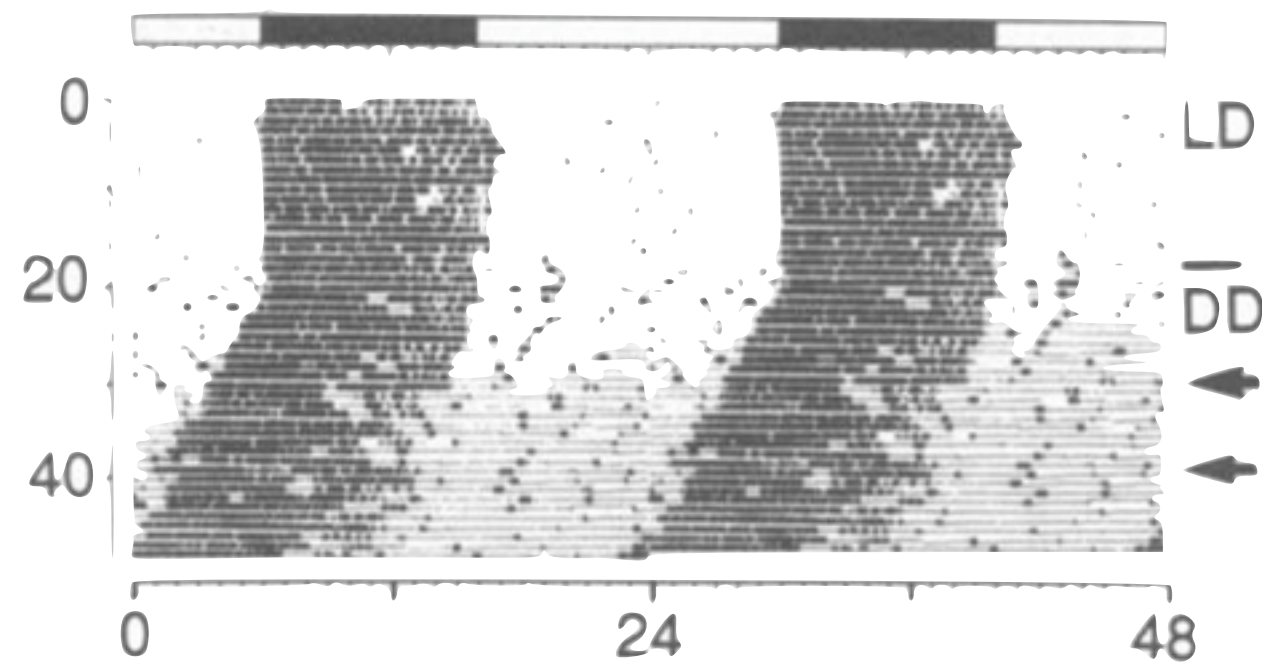
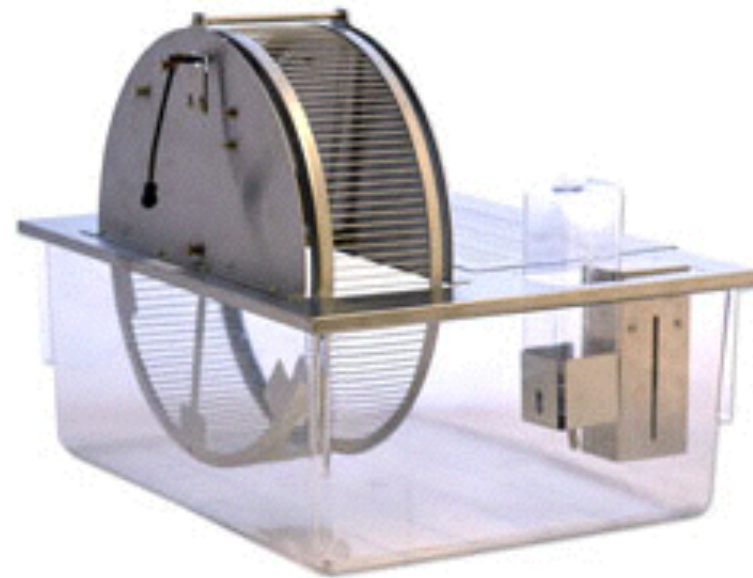
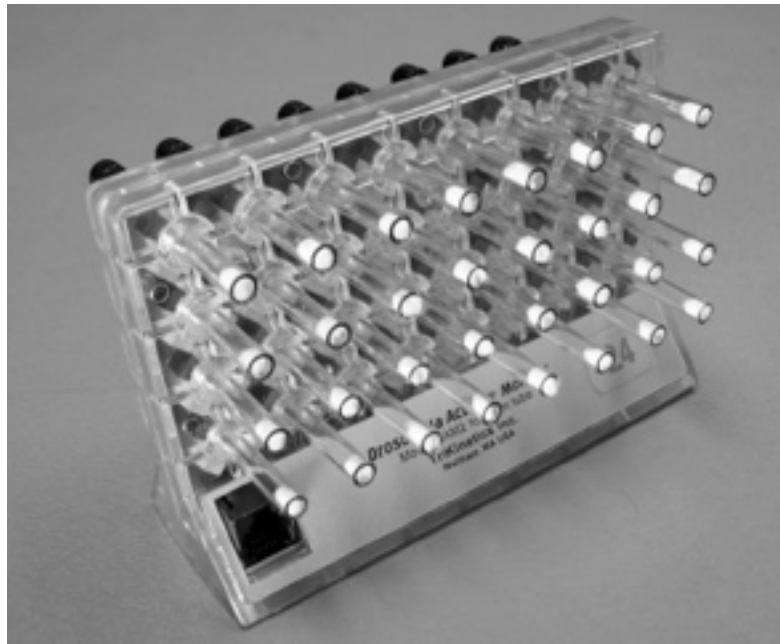
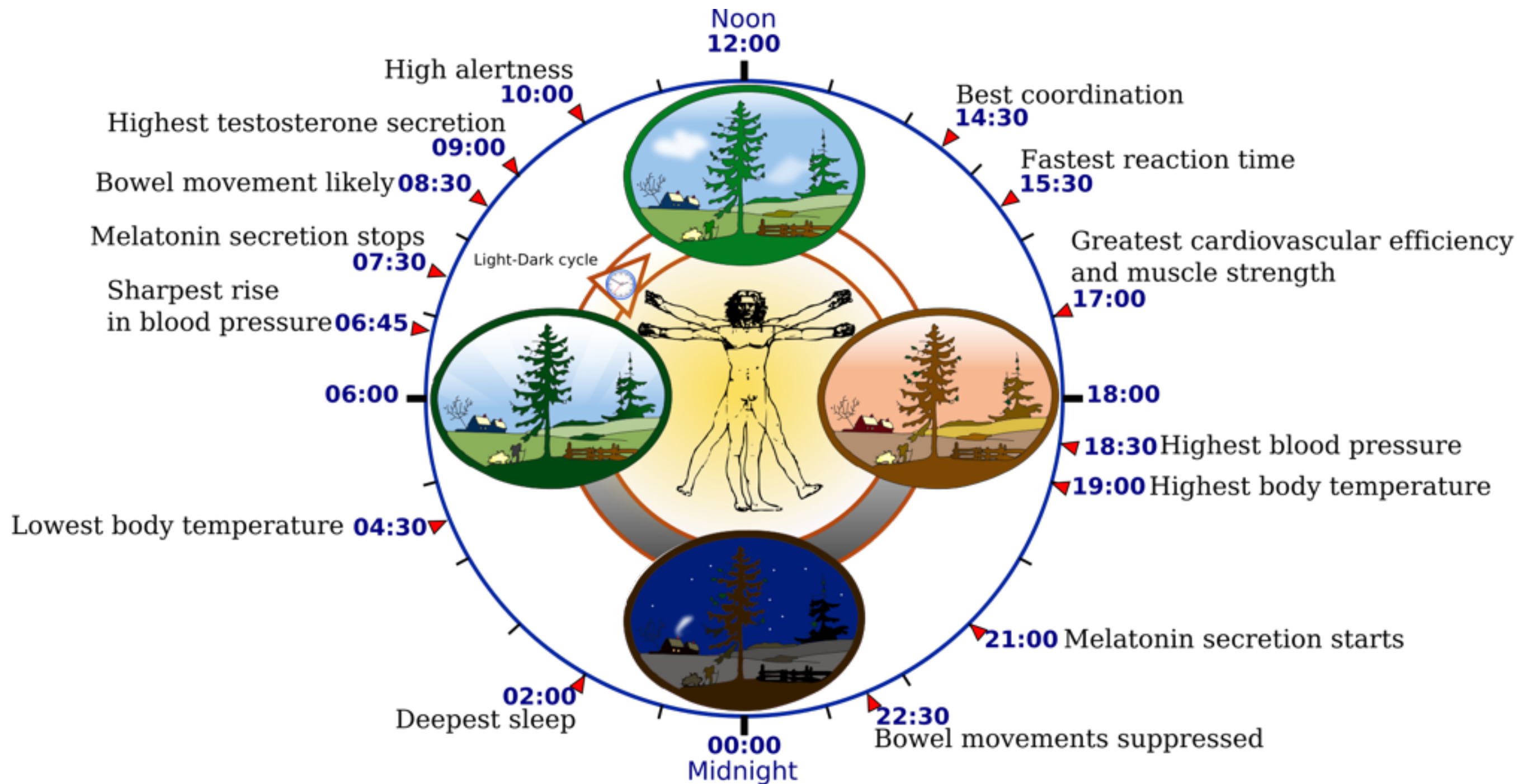


Bio393: Genetic Analysis

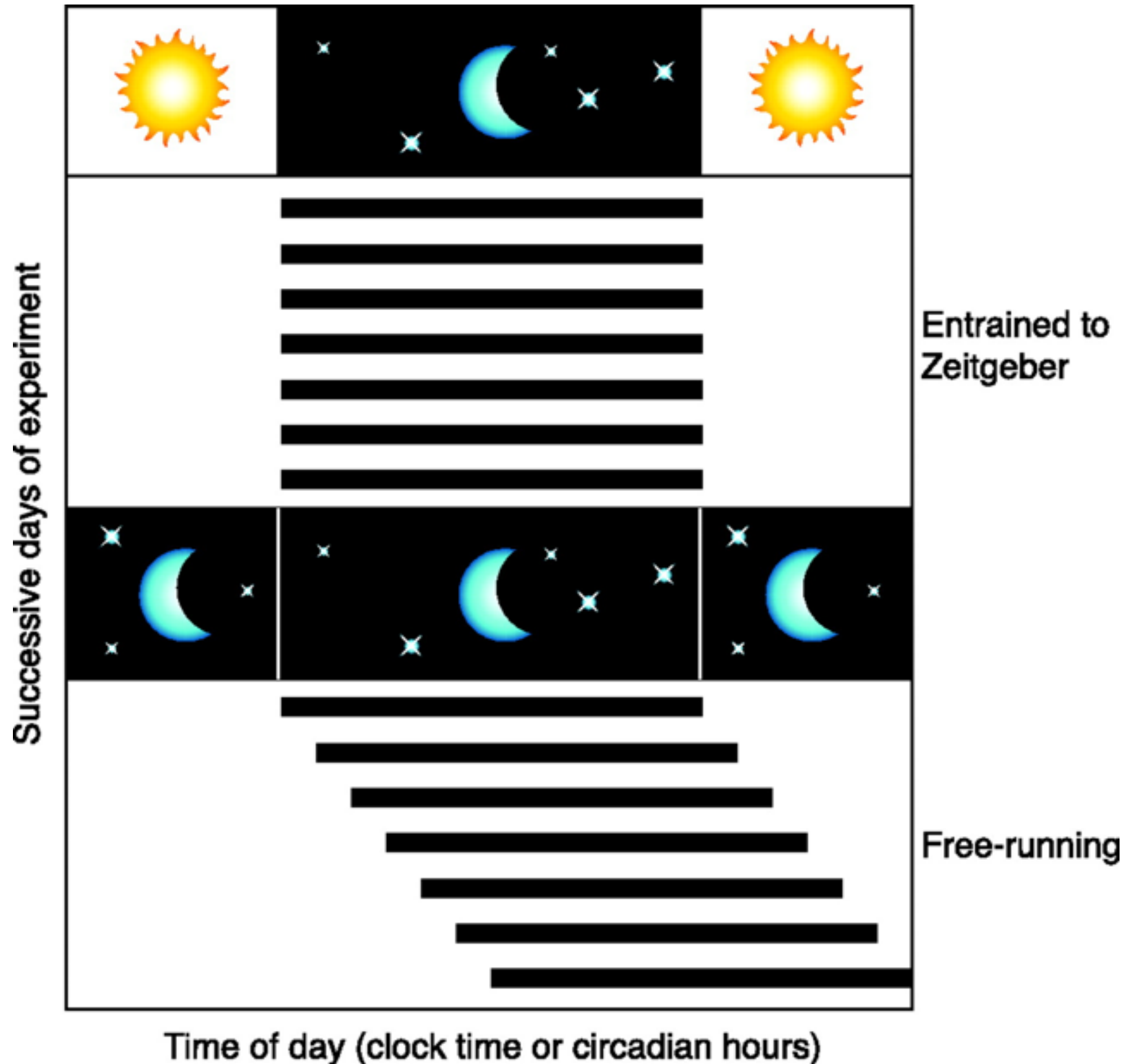
Behavioral genetics



Nearly all organisms have a natural cycle of activity



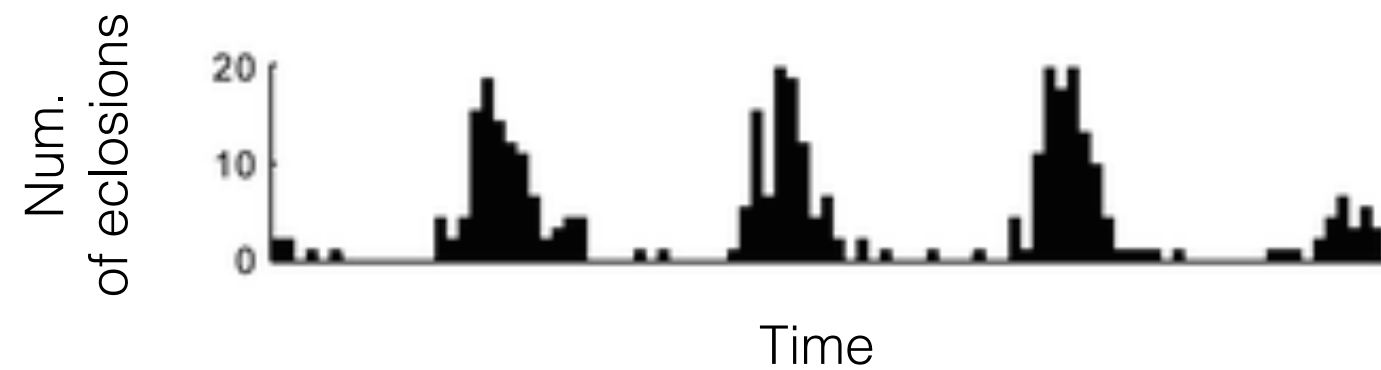
Light and/or temperature can entrain the cycle



