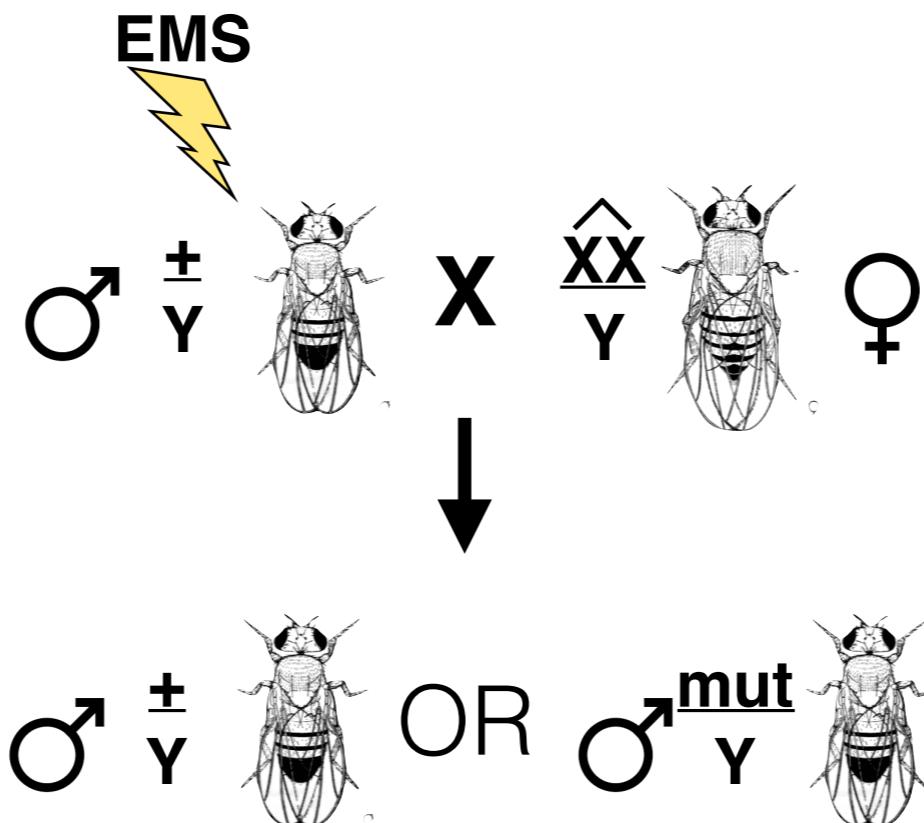
You need to watch the flies a lot of the time



Drosophila movement cycles and is much easier to score



The first genetic screen for behavioral mutants

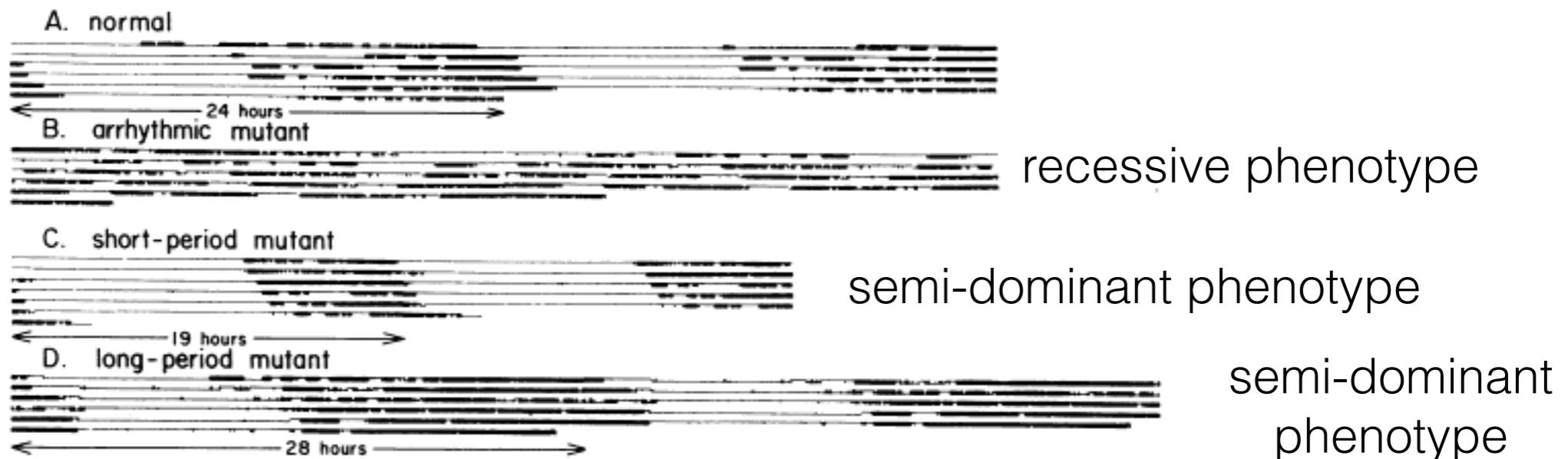


Screened 2,000 males

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

got three mutants
that affected all cyclic behaviors

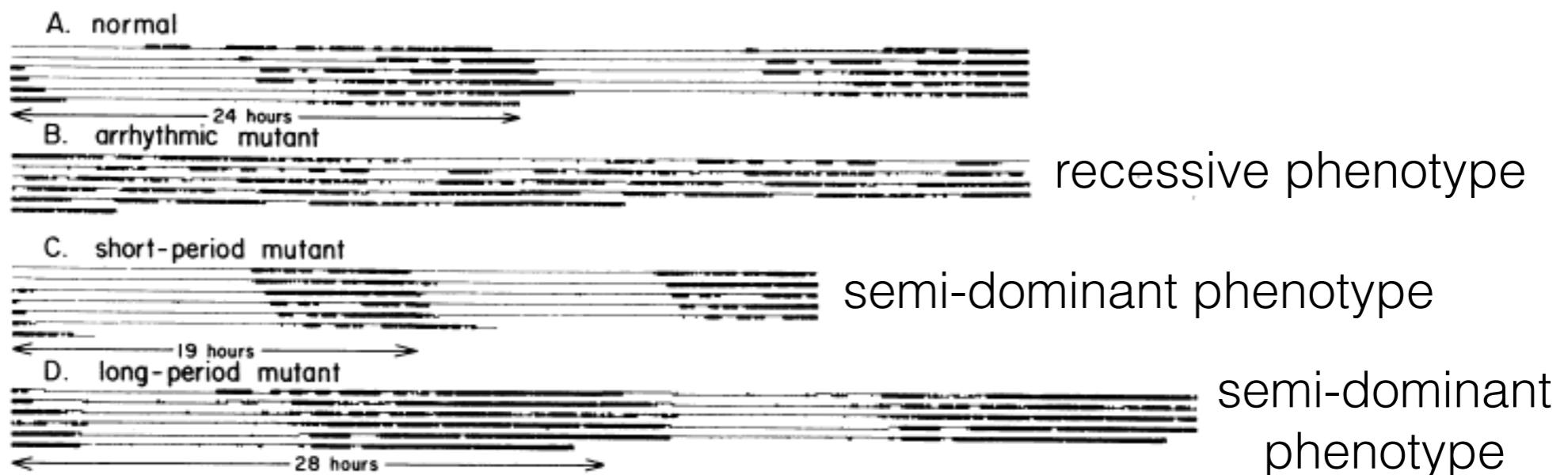
period mutants



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



period mutants

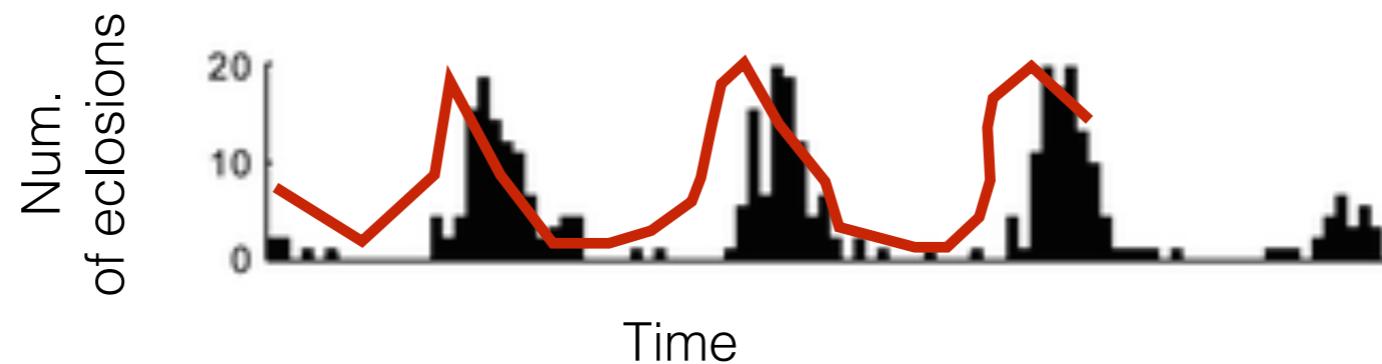


arrhythmic = arrhythmic
arrhythmic deficiency

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

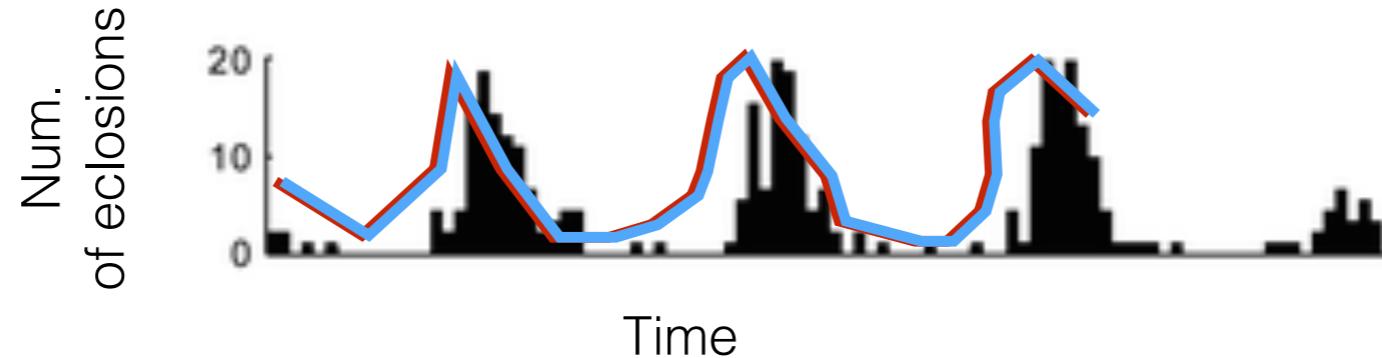
long phenotype long = long = long > long > ±
 long deficiency arrhythmic + +

***period* encoded a novel protein at the time**



period transcription and translation cycles

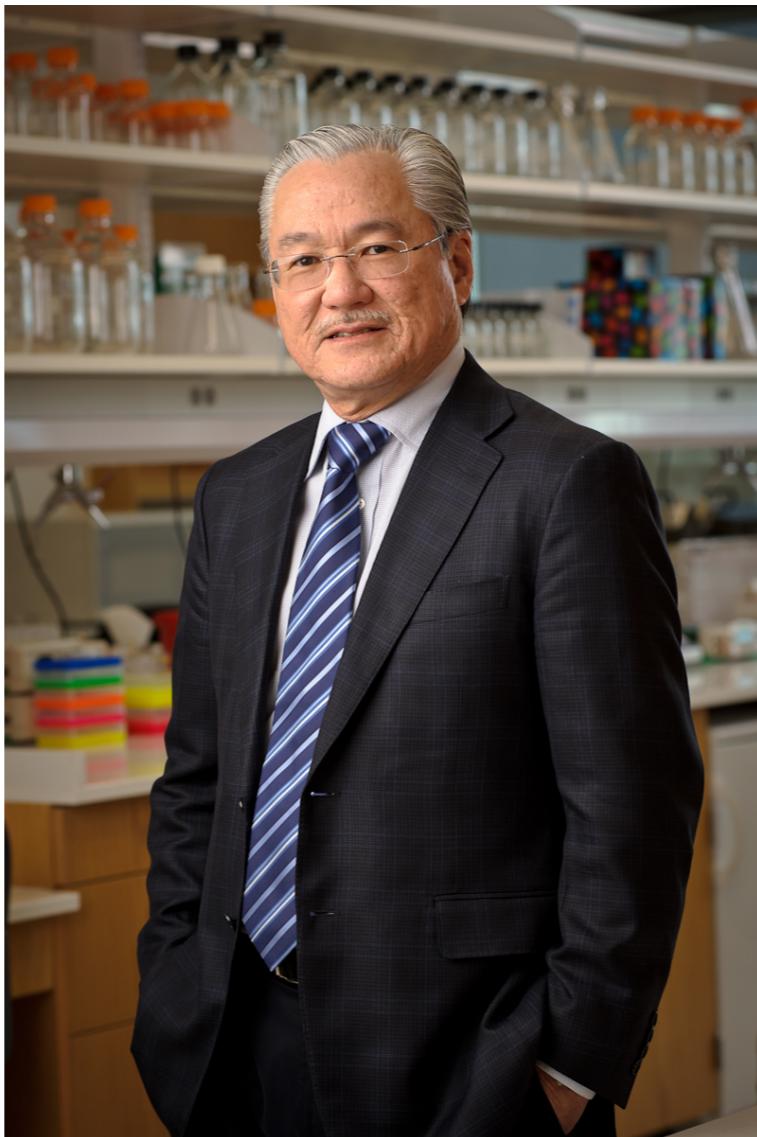
Another genetic screen with a focus on chromosome 2 found the gene *timeless*



