Introducing Temperature-Compensation in Any Reaction Kinetic Oscillator Model

by

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ABSTRACT

The positive and negative feedback loops in oscillatory reactions provide a basis for obtaining temperature-compensation in any reaction-kinetic model of chemical or biological oscillators. The present paper shows that positive and negative feedback reactions play the role of "opposing reactions" whose existence was suggested by Hastings and Sweeney for more than 30 years ago. The principle is illustrated with the Brusselator model.

INTRODUCTION

Many circadian rhythms (Bünning, E., 1964; Edmunds, Jr., L. N., 1988; Engelmann, W., 1988; Hastings, J. W. and Schweiger, H.-G., 1976; Sweeney, B. M., 1987; Winfree, A. T., 1980) although not all (Engelmann, W., 1988) can exhibit so-called temperature-compensation, i.e., the period length of the rhythm is little affected to temperature changes which occur within a certain physiological range. The influence of temperature is normally reported by Q_{10} values (Bünning, E., 1964; Edmunds, Jr., L. N., 1988; Engelmann, W., 1988; Hastings, J. W. and Schweiger, H.-G., 1976; Sweeney, B. M., 1987; Winfree, A. T., 1980) which describe the relative frequency or period change when the temperature is increased by 10 centigrades. For temperature-compensated circadian rhythms typical Q_{10} values are between 1 and 1.1. In a few cases, Q_{10} values are greater than 1.2 or lower than 1 (Bünning, E., 1964). This temperature insensitivity of circadian rhythms is in considerable contrast to chemical or biochemical oscillatory systems where Q_{10} values normally lie between 2-4 as expressed by Van't Hoff's rule (Neumüller, O.-A., 1988). It should be noted, however, that there are examples of purely chemical systems which have Q_{10} values lower than 1 (Skrabal, A., 1915).

To rationalize temperature-compensation in reaction kinetic terms, Hastings and Sweeney (Hastings, J. W. and Sweeney, B. M., 1957) proposed in 1957 the general idea of two opposing and compensating reactions. During the 1960's and

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1970's several approaches to explain temperature-compensation in several models appeared (Engelmann, W. et al., 1974; Johnsson, A., 1983; Johnsson, A. and Karlsson, H. G., 1972; Pavlidis, T., 1973; Pavlidis, T. and Kauzmann, W., 1969; Pavlidis, T. et al., 1968; Rössler, O. E., 1975), where each of the studies were emphasizing specific aspects of the investigated model oscillators.

As a result of an earlier study of light-induced circadian rhythms in higher plants (Lillo, C., 1984; Lillo, C. and Henriksen, A., 1984; Lillo, C. and Ruoff, P., 1984), we were considering the problem how temperature-compensation can be achieved in reaction kinetic terms. This paper describes a general method how temperature-compensation can be obtained in *any* reaction kinetic model: the positive and negative feedback loops of the oscillator act as the "opposing" reactions, where a practically unlimited number of different combinations of rate constant values can lead to temperature-compensation.

THE CONSTRUCTION OF A TEMPERATURE-COMPENSATED REACTION KINETIC OSCILLATOR MODEL

A necessary condition for the existence of *any* physico-chemical oscillatory system is the presence of at least one destabilizing positive feedback and one stabilizing negative feedback both acting simultaneously on one of the kinetic variables in the system. This rule is known as the antagonistic feedback concept, which was formulated by Franck in the late 1970's (Franck, U. F., 1978; Franck, U. F., 1980).

Here we describe that an increase of rate constants belonging to positive feedback reactions increase frequency (decrease period length), while increasing rate constants of negative feedback reactions will lower frequency (increase period length). Thus, for a certain set of activation energies, positive and negative feedback reactions will, due to their opposing temperature-behaviours, tend to compensate the influence of temperature on period length. We illustrate this behaviour with the Brusselator model which is one of the simplest chemical model oscillators (Prigogine, I. and Lefever, R., 1968).

The Brusselator consists of four irreversible reaction steps R1-R4 with two kinetic variables X and Y and the rate constants k_1-k_4. Pool chemicals A, B, D, and E are assumed to be present with constant concentrations:

$$A \xrightarrow{k_1} X \tag{R1}$$

$$2X + Y \xrightarrow{k_2} 3X \tag{R2}$$

$$B + X \xrightarrow{k_3} Y + D \tag{R3}$$

$$X \xrightarrow{k_4} E \tag{R4}$$

Process R2, the autocatalytic generation of X, is the necessary destabilizing positive feedback in order to get oscillations. Process R1 represents another positive feedback relative to X, while processes R3 and R4 consume X and therefore represent negative feedback reactions.