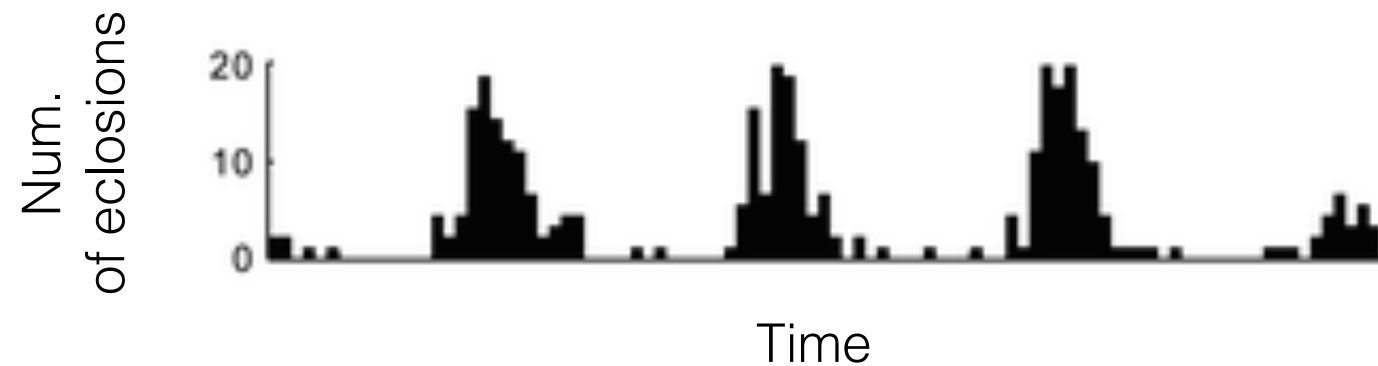


Seymour Benzer

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

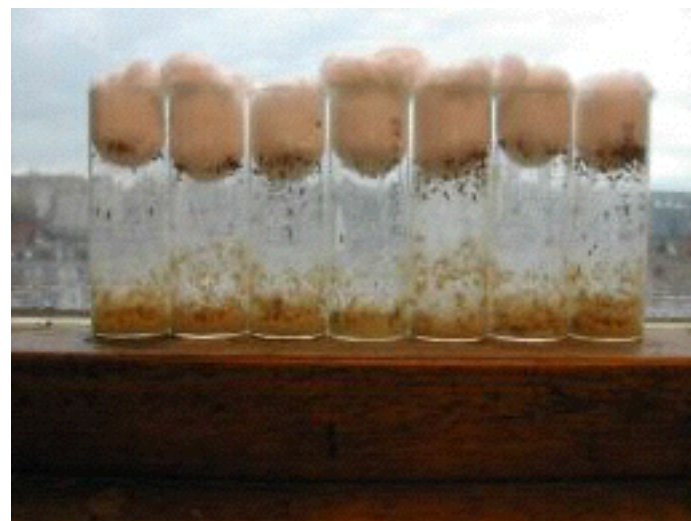


***Drosophila* eclose from the pupal case with a reproducible cycle**

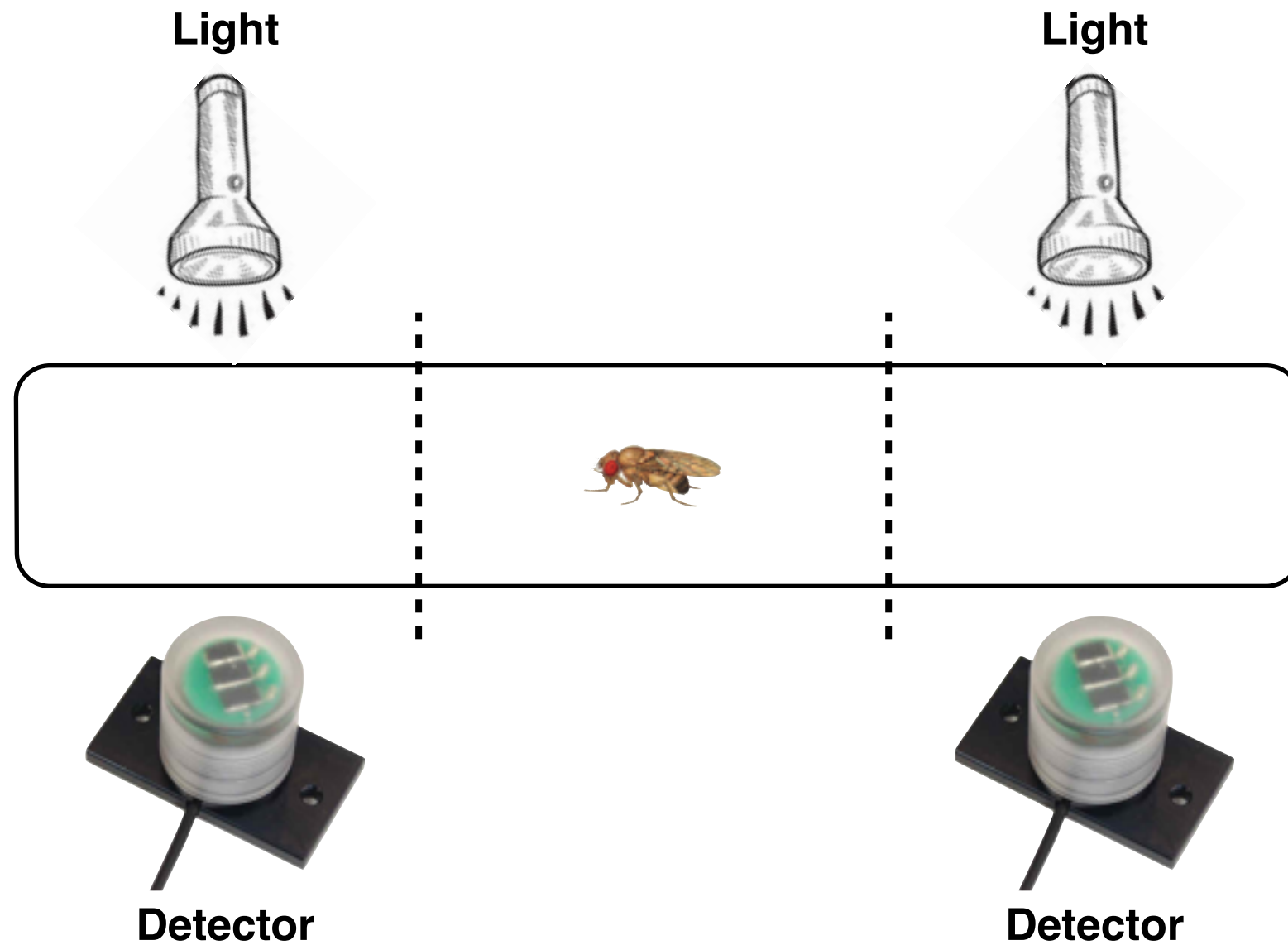


Difficult assay

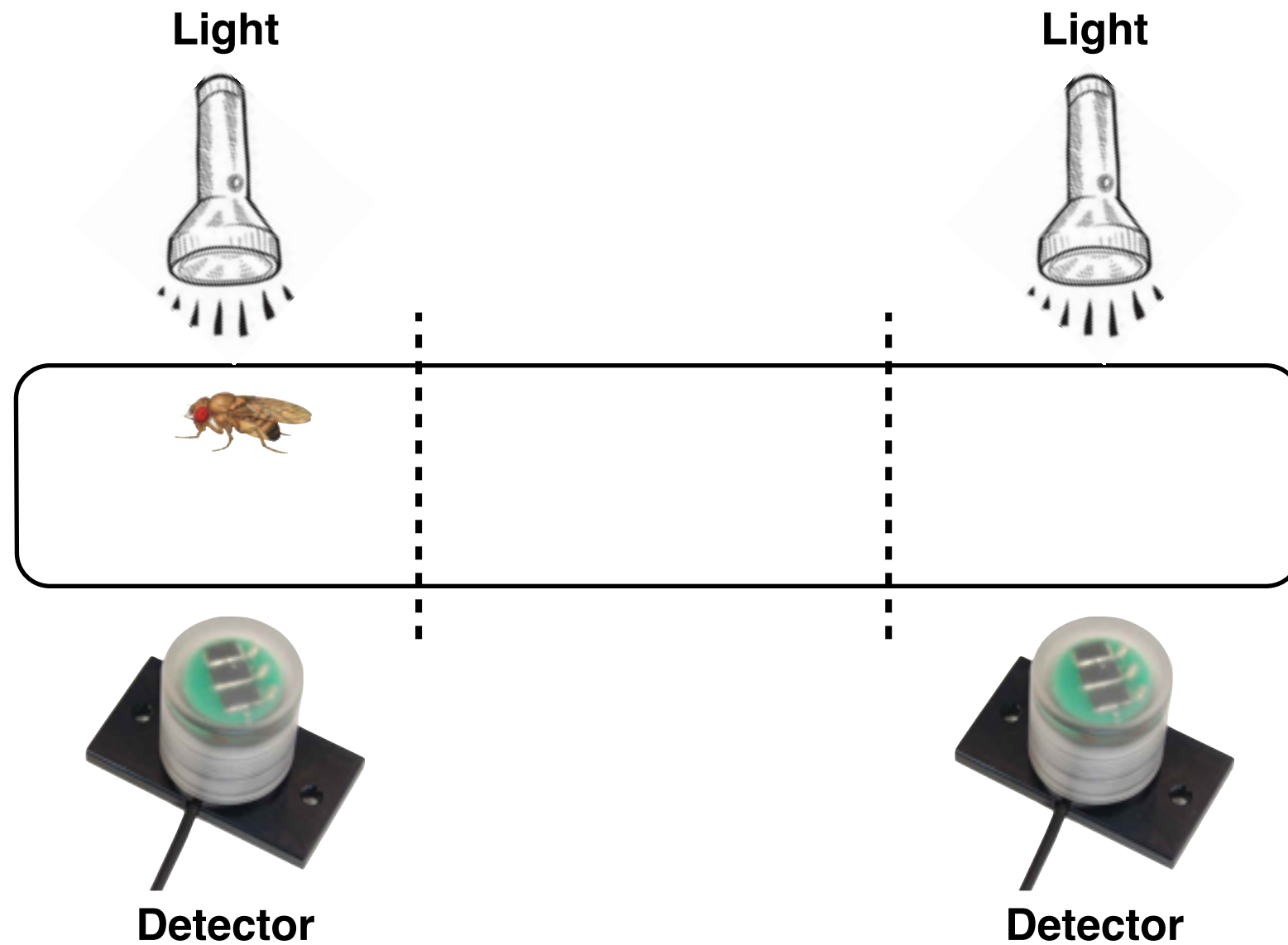
You need to watch the flies a lot of the time



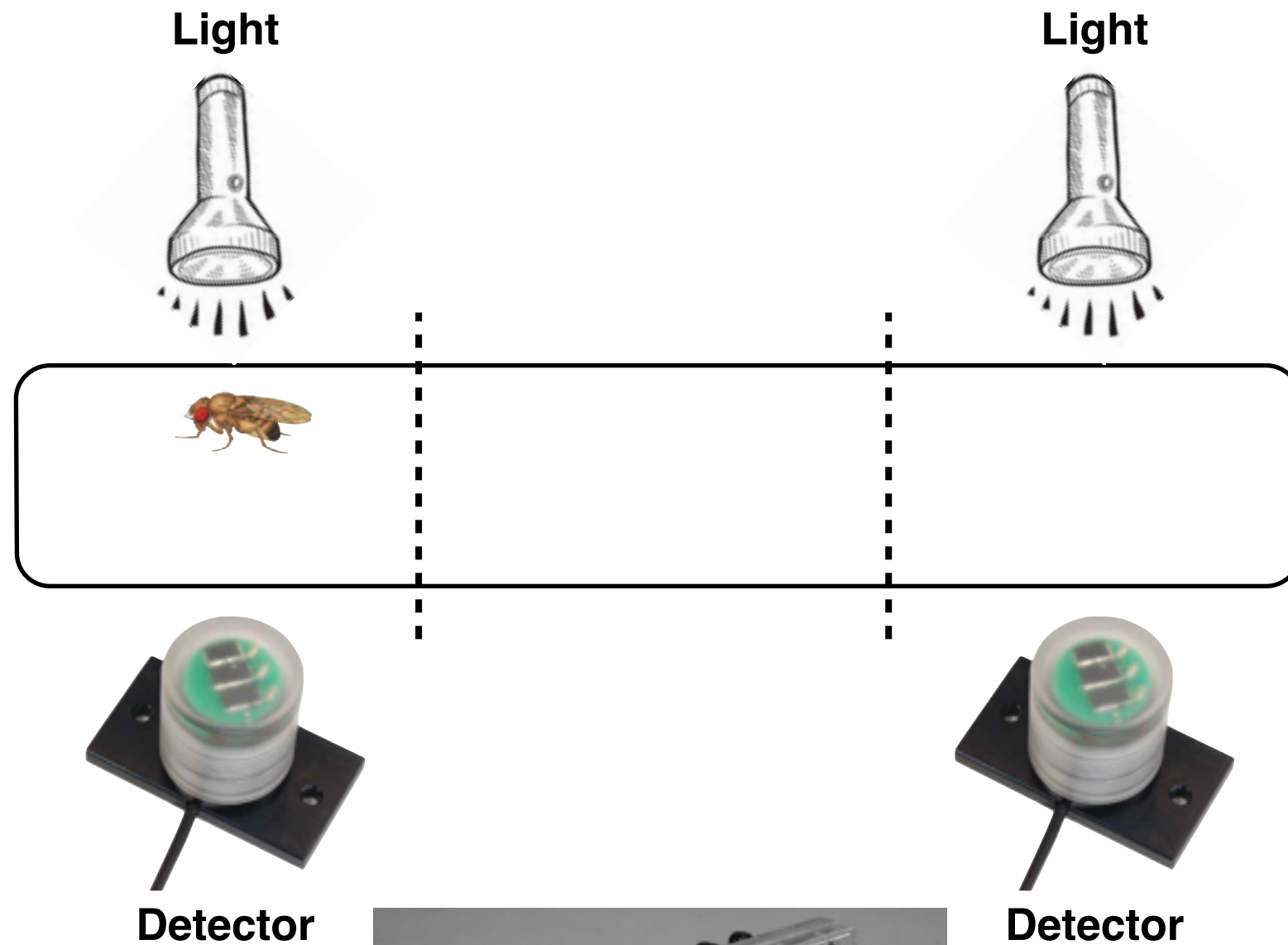
***Drosophila* movement cycles and is much easier to score**



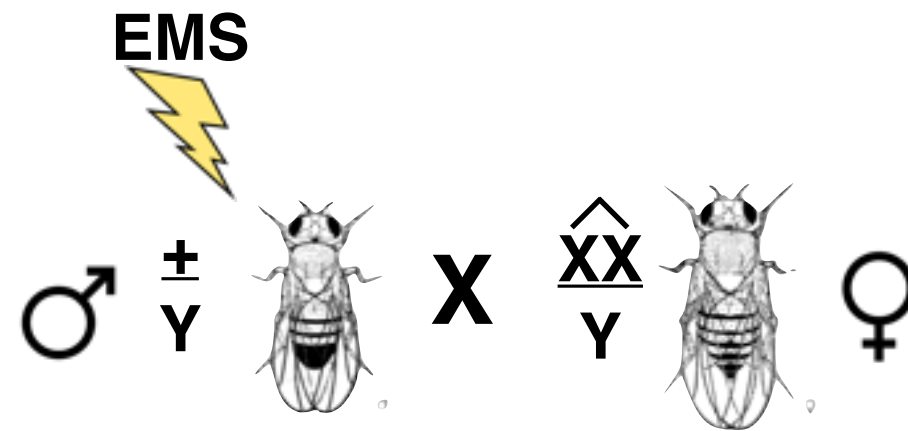
***Drosophila* movement cycles and is much easier to score**



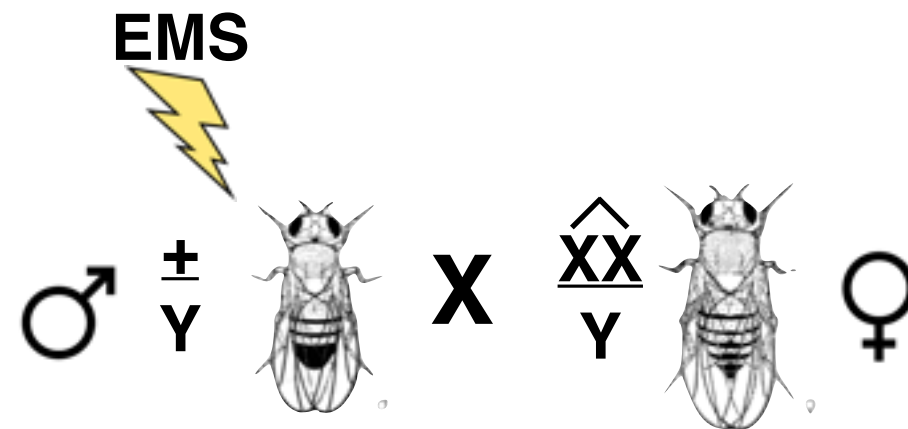
***Drosophila* movement cycles and is much easier to score**



The first genetic screen for behavioral mutants

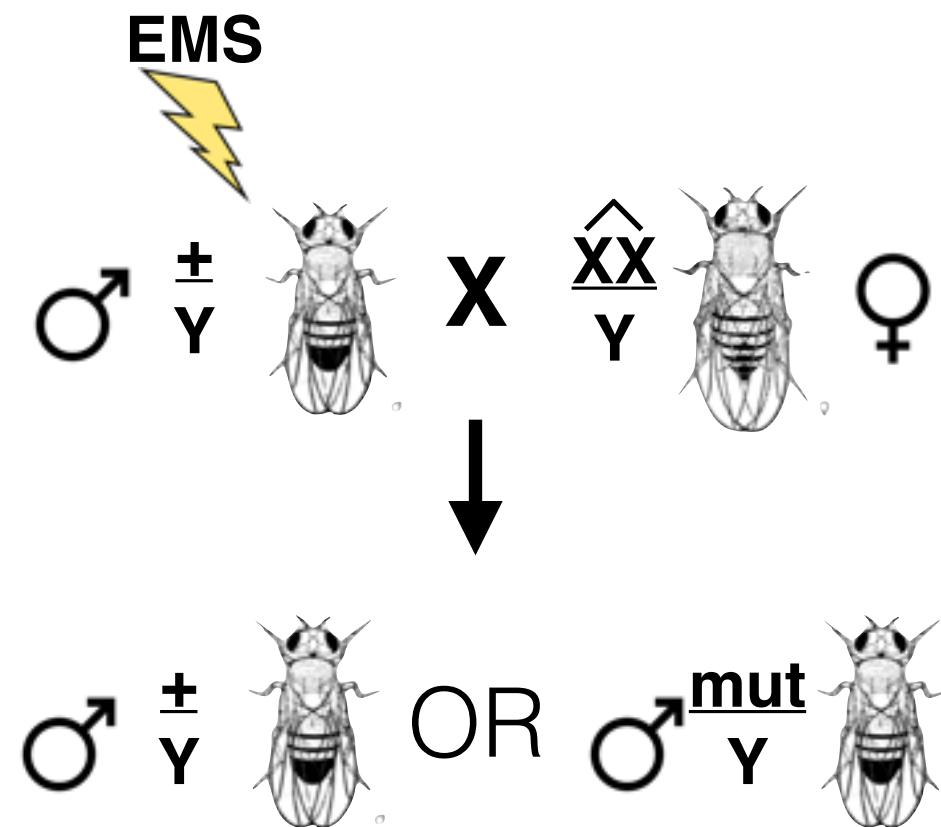


The first genetic screen for behavioral mutants



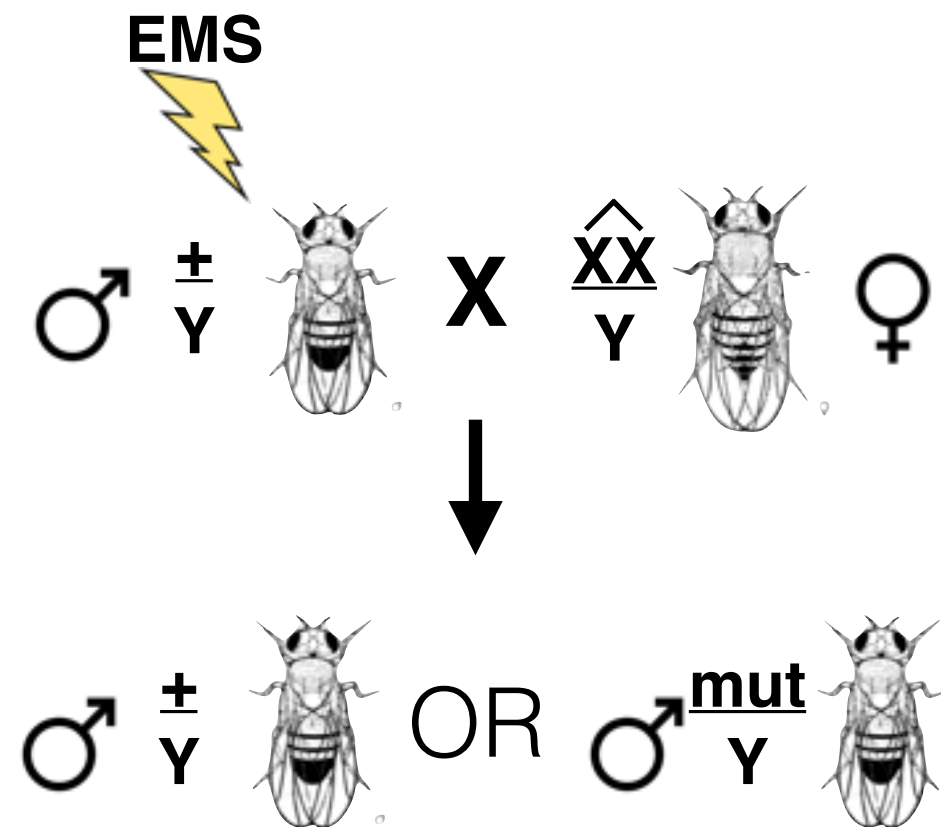
	\widehat{XX}	Y
X	\widehat{XXX} dead	XY ♂
Y	\widehat{XXY} ♀	YY dead