period transcription and translation cycles

timeless transcription and translation cycles

Period Timeless

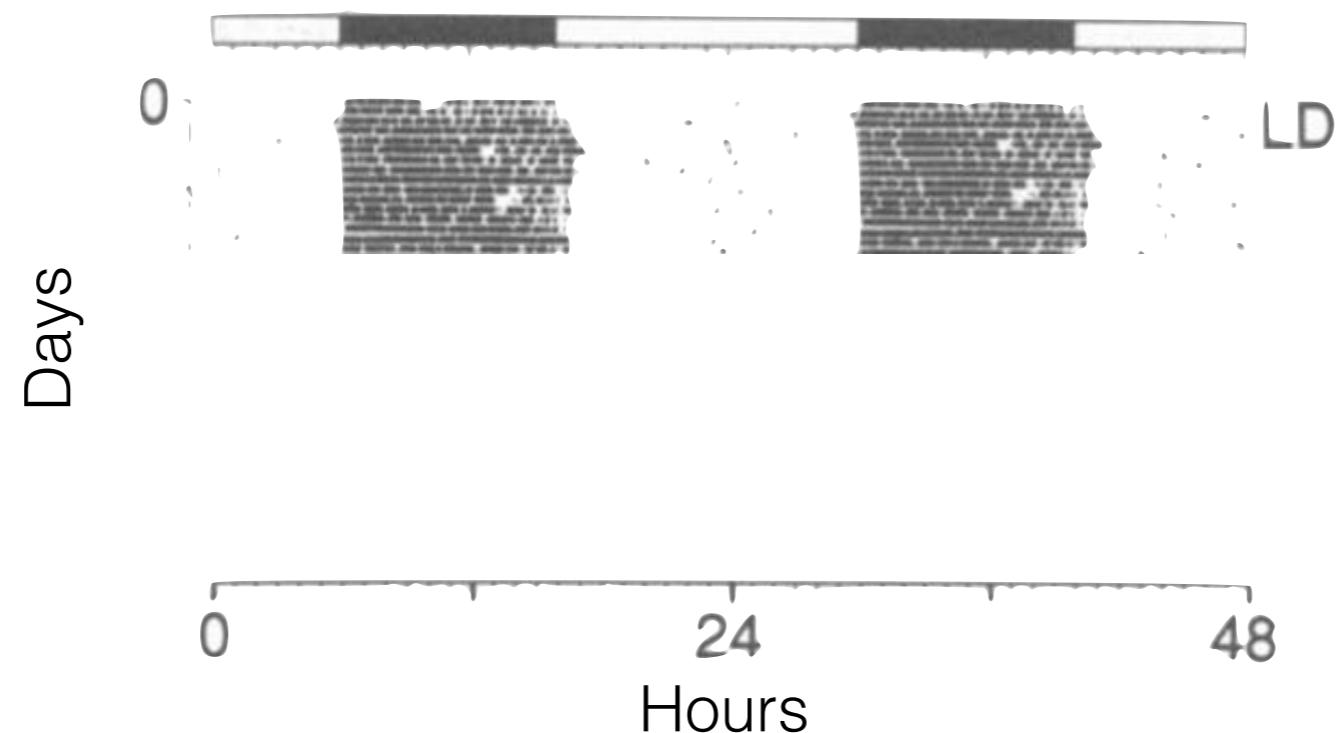


Joe Takahashi

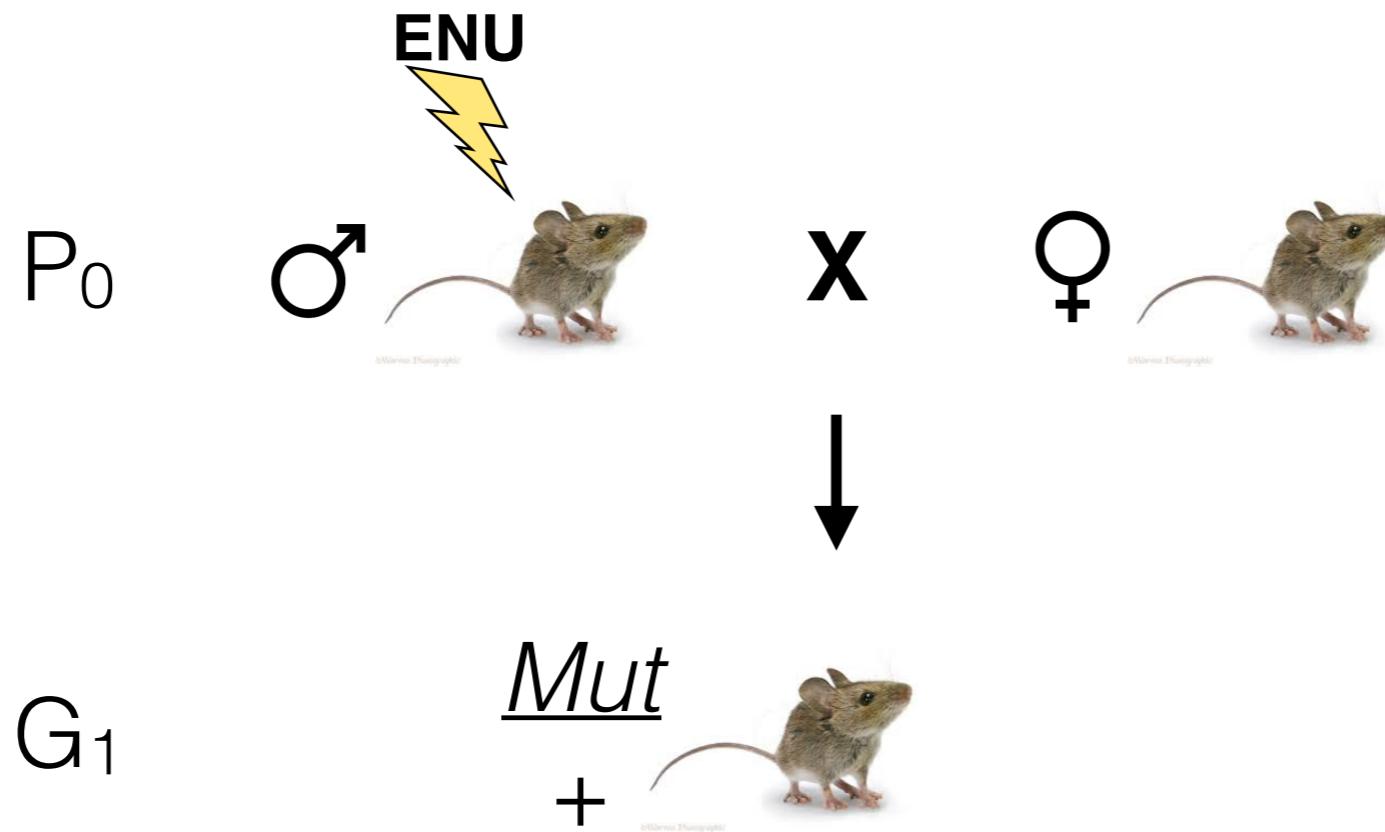
Mice love to run at night



©Warren Photographic



Circadian rhythm screen

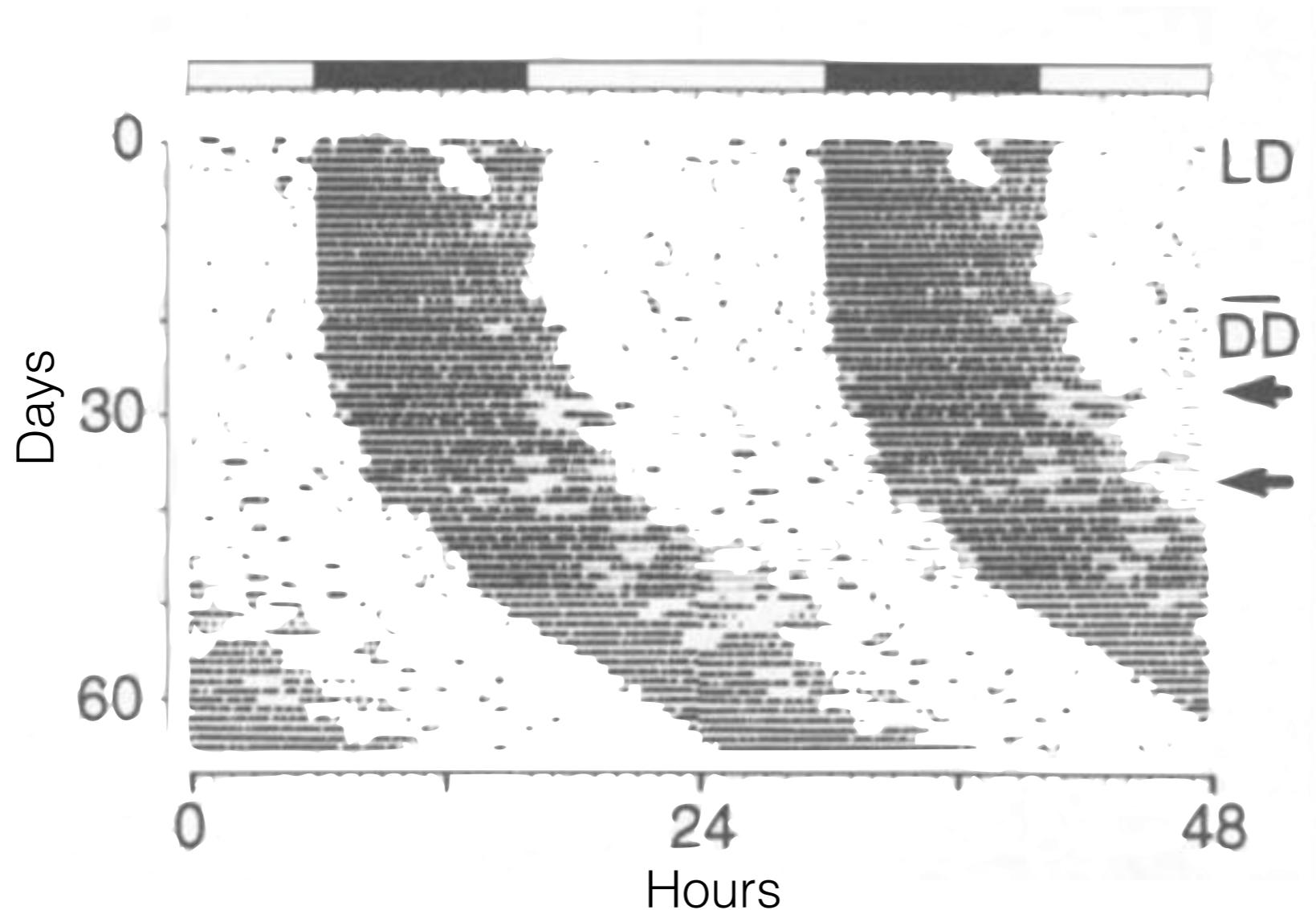


304 mutant mice screened

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**

