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Antagonistic balance in the oregonator: about the possibility of temperature-compensation in the Belousov–Zhabotinsky reaction

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Abstract

The temperature behavior of the Oregonator has been investigated and compared with experimental data. Conditions that lead to temperature-compensation in the Oregonator model are presented and some implications to biological systems are discussed.

1. Introduction

Chemical and biochemical oscillatory systems [1–8] are often considered as "simple" experimental models for biological rhythms. Among biological oscillations, circadian rhythms [9–18] are considered to have physiological clock functions (for example measurement of day length in order to induce important physiological processes as flowering, hibernation, etc. at the correct time). As a consequence, circadian rhythms show temperature-compensation. Temperature-compensation, discovered by Pittendrigh during the early 1950s, [19] implies that the oscillator period, within a physiological range, is little affected by variation in temperature, as long as the temperature is kept constant.

However, temperature-compensation observed in biological rhythms stands in marked contrast to the temperature behavior found in most of the purely chemical or biochemical oscillators. These latter systems are highly dependent on temperature, and in fact, they are often illustrative examples of Van't Hoff's rule. Van't Hoff's rule [20] is an empirical statement saying that when the temperature of a chemical system is increased by 10 centigrades, the reaction rate normally increases with a factor (Q_{10}) of 2 to 4.

The Belousov[21]–Zhabotinsky[22] (BZ) reaction [23,24] is a typical example. Fig. 1 shows the increase in frequency of a batch BZ system as temperature is increased. It is seen that the BZ system follows the Arrhenius equation with high precision. From this Arrhenius plot a Q_{10} value of 2.5 has been calculated together with an overall activation energy of 73 kJ/mol.

If the component processes in biological oscillations are (bio)chemical reactions that follow Van't Hoff's rule, how then can temperature-compensation in circadian rhythms be explained? Several suggestions to solve this problem have been proposed earlier. Hastings and Sweeney [25] postulated the existence of "opposing reac-

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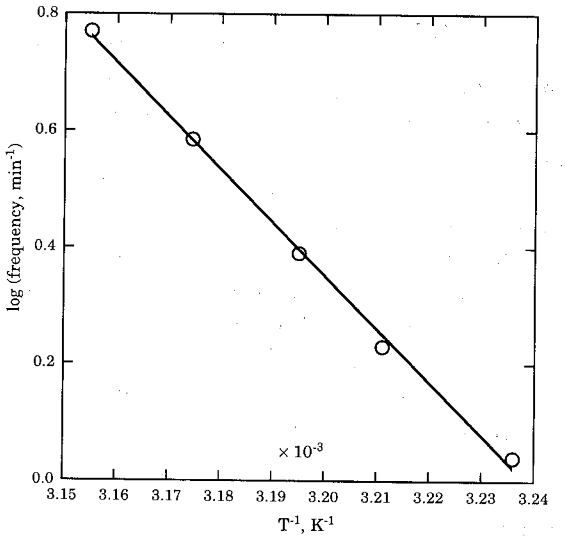

Fig. 1. Arrhenius plot (here: natural logarithm of inverse of period length versus inverse of absolute temperature) of a batch Belousov–Zhabotinsky reaction. Reaction volume is 100 mL. Initial reagent concentrations: malonic acid 0.3 M, potassium bromate 0.1 M, $(NH_4)_2Ce(NO_3)_6$ 2.1×10^{-3} M, sulfuric acid 1.0 M. The calculated $Q_{10} = (P_2/P_1)^{10/(T_1-T_2)}$ is 2.5, where P_1 and P_2 are period lengths at temperatures T_1 and T_2, respectively. The calculated activation energy is 73 kJ/mol.

tions" which somehow influence the period, while Pavlidis and Kauzmann [26] introduced the involvement of diffusion-controlled reactions and the existence of temperature-independent rate constant ratios. Later, Hastings and coworkers [27] suggested that certain membrane processes may be responsible for temperature-compensation.

In the following we show how temperature-compensation can be explained as the balance between two groups of antagonistic (opposing) reactions that are present in any physico-chemical oscillator. The derived concept, which we call "antagonistic balance" [28,29] can be considered as a quantitative formulation of a suggestion by Hasting and Sweeney more than 30 years ago [25]. Our approach also shows that *any* physico-chemical oscillator has already all the necessary elements to obtain temperature-compensation. There is no need to postulate additional controlling reactions other than the component processes of the oscillator.

The BZ reaction is a "simple" chemcial non-living system with most complex dynamic behaviors, including oscillations, excitability, multistability, chaos, chemical (wave) signal transmission and light signal storage capabilities. The author therefore wondered whether the BZ reaction could also exhibit temperature-compensation.

2. Antagonistic balance: conditions for temperature-compensation in the Oregonator model

The component processes of a physico-chemical oscillator can be divided into 2 classes: those reactions that increase the period P when the rate constant of the process is increased ("P-positive processes") and those reactions that decrease the period when the rate constant of those reactions are increased ("P-negative processes").