Reactions R1-R4 are treated as elementary processes (Prigogine, I. and Lefever, R., 1968) which results in the following rate equations:

$$\frac{d[X]}{dt} = k_1 \cdot [A] + k_2 \cdot [X]^2 \cdot [Y] - k_3 \cdot [B] \cdot [X] - k_4 \cdot [X] \tag{1}$$

$$\frac{d[Y]}{dt} = -k_2 \cdot [X]^2 \cdot [Y] + k_3 \cdot [B] \cdot [X] \tag{2}$$

Equations 1 and 2 are solved numerically by using the FORTRAN-program LSODE (Hindmarsh, A. C., 1980).

Analogous to empirical chemical rate equations (Laidler, K. J., 1987), we express the period length P of the Brusselator by the following *approximate* relationship:

$$P = \tau_0 \cdot k_1^{\alpha_1} \cdot k_2^{\alpha_2} \cdot k_3^{\alpha_3} \cdot k_4^{\alpha_4} \tag{3}$$

where τ_0 and α_i's are constants. Because α_1 and α_2 belong to positive feedback reactions they are negative, while α_3 and α_4 have positive values. When the oscillator is temperature-compensated, P is approximately independent of temperature T such that

$$\frac{\partial P}{\partial T} \approx 0 \tag{4}$$

Assuming an Arrhenius-type dependence of the k_i's on T, i.e.,

$$k_i = A_i e^{-\frac{E_i}{R \cdot T}} \tag{5}$$

equation 2 leads to the condition:

$$\sum_i \alpha_i \cdot E_i \approx 0 \tag{6}$$

However, because equation 3 is an approximation, equation 6 is generally not fulfilled over an extended temperature-range, and further "fine-tuning" of one or several activation energies (E_i's) is normally necessary to obtain the desired degree of temperature-compensation.

Fig. 1 shows the contributions of the positive and negative feedback reactions to the period length in a temperature-compensated situation. Actually, we have used the logarithm of the period P, because if equation 3 is an exact representa-
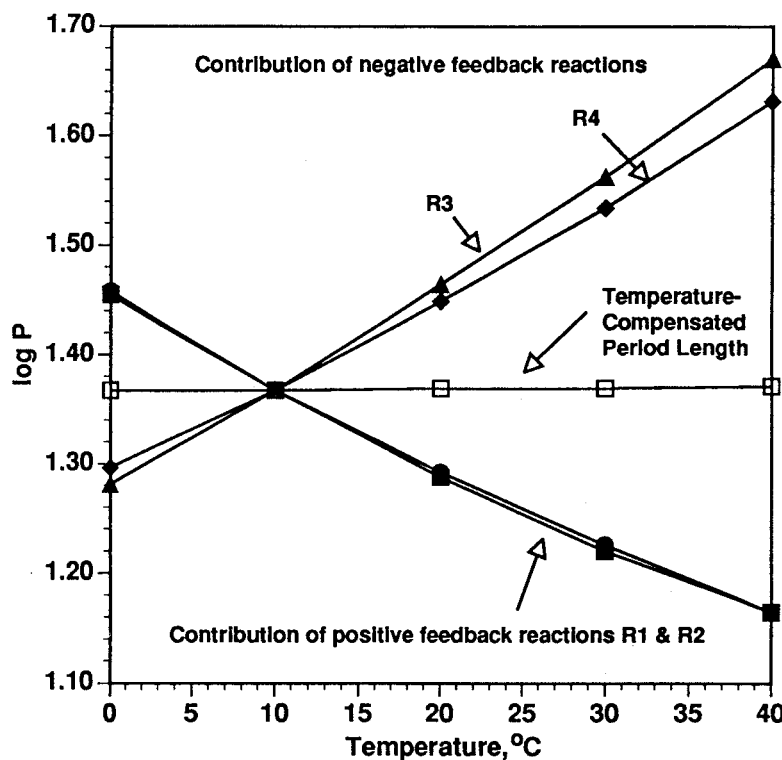
Fig. 1. Logarithm of period length (log P) of a temperature-compensated Brusselator. Values of [A] and [B] are fixed to 0.5 and 3.0 (arbitrary concentration units), respectively.

tion, simulated log P -T plots should be straight lines. The fact that the log P -T plots in Fig.1 are curved shows that equation 3 is indeed only an approximation.