The first genetic screen for behavioral mutants



	\widehat{XX}	Y
X	\widehat{XXX} dead	XY ♂
Y	\widehat{XXY} ♀	YY dead

The first genetic screen for behavioral mutants

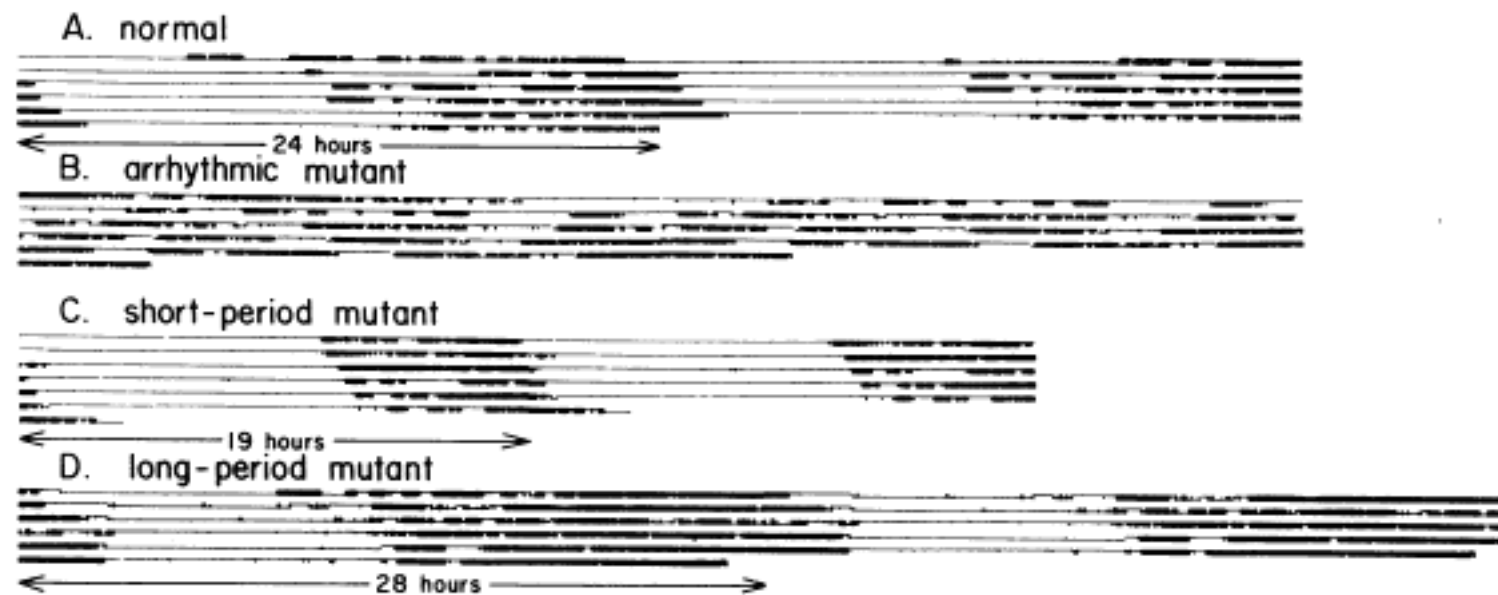


Screened 2,000 males

got three mutants
that affected all cyclic behaviors

	\hat{XX}	Y
X	\hat{XXX} dead	XY ♂
Y	\hat{XXY} ♀	YY dead

period mutants



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

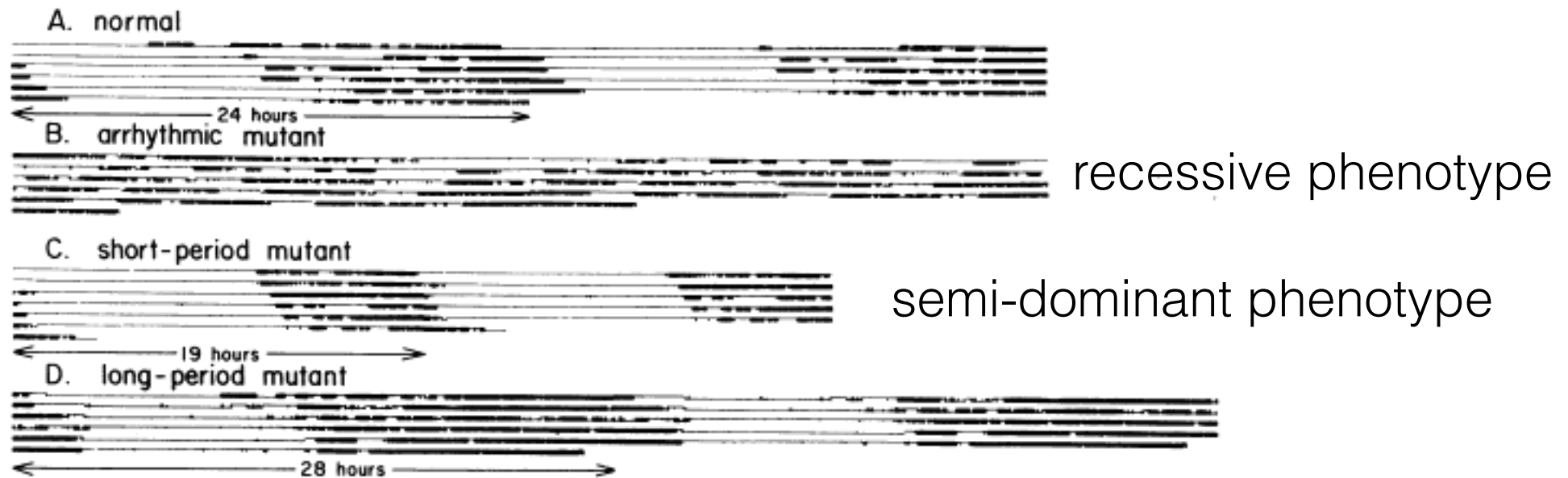
period mutants



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

$$\frac{\text{arrhythmic}}{\text{arrhythmic}} > \frac{\text{arrhythmic}}{+}$$

period mutants

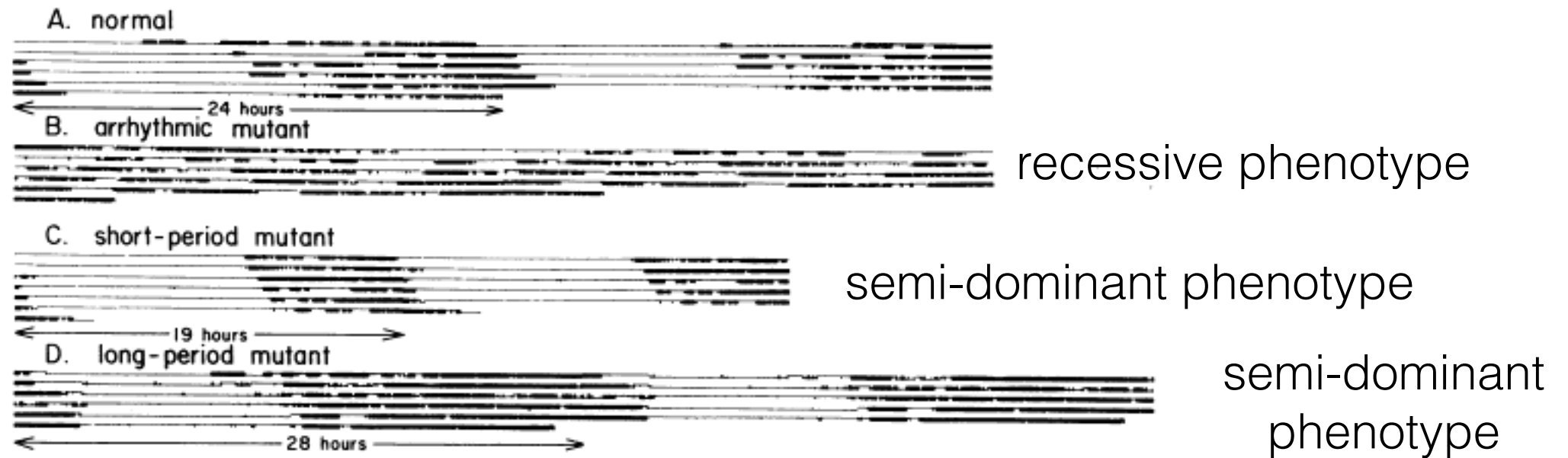


All three mutations mapped to the same place
on the X chromosome

arrhythmic > arrhythmic
arrhythmic +

short > ±
+ +

period mutants



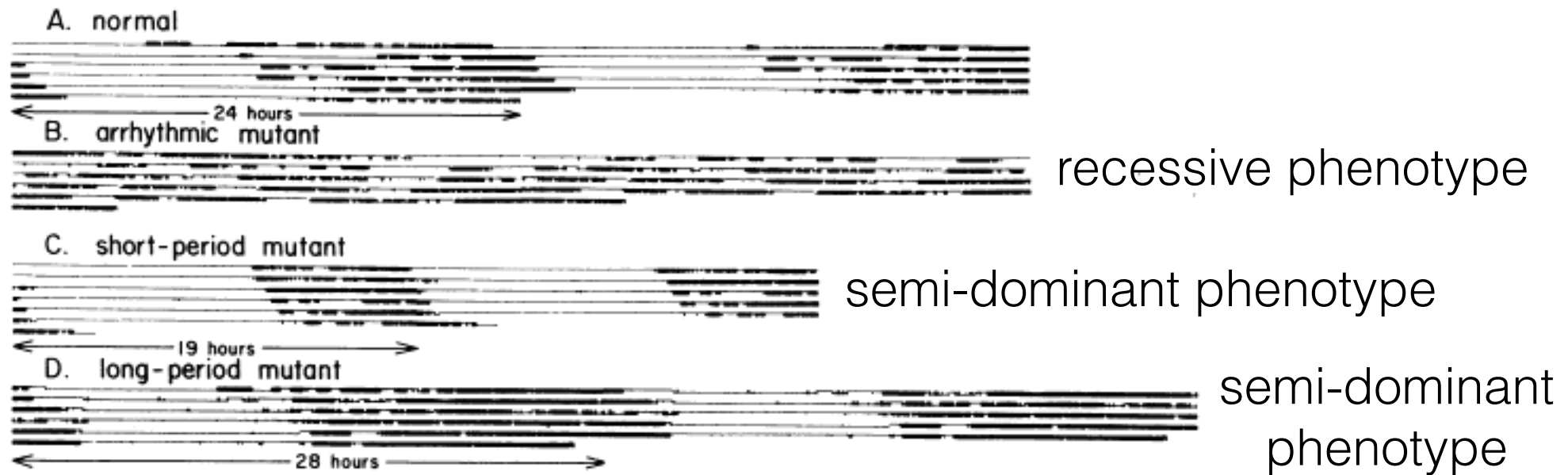
All three mutations mapped to the same place
on the X chromosome

arrhythmic > arrhythmic
arrhythmic +

short > \pm
+ +

long > \pm
+ +

period mutants

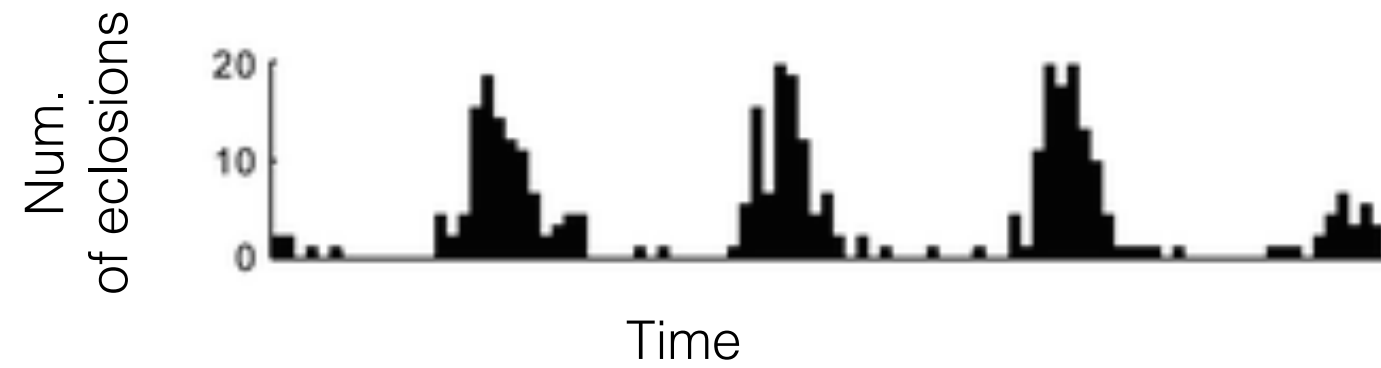


$\frac{\text{arrhythmic}}{\text{arrhythmic}} = \frac{\text{arrhythmic}}{\text{deficiency}}$

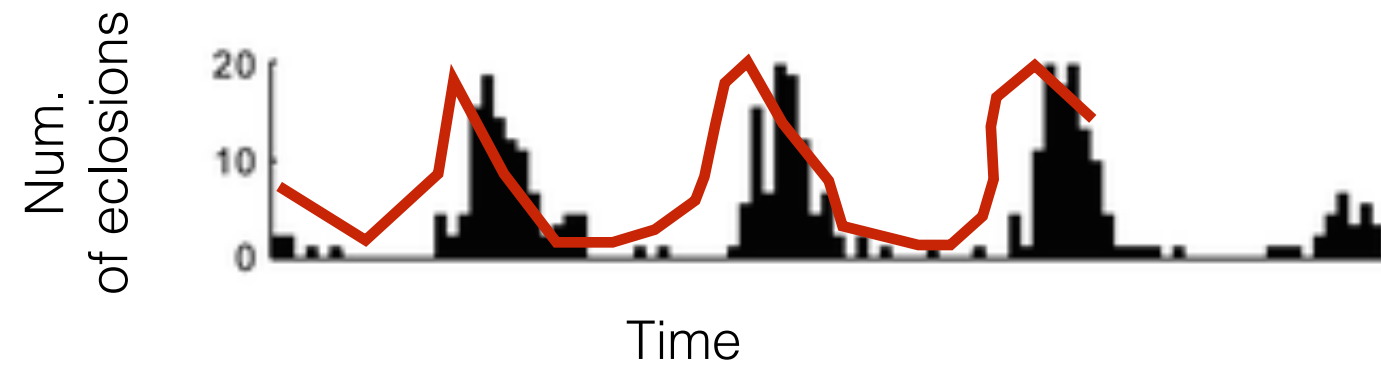
$\frac{\text{short}}{\text{short}} = \frac{\text{short}}{\text{deficiency}} = \frac{\text{short}}{\text{arrhythmic}} > \frac{\text{short}}{+} > \frac{\pm}{+}$

$\frac{\text{long}}{\text{long}} = \frac{\text{long}}{\text{deficiency}} = \frac{\text{long}}{\text{arrhythmic}} > \frac{\text{long}}{+} > \frac{\pm}{+}$

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

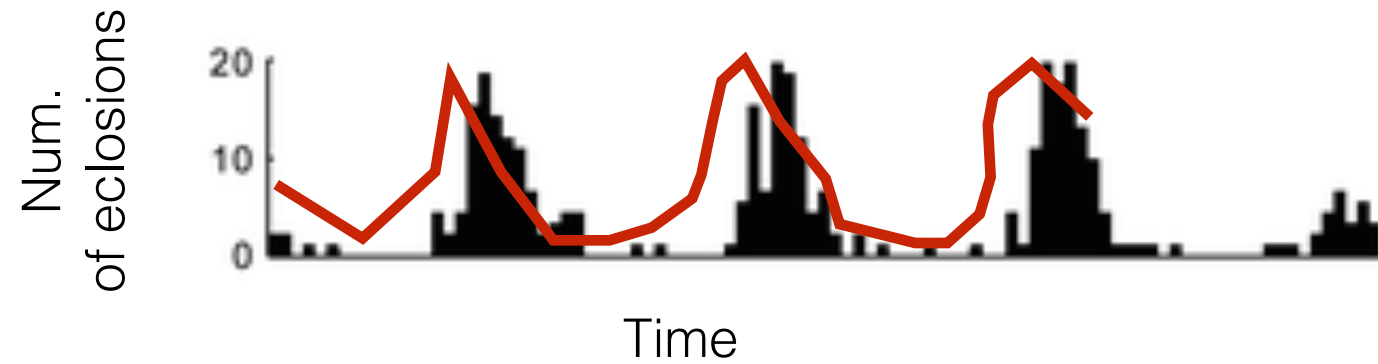


***period* encoded a novel protein at the time**



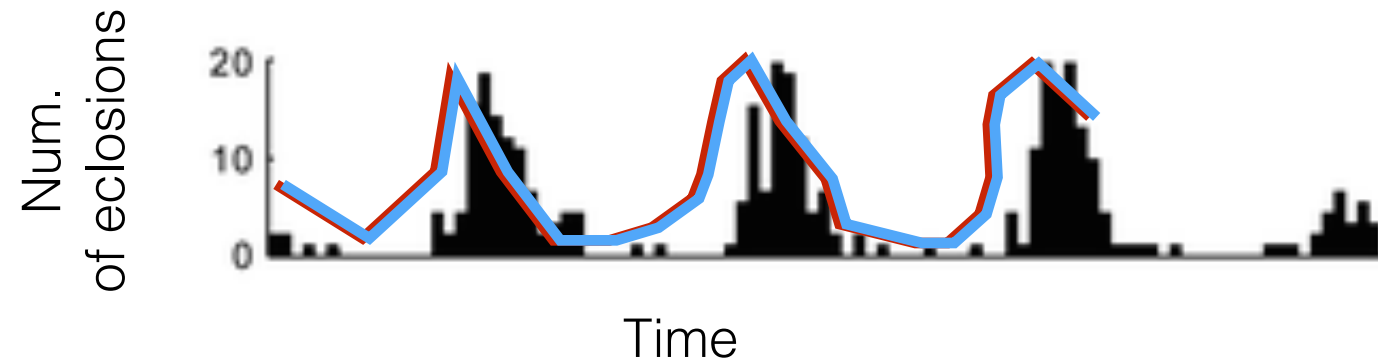
period transcription and translation cycles

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



period transcription and translation cycles

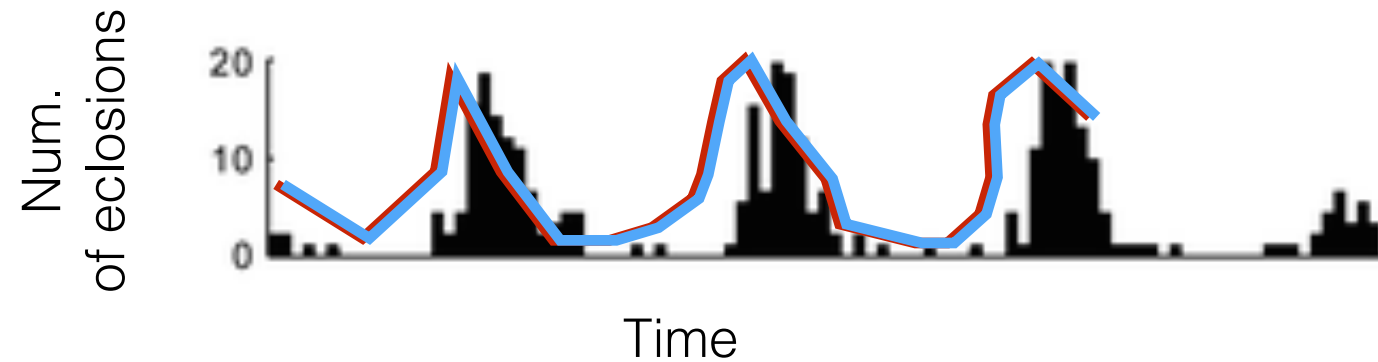
Another genetic screen with a focus on chromosome 2 found the gene *timeless*



