

The Mechanism of Circadian Clock

丁啟祐¹ and 邱紹庭²

¹昆蟲系

²生醫電資所

1/7, 2019. NTU

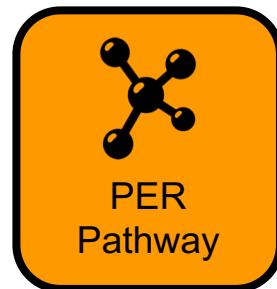
Outline

The Mechanism of Circadian Clock

Part I - What is *Circadian Clock*? What makes it ticks?



History of
Discovery



PER
Pathway



Part II - Why molecular clock ticks?



Negative
Feedback



Delay

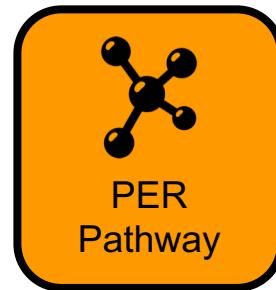


Limit Cycle

Outline

The Mechanism of Circadian Clock

Part I - What is *Circadian Clock*? What makes it ticks?



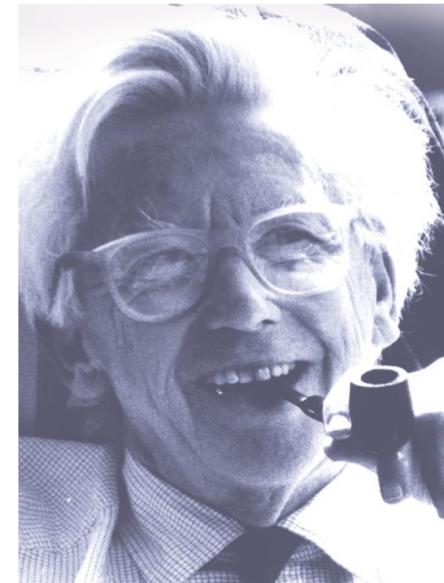
Part II - Why molecular clock ticks?



History of Circadian Discovery



Colin Pittendrigh (1918-1996)

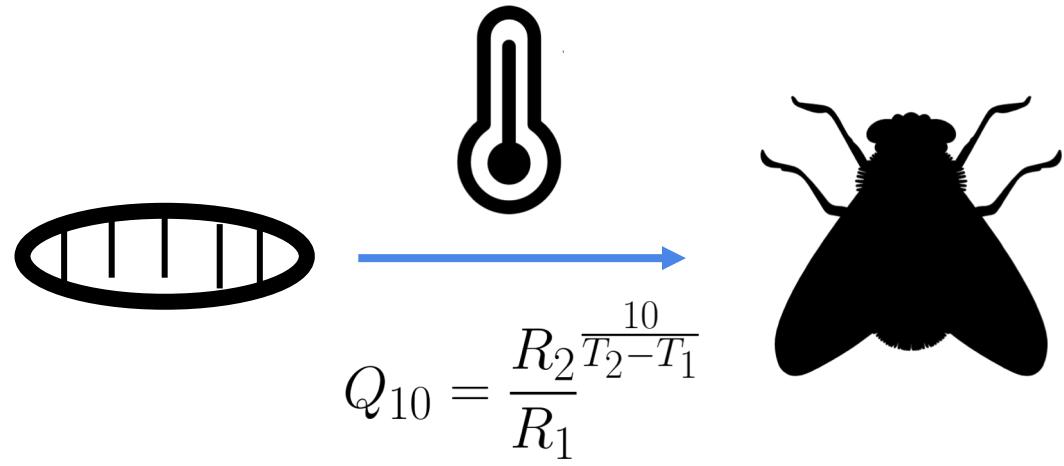


Jürgen Aschoff (1913-1998)

<https://www.nature.com/articles/381024a0>
<https://www.nature.com/articles/24750>

History of Circadian Discovery

生物時鐘受到溫度補償效應

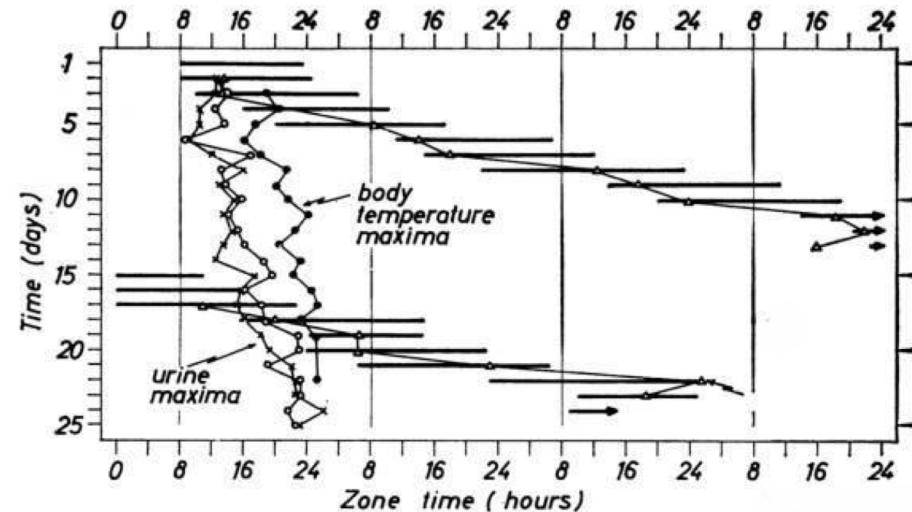


Colin Pittendrigh (1918-1996)

R : Rate ; T: Temperature ; Q : ratio of rates

<https://www.nature.com/articles/381024a0>

History of Circadian Discovery

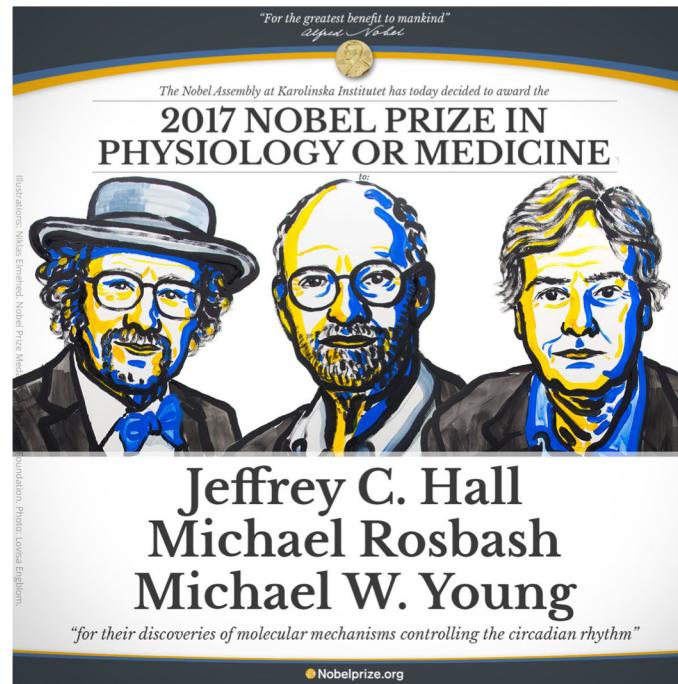


<https://www.pravda-tv.com/2013/07/chronobiologie-schlaflabor-im-bunker/>

<https://www.britannica.com/video/179763/subjects-bunker-experiment-exposure-rhythms-light>

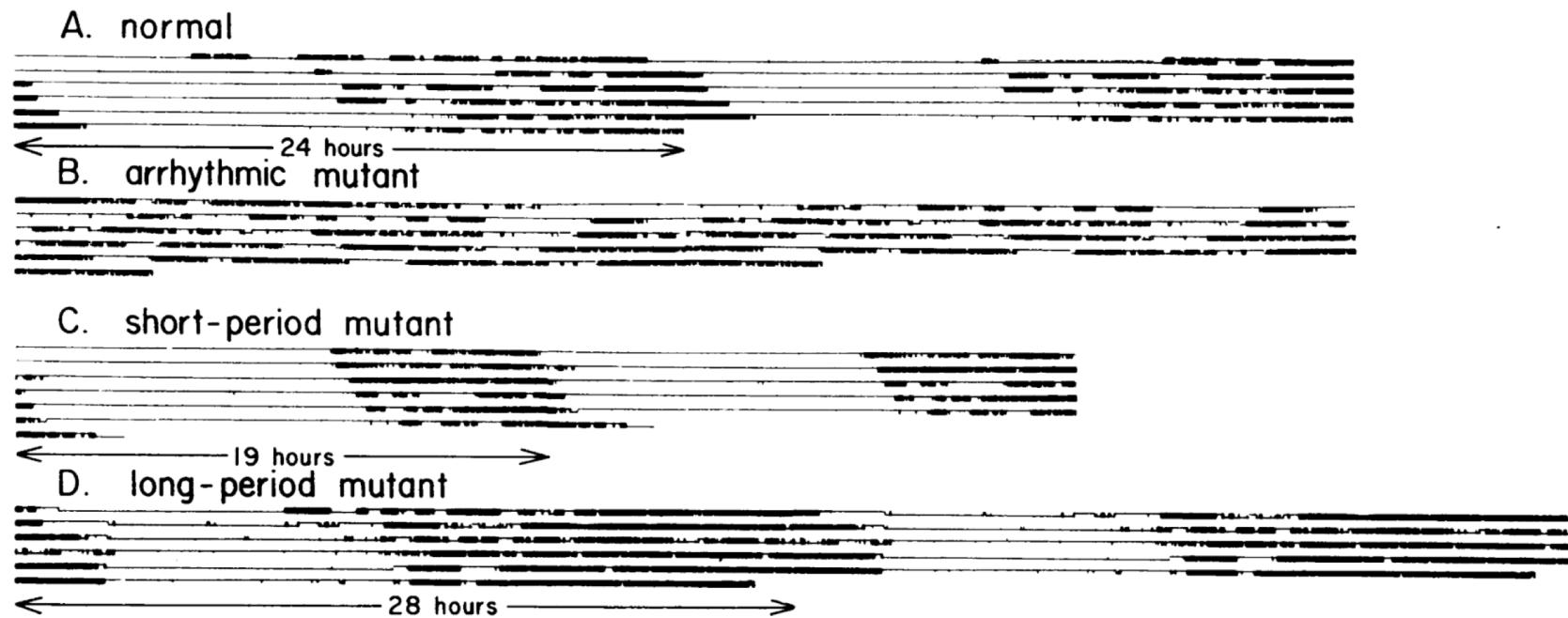
Jürgen Aschoff (1913-1998)