At T= 283 K, all rate constants are arbitrary set to 1.0, which results in a period length of 23.3 time units. This refers to the intersection point in Fig.1. The α_i's are determined by calculating the slope of the numerical log$P$ - log(k_i) function, while keeping the other $k_{j \neq i}$ at 1.0. The obtained α_i values are listed in Table 1.

Activation energies E_2, E_3, E_4 are (arbitrary) set to 14.00 kJ/mol, and the pre-exponential factors A_i in the Arrhenius equation are determined according to the condition $k_i(283K)=1.0$. When E_1 is finally calculated according to equation 6 (which results in $E_1=9.02$ kJ/mol), a decrease in period length with increasing temperature is observed, where the average Q_{10} is 1.07 over a 0°C-40°C range. Fig. 1 shows the results when E_1 is further "fine-tuned" to 6.57 kJ/mol: the period of the oscillator increases now slightly with increasing temperature and Q_{10} has a value of 0.998. The results are summarized in Table 1. We note that when positive

Table 1. Calculated α_i, A_i, E_i, and Q_{10} values for the Brusselator model[a].

i	α_i	E_i (kJ/mol)	A_i (arbitary units)	Q_{10}
2	-0.954	14.00[b]	383.83	–
3	1.175	14.00[b]	383.83	–
4	0.984	14.00[b]	383.83	–
1	-1.870	9.02	46.25	1.07
1	-1.870	6.57	16.32	0.998

[a] [A]=0.5, [B]=3.0 (arbitrary concentration units)
[b] fixed values

feedback reactions dominate, the Q_{10} values are greater than 1, and the period length decreases with increasing temperature. When negative feedback reactions dominate (like in Fig. 1), we get Q_{10} values lower than 1. In this case the period increases with increasing temperature.

PHASE AND AMPLITUDE SHIFTS

Although period lengths in temperature-compensated oscillators may be remarkably constant over a certain temperature range, phases and amplitudes are generally altered by temperature changes. In the temperature-compensated Brusselator, positive temperature-steps lead to a phase delay and to an increase in amplitude, while negative temperature-steps lead to the opposite (Fig. 2). Fig. 3 illustrates the origin of the phase delay and amplitude increase for the 0°C → 40°C temperature-step shown in Fig. 2.

The choice of activation energies E_i (Table 1) which leads to the temperature-compensation of Fig. 1 is only one possibility out of many other combinations as to how temperature-compensation can be achieved. Equation 6, although not strictly valid over an extended temperature range, can serve as a guideline for obtaining other E_i-combinations.

GENERALIZATION AND FURTHER WORK

For a model oscillator with n reaction kinetic component processes, period P can be expressed by an extended equation 3:

$$P = \tau_0 \prod_{i=1}^{n} k_i^{\alpha_i} \tag{8}$$

As long as the period length P is a smooth and not too rapidly changing function of the rate constants k_i, equation 8 appears to be a satisfactory description of P of any reaction kinetic oscillator model.
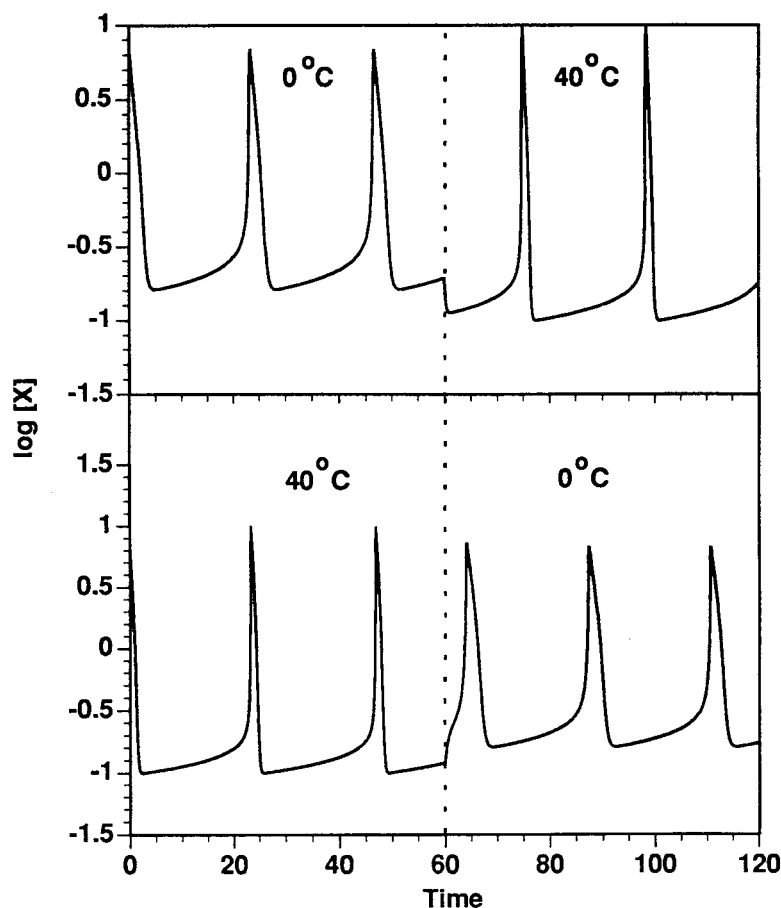
Fig. 2. Effect of temperature-steps in the temperature-compensated Brusselator. The logarithm of the X-concentration, [X], against time (both in arbitrary units) is shown. The dashed line indicates the sudden change in temperature.