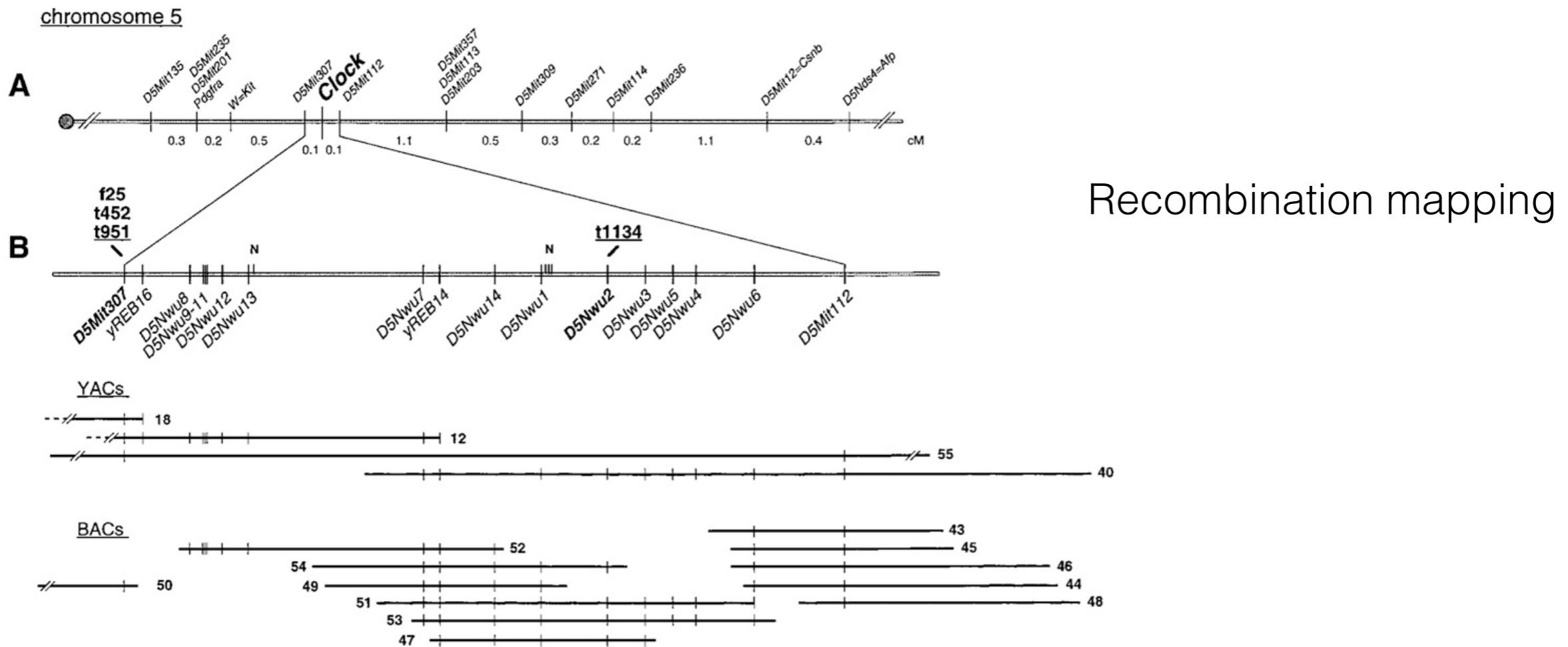


Clock = circadian locomotor output cycles kaput

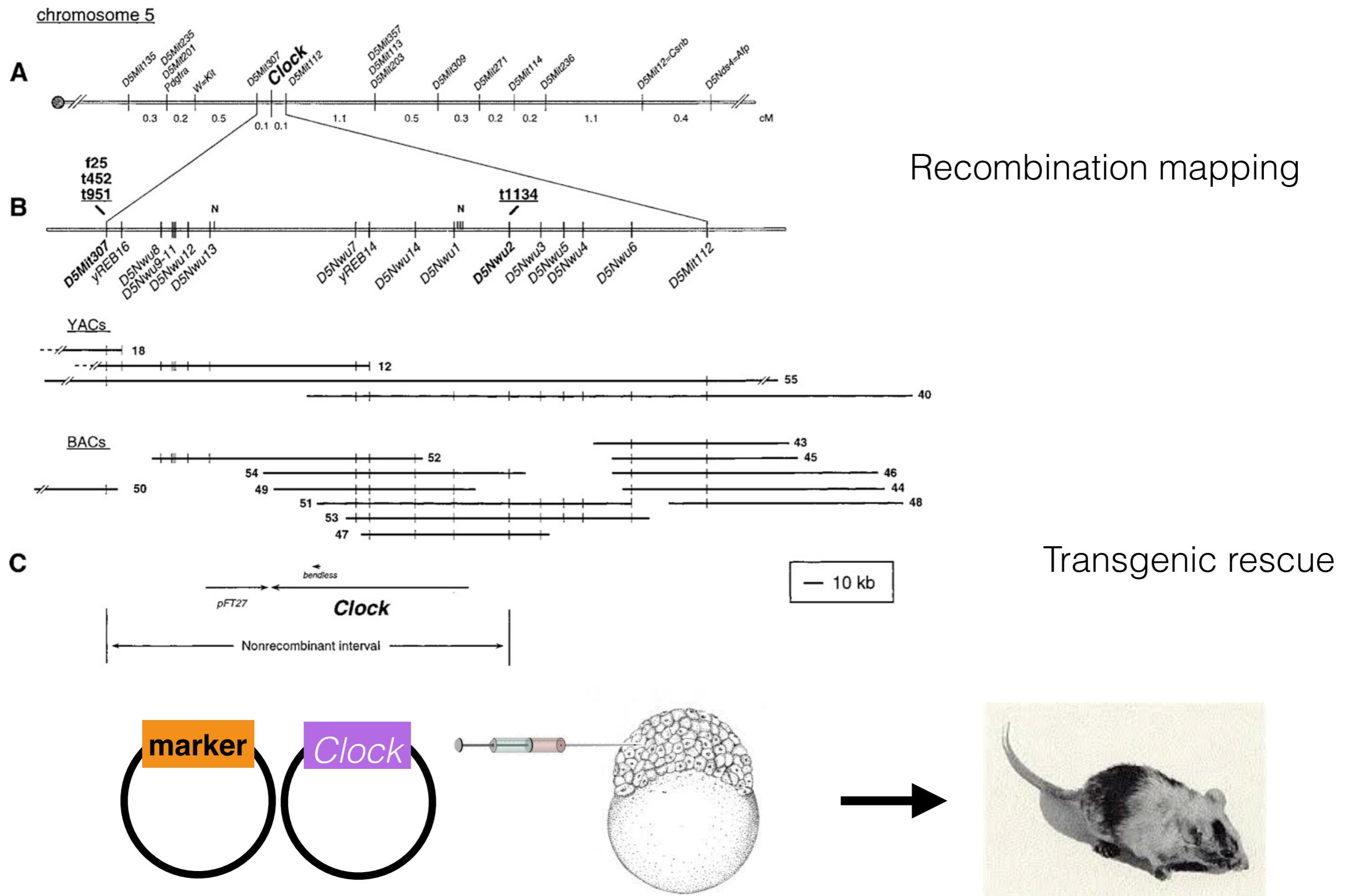
Clock mutants have a semi-dominant phenotype

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

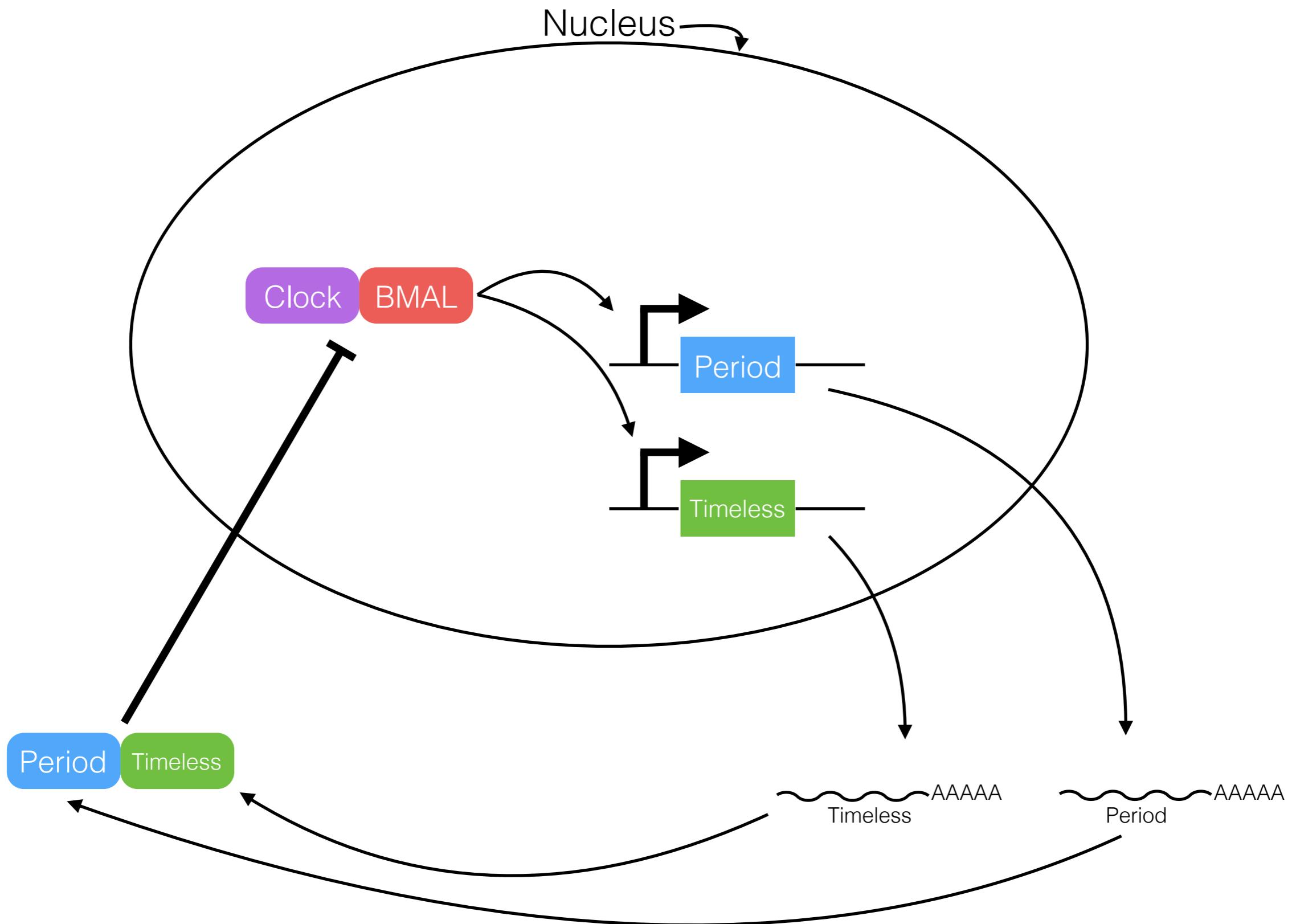
***Clock* was cloned and encodes a transcription factor**



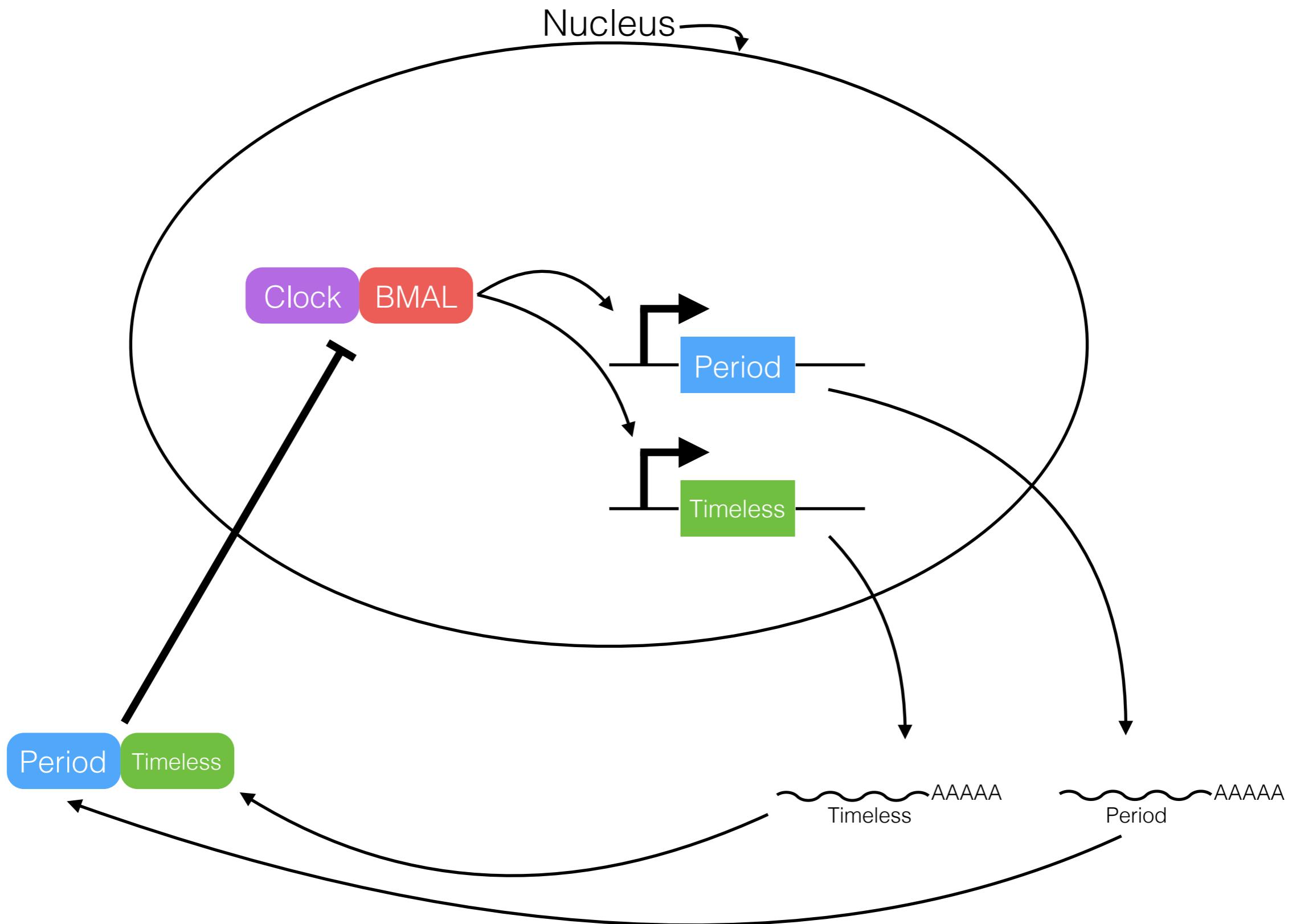
***Clock* was cloned and encodes a transcription factor**