Molecular Mechanism of Circadian Pathway



<https://www.thenewslens.com/article/103382>

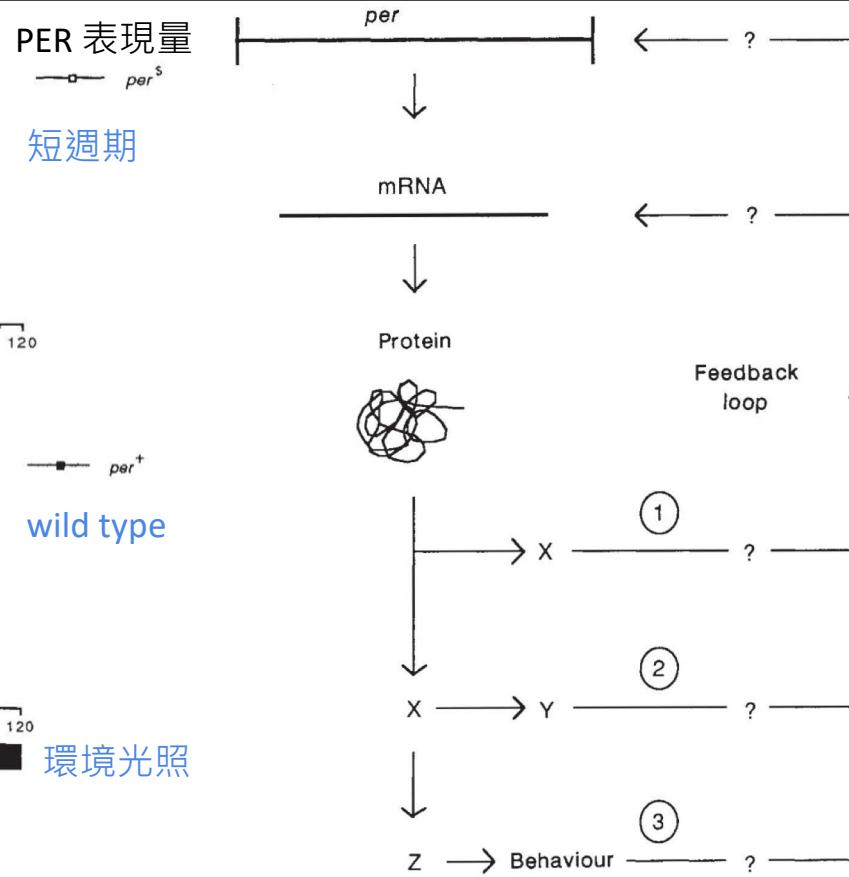
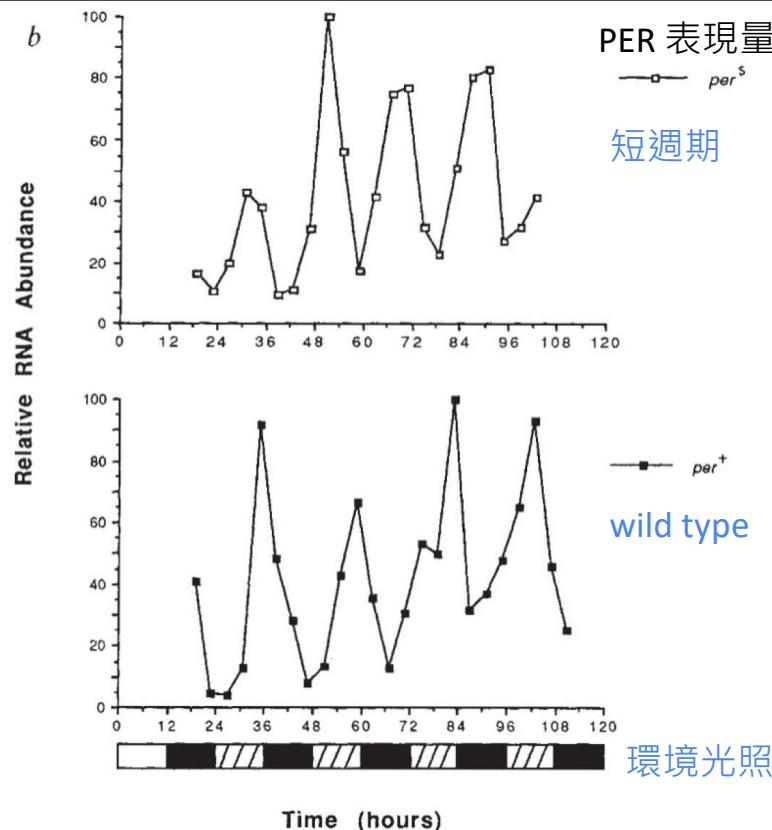
Molecular Mechanism of Circadian Pathway



(J. Konopka, 1971)

黑點: 活動時間; 白:無活動時間

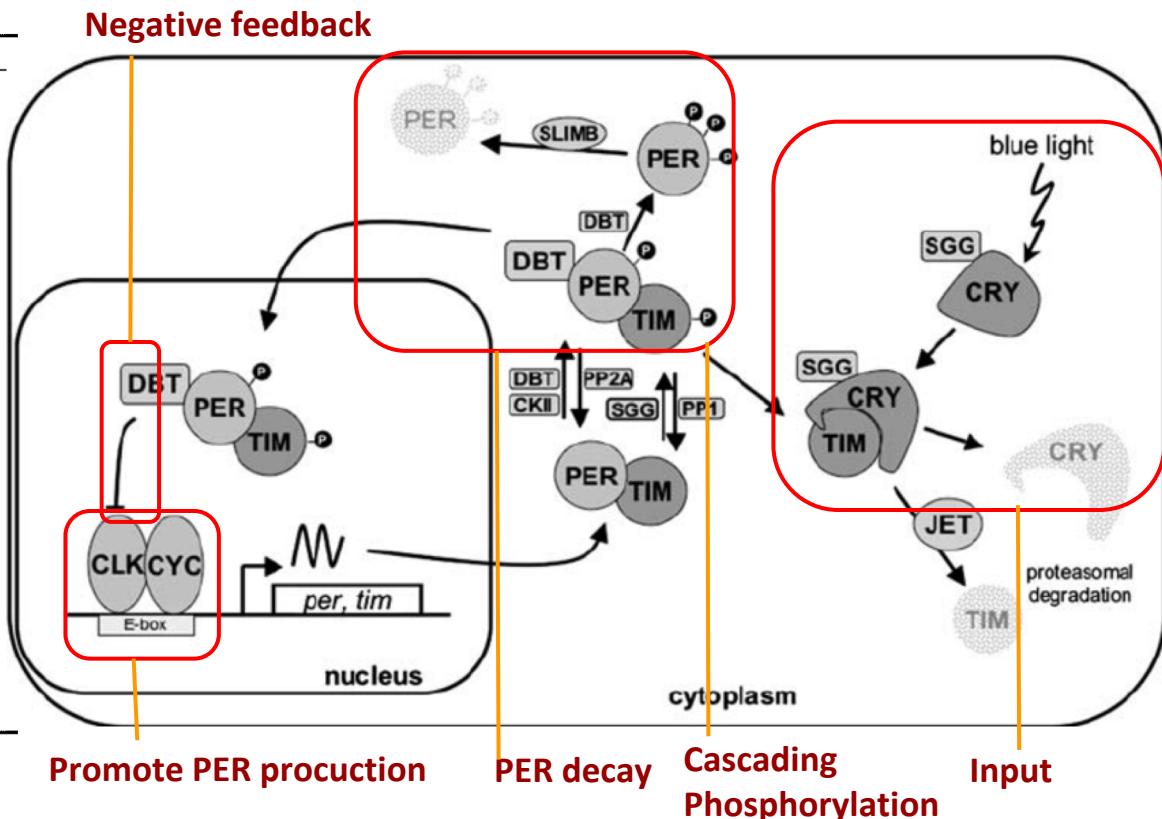
Molecular Mechanism of Circadian Pathway



(C. Hall&Michael Rosbash,1990)

Molecular Mechanism of Circadian Pathway

Gene	Clock role
<i>period</i>	PER
<i>timeless</i>	TIM
<i>Clock cycle</i>	
<i>doubletime</i>	DBT
<i>vrielle</i>	
<i>cryptochromes</i>	CRY
<i>lark</i>	
<i>pigment dispersing factor</i>	
<i>takeout</i>	



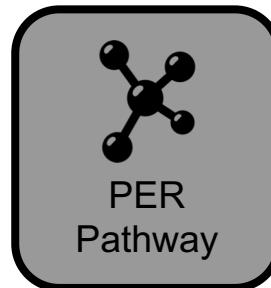
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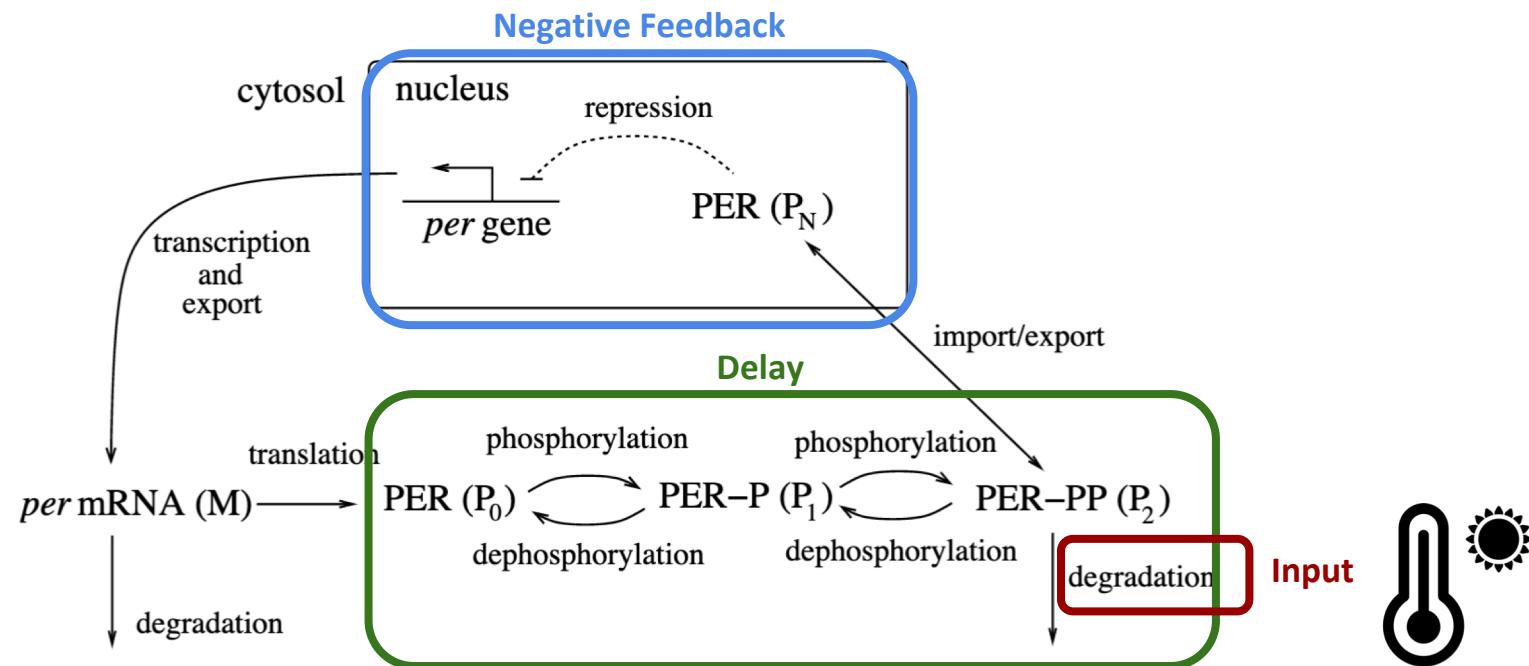
Delay



Limit Cycle

Model of Circadian Clock

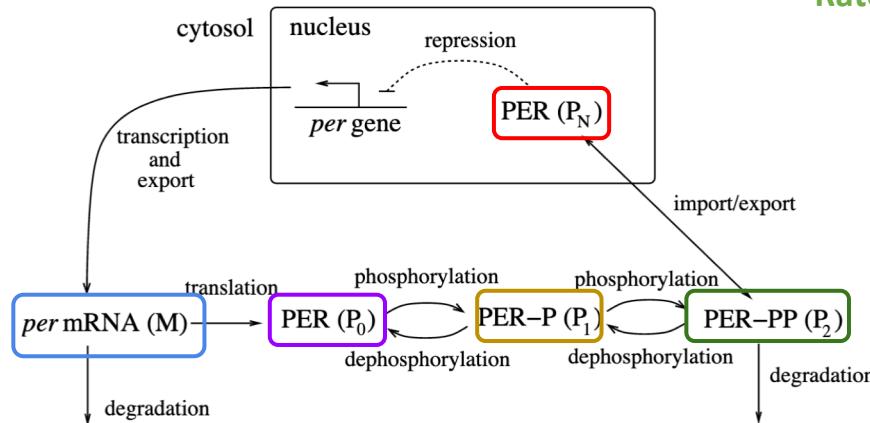
Why circadian clock ticks?



[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. Mathematical Modeling in Systems Biology - an Introduction (2016)

Mathematical Model of Circadian Clock

Why circadian clock ticks?