In a first approximation, E_i values can be determined by equation 6, but further "fine-tuning" of the E_i's will normally be necessary to obtain better temperature-compensation.

We may speculate whether chemical oscillatory reactions (Field, R. J. and Burger, M., 1985; Gray, P. and Scott, S. K., 1990) may be able to act as temperature-compensated "in-vitro" systems. In view of the findings by Skrabal (Skrabal, A. 1915) that also purely chemical systems seem to be able to exhibit Q_{10} values lower than 1, it appears interesting to try to design or modify chemical oscillatory reactions such that they show Q_{10} values close to one.
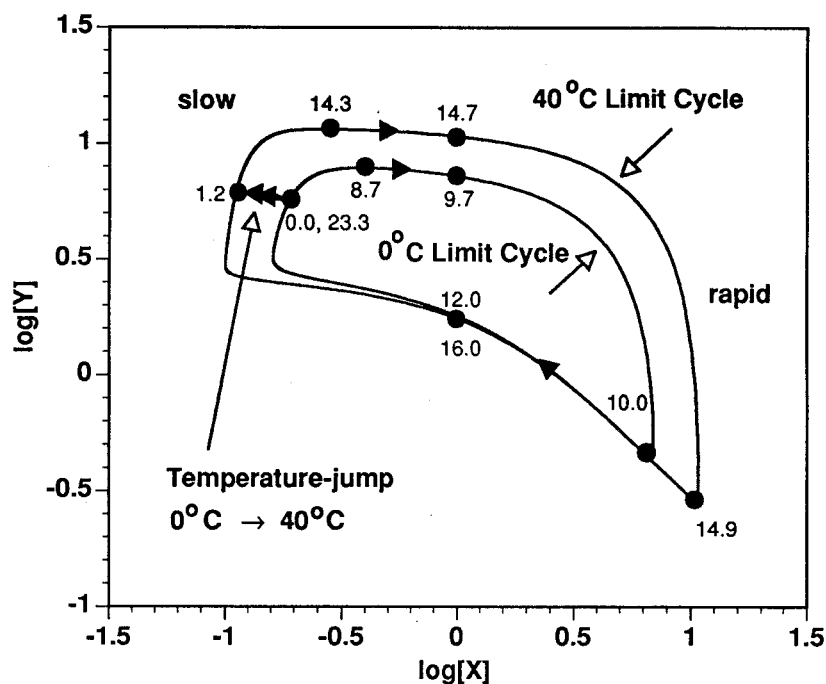
Fig. 3. Log[Y] - log[X] phase plane plot corresponding to the upper trace of Fig. 2. The two oscilla-
tory states at 0°C and 40°C are represented by the indicated limit cycles. Numbers at points
along the 40°C limit cycle show times relative to the 0°C → 40°C step, while numbers at the
inner 0°C limit cycle show times if no temperature-jump would have occurred. The delay in
phase due to the 0°C → 40°C step occurs, because at high [Y] and low [X] values velocities
on the 40°C limit cycle are substantially lower than on the 0°C limit cycle. Velocities in the
rapid region of the phase plane (high [X], low [Y]) are only marginally higher on the 40°C limit
cycle. Positive temperature-steps in this region of the phase plane lead only to very small
phase advances.

More than 30 years ago, the existence of opposing reactions to explain tem-
perature-compensation in circadian rhythms was suggested (Hastings, J. W. and
Sweeney, B. M., 1957). The present paper shows that positive and negative
feedback reactions in fact play such a role, and that temperature-compensation
can be accomplished by these elements which form the oscillatory reaction.
Further work will investigate whether the principles derived in this paper are
sufficient to explain experimentally observed phase resetting behaviors in tem-
perature-perturbed circadian rhythms.

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