period transcription and translation cycles

timeless transcription and translation cycles

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

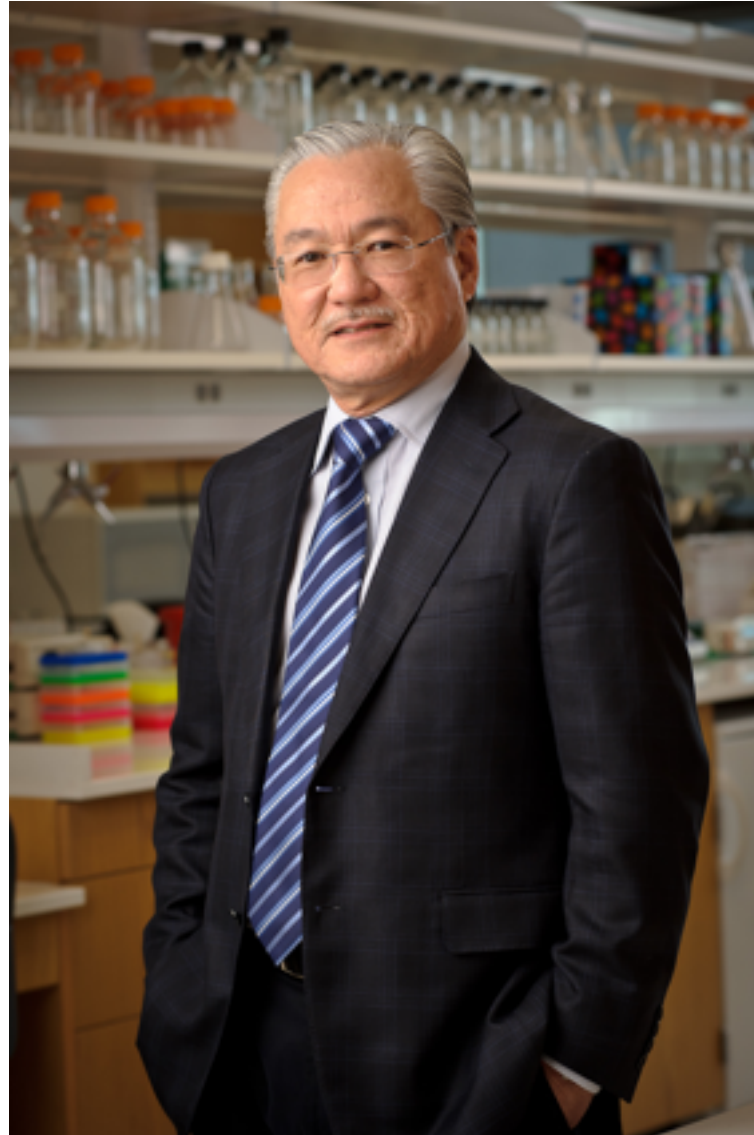


period transcription and translation cycles

timeless transcription and translation cycles

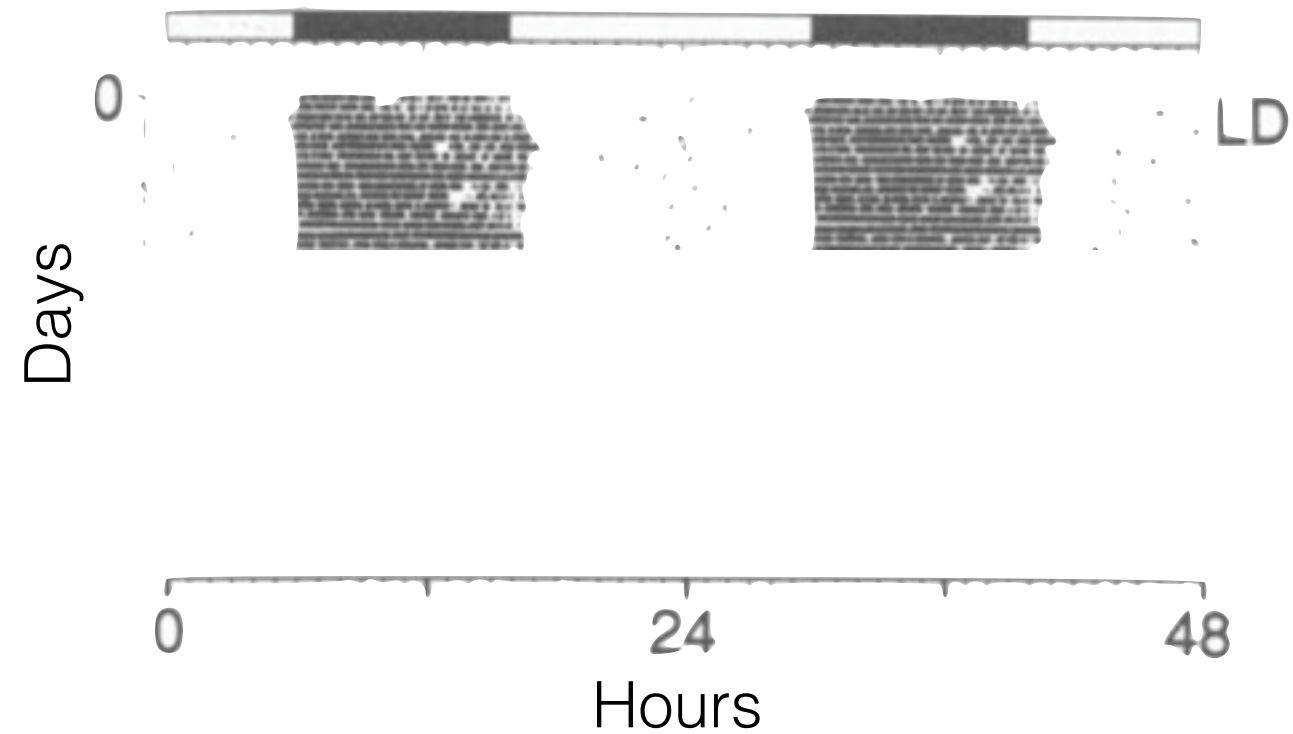
Period

Timeless

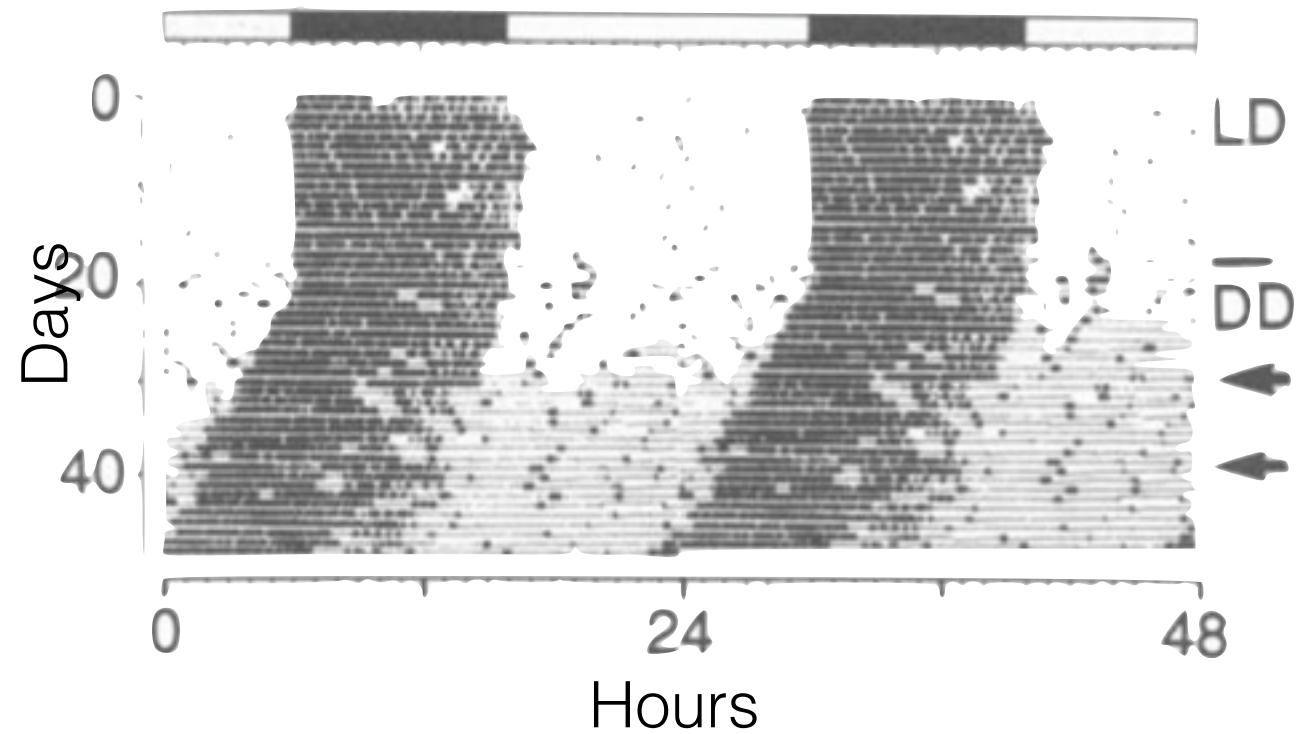


Joe Takahashi

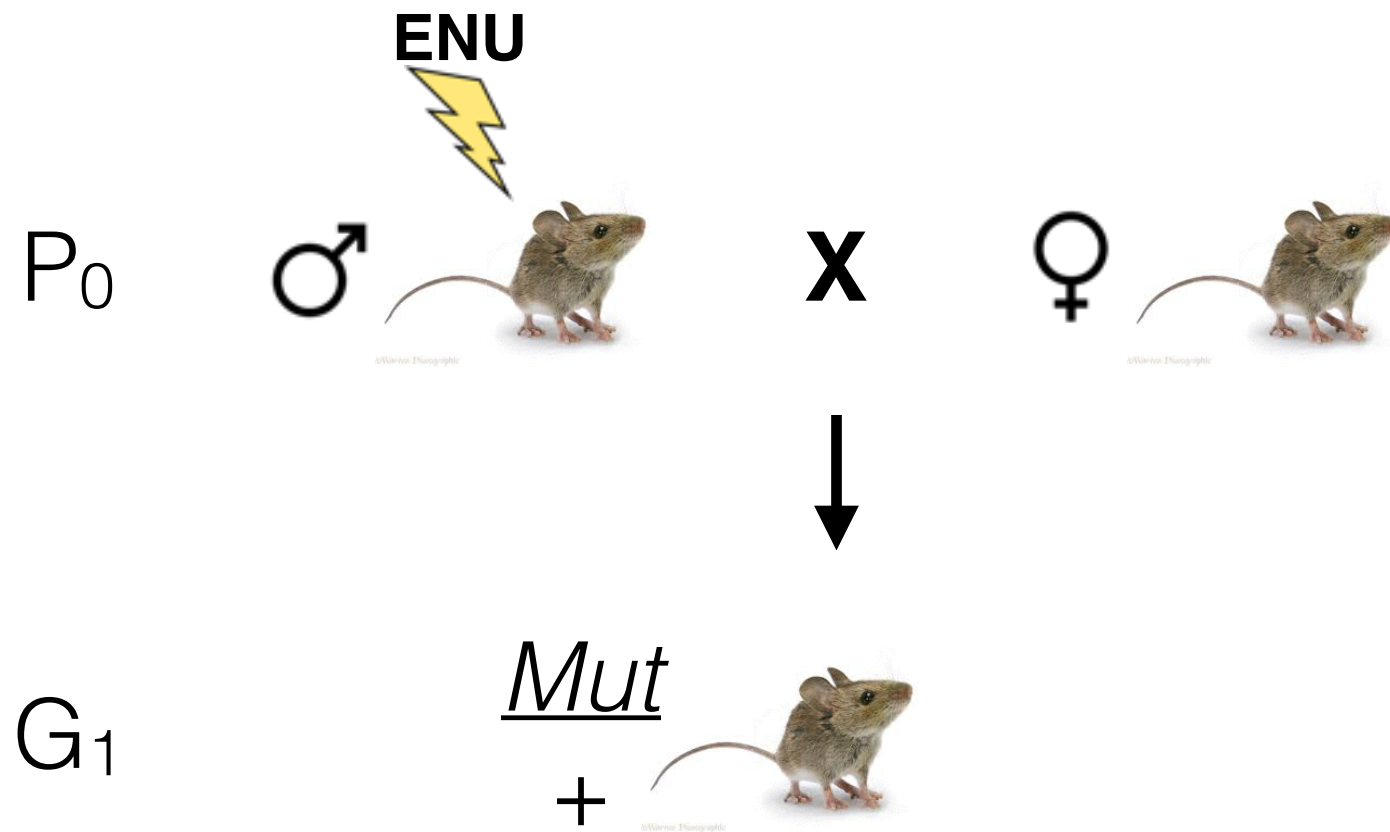
Mice love to run at night



Mice love to run at night



Circadian rhythm screen

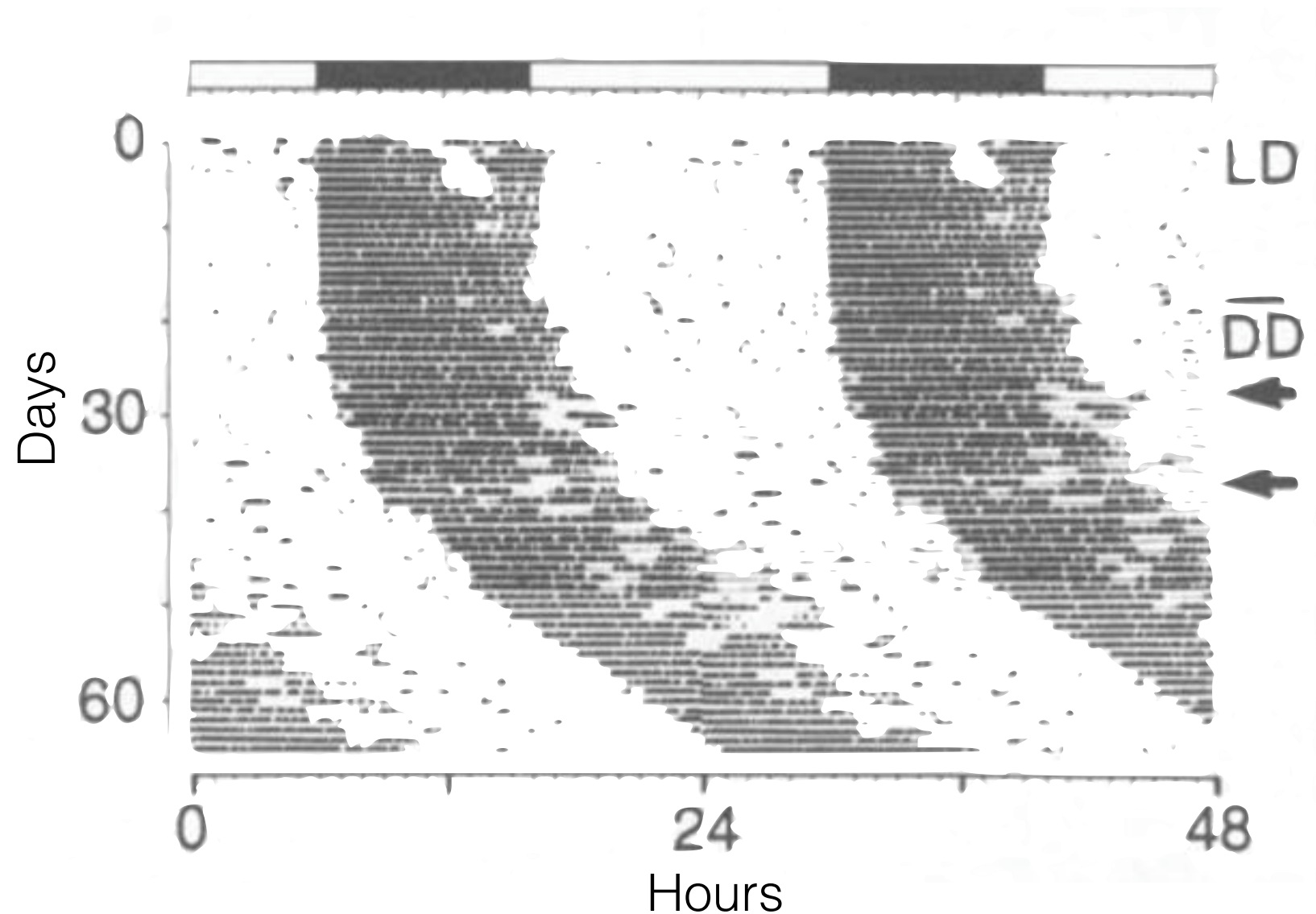


304 mutant mice screened

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**

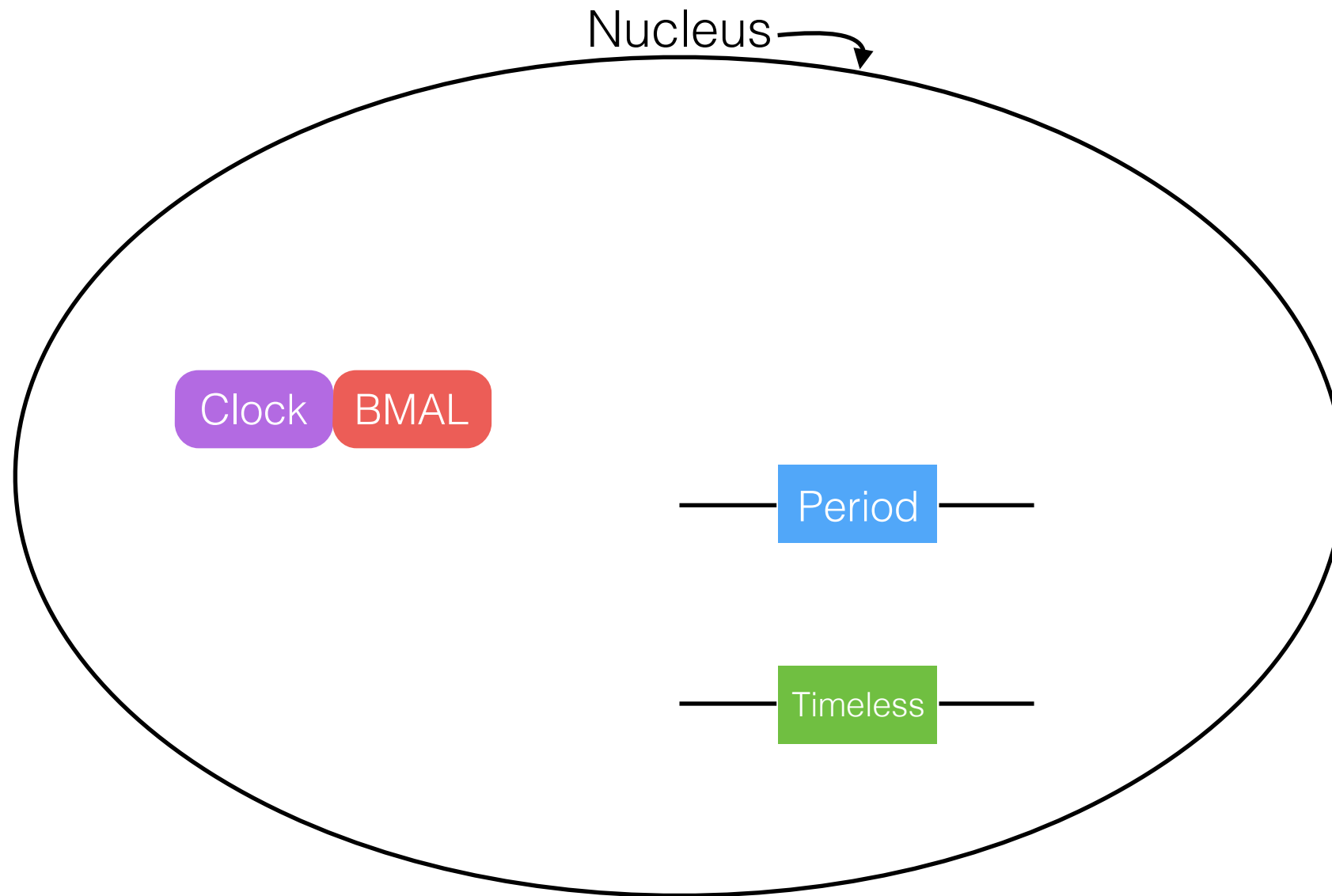


Clock = circadian locomotor output cycles kaput

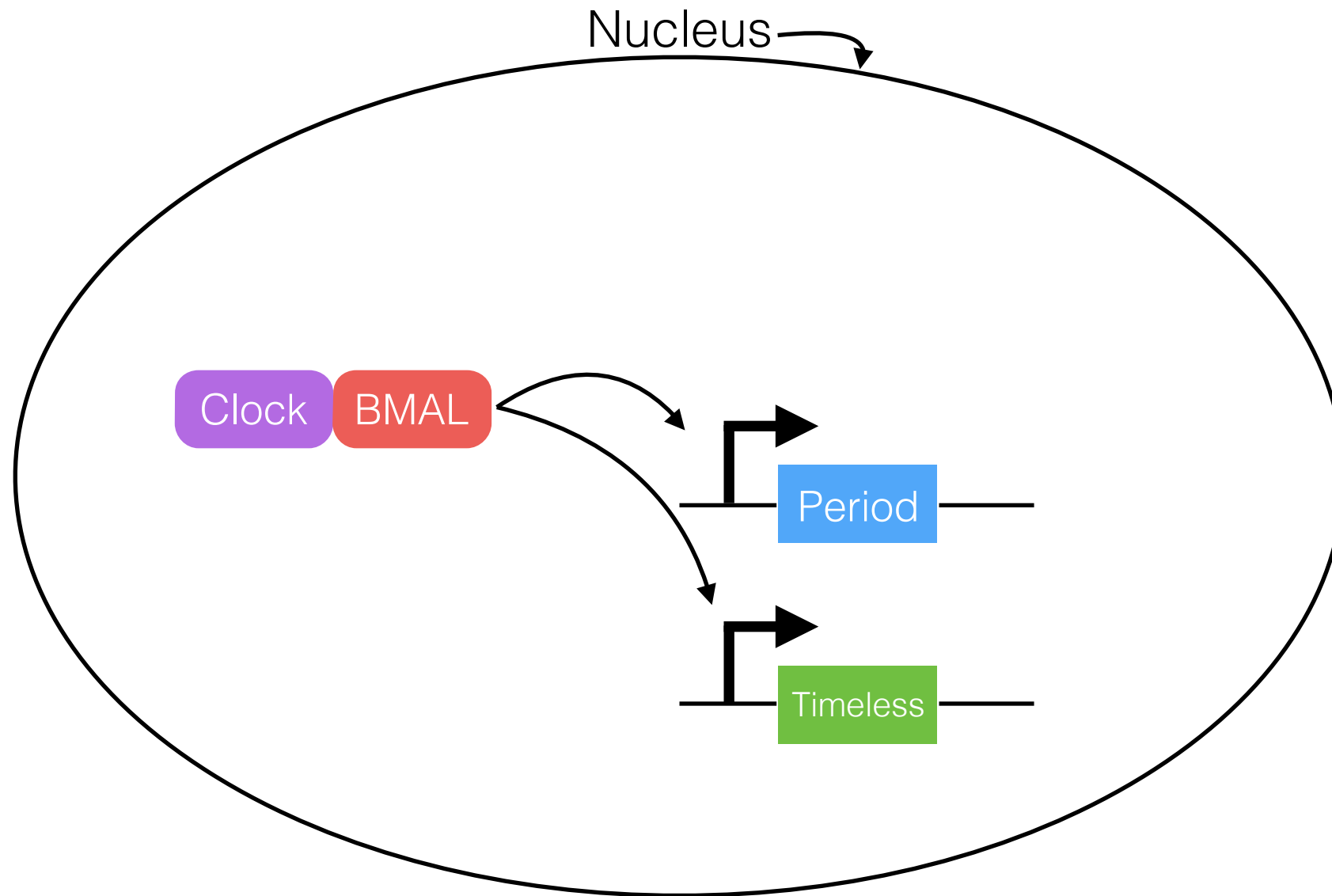
***Clock* mutants have a semi-dominant phenotype**