Rate of reaction



$$\frac{d}{dt}m(t) = \frac{v_s}{1 + (p_N(t)/K_I)^n} - \frac{v_m m(t)}{K_{m1} + m(t)}$$

$$\frac{d}{dt}p_0(t) = k_s m(t) - \frac{V_1 p_0(t)}{K_1 + p_0(t)} + \frac{V_2 p_1(t)}{K_2 + p_1(t)}$$

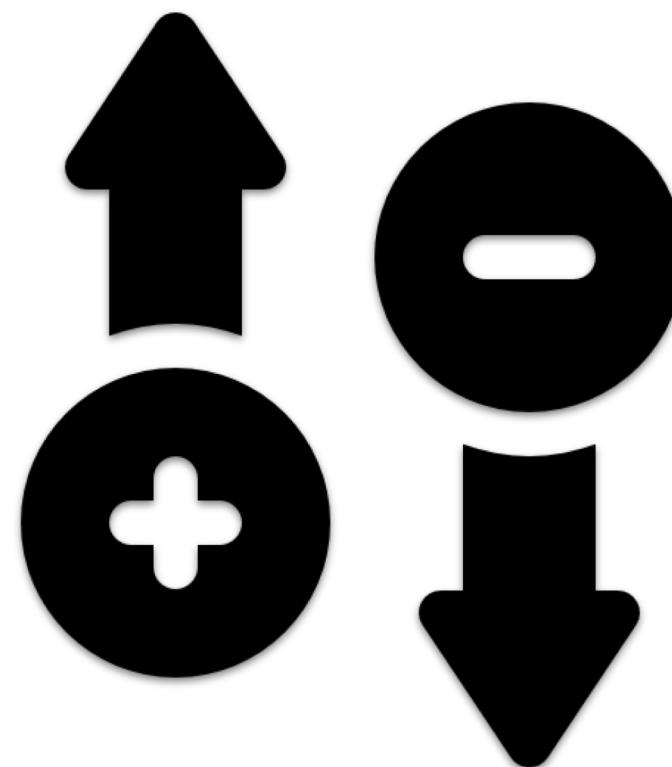
$$\frac{d}{dt}p_1(t) = \frac{V_1 p_0(t)}{K_1 + p_0(t)} - \frac{V_2 p_1(t)}{K_2 + p_1(t)} - \frac{V_3 p_1(t)}{K_3 + p_1(t)} + \frac{V_4 p_2(t)}{K_4 + p_2(t)}$$

$$\frac{d}{dt}p_2(t) = \frac{V_3 p_1(t)}{K_3 + p_1(t)} - \frac{V_4 p_2(t)}{K_4 + p_2(t)} - k_1 p_2(t) + k_2 p_N(t) - \frac{v_d p_2(t)}{K_d + p_2(t)}$$

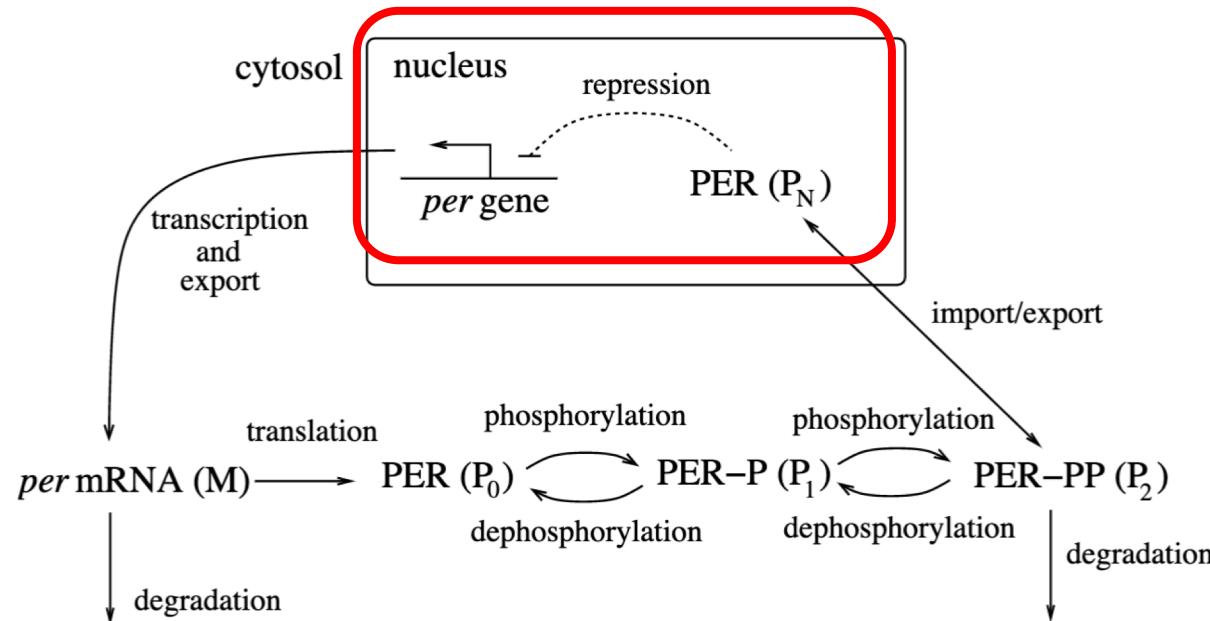
$$\frac{d}{dt}p_N(t) = k_1 p_2(t) - k_2 p_N(t)$$

[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. Mathematical Modeling in Systems Biology - an Introduction (2016)

Negative Feedback

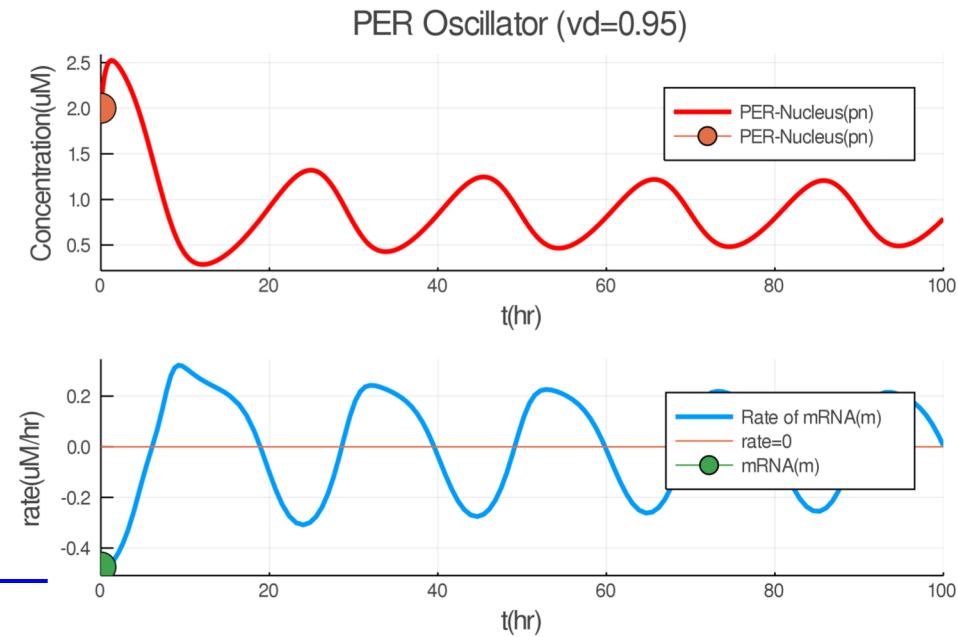
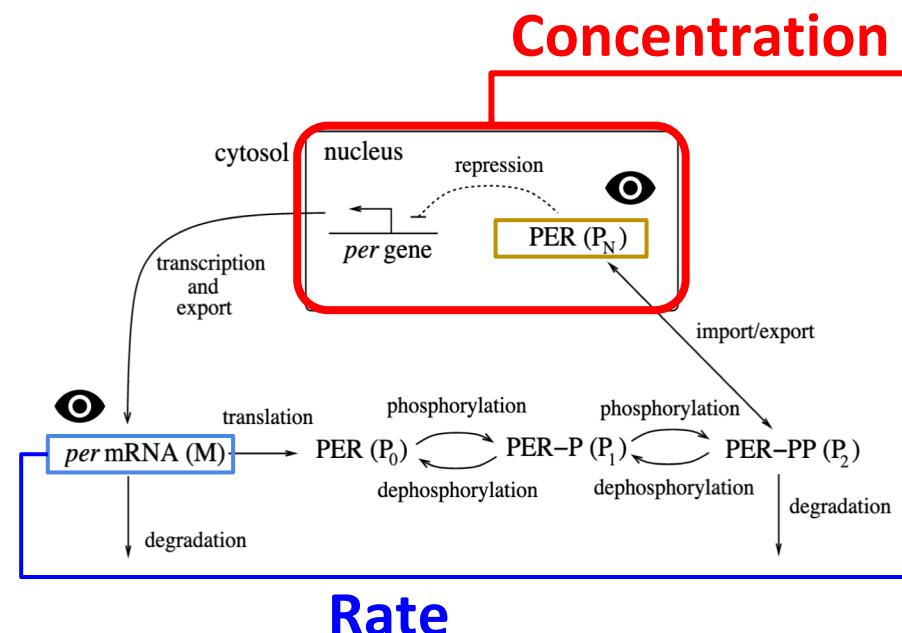


Negative Feedback



[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. Mathematical Modeling in Systems Biology - an Introduction (2016)

Negative Feedback

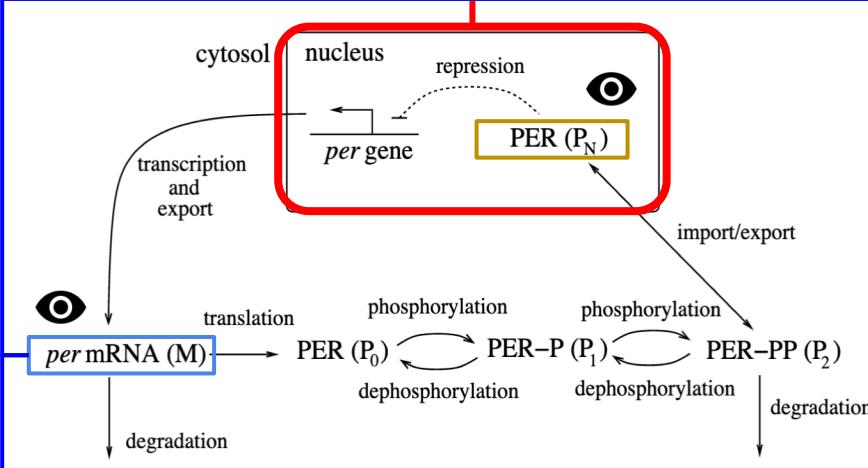


Goldbeter, A. and Berridge, M.J. 1996.

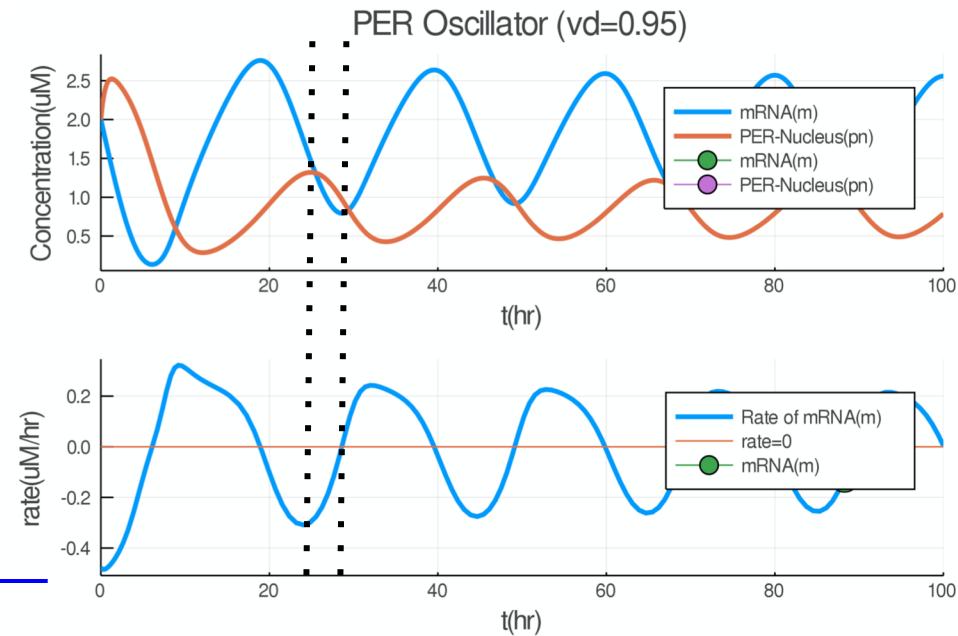
Negative Feedback

Negative feedback makes the system stable.

