A well-know mathematical model of circadian rhythms that also serves as an example paper for the research project

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A Simple Model of Circadian Rhythms Based on Dimerization and Proteolysis of PER and TIM

John J. Tyson,* Christian I. Hong,* C. Dennis Thron,# and Bela Novak§ *Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061 USA; [#]5 Barrymore Road, Hanover, New Hampshire 03755 USA; and [§]Department of Agricultural Chemical Technology, Technical University, Budapest 1521, Hungary

ABSTRACT Many organisms display rhythms of physiology and behavior that are entrained to the 24-h cycle of light and darkness prevailing on Earth. Under constant conditions of illumination and temperature, these internal biological rhythms persist with a period close to 1 day ("circadian"), but it is usually not exactly 24 h. Recent discoveries have uncovered stunning similarities among the molecular circuitries of circadian clocks in mice, fruit flies, and bread molds. A consensus picture is coming into focus around two proteins (called PER and TIM in fruit flies), which dimerize and then inhibit transcription of their own genes. Although this picture seems to confirm a venerable model of circadian rhythms based on time-delayed negative feedback, we suggest that just as crucial to the circadian oscillator is a positive feedback loop based on stabilization of PER upon dimerization. These ideas can be expressed in simple mathematical form (phase plane portraits), and the model accounts naturally for several hallmarks of circadian rhythms, including temperature compensation and the *per*^L mutant phenotype. In addition, the model suggests how an endogenous circadian oscillator could have evolved from a more primitive, light-activated switch.

The Tyson et al model focuses on the negative feedback of dimers of PER protein on the transcription of the *per* gene

They do not model TIM but focus on PER.

with Michaelis-Menten reactions and, denoting *P*¹ for PER monomers and *P*² for PER dimers, and $h \land h$ phosp They use Michaelis-Menten to model DBT phosphorylating PER monomers and dimers

$$
D+P_1 \underset{b_1}{\overset{f_1}{\rightleftharpoons}} C_1 \overset{k_1}{\rightarrow} P_1^*+D
$$

$$
D + P_2 \xrightarrow[b_2]{f_2} C_2 \xrightarrow{k_2} P_2^* + D
$$

As before (see Eq 2.69), we assume that both *C*¹ and *C*2, the kinase-substrate complexes, As before (see Eq 2.69), we assume that both *C*¹ and *C*2, the kinase-substrate complexes, where the kinase DBT is denoted *D*. Quasi-steady state implies As before (see Eq 2.69), we assume that both *C*¹ and *C*2, the kinase-substrate complexes,

$$
\frac{dC_1}{dt} = f_1 DP_1 - (b_1 + k_1)C_1 \simeq 0
$$
\n
$$
\frac{dC_2}{dt} = f_2 DP_2 - (b_2 + k_2)C_2 \simeq 0
$$
\n
$$
C_1 \simeq \frac{f_1 DP_1}{b_1 + k_1} \quad ; \quad C_2 \simeq \frac{f_2 DP_2}{b_2 + k_2}
$$

Conservation of the enzyme DBT implies and therefore *c*1 implies The total amount of kinase, *D^T* , is fixed, and *D* + *C*¹ + *C*² = *D^T* . This conservation law with

using Eqs 5.8 and 5.9. We can thus write

$$
D + C_1 + C_2 = D_T \qquad \text{and} \qquad D = \frac{D_T}{1 + \frac{f_1 P_1}{b_1 + k_1} + \frac{f_2 P_2}{b_2 + k_2}}
$$

n of phosphorylated monomer is 1 + *^f*1*P*¹ *b*1+*k*¹ + *^f*2*P*² *b*2+*k*² Consequently, the rate of formation of *P*⇤ ¹ , which is *k*1*C*1, equals *k* e of formation of phosphorylated monomer is 1 + *^f*1*P*¹ + *^f*2*P*² and so the rate of formation of phosphorylated monomer is 1 + *^f*1*P*¹ *b*1+*k*¹ + *^f*2*P*² *b*2+*k*² 1 , which is *k*¹ , which is *k*¹, equals in *k*² Consequently, the rate of formation of *P*⇤

$$
k_1 C_1 \qquad k_1 \times \frac{f_1 P_1}{b_1 + k_1} \times \frac{D_T}{1 + \frac{f_1 P_1}{b_1 + k_1} + \frac{f_2 P_2}{b_2 + k_2}}
$$

*^k*¹ ⇥ *^f*1*P*¹

Monomers prevent dimers from being phosphorylated and dimers prevent monomers from being phosphorylated 1 + *^f*1*P*¹ *^b*1+*k*¹ ⁺ *^f*2*P*² *b*2+*k*² Consequently, the rate of formation of *P*⇤ ¹ , which is *k*1*C*1, equals λ *m* being pho omers prevent dimers from beina r *D^T* 1 + *^f*1*P*¹ *^b*1+*k*¹ ⁺ *^f*2*P*² *b*2+*k*² *dimers from being phosphorylated and dimer f*1 + *P*¹ + *^f*2(*b*1+*k*1) *^f*1(*b*2+*k*2)*P*²