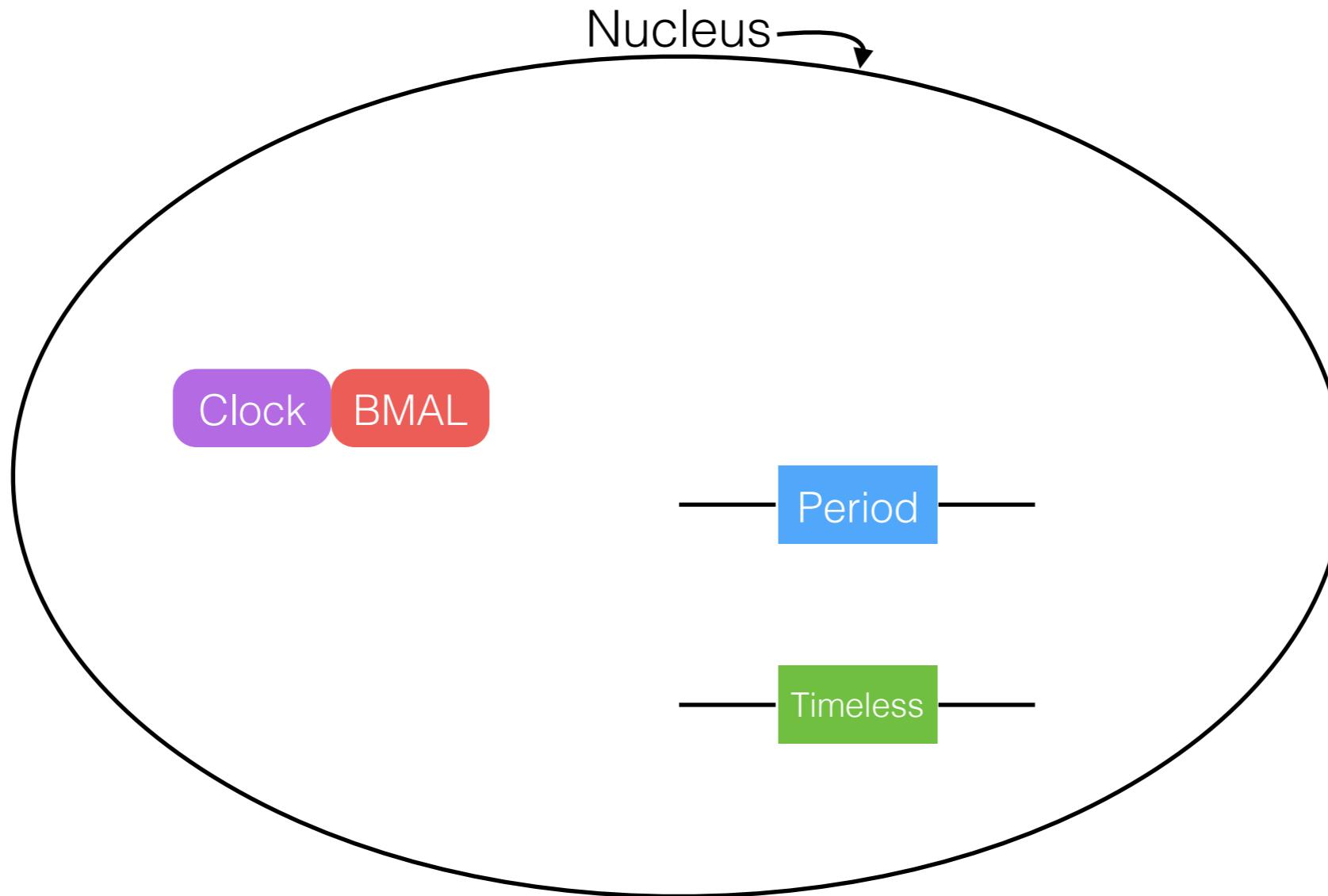
A simplified model of the circadian clock



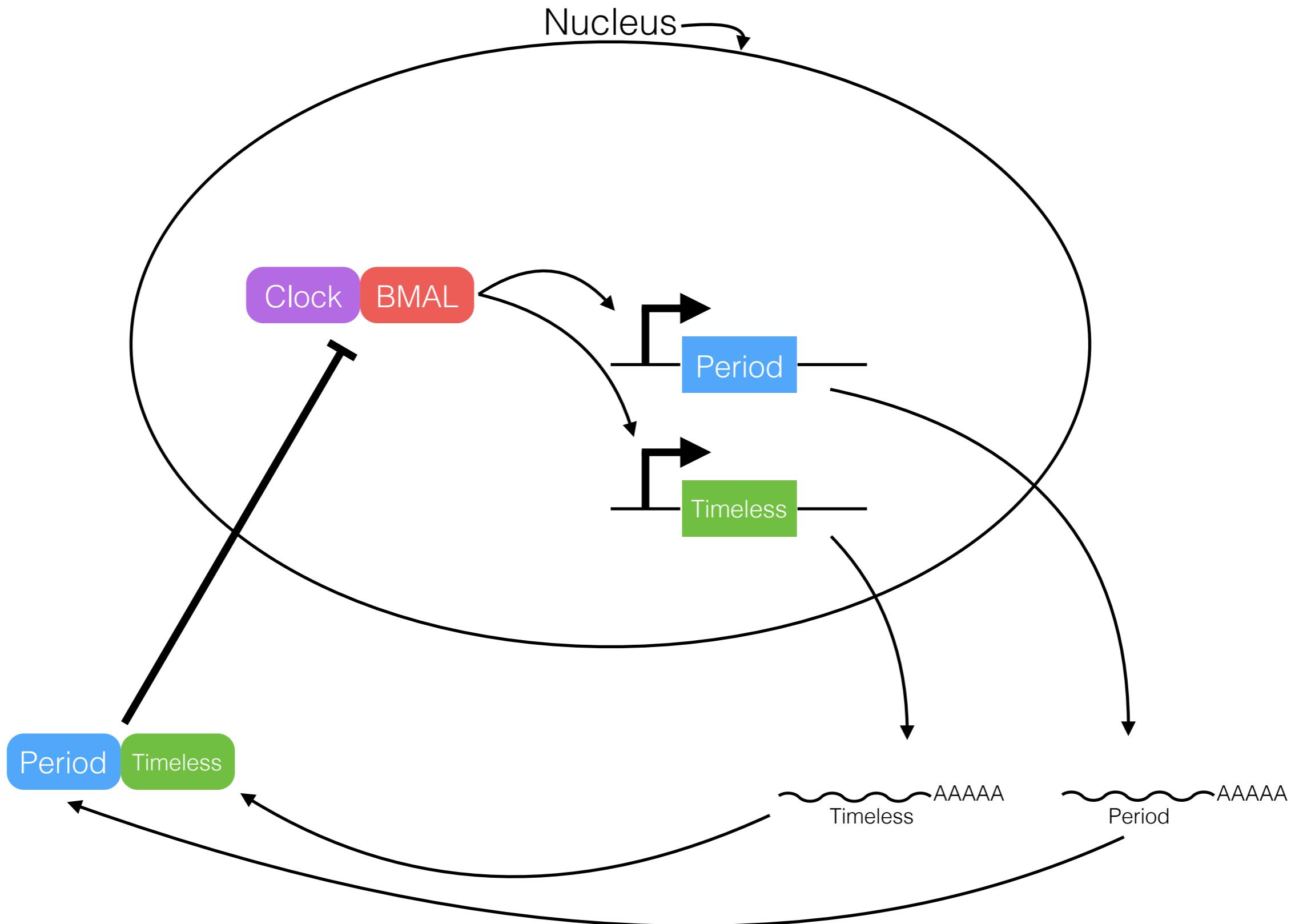
A simplified model of the circadian clock



A simplified model of the circadian clock

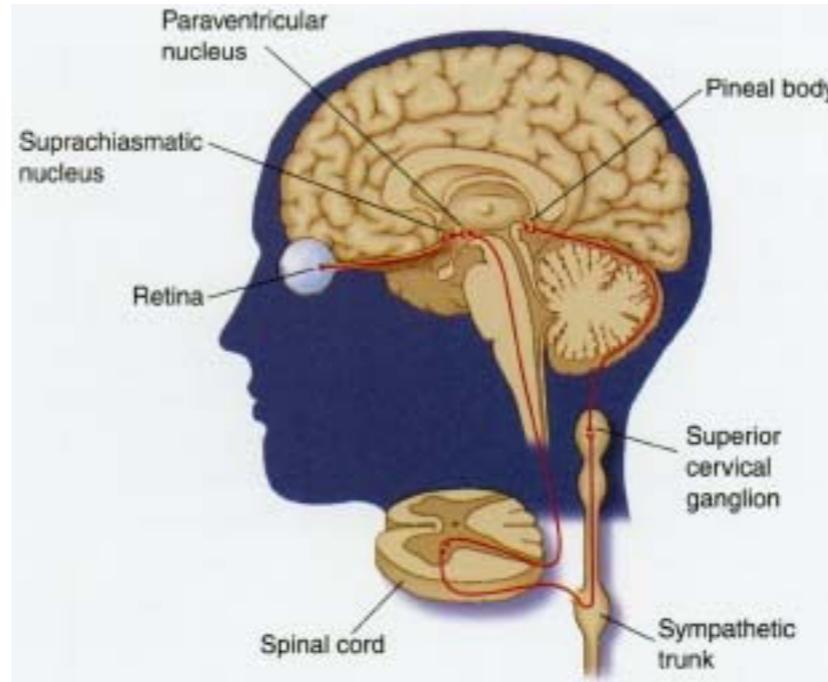


A simplified model of the circadian clock



How do you think light entrains the system?

In humans, the suprachiasmatic nucleus regulates sleep and wakefulness



Do blind people have circadian cycles?

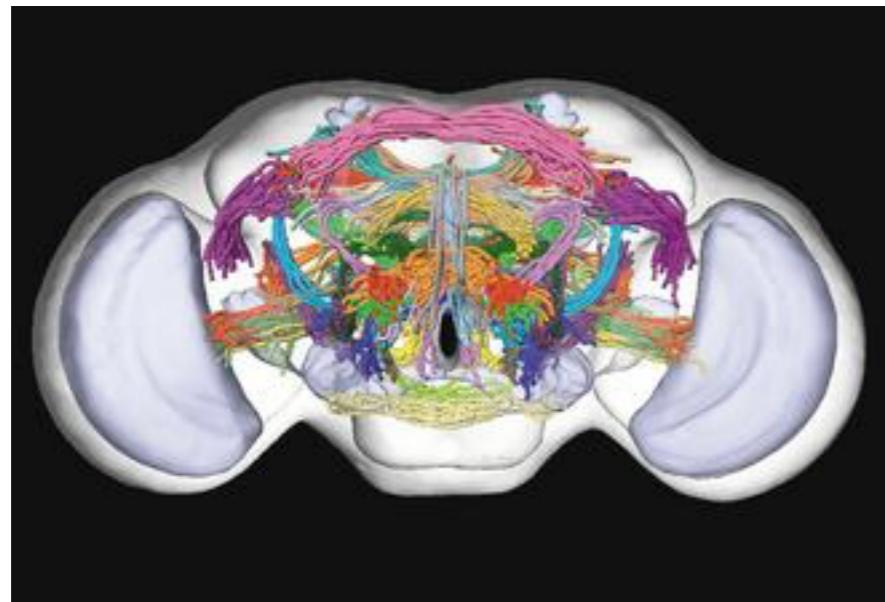
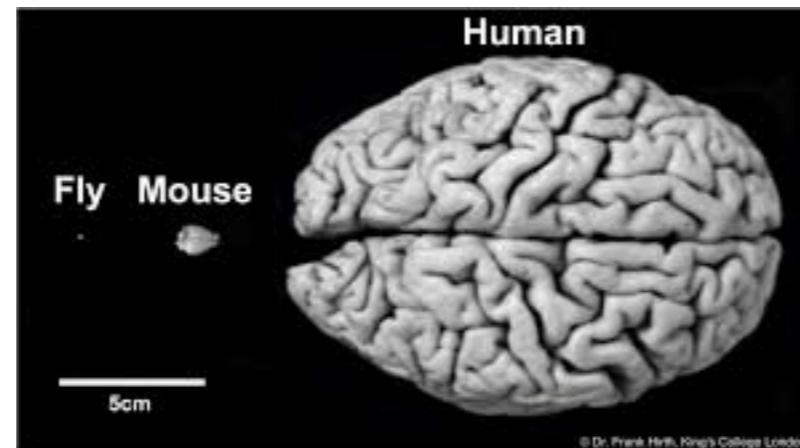
Using narcoleptic dogs, researchers found the gene underlying narcolepsy



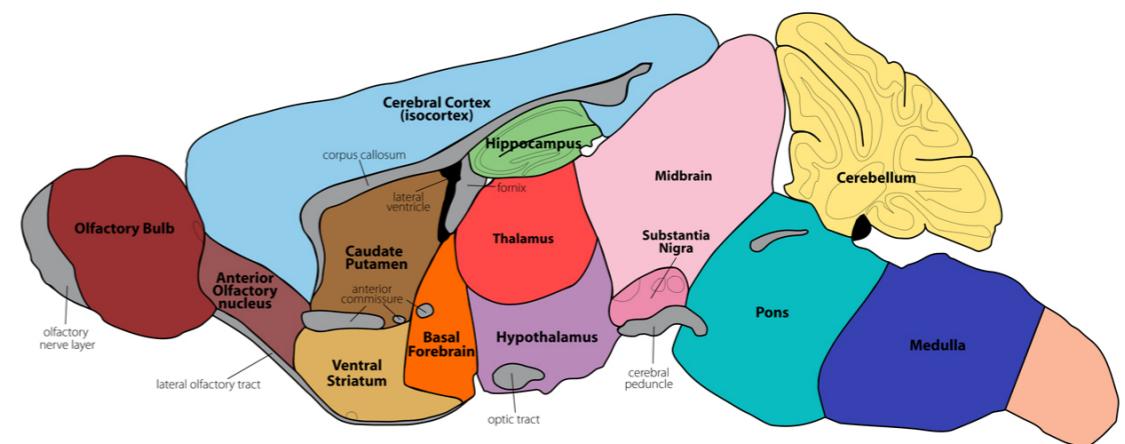
How?