Concentration

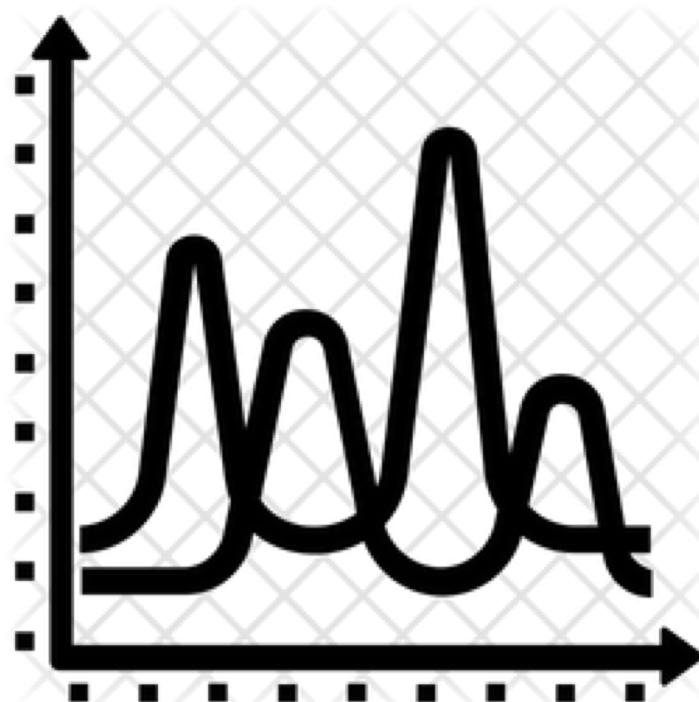


Rate



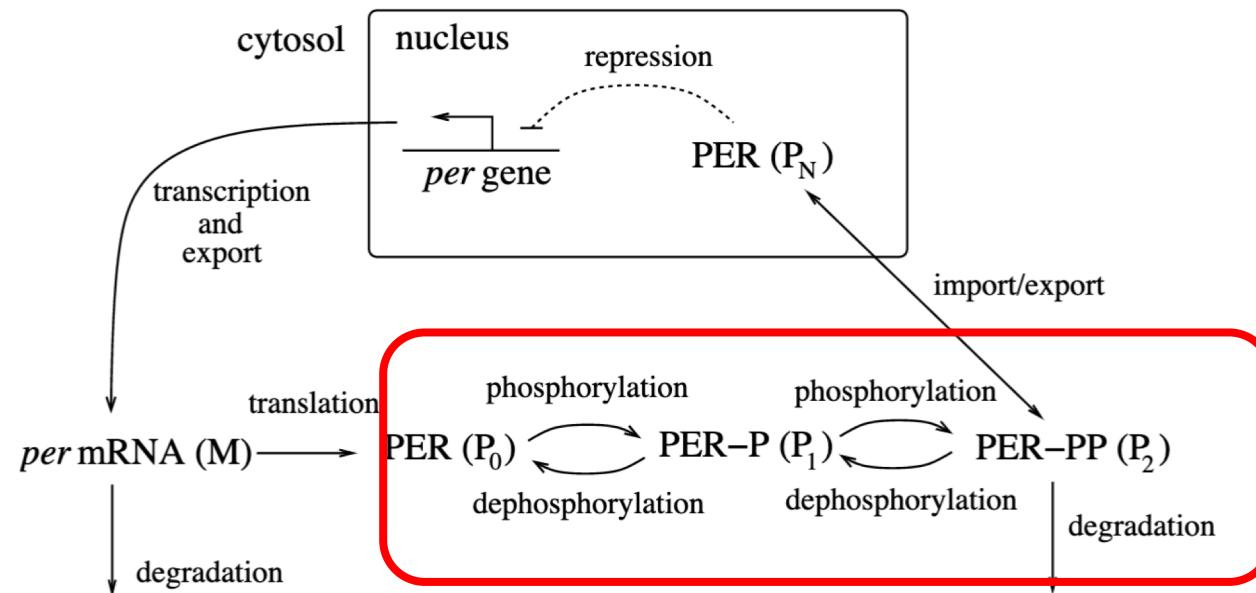
Goldbeter, A. and Berridge, M.J. 1996.

Delay



Delay

Delayed feedback is made by cascading phosphorylation.

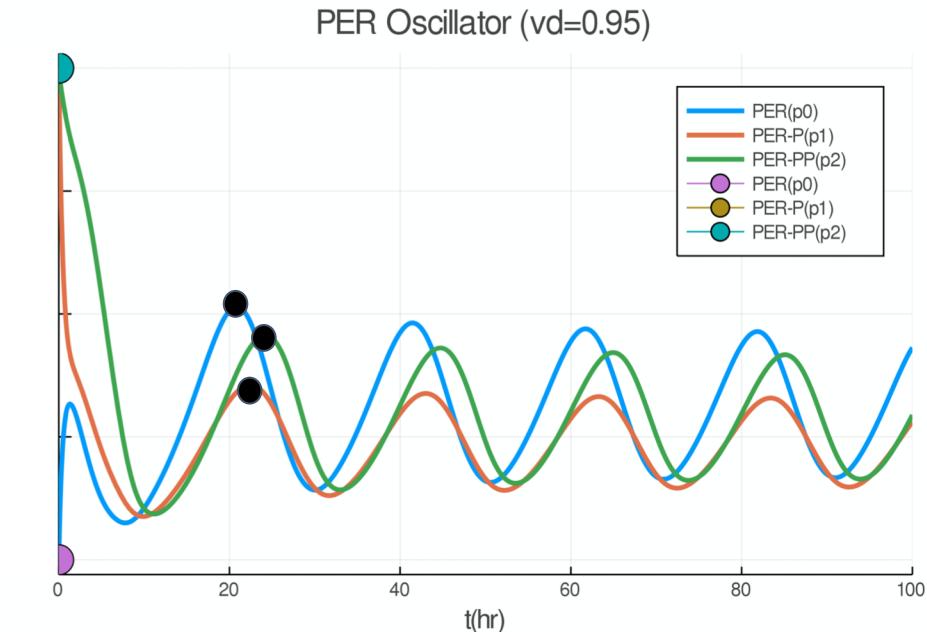
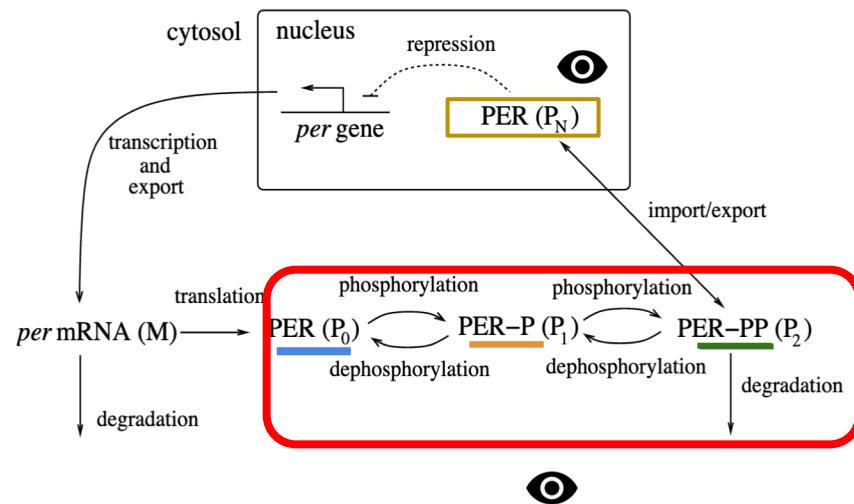


[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. Mathematical Modeling in Systems Biology - an Introduction (2016)

Delay

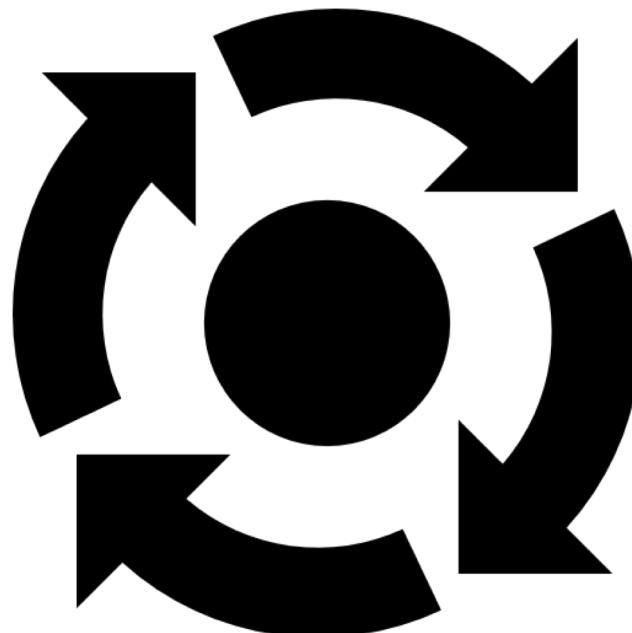
Delayed feedback made the system unstable.

Cascading phosphorylation



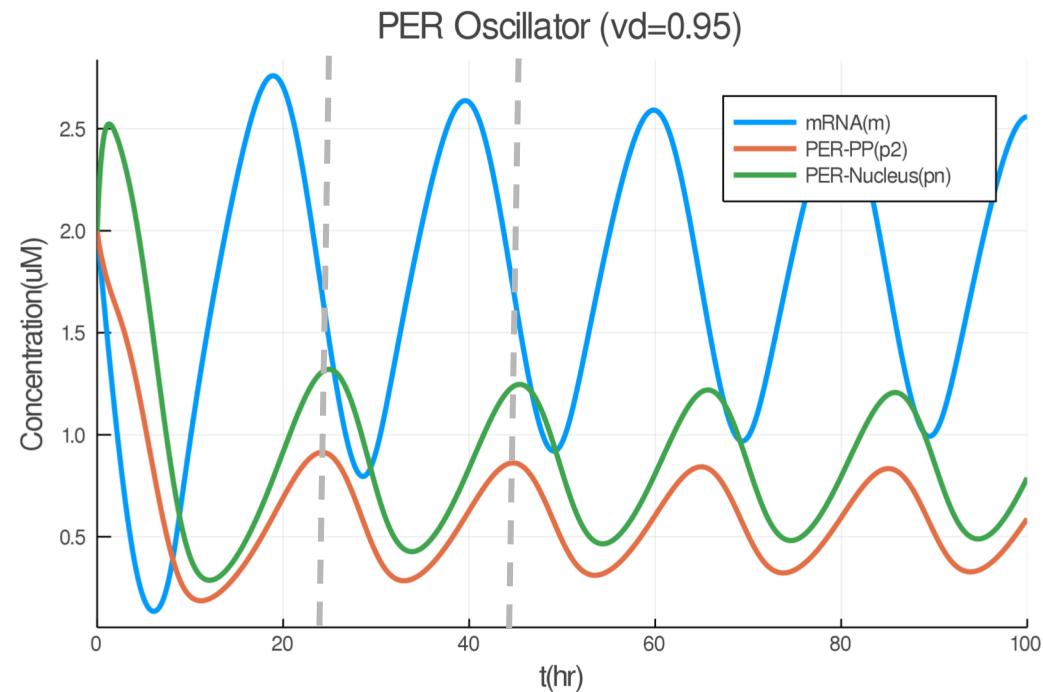
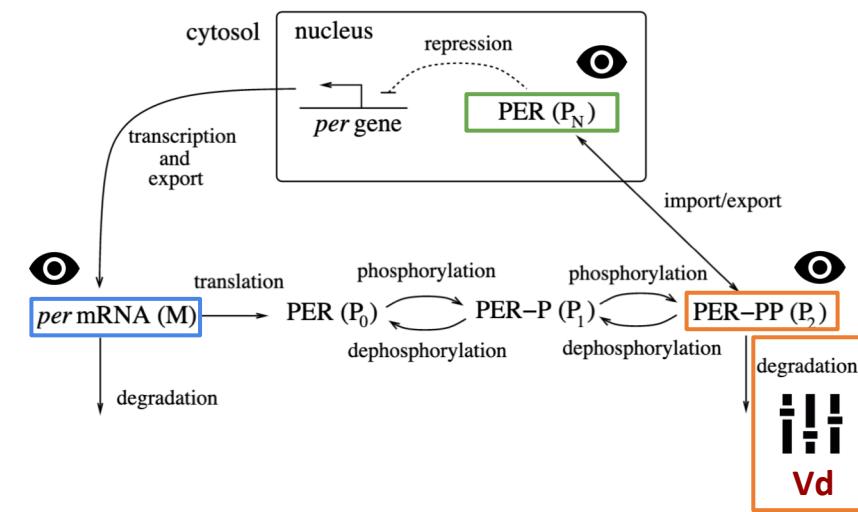
Goldbeter, A. and Berridge, M.J. 1996.