<u><i>Clock</i></u> <i>Clock</i>	<u><i>Clock</i></u> <i>Deficiency</i>	<u><i>Clock</i></u> +	<u>±</u> +	<u>±</u> <i>Deficiency</i>
27.3 hr	27.0 hr	24.7 hr	23.8 hr	23.8 hr

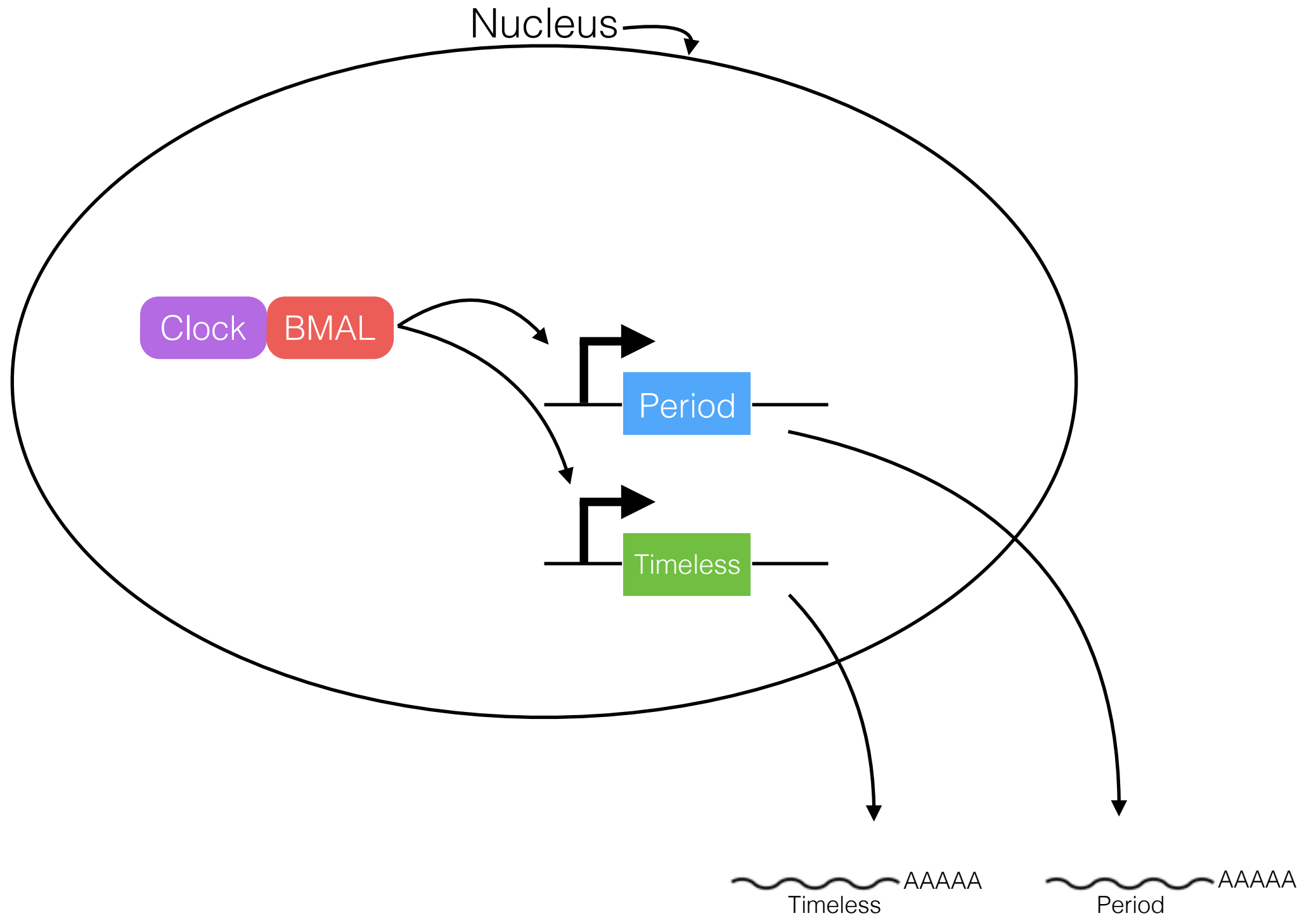
A simplified model of the circadian clock



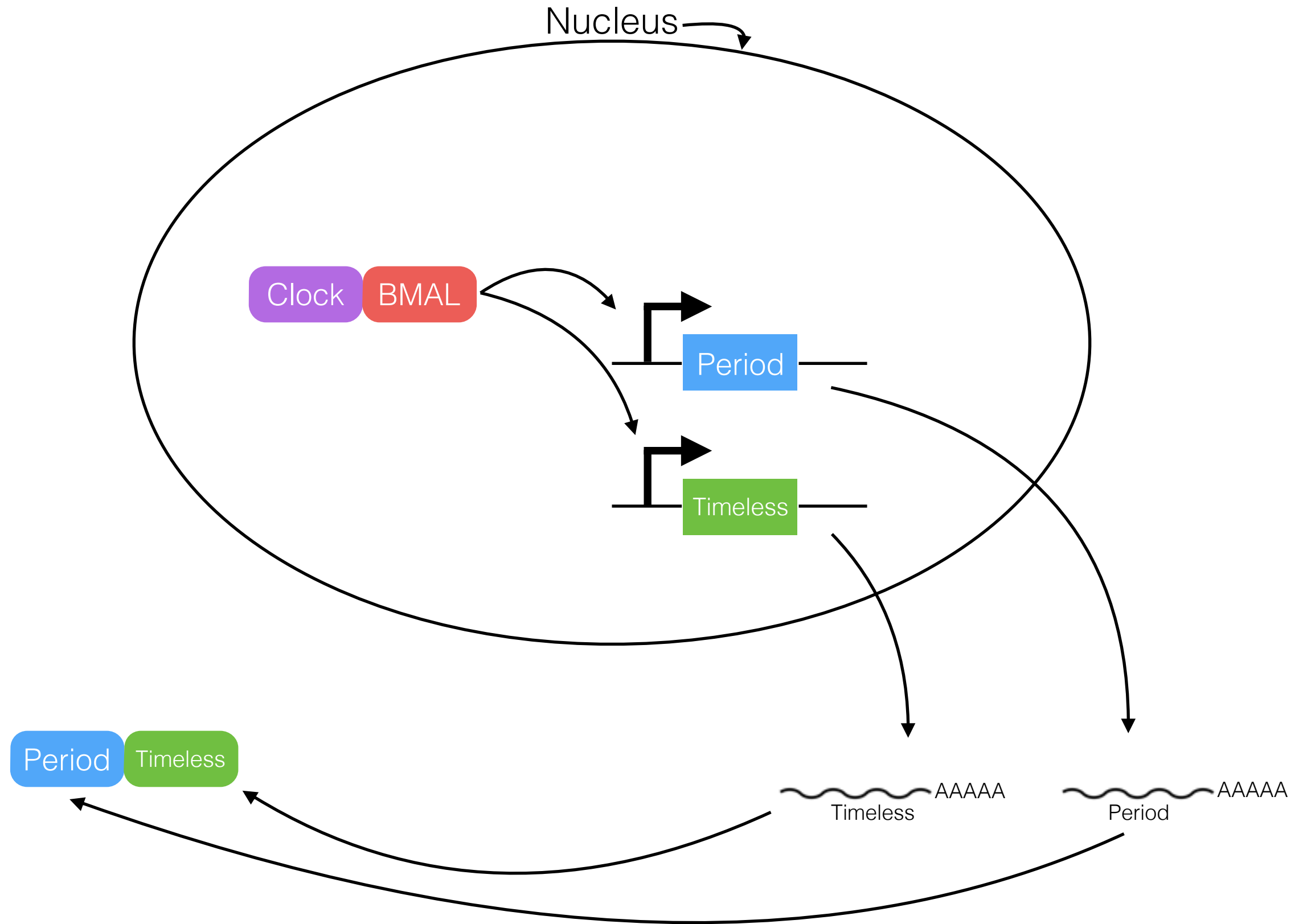
A simplified model of the circadian clock



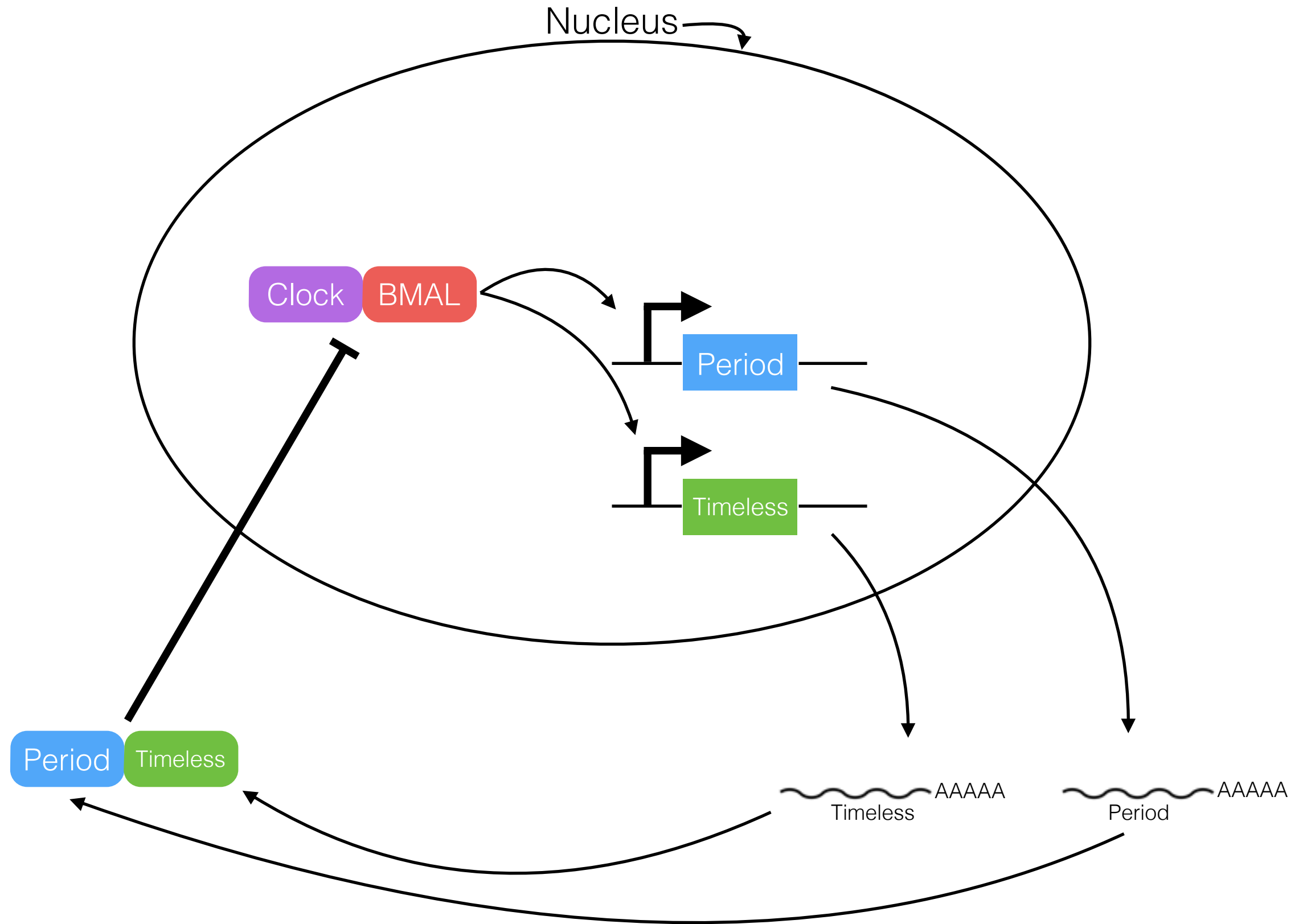
A simplified model of the circadian clock



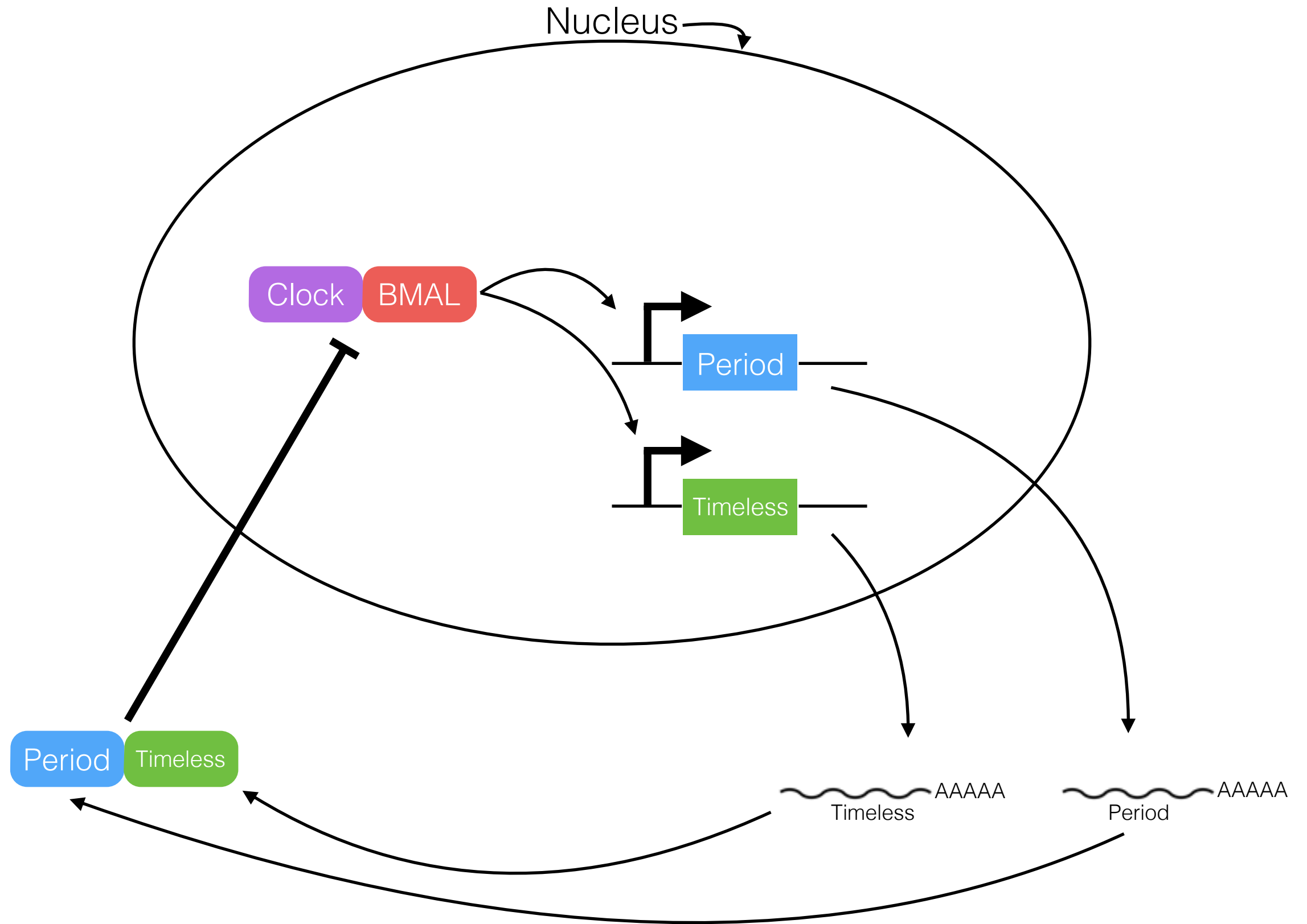
A simplified model of the circadian clock



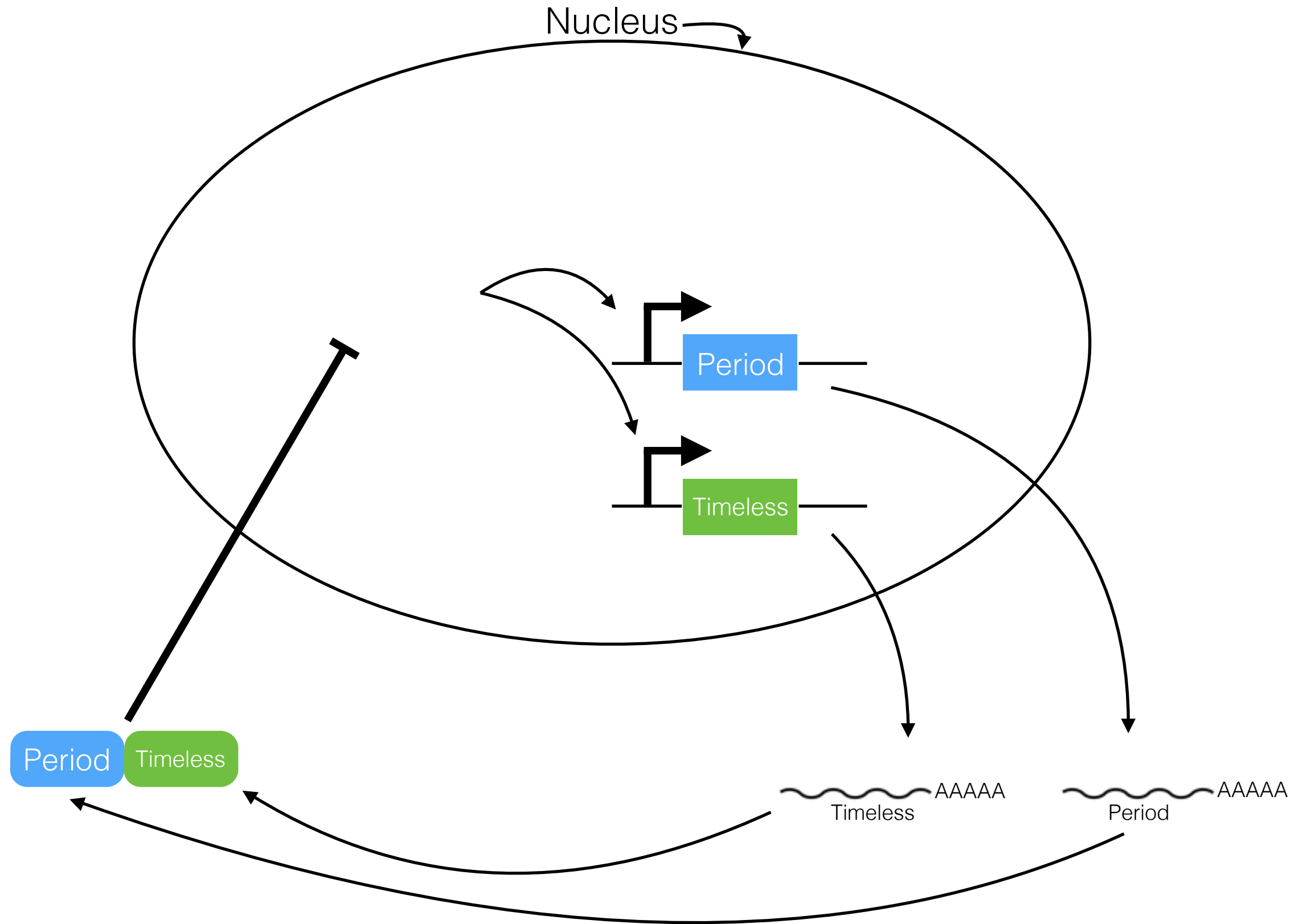
A simplified model of the circadian clock