*^b*1+*k*¹ ⁺ *^f*2*P*²

1 + *^f*1*P*¹

$$
\frac{dP_1^*}{dt} = \frac{k_1 D_T P_1}{\frac{b_1 + k_1}{f_1} + P_1 + \frac{f_2(b_1 + k_1)}{f_1(b_2 + k_2)}P_2}
$$

$$
\frac{dP_2^*}{dt} = \frac{k_2 D_T P_2}{\frac{b_2 + k_2}{f_2} + P_2 + \frac{f_1(b_2 + k_2)}{f_2(b_1 + k_1)}P_1}
$$

extended Michaelis-Menten equations dP_{α}^{*} dimers the phosphorylation of Persons in Persons *d*equations **equations**

$$
\frac{dP_1^*}{dt} = \frac{V_1 P_1}{K + P_1 + P_2}
$$

$$
\frac{dP_2^*}{dt} = \frac{V_2 P_2}{K + P_1 + P_2}
$$

Each substrate inhibits the other by sequestering the enzyme DBT.

The *per* gene is repressed by PER dimers

$$
\frac{dM}{dt} = \frac{u}{1 + \frac{P_2^2}{P_c^2}} - d_M M
$$

active
Autorenression is modelled through a Hill funct Autorepression is modelled through a Hill function with *n= 2* There are three rate equations

$$
\frac{dP_1}{dt} = vM - \frac{V_1P_1}{K+P_1+P_2} - d_PP_1 - 2fP_1^2 + 2bP_2
$$

$$
\frac{dP_2}{dt} = -\frac{V_2 P_2}{K + P_1 + P_2} - d_P P_2 + f P_1^2 - b P_2
$$

$$
\frac{dM}{dt} = \frac{u}{1 + \frac{P_2^2}{P_c^2}} - d_M M
$$

To simplify, they assume that PER monomer and dimers are in equilibrium where the factor of two arises because the forward reaction decreases the number of $\mathcal P1 molecules$ Second, we investigate the equilibrium properties of the dimerization reaction of PER proteins. *dt* = *fp*₂ *de* that PER monomer and dimers are in where the factor of two arises because the forward reaction decreases the number of *P*¹ molecules by two and the backward reaction increases the number of *P*¹ molecules by two. The dimer obeys *P*y assume tha *b* ¹ (5.16) and if we let

$$
P_1 + P_1 \underset{b}{\overset{f}{\rightleftharpoons}} P_2 \hspace{3cm} P_2 = \frac{f}{b} P_1^2
$$

tal Let the total number of monomers be P_T Let the total number of monomers be P_T *b* P_{τ} rmber of mon<mark>t</mark> σ *be*

$$
P_T = P_1 + 2P_2
$$

the these equations gives **the sequent of the sequence of the sequence of the sequence of** \mathcal{D} *^P^T* ⁼ *^P*¹ + 2*^f* Combining these equations gives where we have depended by 2*/2*

$$
P_1^2 + \frac{b}{2f}P_1 - \frac{b}{2f}P_T = 0
$$

and so both can be expressed in terms of P_{τ} and so both can be expressed in terms of $P_{\mathcal{T}}$ an be expressed in terms of η

$$
P_1 = qP_T \quad ; \quad P_2 = \frac{1}{2}(1-q)P_T \qquad \text{with } q = \frac{2}{1 + \sqrt{1 + 8\frac{f}{b}P_T}}
$$

By assuming dimerisation is at equilibrium, only two rate equations are necessary dynamics. By assuming equilibrium between PER monomers and dimers, Tyson *et al.* were able to Once phosphorylated, the PER dimers rapidly degrade too and are no longer relevant for the Once phosphorylated, the PER dimers rapidly degrade too and are no longer relevant for the

$$
\frac{dP_T}{dt} = vM - \frac{V_1q + V_2(1-q)}{K + \frac{1}{2}(1+q)P_T}P_T - d_PP_T
$$

$$
\frac{dM}{dt} = \frac{u}{1 + \frac{(1-q)^2P_T^2}{4P_c^2}} - d_MM
$$

 E one point is unstable for certain values of the parameters α and the system values of the sys Using

found an equation for *P^T* = *P*¹ + 2*P*2:

$$
P_T = P_1 + 2P_2
$$

The system has negative feedback because of the repression of the *per* gene by PER dimers, and so delayed because PER must be seen the synthesized and then converted into dimersized and then converted in and so and the synthesized and then converted and then converted into dimersized and then converted into dimer and so

$$
\frac{dP_T}{dt} = \frac{dP_1}{dt} + 2\frac{dP_2}{dt}
$$