No genetic screens,
no balancers,
small numbers of offspring

Gene products act in neurons and neuronal circuits

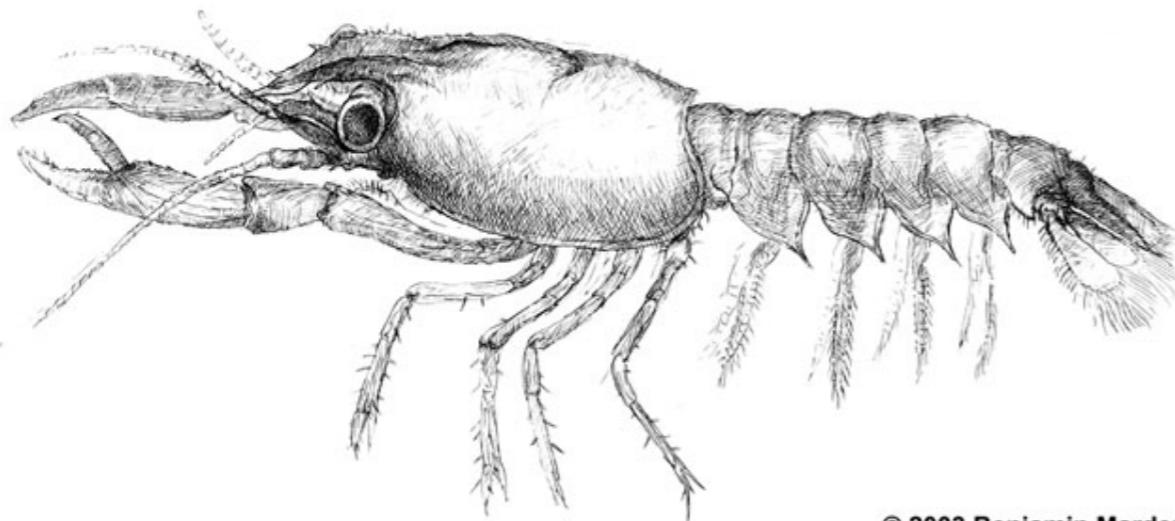


Drosophila brain

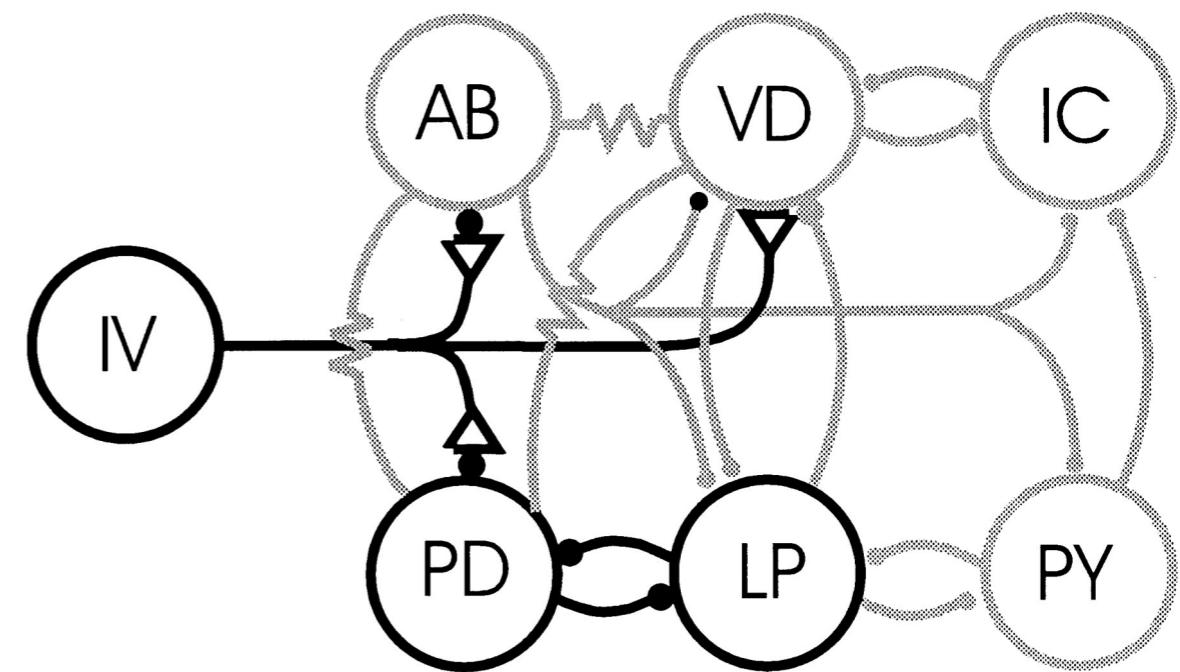


Mouse brain

The activities of neurons AND their connections regulate behavior

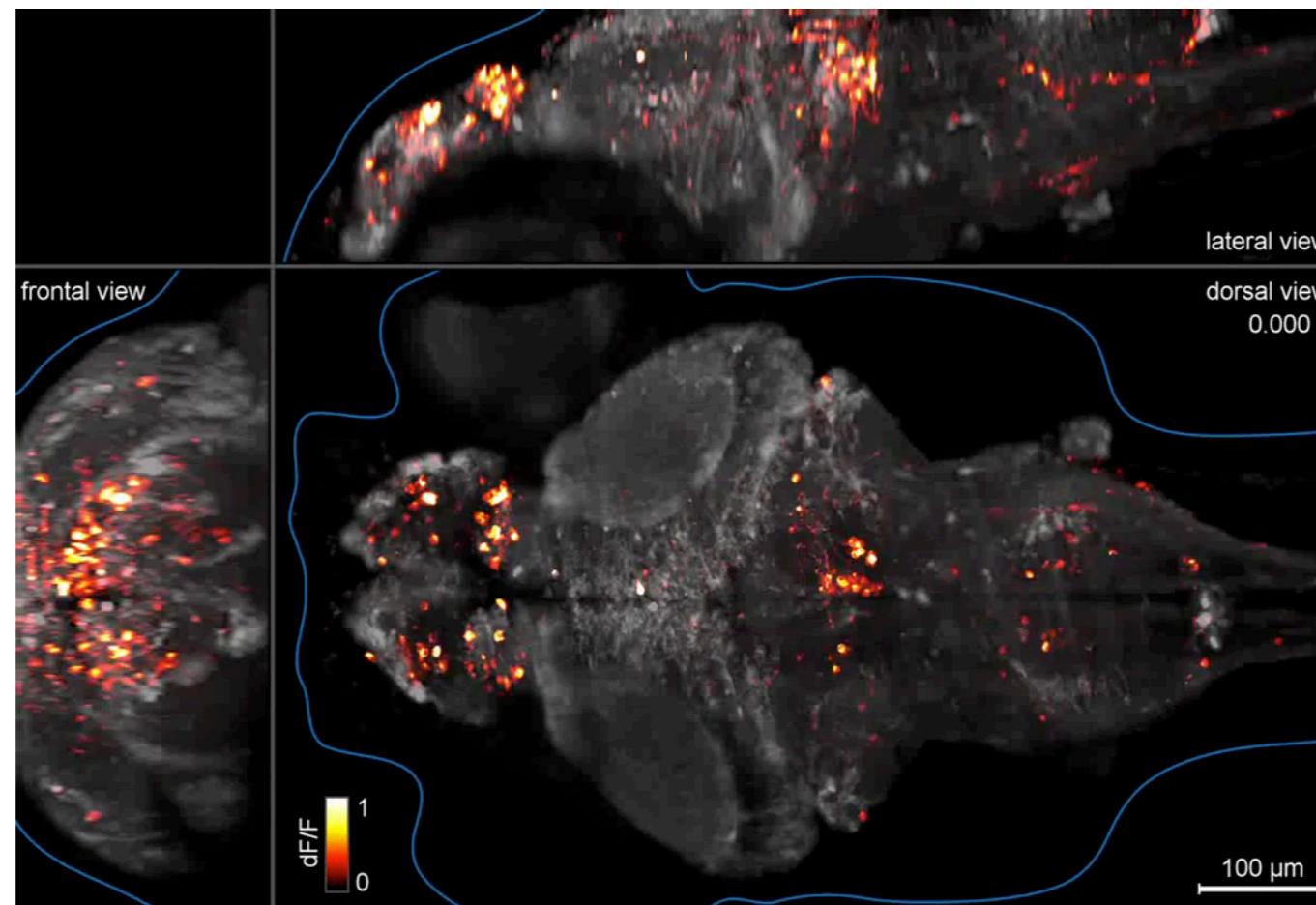
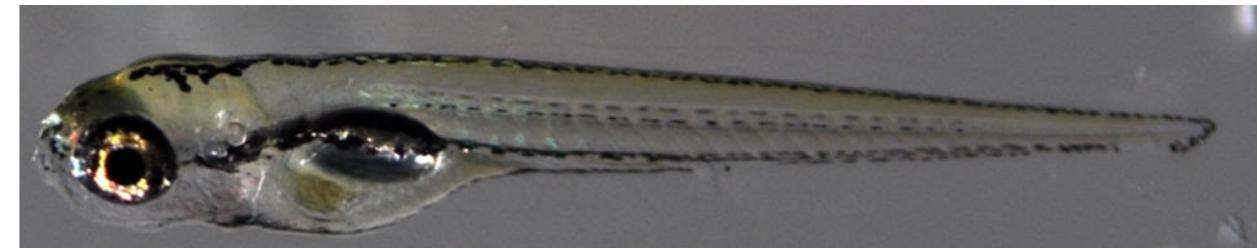
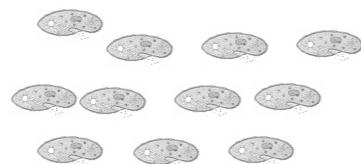


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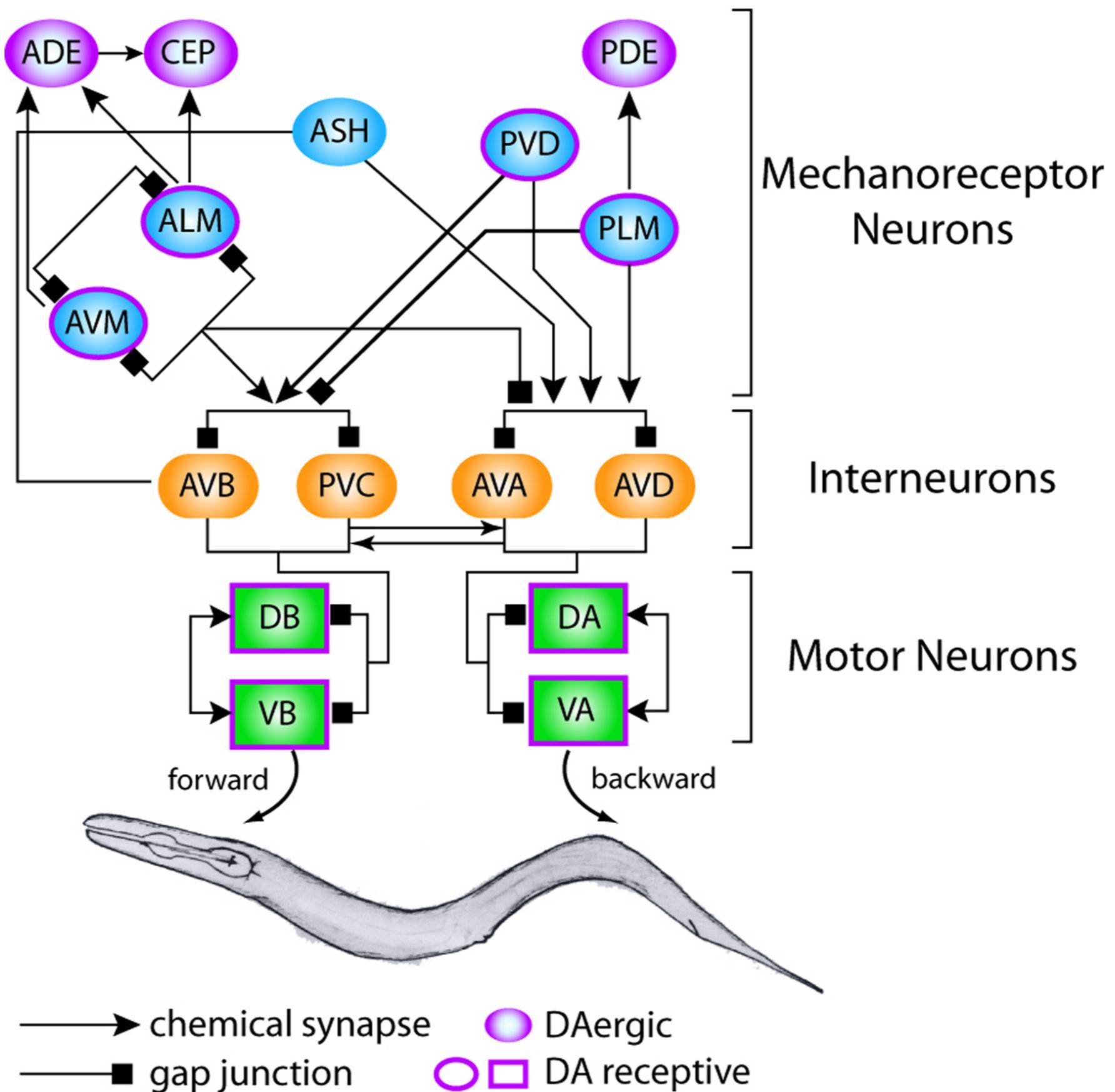


When neurons are active,
intracellular calcium concentration increases

Genetically encoded calcium indicators show neuronal activity



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



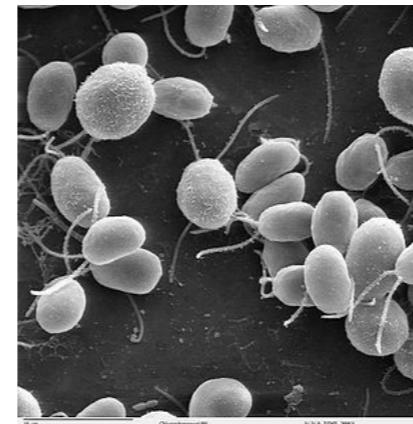
What if you want to turn neurons ON or OFF at will?