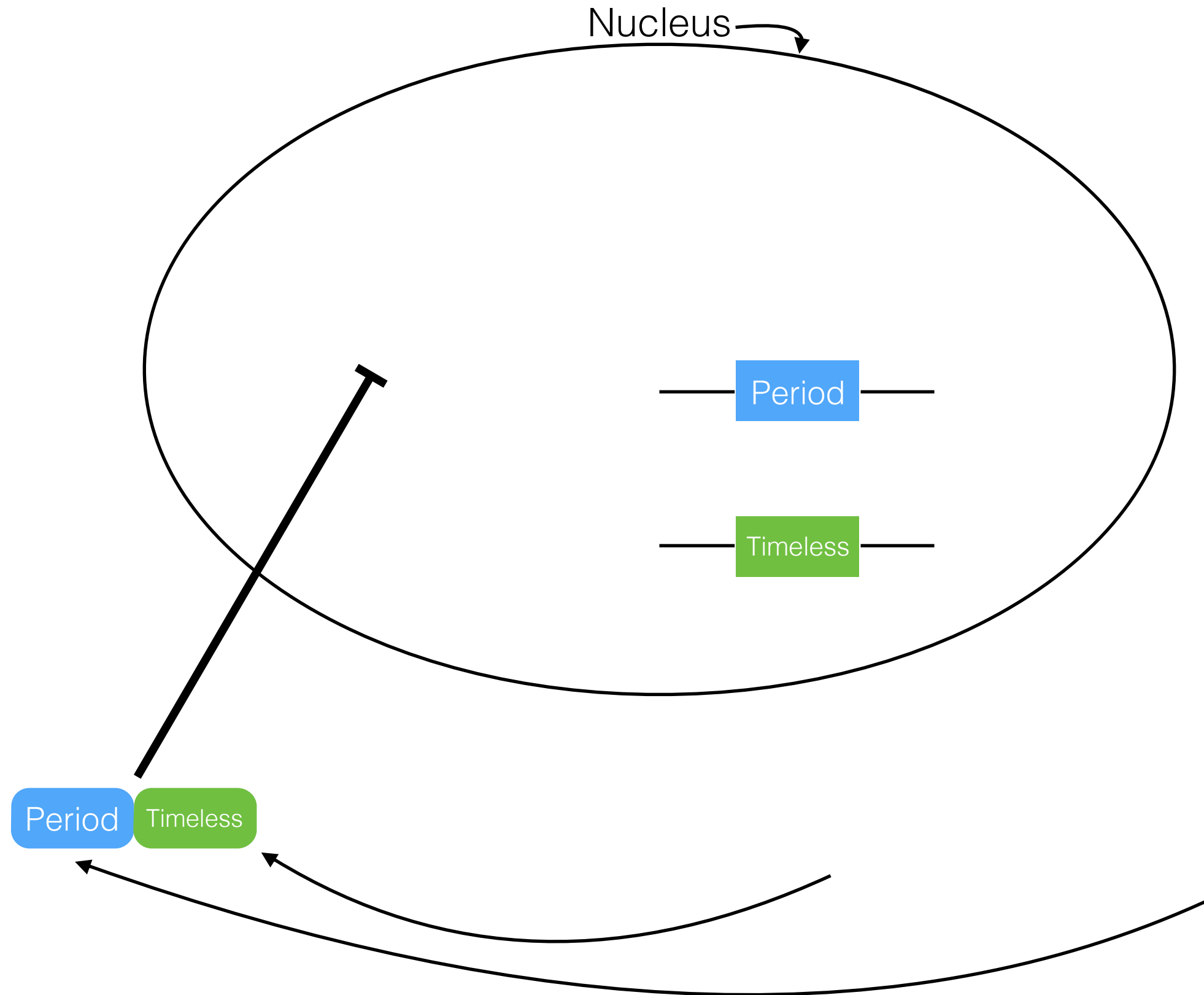
A simplified model of the circadian clock



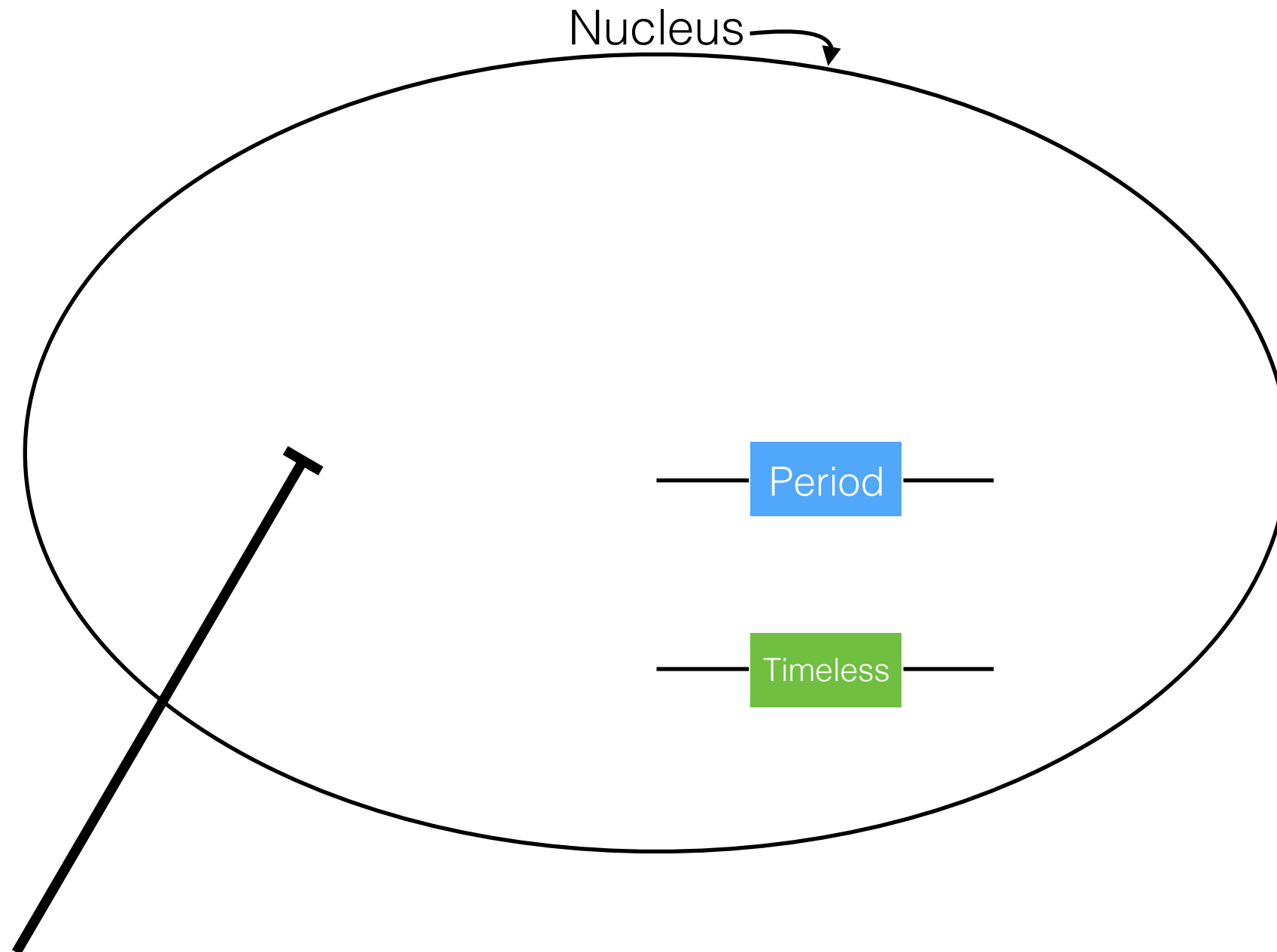
A simplified model of the circadian clock



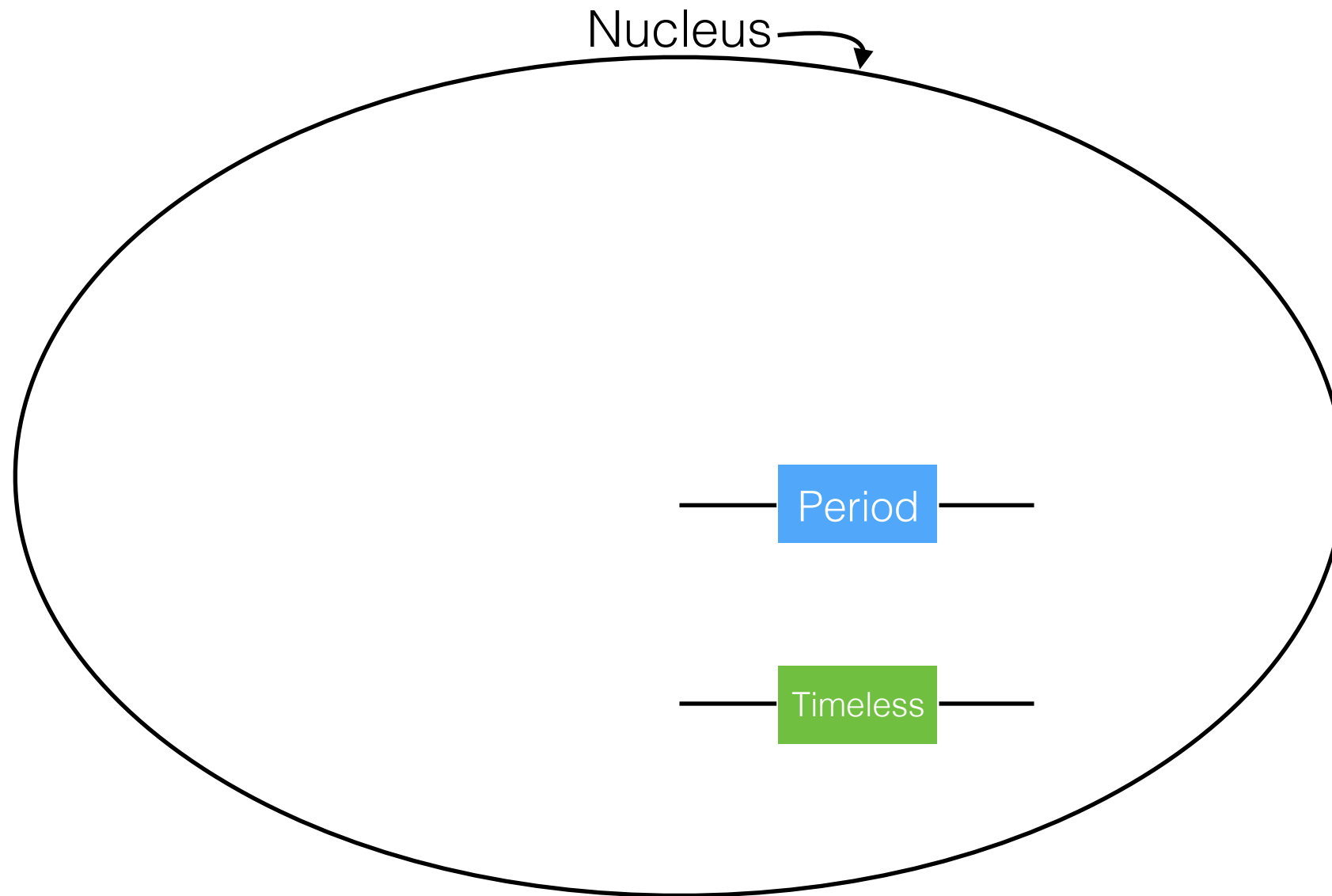
A simplified model of the circadian clock



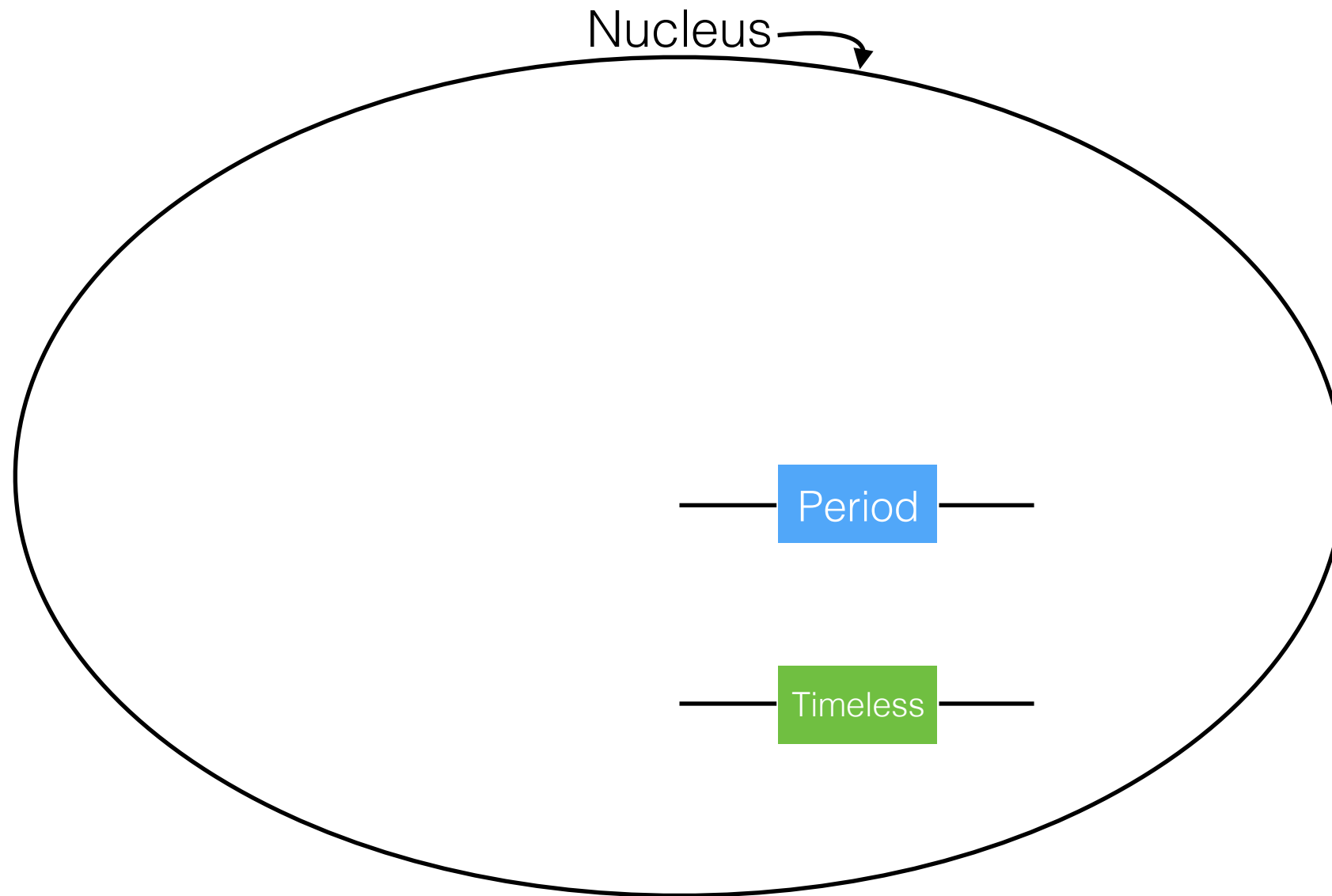
A simplified model of the circadian clock



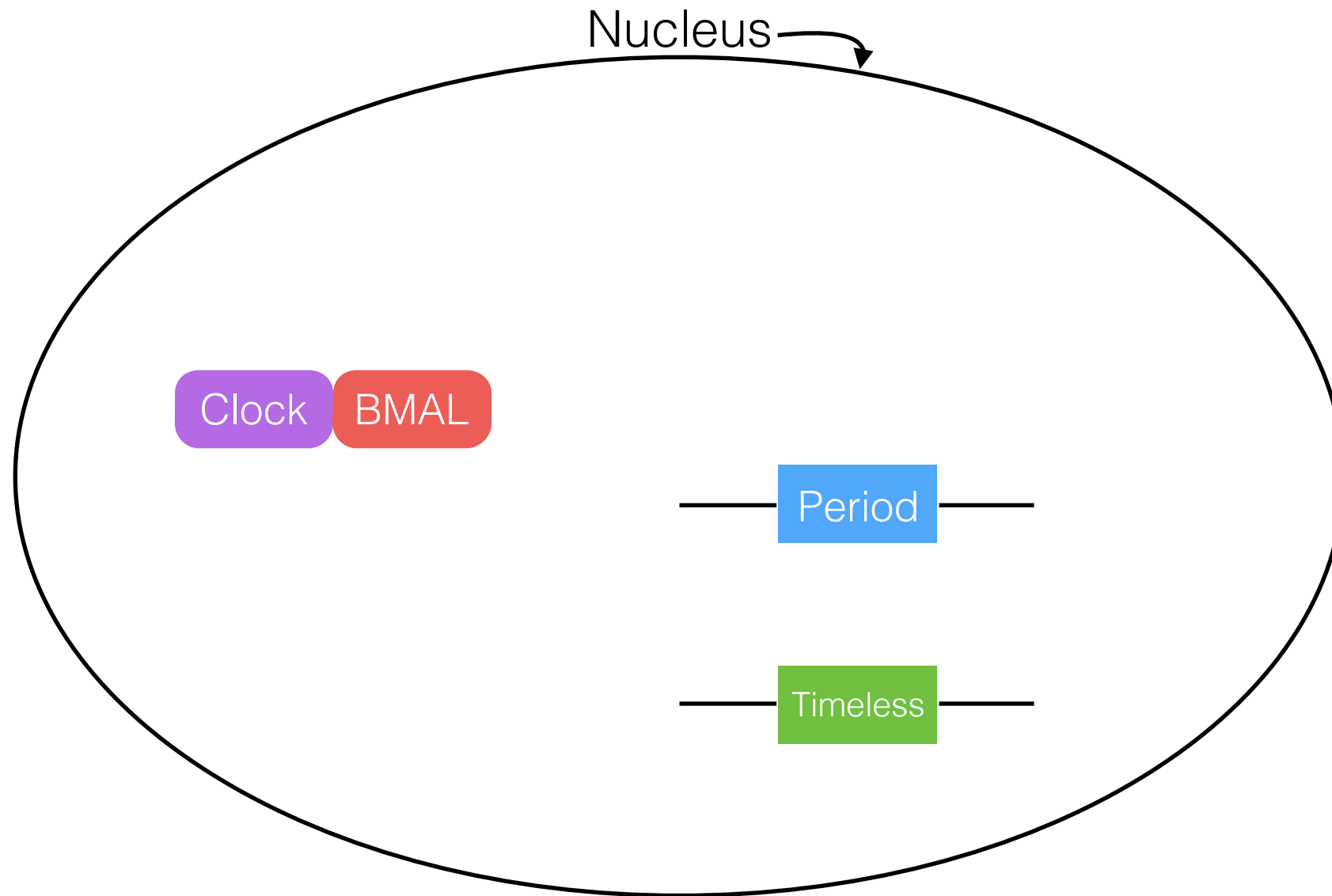
A simplified model of the circadian clock