Limit Cycle



Limit Cycle

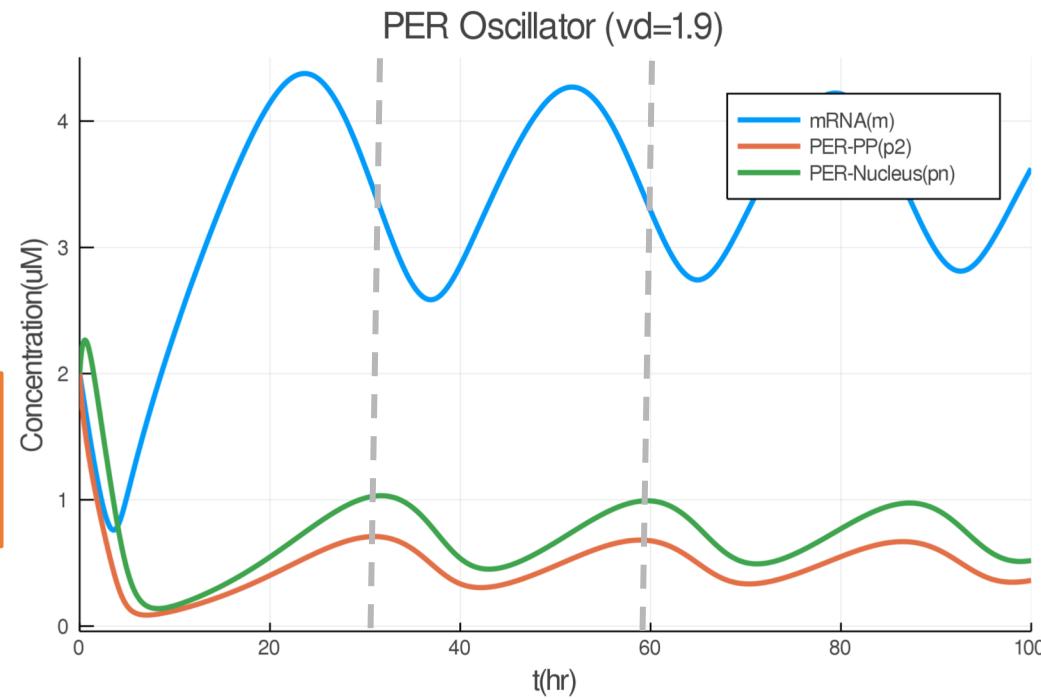
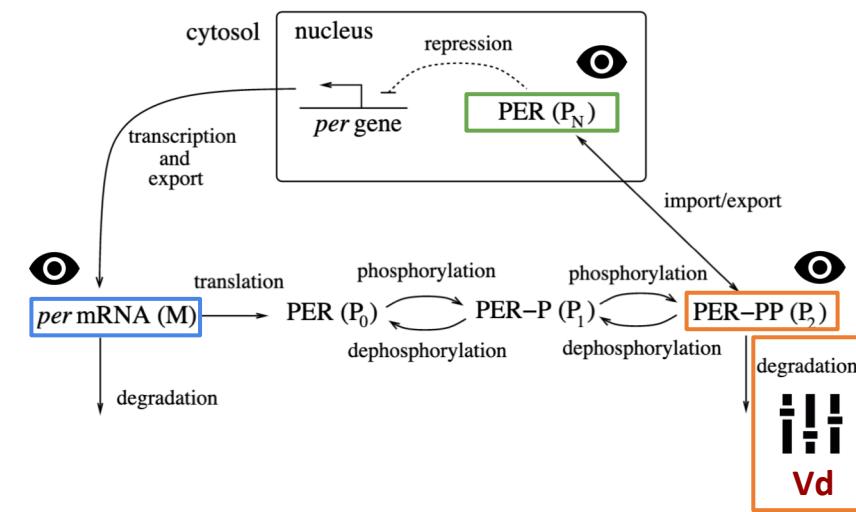
The Period of Circadian Clock can be Modulated by Decay of PER



[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. 2016

Limit Cycle

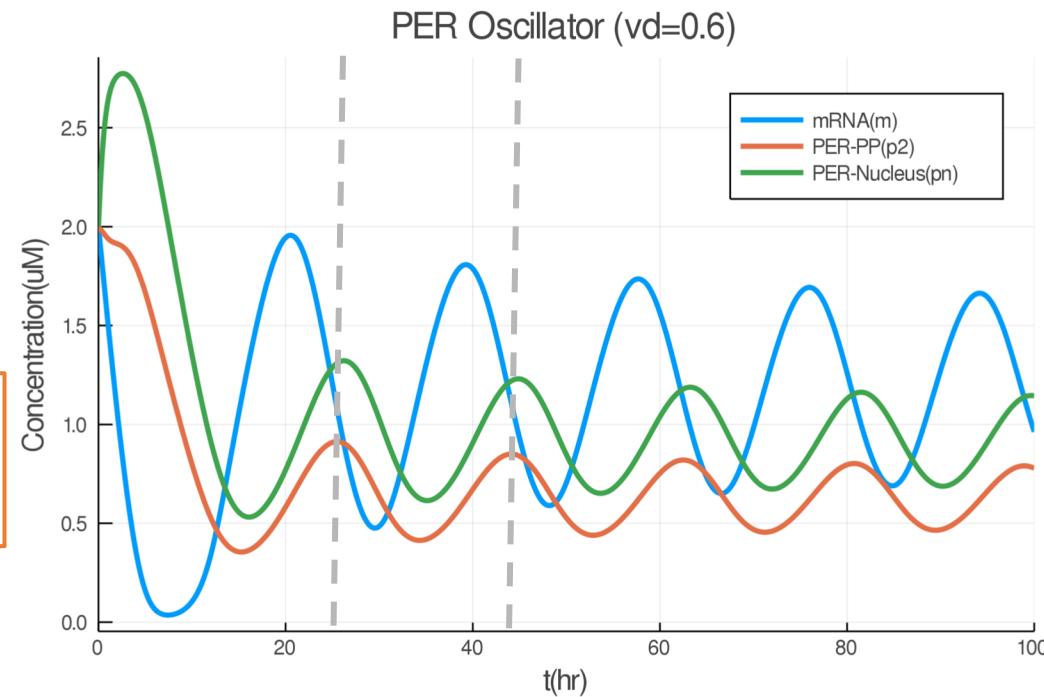
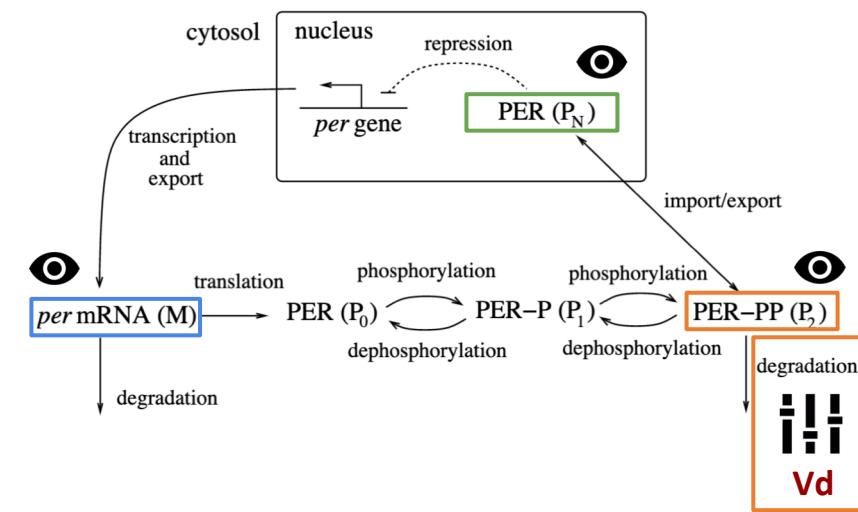
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Limit Cycle

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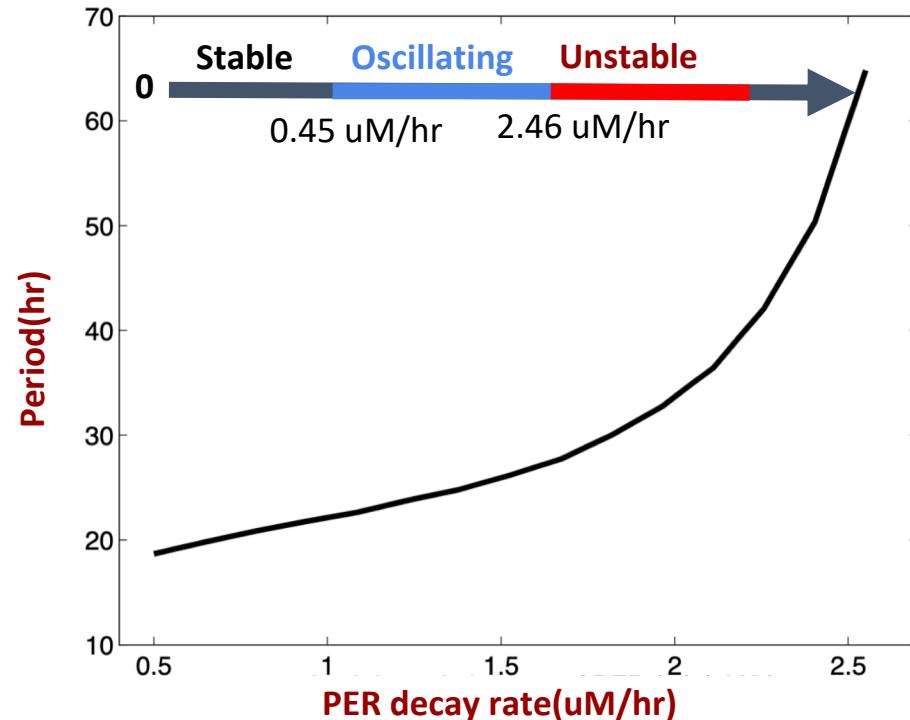
[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. 2016

Limit Cycle

The PER clock doesn't always oscillate.

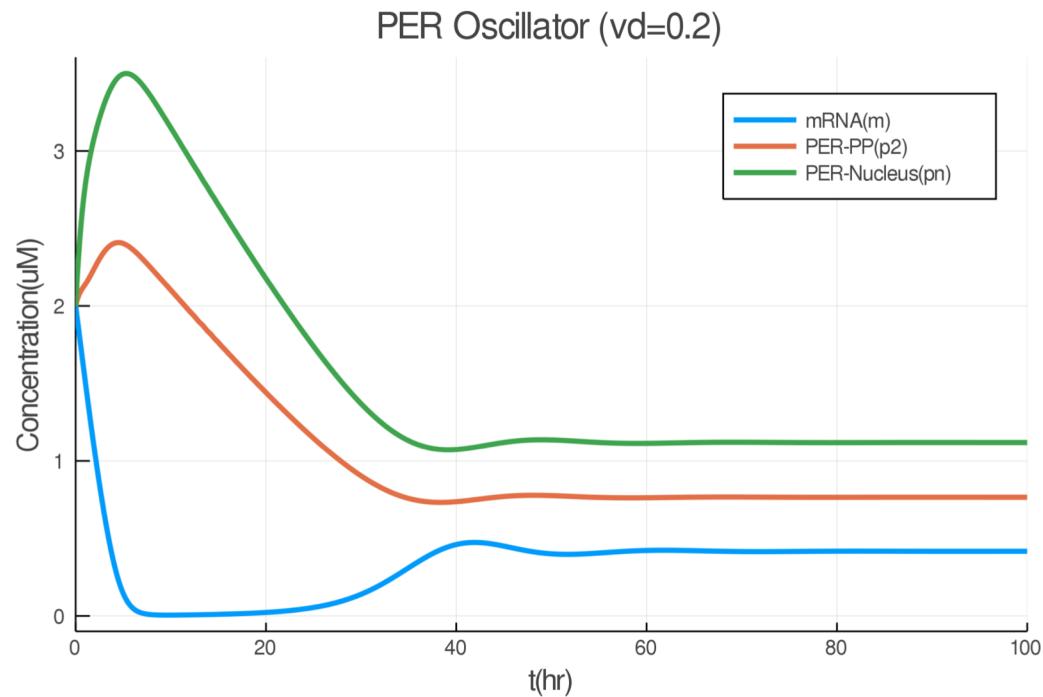
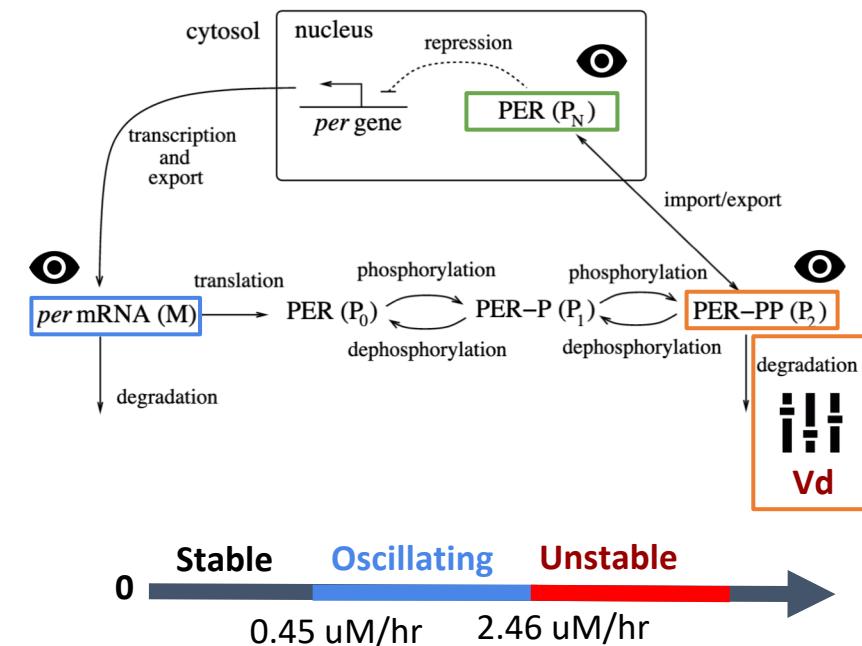
Does circadian clock oscillate with any PER decay rate?