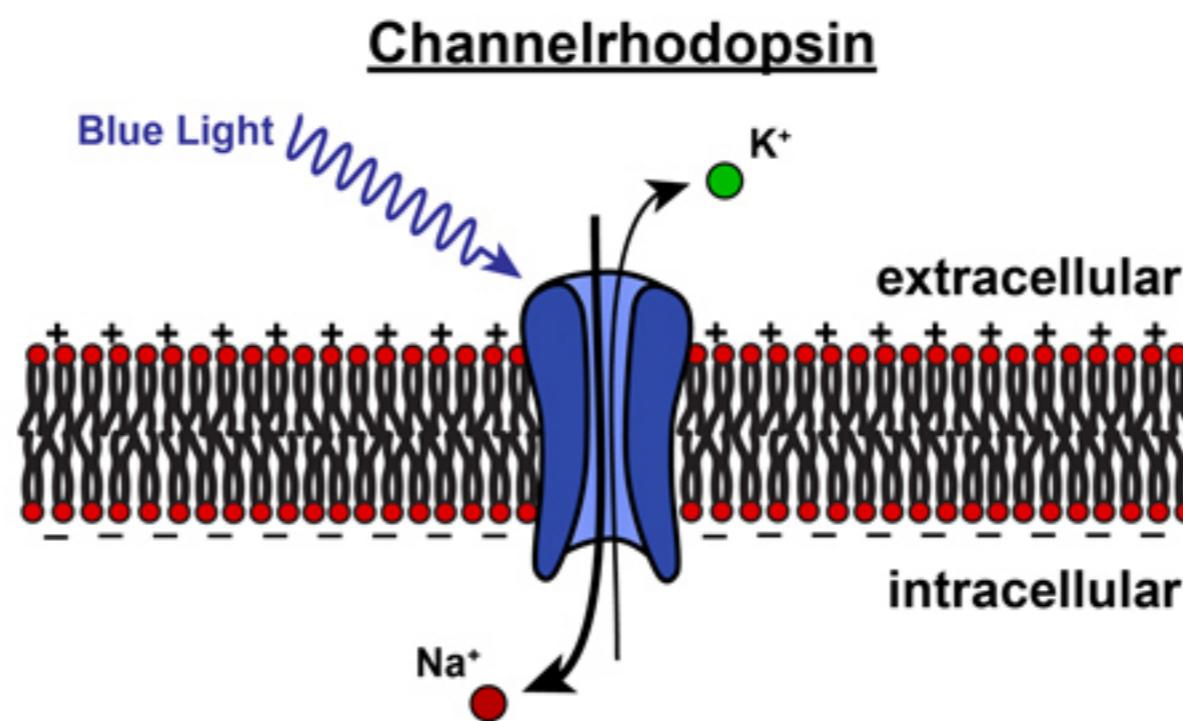
Karl Deisseroth

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

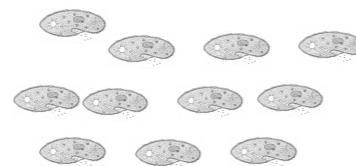
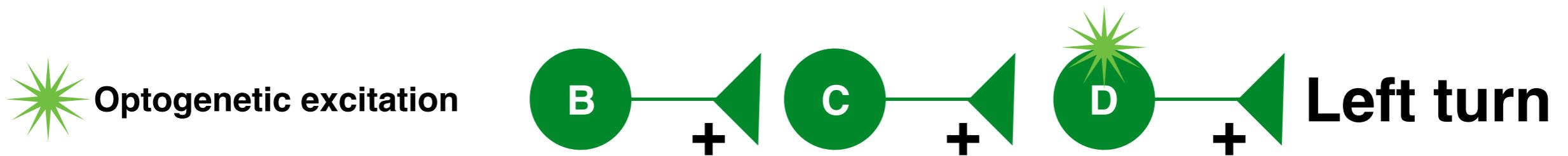
Channelrhodopsin for turning cells ON



Chlamydomonas reinhardtii



Ontogenetic control of neuronal activity



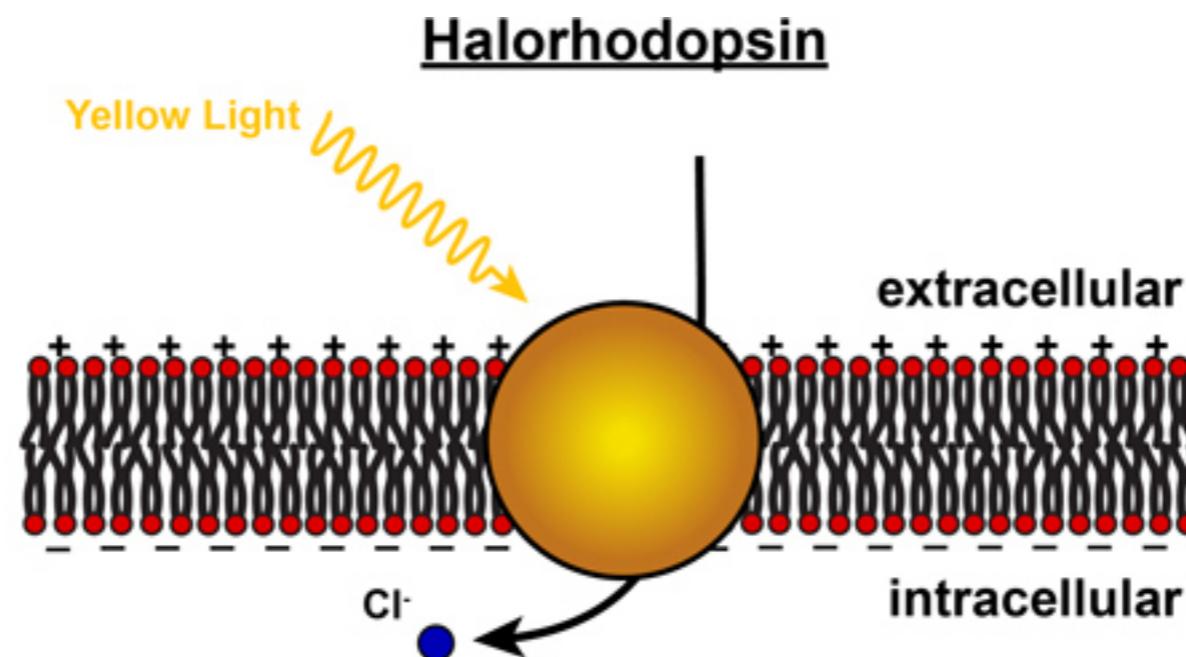
Sodium ions polarize neurons and activate them

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

Halorhodopsin for turning cells OFF



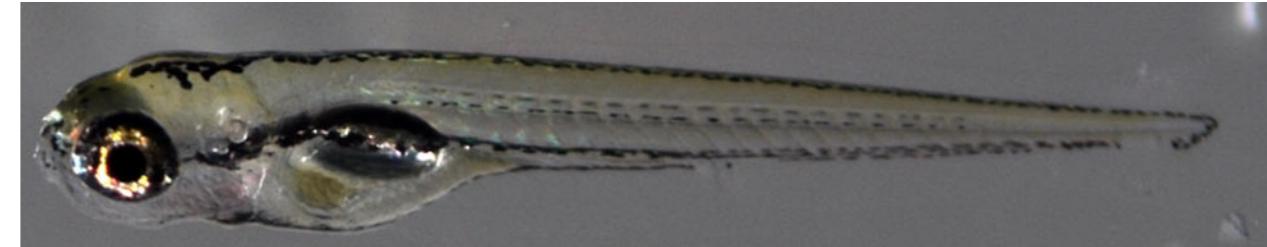
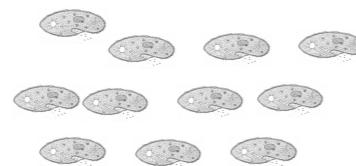
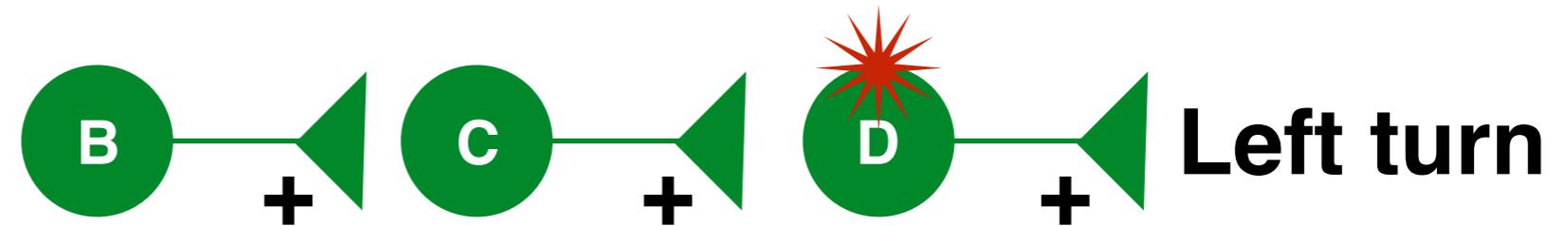
Halobacterium salinarum



Ontogenetic control of neuronal activity

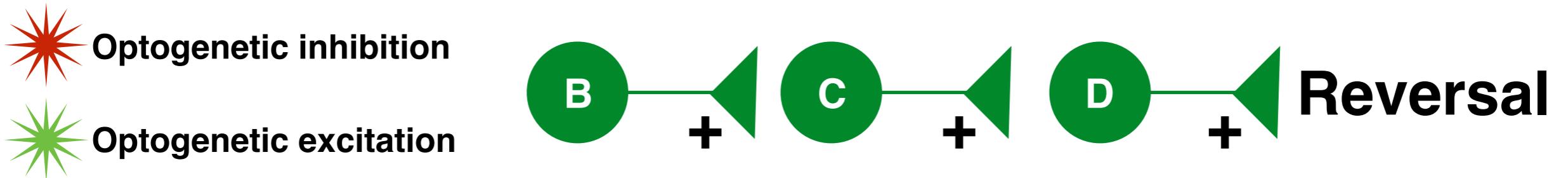


Optogenetic inhibition



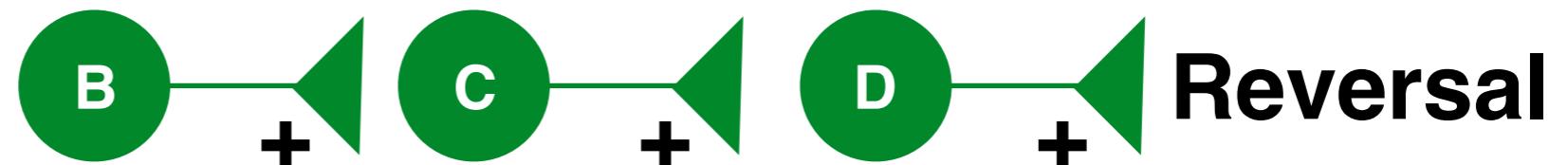
Chloride ions depolarize neurons and inhibit them

Ontogenetic control of neuronal activity



Ontogenetic control of neuronal activity

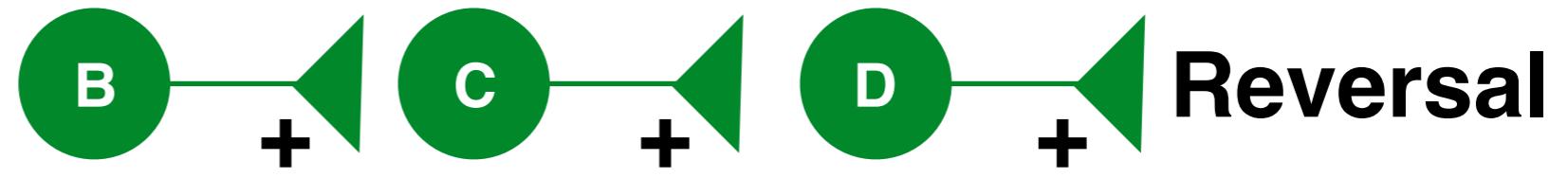
-  Optogenetic inhibition
-  Optogenetic excitation