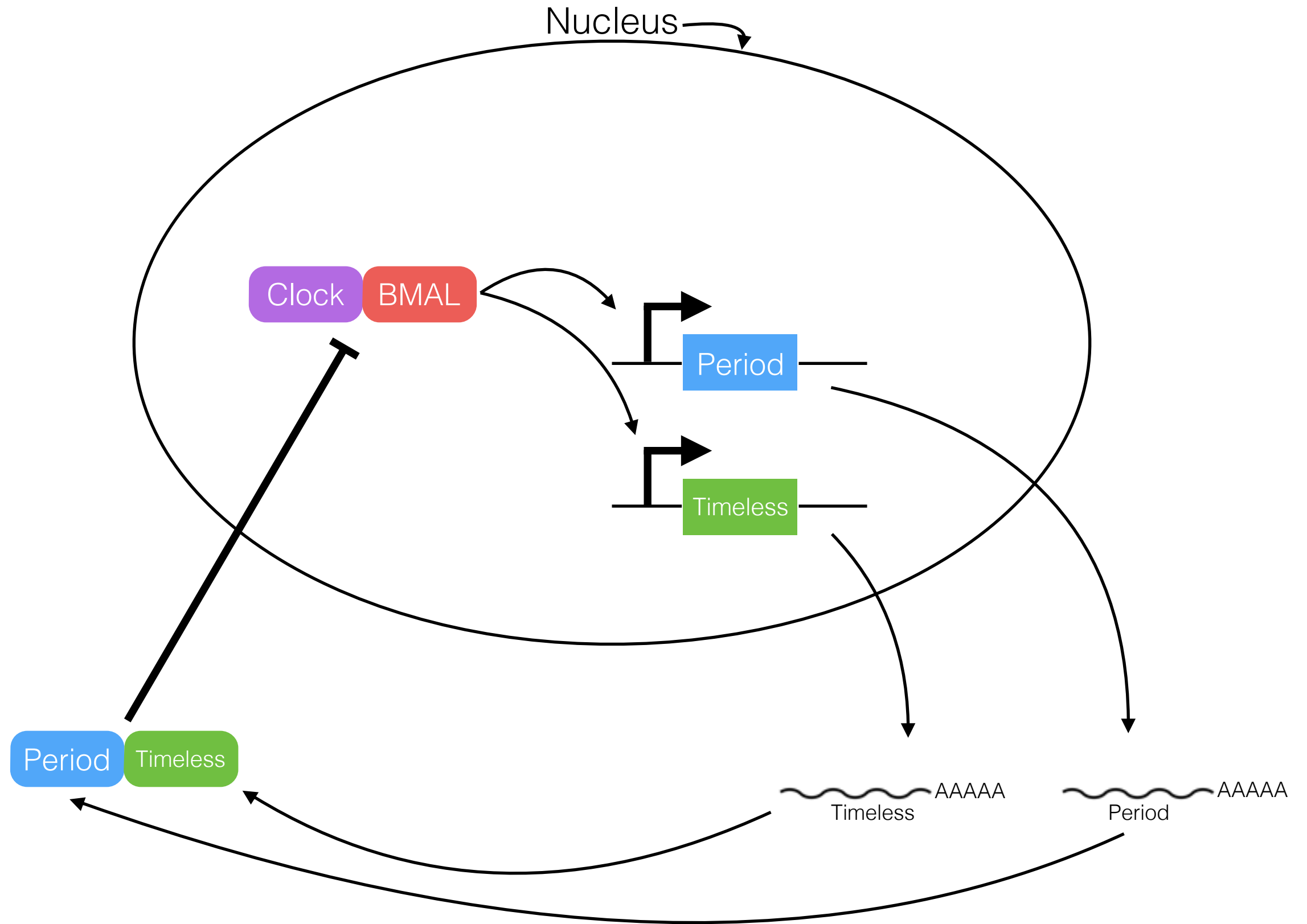
A simplified model of the circadian clock



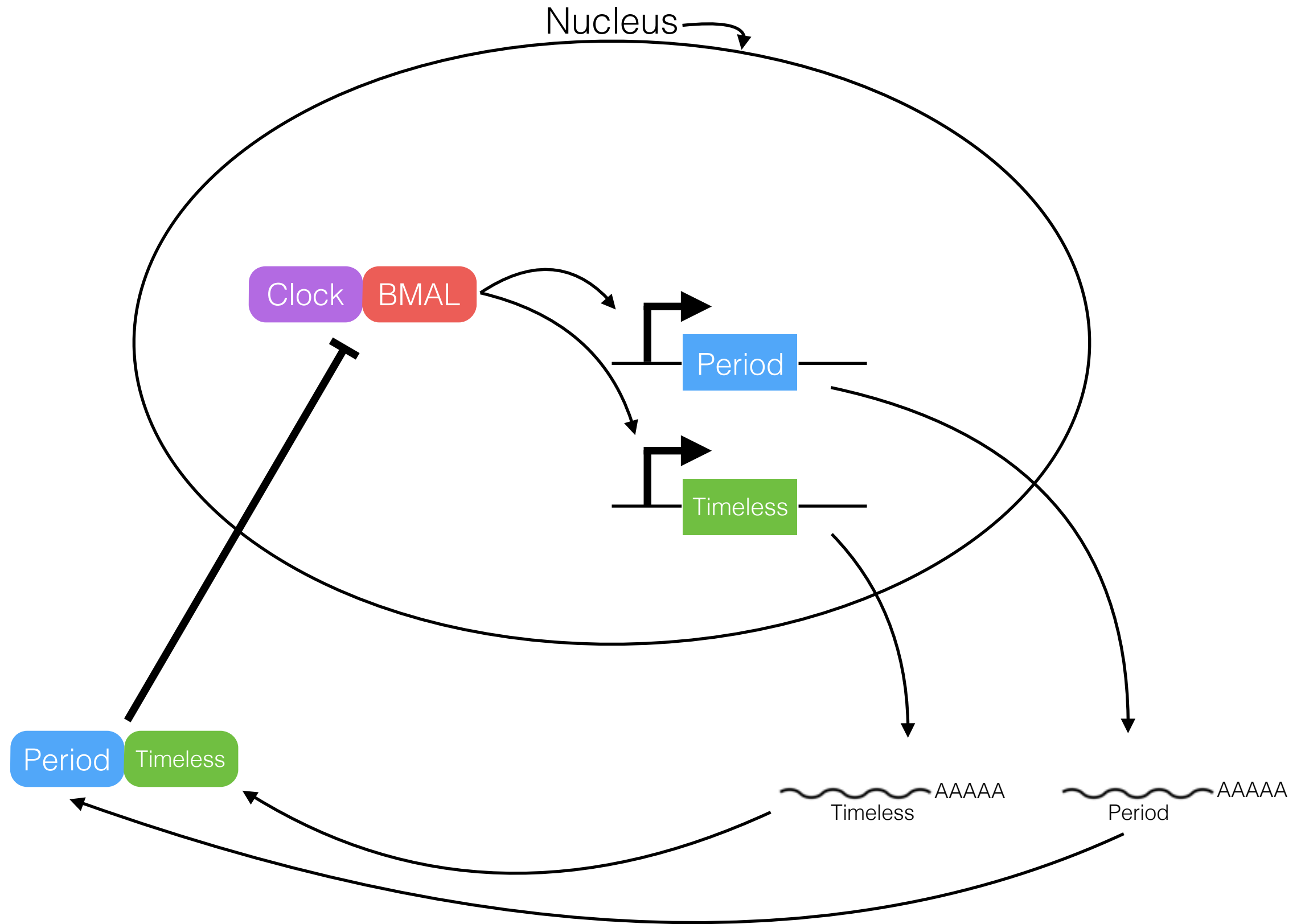
A simplified model of the circadian clock



A simplified model of the circadian clock

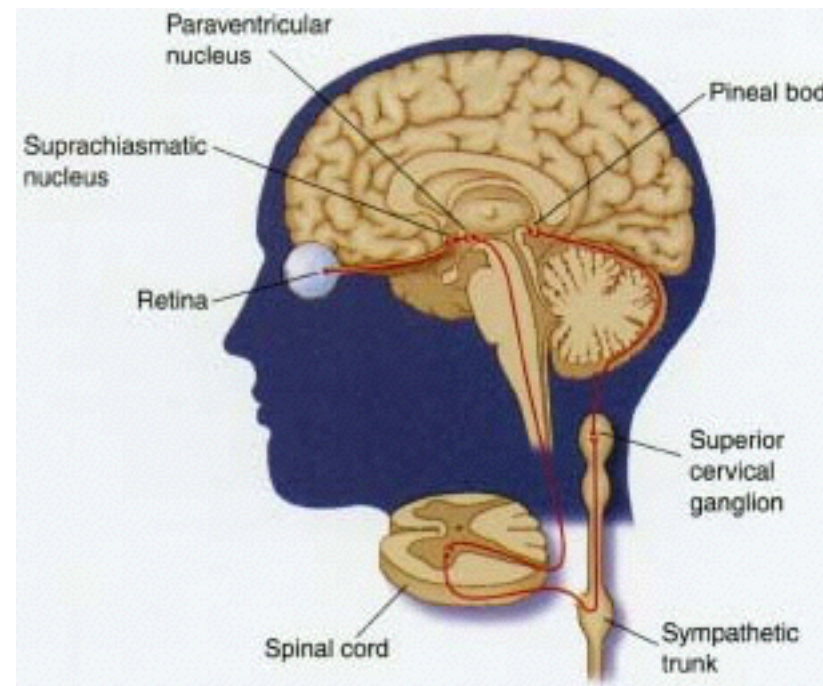


A simplified model of the circadian clock

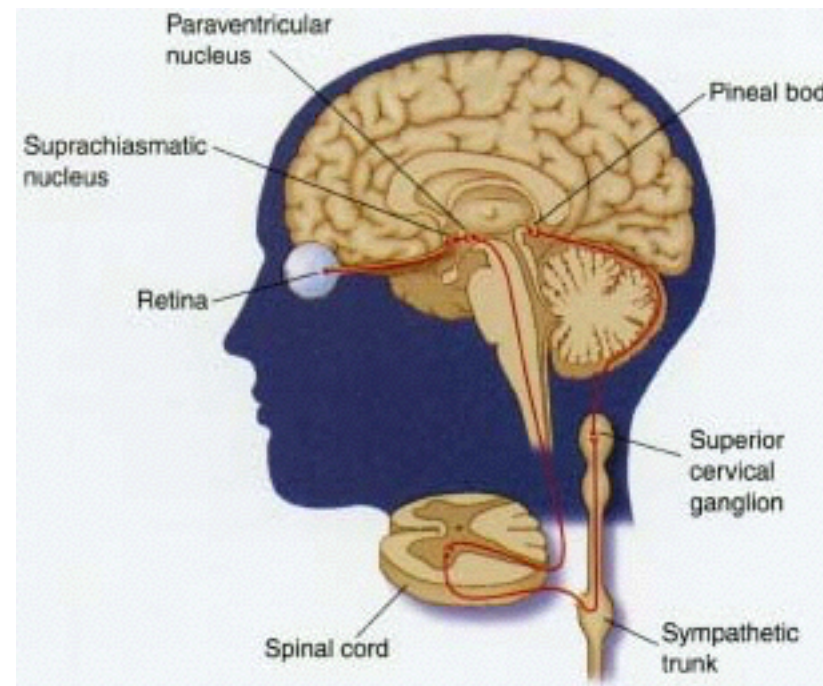


How do you think light entrains the system?

In humans, the suprachiasmatic nucleus regulates sleep and wakefulness

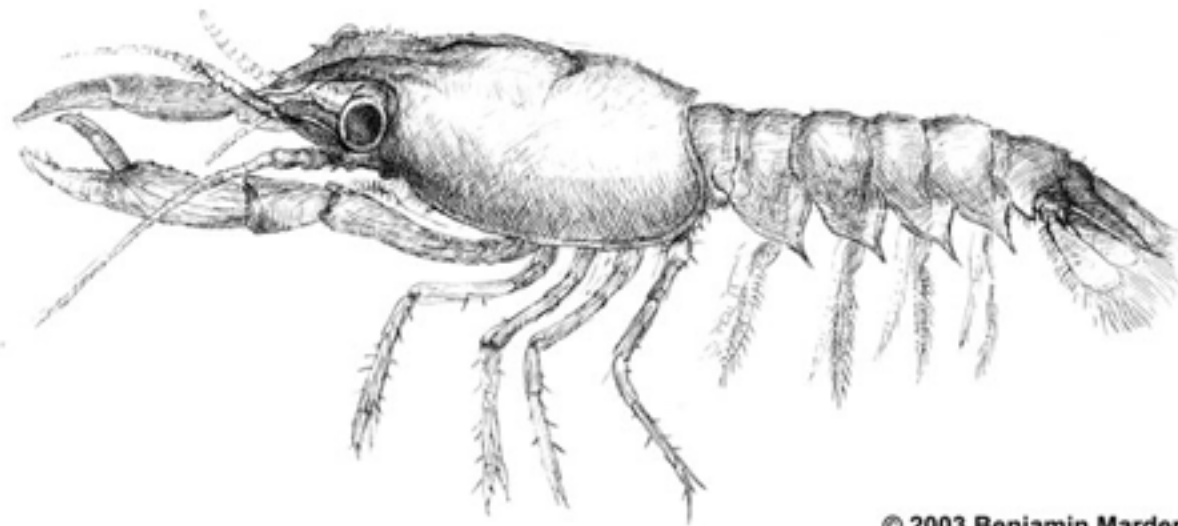


In humans, the suprachiasmatic nucleus regulates sleep and wakefulness

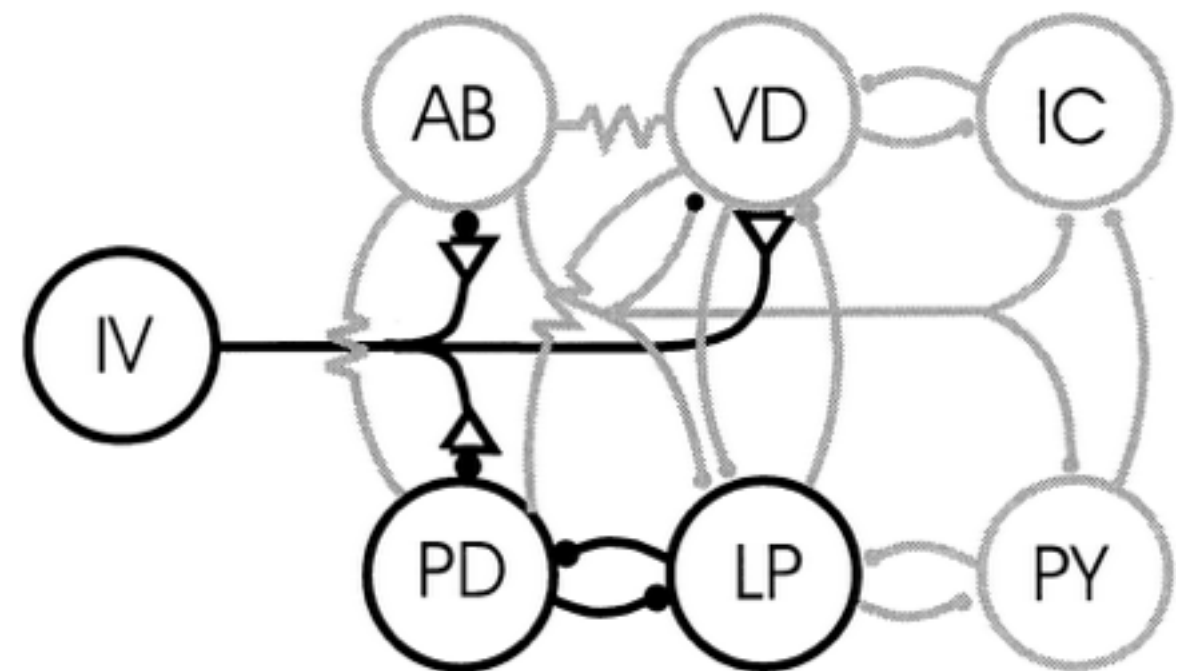


Do blind people have circadian cycles?

The activities of neurons and their connections regulate behavior

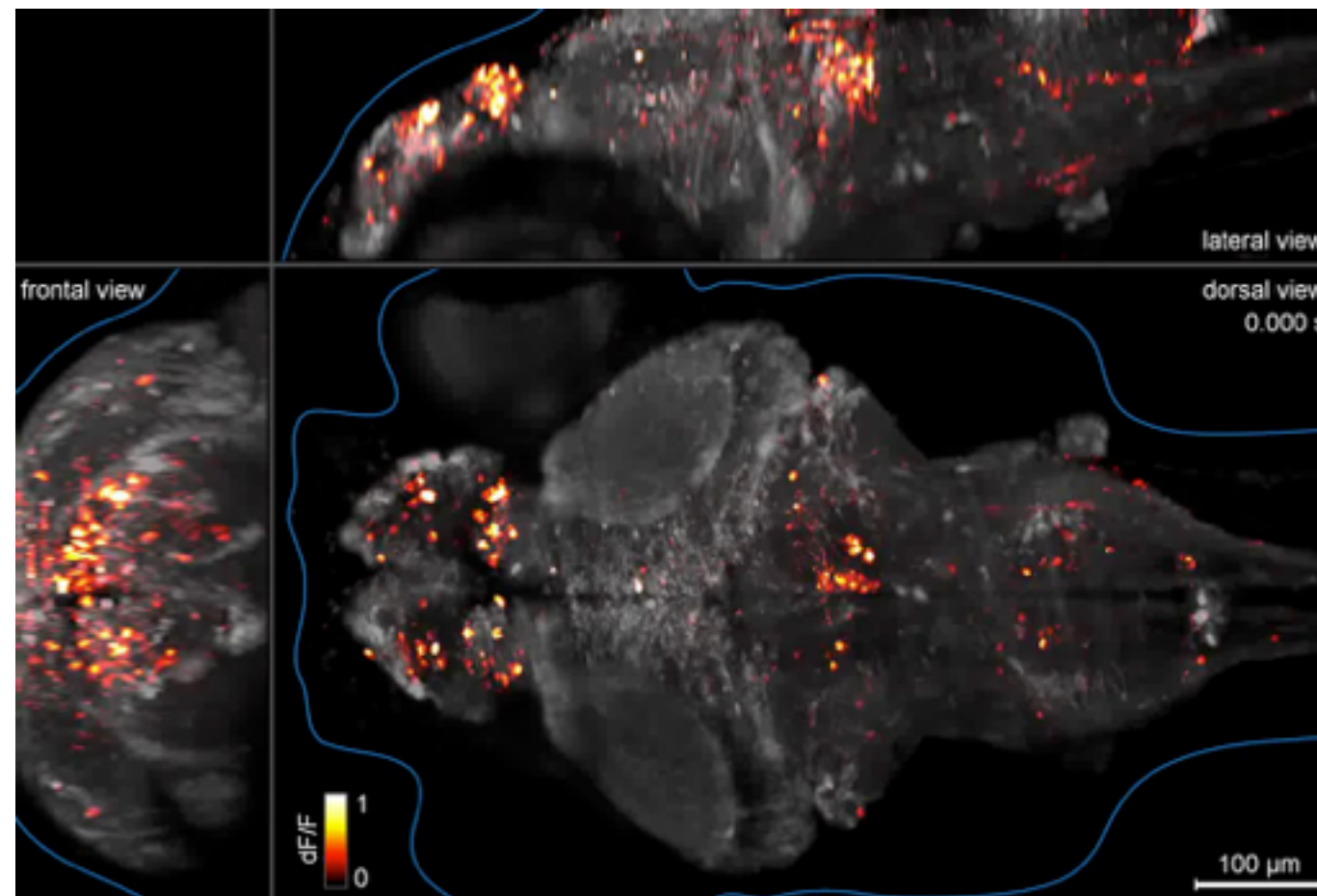
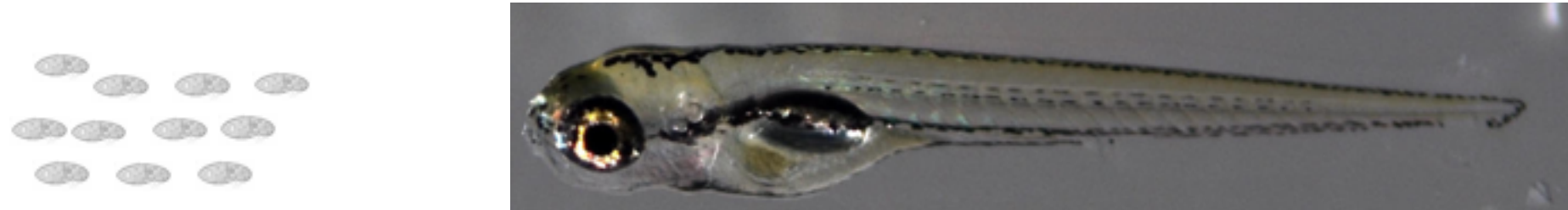