No, circadian clock can't achieve any duration of period either.



Limit Cycle

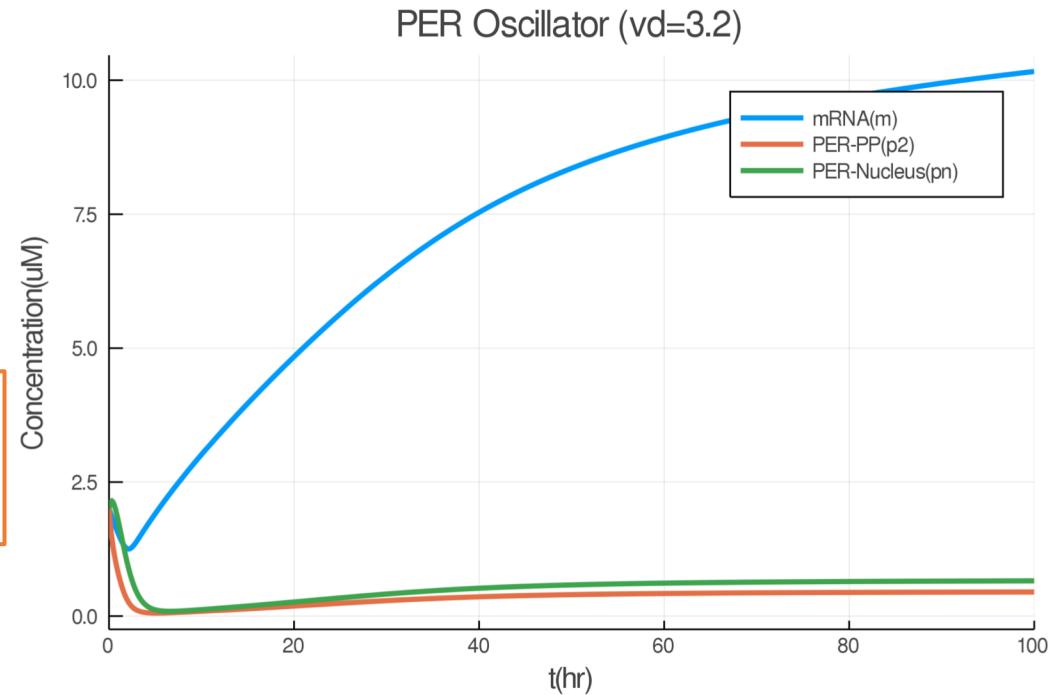
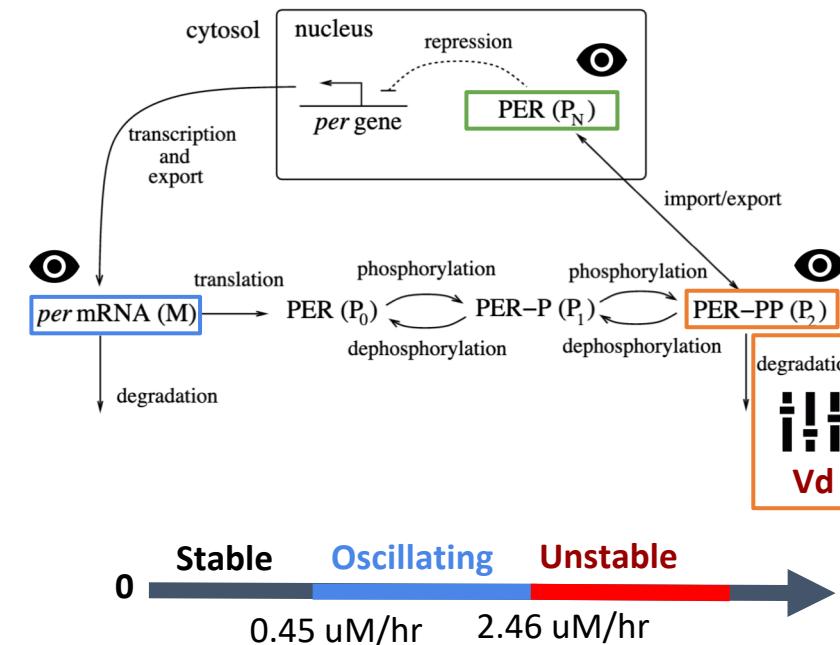
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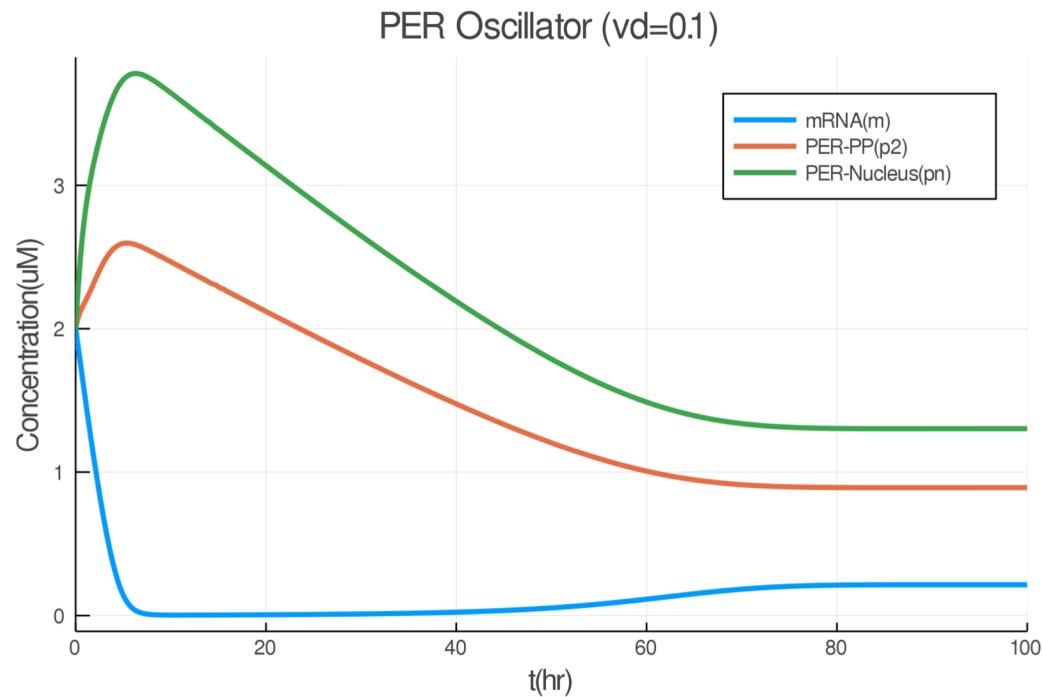
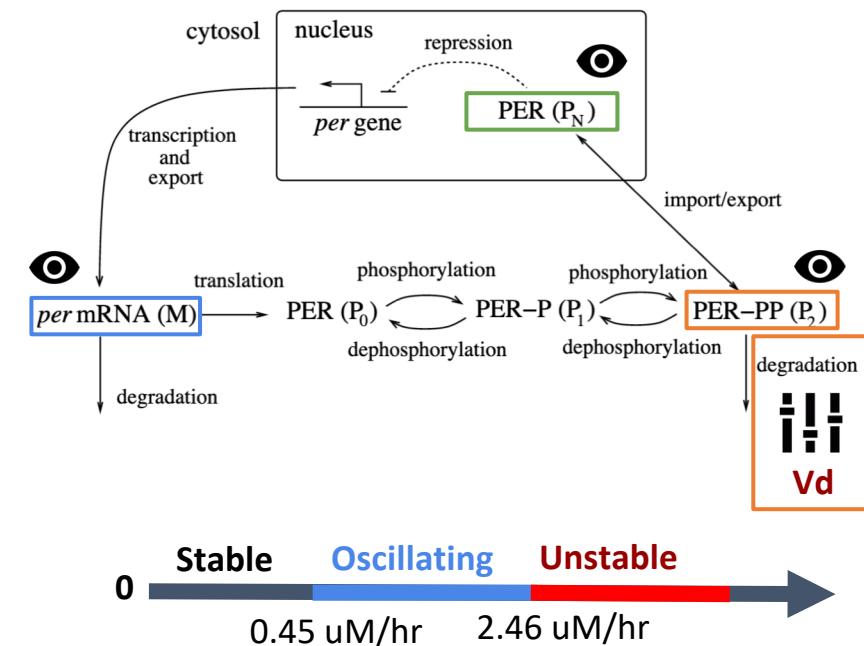
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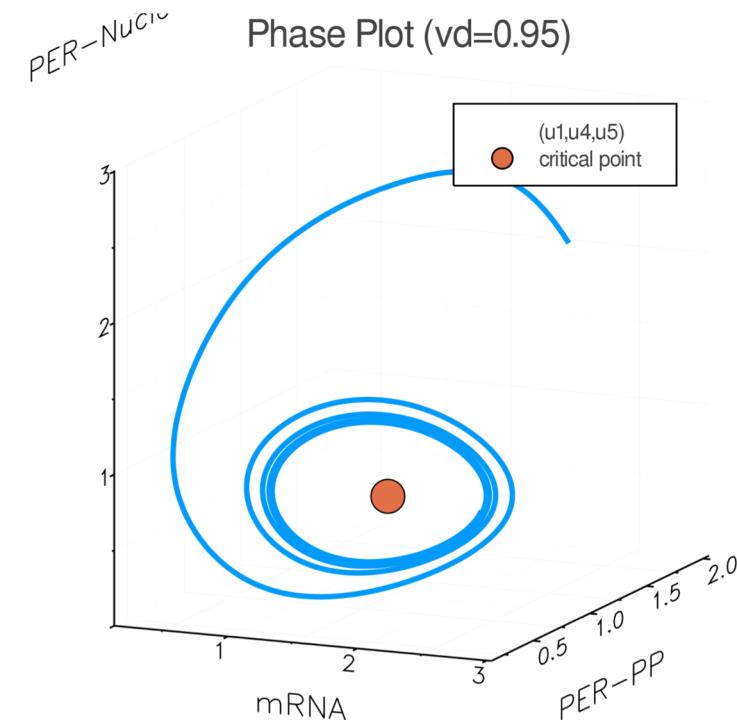
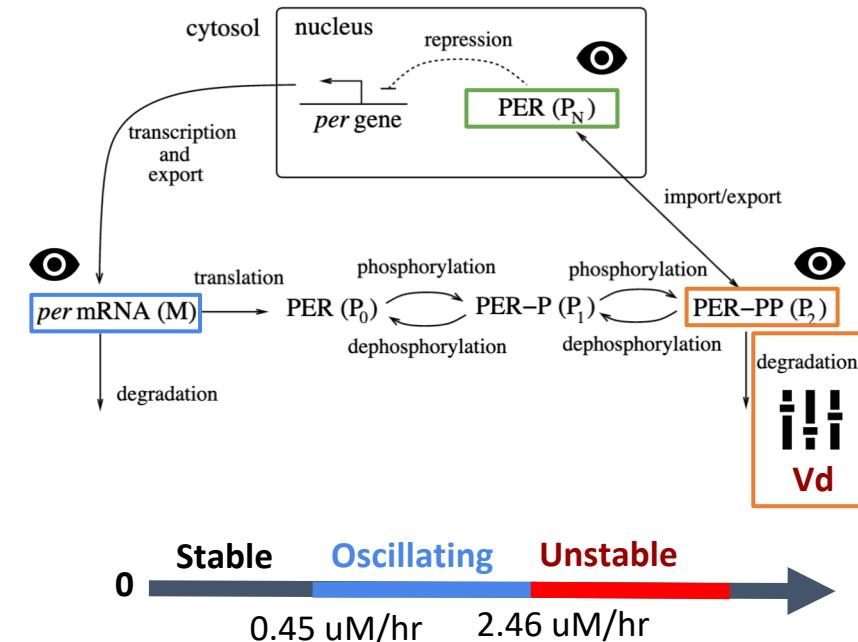
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[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. 2016

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The PER clock doesn't always oscillate.



[1] Goldbeter, A. and Berridge, M.J. 1996. [2] Ingalls B. 2016

Conclusions

1. 生物時鐘由 PER 蛋白調控，其包含溫度, 藍光等因素影響 PER 與 TIM (防止PER降解的蛋白) 的結合。
1. 生物時鐘的震盪需要 negative feedback 和 delay 匹配提供穩定與不穩定的因子。



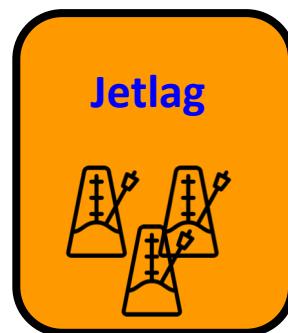
Thank you.