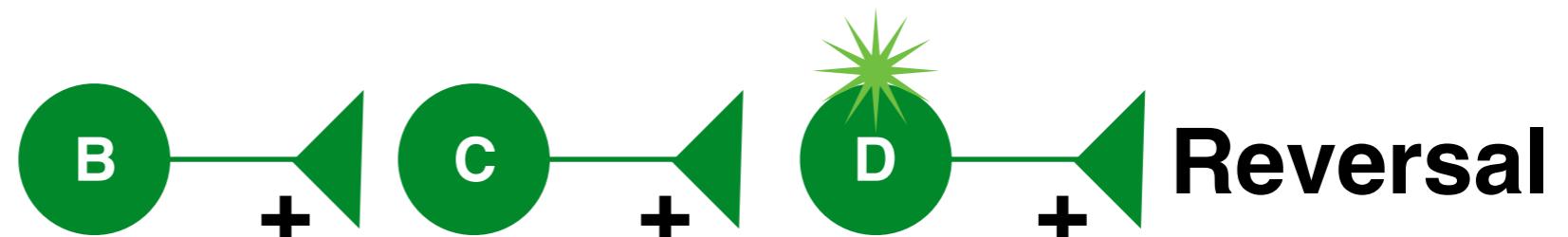
Animal crawls straight

Ontogenetic control of neuronal activity

-  Optogenetic inhibition
-  Optogenetic excitation



Animal crawls straight



Animal reverses

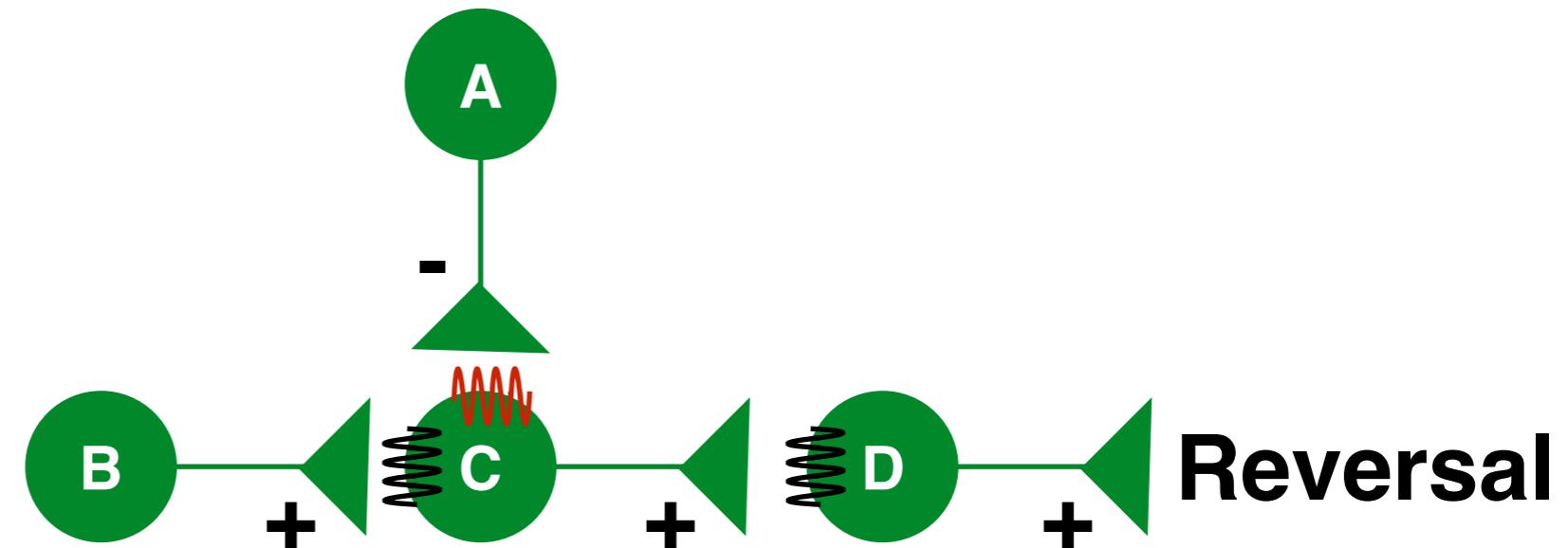
Using optogenetics to probe gene and neuronal functions

 Inhibitory receptor

 Excitatory receptor

 Optogenetic inhibition

 Optogenetic excitation



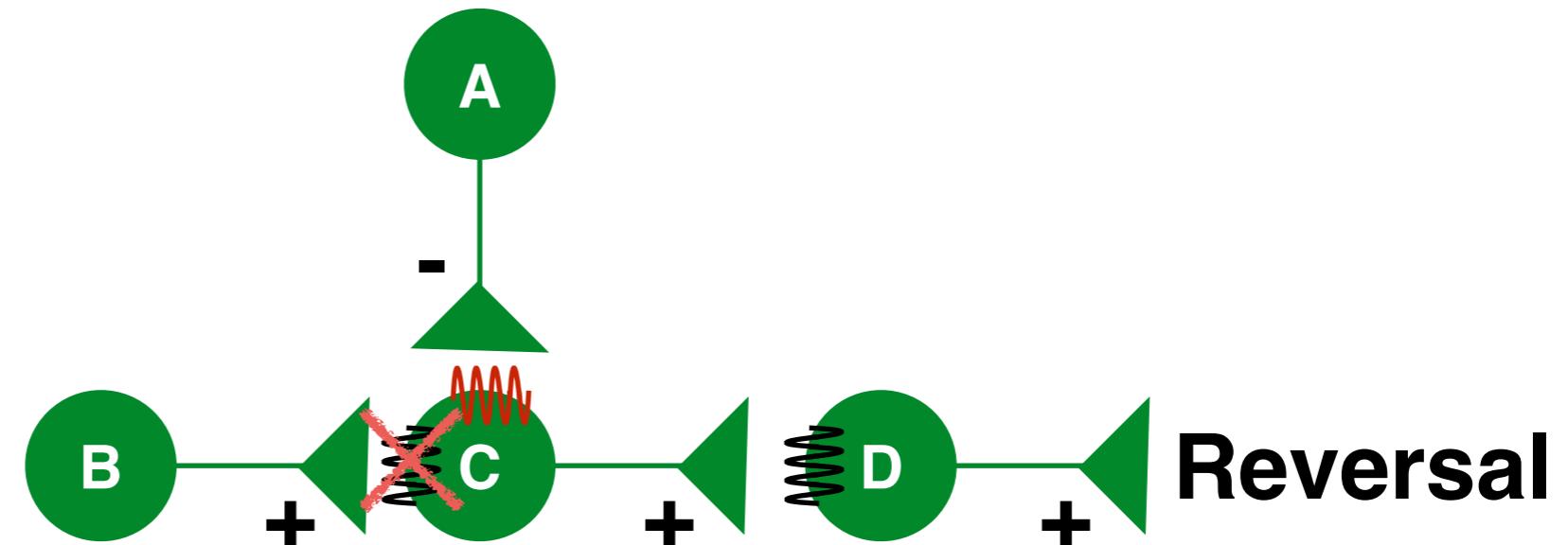
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Mutant in excitatory receptor = Animal fails to reverse

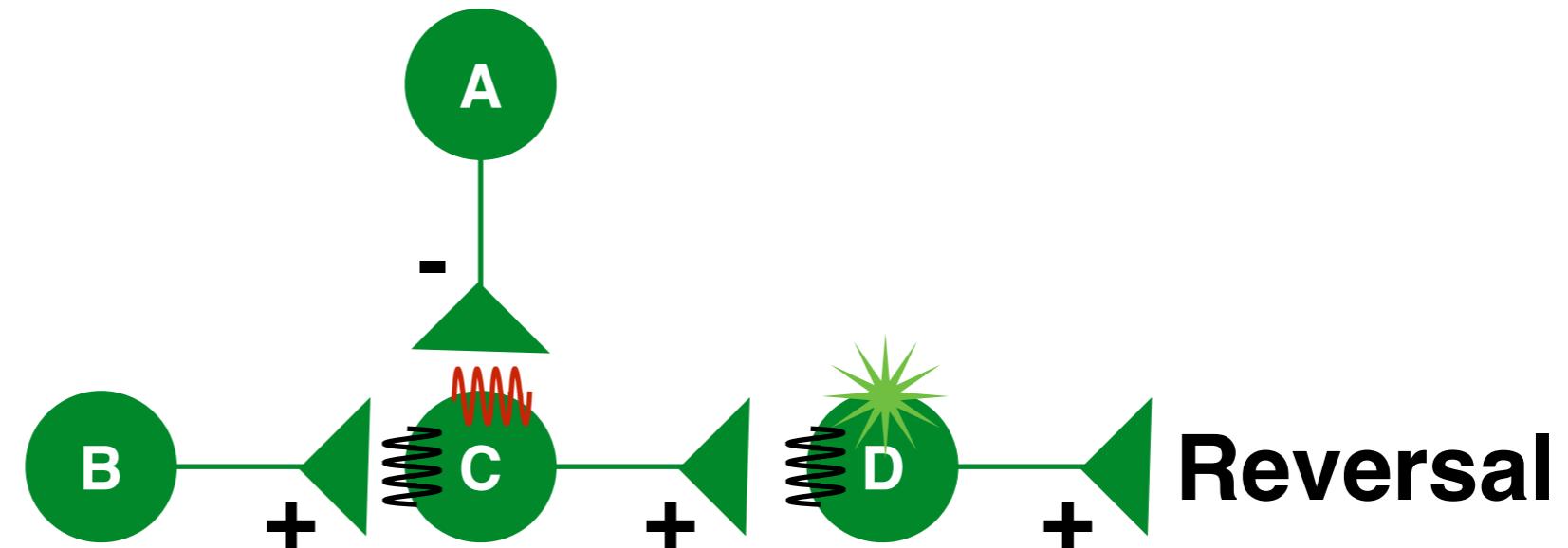
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Optogenetic excitation of D = Animal reverses

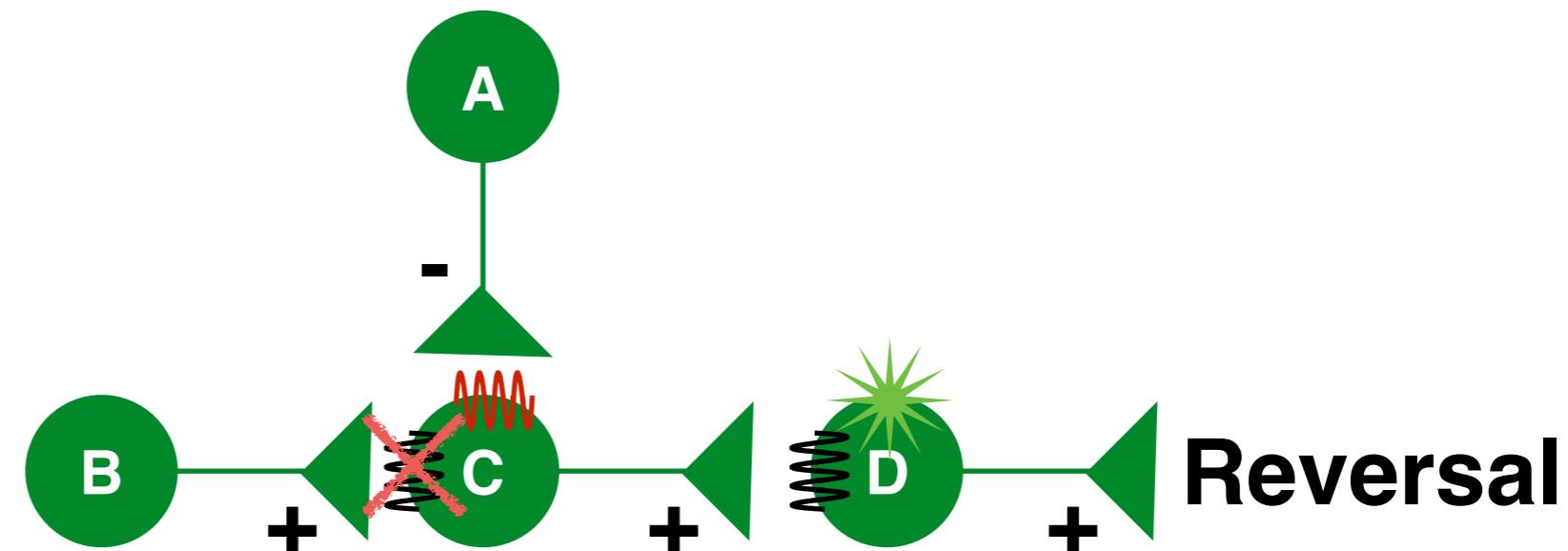
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Mutant in excitatory receptor = Animal fails to reverse

Optogenetic excitation of D = Animal reverses

D activation is epistatic to loss of receptor in C

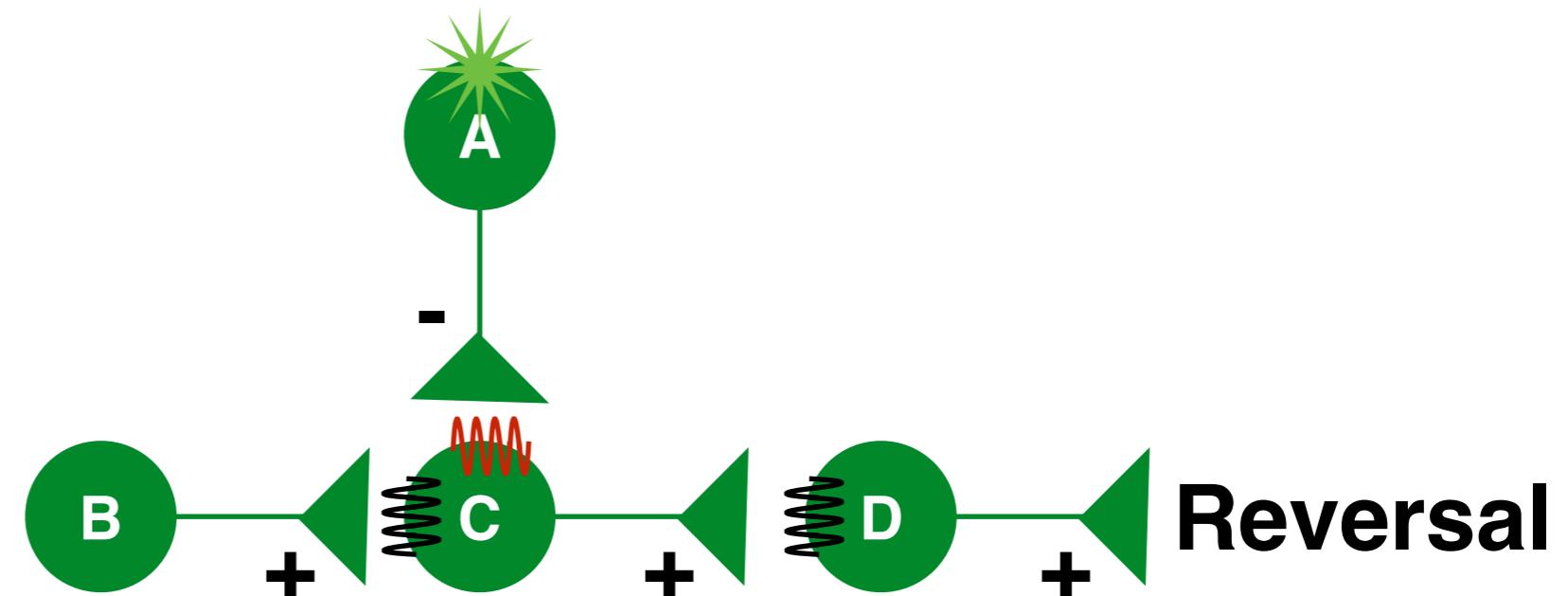
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Excitation of A = animal fails to reverse