© 2003 Benjamin Marder

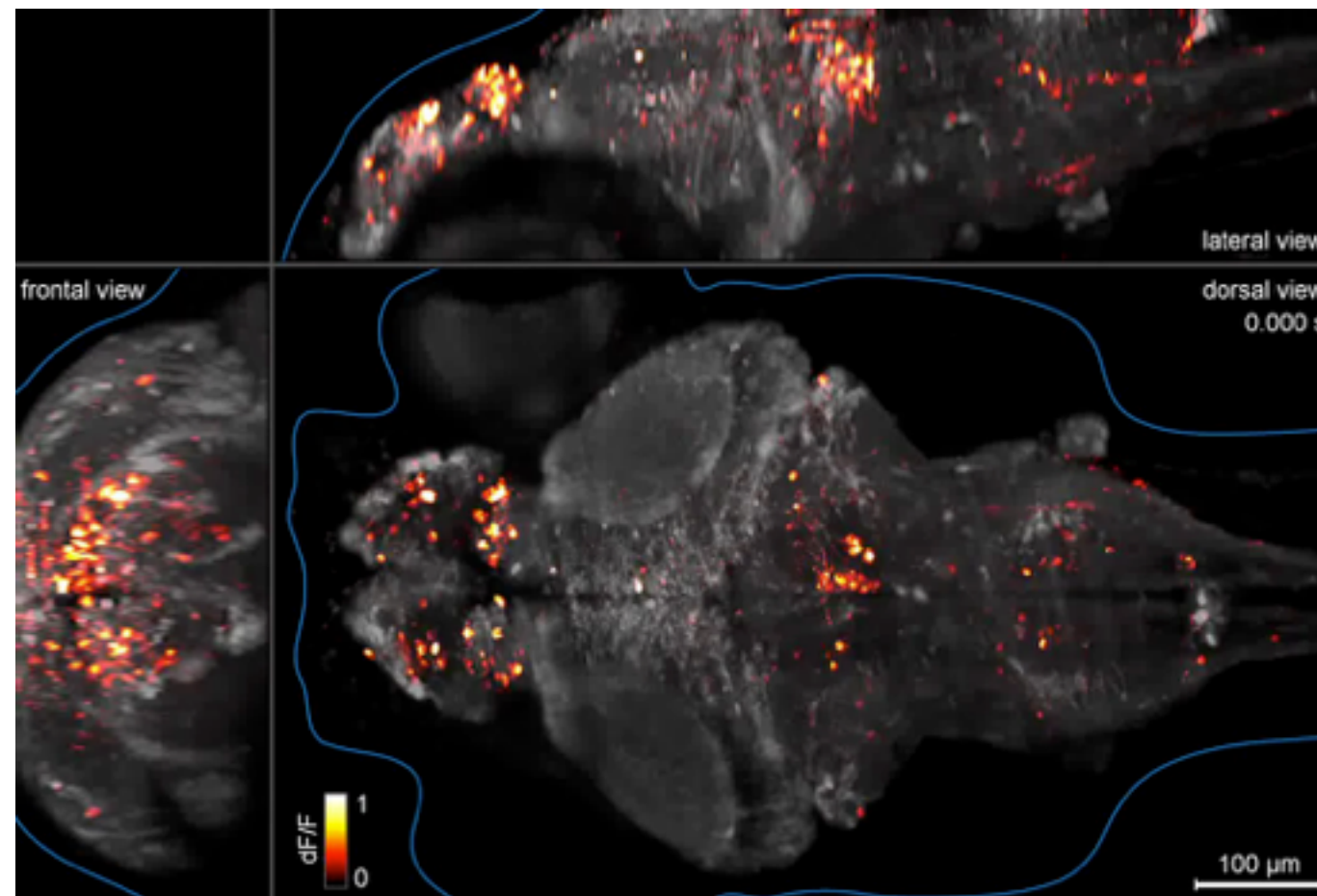


When neurons are active,
intracellular calcium concentration increases

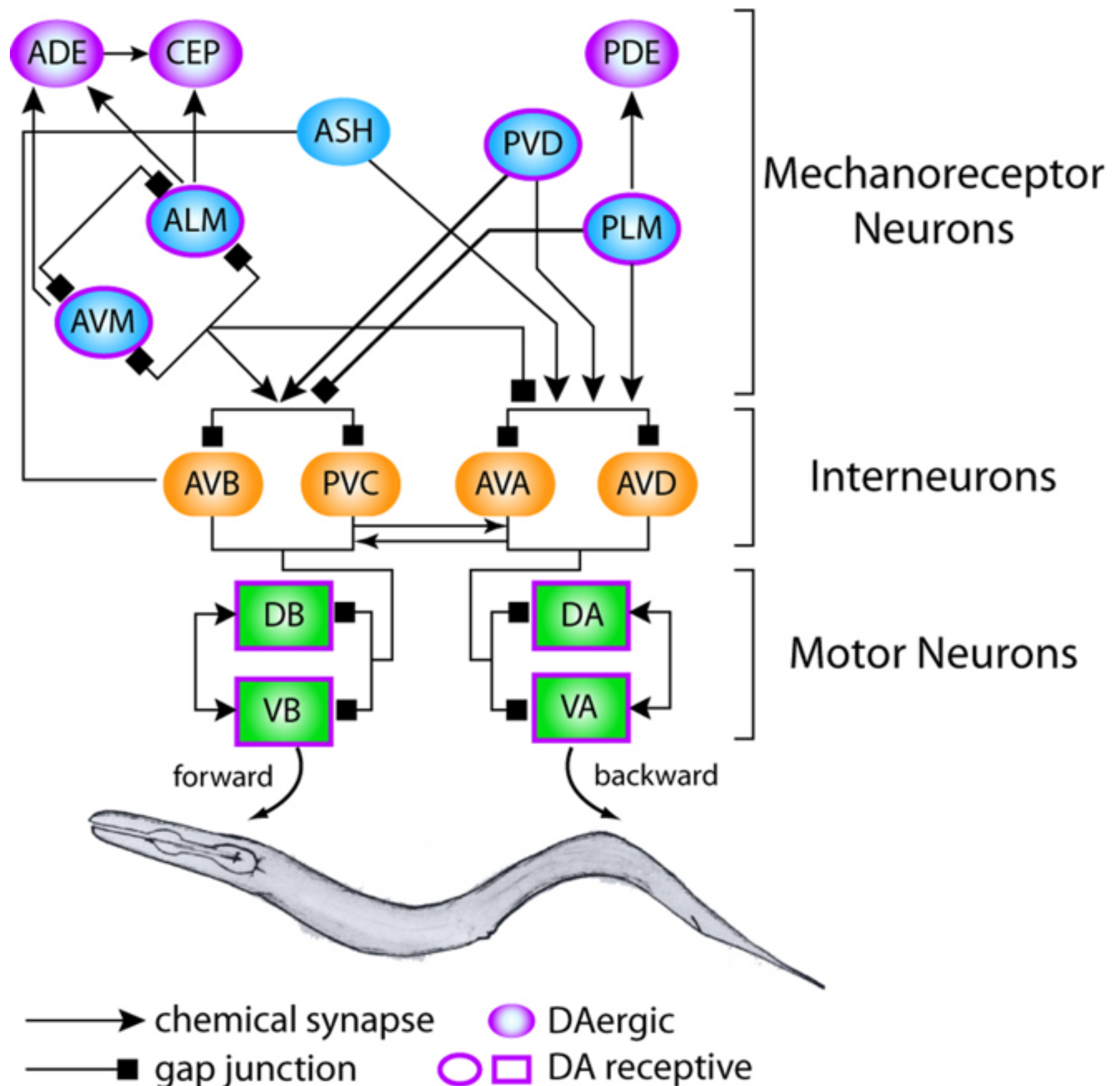
Genetically encoded calcium indicators show neuronal activity



Genetically encoded calcium indicators show neuronal activity



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

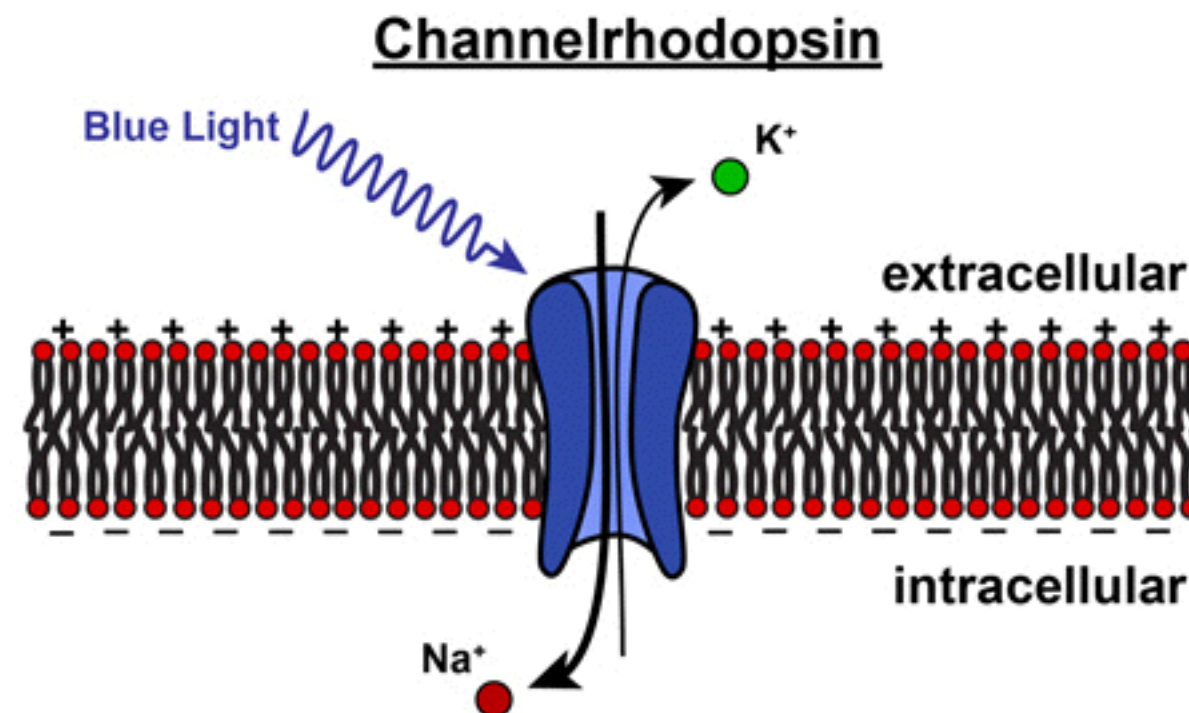


What if you want to turn neurons ON or OFF at will?

Channelrhodopsin for turning cells ON

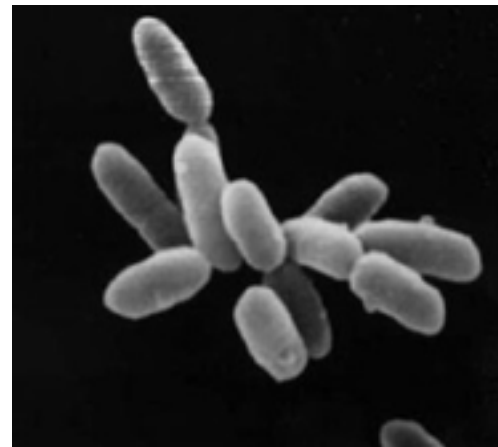


Chlamydomonas reinhardtii

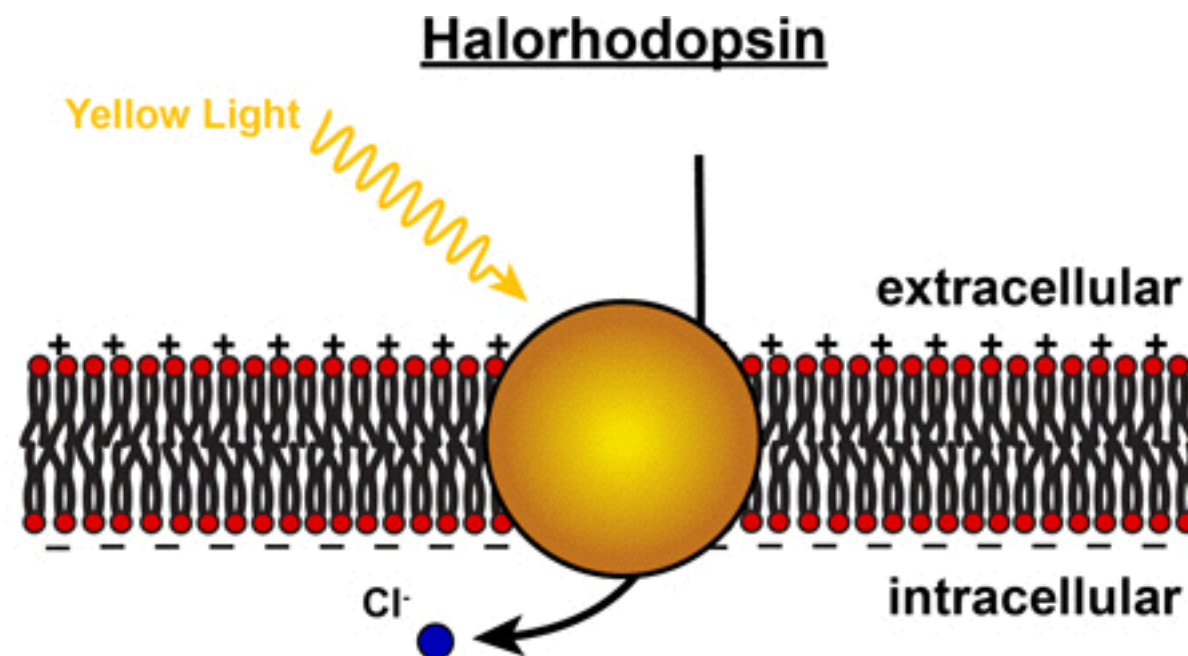


What if you want to turn neurons ON or OFF at will?

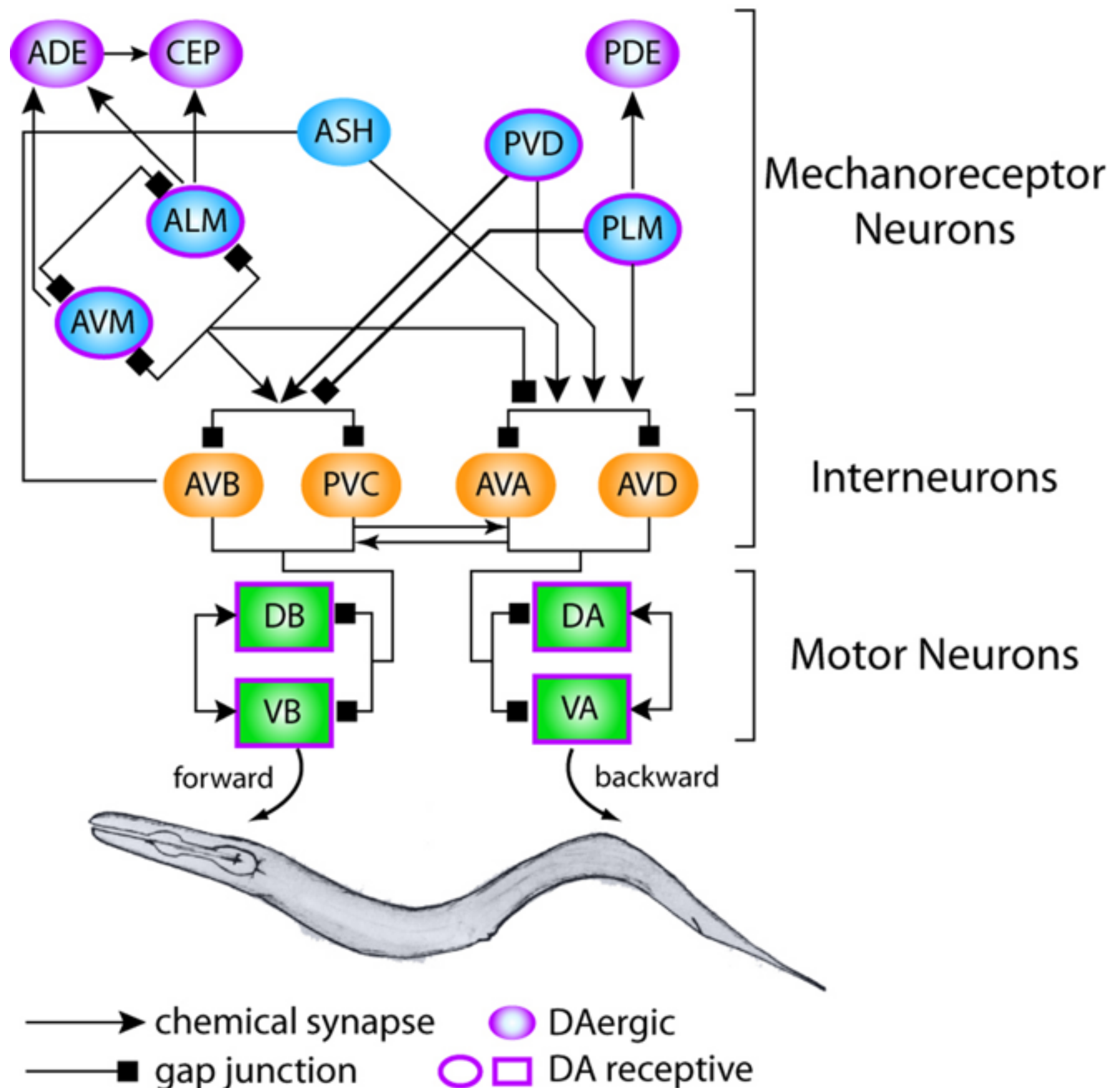
Halorhodopsin for turning cells OFF



Halobacterium salinarum



Using cell lineage, genetics, calcium indicators, and rhodopsins, we can control neuronal circuits



Using narcoleptic dogs, researchers found the gene underlying narcolepsy



How?

No genetic screens,
no balancers,
small numbers of offspring

Using narcoleptic dogs, researchers found the gene underlying narcolepsy



How?

No genetic screens,
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