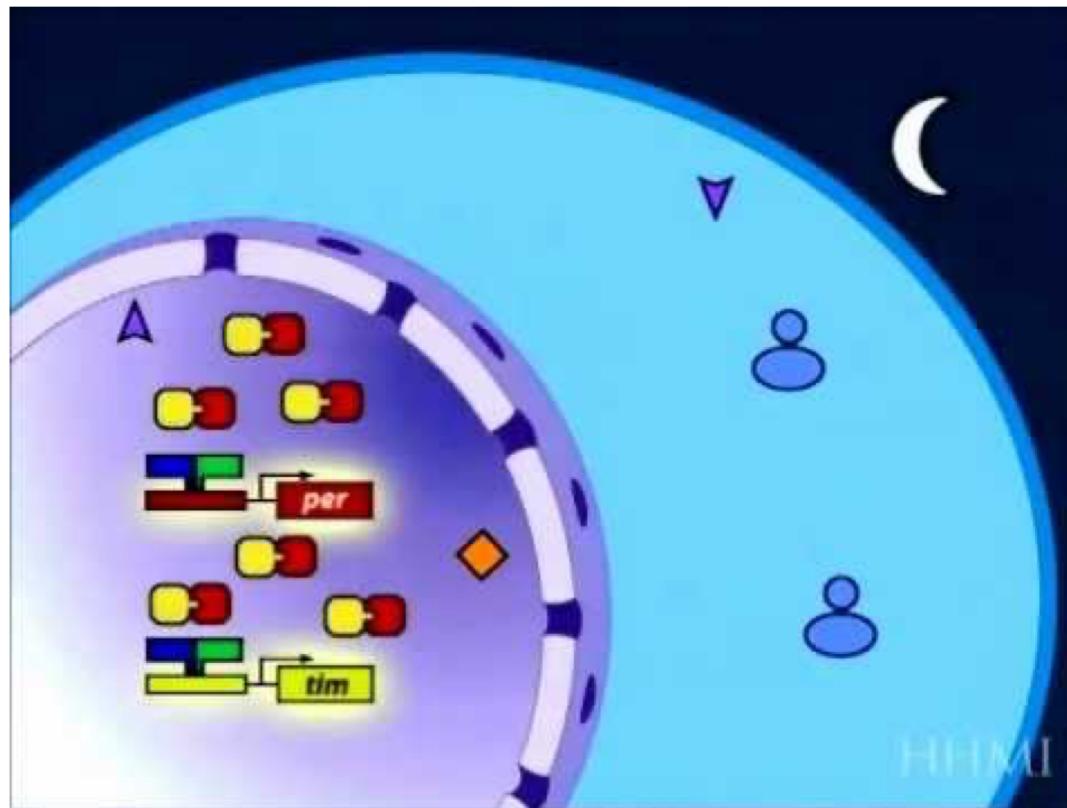
Snap it if you want to know more...



Source code and supplemental material.
<https://github.com/stevengogogo/CircadianSimulation>

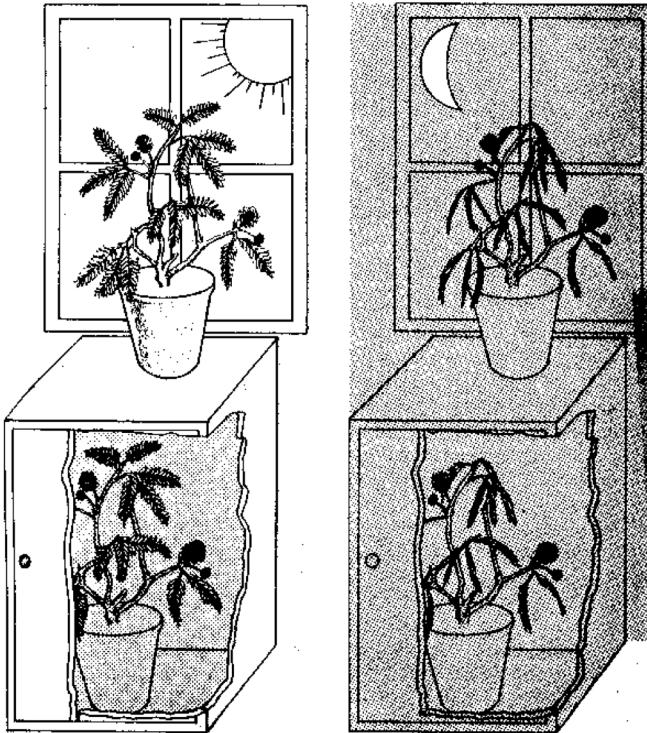
Supplemental Material





<https://www.youtube.com/watch?v=zB4VBpv9rn4>

History of Circadian Discovery



DES SCIENCES

35

OBSERVATION BOTANIQUE.

ON fait que la Sensitive est *heliotrope*, c'est-à-dire que ses rameaux & ses feuilles se dirigent toujours vers le côté d'où vient la plus grande lumière, & l'on fait de plus qu'à cette propriété qui lui est commune avec d'autres Plantes, elle en joint une qui lui est plus particulière, c'est à dire Sensitive à l'égard du Soleil ou du jour, ses feuilles & leurs pédicules se replient & se contractent vers le coucher du Soleil, de la même manière dont cela se fait quand on touche la Plante, ou qu'on l'agit. Mais M. de Maïran a observé qu'il n'est point nécessaire pour ce phénomène qu'elle soit au Soleil ou au grand air, il est seulement un peu moins marqué lorsqu'on la tient toujours enfermée dans un lieu obscur, elle s'épanouit encore très-sensiblement pendant le jour, & se replie ou se referme régulièrement le soir pour toute la nuit. L'expérience a été faite sur la fin de l'Eté, & bien répétée. La Sensitive sent donc le Soleil sans le voir en aucune manière ; & cela paroît avoir rapport à cette malheureuse délicatesse d'un grand nombre de Malades, qui s'appreçoient dans leurs Lits de la différence du jour & de la nuit.

Il ferait curieux d'éprouver si d'autres Plantes, dont les feuilles ou les fleurs s'ouvrent le jour, & se ferment la nuit, conserveroient comme la Sensitive cette propriété dans des lieux obscurs ; si on pourroit faire par art, par des fourneaux plus ou moins chauds, un jour & une nuit qu'elles sensent ; si on pourroit renverser par l'ordre des phénomènes du vrai jour & de la vraye nuit, &c. Mais les occupations ordinaires de M. Maïran ne lui ont pas permis de pousser les expériences jusque-là, & il se contente d'une simple invitation aux Botanistes & aux Phisiciens, qui pourront eux-mêmes avoir d'autres choses à suivre. La marche de la véritable Phisique, qui est l'Expérimentale, ne peut être que fort lente.

E ii

36 HISTOIRE DE L'ACADEMIE ROYALE

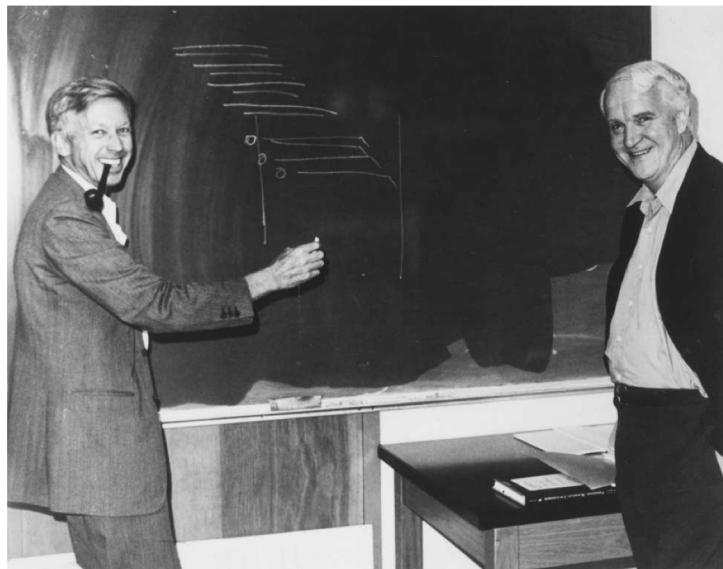
M. Marchant a lú la Description
De l'*Alchora Dioica*. & Plin. C. B. Pin. 315.
Guimauve, avec la Critique des Auteurs Botanistes sur cette
Plante.

De la *Mutella Americana*, *florum foliis fimbriatis*. Inst. Raïl
Herb. 242.

Et de la *Sanicula*, seu *Cortusa Americana*, *altera*, *flore mi-*
nuto, *fimbriato*. Hort. Reg. Par.



History of Circadian Discovery

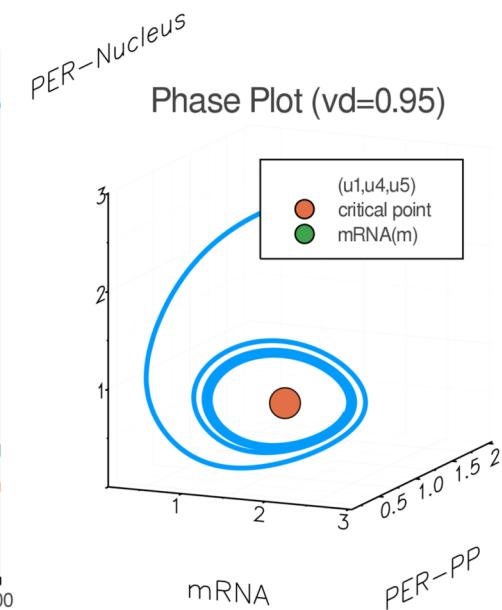
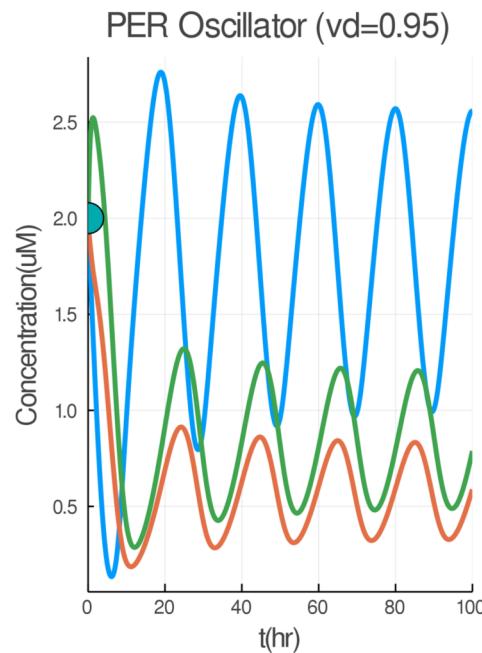


- 1)Free running period和Entrainment的證實
- 2)將行為學建立出數學公式

Limit Cycle

What is the phase plot?

Time-series



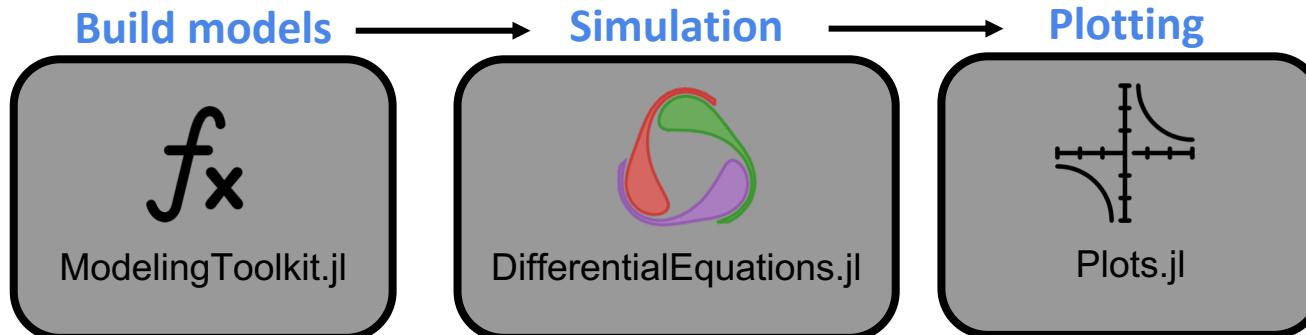
Phase Plane

1. Trajectory of dynamical systems

2. Indicate the system behavior.
Like limit cycle.

Method

How did I construct a PER model?