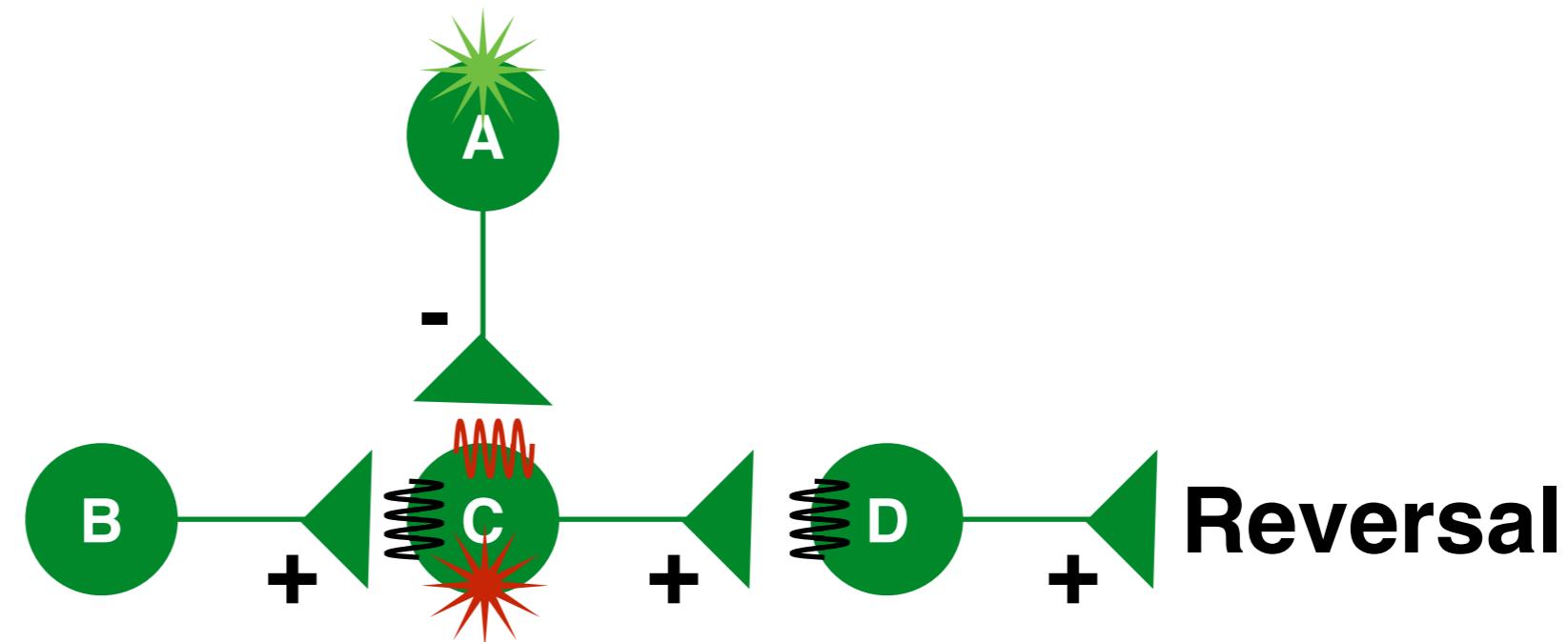
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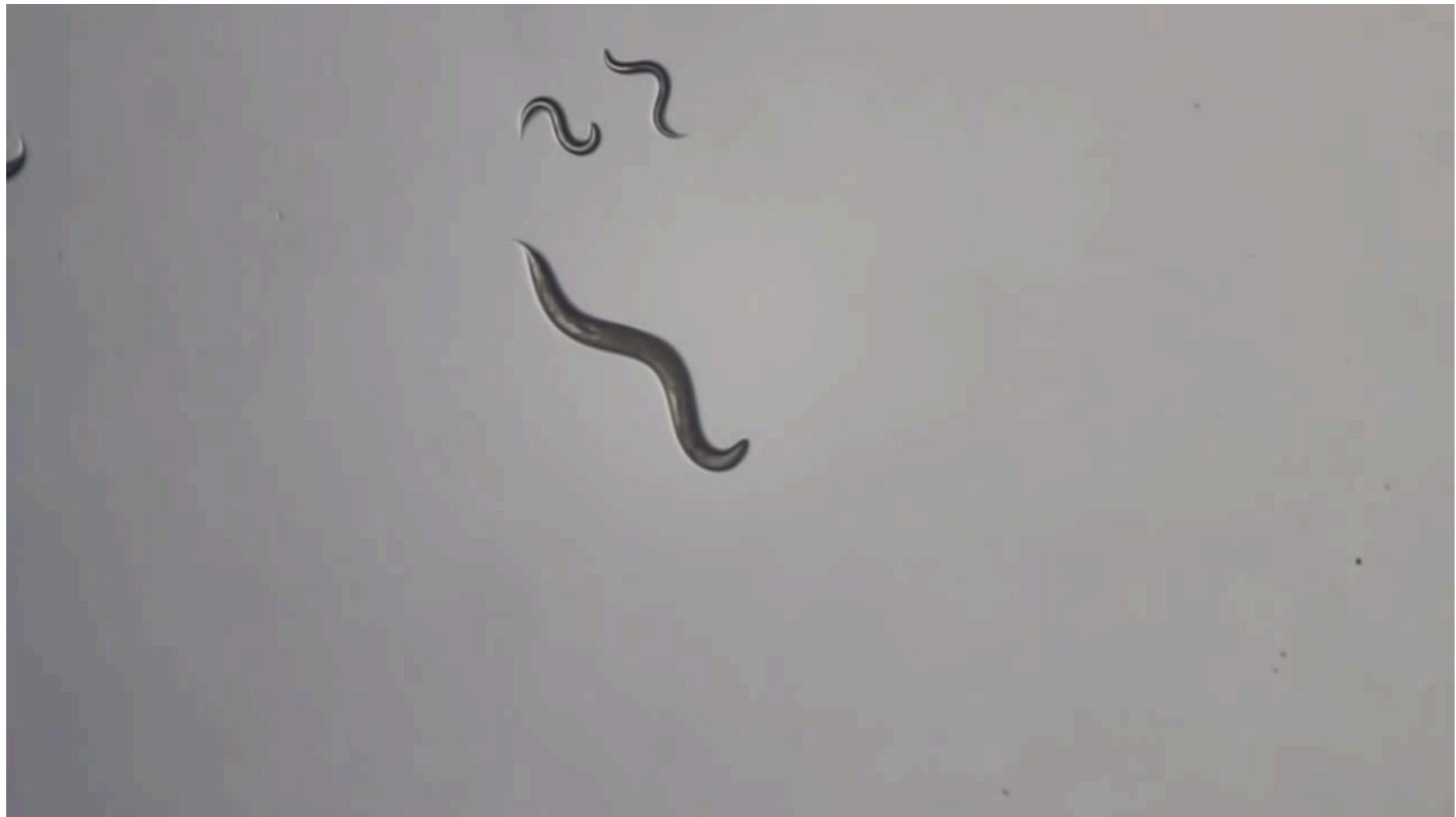


Excitation of A = animal fails to reverse

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

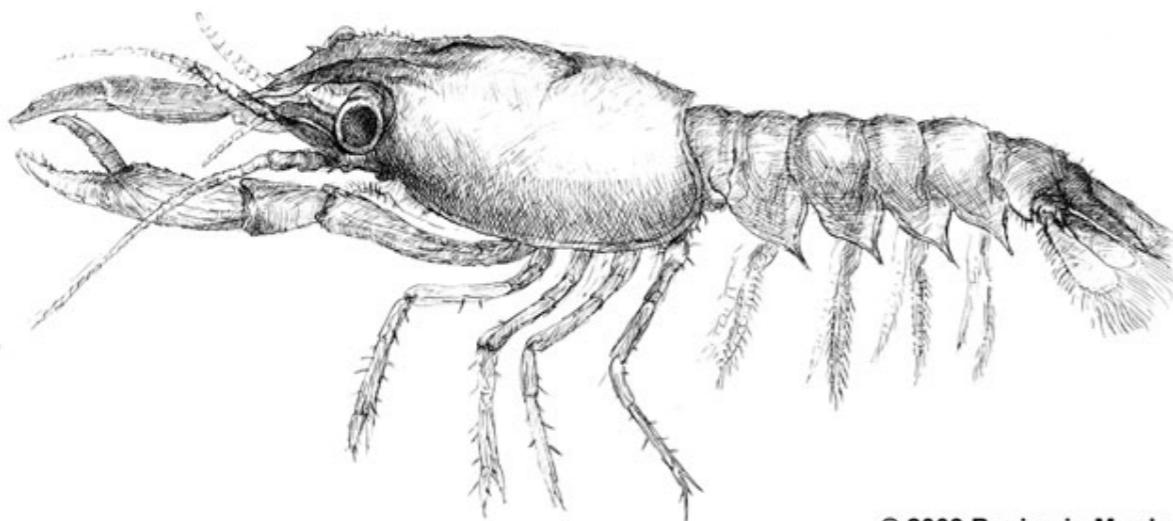


These tools allow researchers to make remote control animals

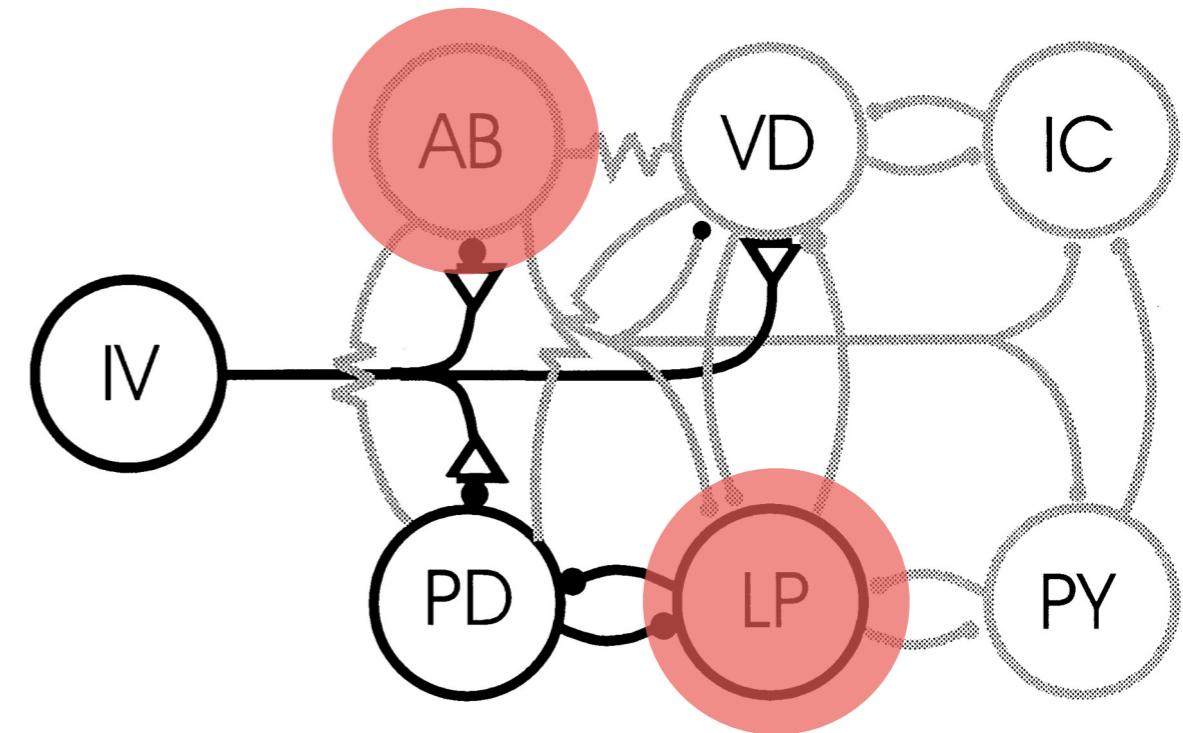
Why useful?

Build a model of how nervous systems work

The activities of neurons AND their connections regulate behavior



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Context of neurons (not just connections) matters!

The BRAIN Initiative

Brain Research through Advancing Innovative Neurotechnologies