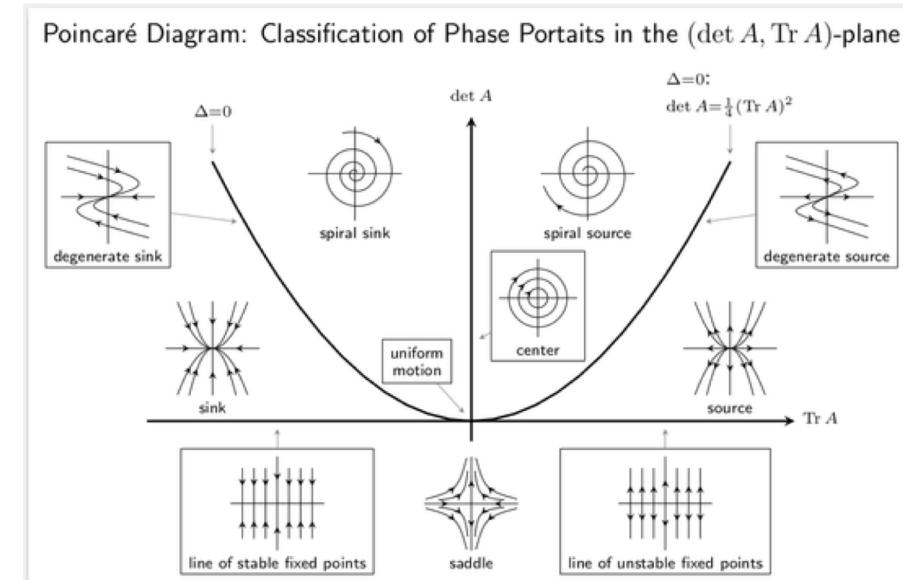
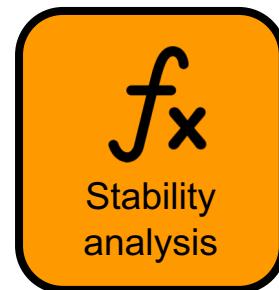


<https://julialang.org/>

Source code: <https://github.com/stevengogogo/CircadianSimulation>

Limit Cycle

How to predict if a circadian clock ticks or not?

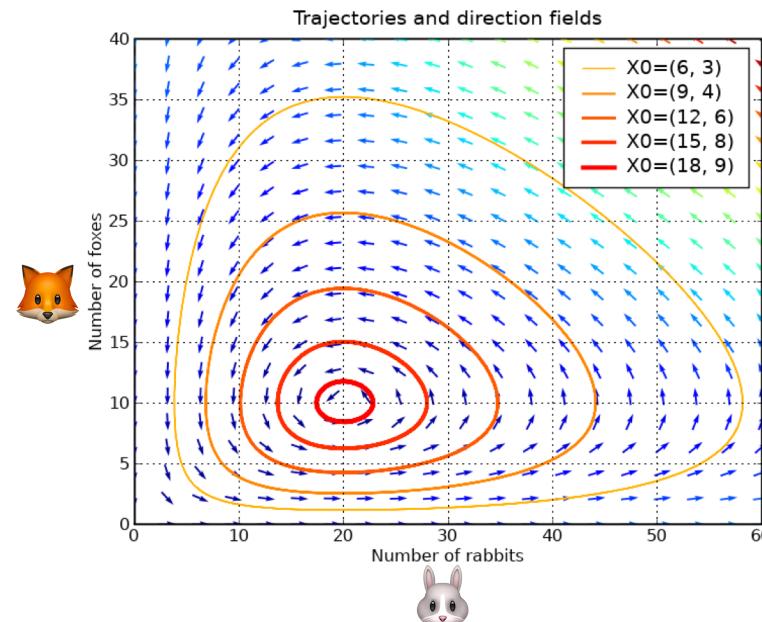


$$dx/dt = Ax, \text{ where } x \text{ is vector of agents.}$$

Limit Cycle

What is phase plot?

Phase plane can be used to visualize **the gradient of motion**.

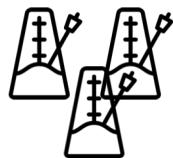


Phase Plane

1. Trajectory of dynamical systems
2. Indicate the system behavior. Like **limit cycle**

What is Jetlag?

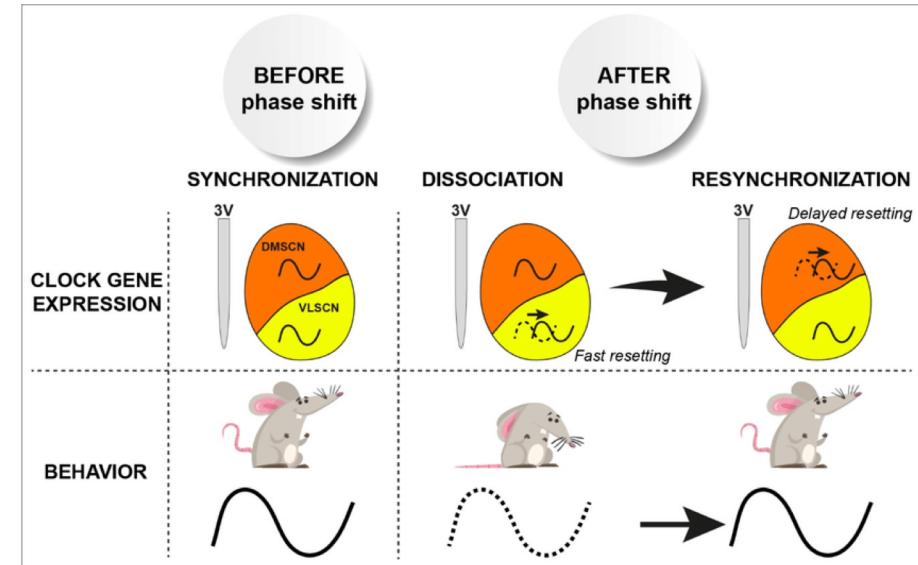
Beyond the cell



Synchronization of SCN is the key to functional regulation.



Phase shift cause heterogeneous impact on SCN cells.



The East-West Jetlag Phenomenon



Flying east gives you more jetlag than flying west



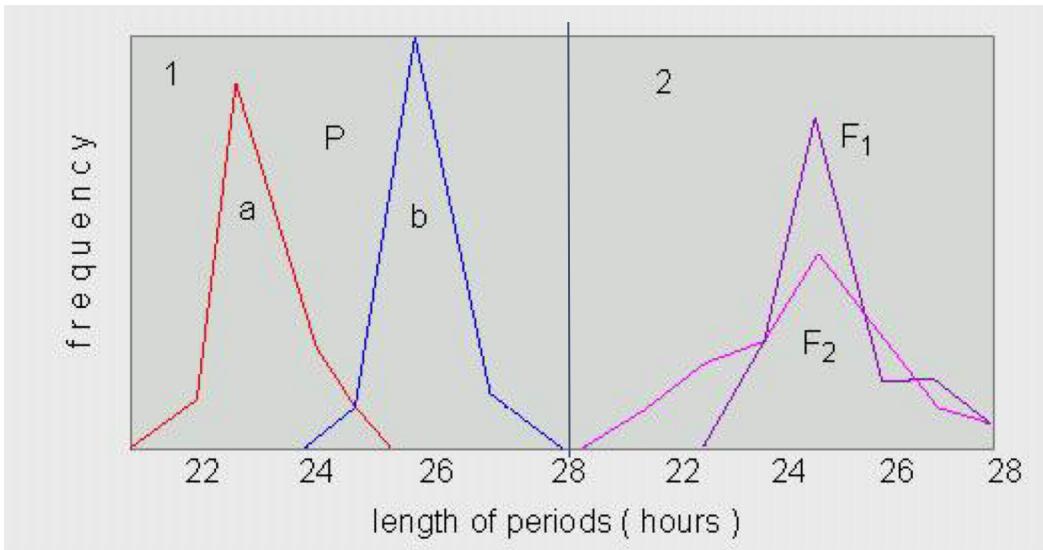
Human has native circadian clock
of 24.5hr/period.



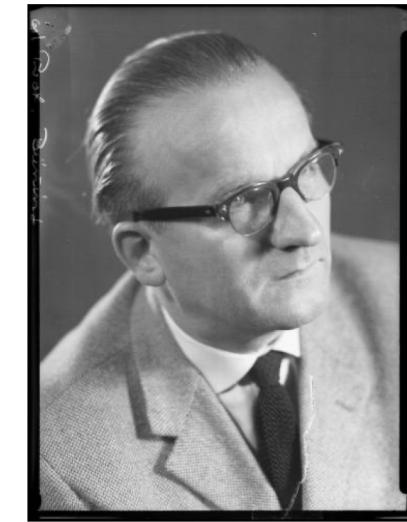
Image: [source](#)

Ref.: [link](#)

History of Circadian Discovery

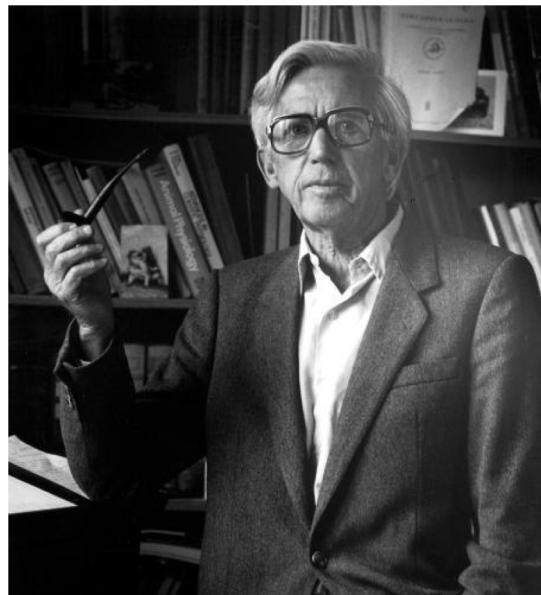


The length of periods comprise 23 hours (a), 26 hours (b) and 25 hours in the F₁ und F₂ - hybrids (E.BÜNNING, 1932).



Erwin Bünning(1906-1990)

History of Circadian Discovery



Jürgen Aschoff (1913-1998)



<https://www.pravda-tv.com/2013/07/chronobiologie-schlaflabor-im-bunker/>

<https://www.nature.com/articles/24750>

參考模板

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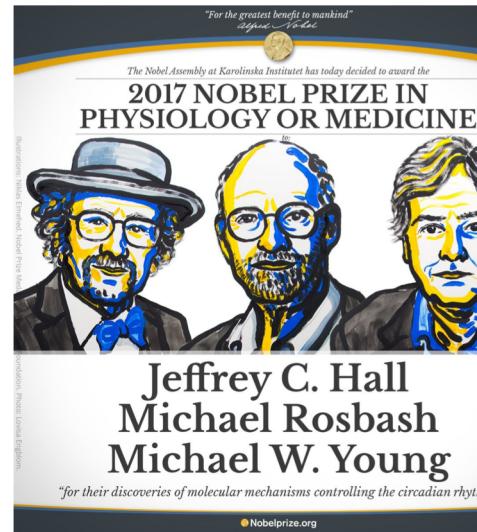


TABLE 4.2. Some mutant phenotypes of important 'clock' genes. L – locomotion; E – eclosion.

Gene	Mutant allele	Mutant phenotype	Key references
<i>period</i>	<i>per</i> ^S	$\tau \sim 19$ h; L and E	Konopka & Benzer, 1971
	<i>per</i> ^{L1}	$\tau \sim 29$ h; L and E	ditto
	<i>per</i> ^{L2}	ditto	Konopka, 1987
	<i>per</i> ⁰¹⁻⁰⁴	arrhythmic; L and E	Konopka & Benzer, 1971 Hamblen-Coyle et al., 1989
<i>timeless</i>	<i>per</i> ^T	$\tau \sim 16$ h; L and E	Konopka et al., 1994
	<i>per</i> ^{clk}	$\tau \sim 22.5$ h; L and E	Dushay et al., 1990
<i>Clock</i>	<i>tim</i> ⁰	arrhythmic	Sehgal et al., 1994
	<i>tim</i> ^S	short period	
	<i>tim</i> ^L	long period	
<i>cycle</i>	<i>cyc</i> ⁰¹⁻⁰²	arrhythmic	Rutila et al., 1998
<i>doubletime</i>	<i>dbt</i> ^S <i>dbt</i> ^L	short period long period	Price et al., 1998
<i>cryptochrome</i>	<i>cry</i> ^b	reduced light sensitivity	Stanewsky et al., 1998
<i>pigment dispersing factor</i>	<i>pdf</i> ⁰¹	arrhythmic or abnormal L and E	Renn et al., 1999

circadian rhythms at different times
across different tissues