The Oregonator [30] represents a skeleton scheme of the Field–Körös–Noyes (FKN) mechanism [23]. Many phenomena observed in the BZ reaction can be at least semiquantitatively simulated with this model. The Oregonator consists of the five pseudo-elementary processes O1–O5:

$$A + Y \xrightarrow{k_1} X + P \tag{O1}$$

$$X + Y \xrightarrow{k_2} 2P \tag{O2}$$

$$A + X \xrightarrow{k_3} 2X + Z \tag{O3}$$

$$2X \xrightarrow{k_4} A + P \tag{O4}$$

$$Z \xrightarrow{k_5} fY \tag{O5}$$

where $A \equiv BrO_3^-$, $X \equiv HBrO_2$, $Y \equiv Br^-$, $Z \equiv 2Ce(IV)$, $P \equiv HOBr$, and f is a stoichiometric factor. X, Y, and Z are the kinetic variables. Rate constant values are those suggested by Field and Försterling [31] (Table 1) and are assumed to refer to 20°C. The influence of

Table 1
Oregonator rate constant values at 20°C (in $M^{-1} s^{-1}$)

k_1	k_2	k_3	k_4	k_5
1.3	2.0×10^6	34	3.0×10^3	0.02

temperature is incorporated into the Oregonator by use of the Arrhenius equation, $k_i = A_i \exp(-E_i/RT)$, using (for simplicity) a temperature-independent pre-exponential factor A_i.

When analyzing the Oregonator, it is found that reactions O2 and O3 are P-positive, while the other reactions are P-negative. A numeric representation of the period dependence on the rate constants [28] of the Oregonator can be given by the (approximative) relationship

$$P_{\mathrm{appr}} = \tau_0 (k_1)^{a_1} (k_2)^{a_2} (k_3)^{a_3} (k_4)^{a_4} (k_5)^{a_5}\,, \tag{1a}$$

$$P_{\mathrm{appr}} = \tau_0 (k_1)^{-0.1964} (k_2)^{0.1629} (k_3)^{0.1075} \times (k_4)^{-0.1528} (k_5)^{-0.9417}\,, \tag{1b}$$

with $\tau_0 = 355/((1.3)^{-0.1964}(2 \times 10^6)^{0.1629}(34)^{0.1075}(3000)^{-0.1528}(0.02)^{-0.9417}) = 2.05550781$. Table 2 shows how the approximate period P_{appr} compares with the numerically computed period of the Oregonator model.

Temperature-compensation is expected whenever the contributions of the P-positive and P-negative reactions balance. This occurs when the a_i-weighted sum of activation energies of P-positive processes is equal to the corresponding sum of P-negtive processes, i.e., when the contributions of P-positive reactions, Σ^+, are equal to the contributions of P-negative reactions, Σ^-, i.e.,

$$0.1629\mathrm{E}_2 + 0.1075\mathrm{E}_3 = 0.1964\mathrm{E}_1 + 0.1528\mathrm{E}_4 + 0.9417\mathrm{E}_5\,. \tag{2}$$

Let us for a moment assume that the activation energies of the five component processes

Table 2
Numerically calculated period length, P_{num}, compared with P_{appr} values, calculated by Eq. (1b).

P_{num} (s)	P_{appr} (s)	k_1 ($M^{-1}s^{-1}$)	k_2 ($M^{-1}s^{-1}$)	k_3 ($M^{-1}s^{-1}$)	k_4 ($M^{-1}s^{-1}$)	k_5 ($M^{-1}s^{-1}$)
355	355	1.3	2.00E + 06	34	3.00E + 03	0.02
323	317	2.3	2.00E + 06	34	3.00E + 03	0.02
281	273	5.0	2.00E + 06	34	3.00E + 03	0.02
414	428	0.5	2.00E + 06	34	3.00E + 03	0.02
618	588	0.1	2.00E + 06	34	3.00E + 03	0.02
244	238	10.0	2.00E + 06	34	3.00E + 03	0.02
401	412	1.3	5.00E + 06	34	3.00E + 03	0.02
436	461	1.3	1.00E + 07	34	3.00E + 03	0.02
517	600	1.3	5.00E + 07	34	3.00E + 03	0.02
205	218	1.3	1.00E + 05	34	3.00E + 03	0.02
171	195	1.3	5.00E + 04	34	3.00E + 03	0.02
384	383	1.3	2.00E + 06	68	3.00E + 03	0.02
410	407	1.3	2.00E + 06	120	3.00E + 03	0.02
324	325	1.3	2.00E + 06	15	3.00E + 03	0.02
303	300	1.3	2.00E + 06	7	3.00E + 03	0.02
300	300	1.3	2.00E + 06	34	9.00E + 03	0.02
411	420	1.3	2.00E + 06	34	1.00E + 03	0.02
265	270	1.3	2.00E + 06	34	1.80E + 04	0.02
445	467	1.3	2.00E + 06	34	5.00E + 02	0.02
230	243	1.3	2.00E + 06	34	3.60E + 04	0.02
128	126	1.3	2.00E + 06	34	3.00E + 03	0.06
690	682	1.3	2.00E + 06	34	3.00E + 03	0.01
242	242	1.3	2.00E + 06	34	3.00E + 03	0.03
185	185	1.3	2.00E + 06	34	3.00E + 03	0.04

O1–O5 can be varied. Assuming further the Arrhenius-type dependence of the reaction rates upon temperature (note that we assume the Field–Försterling values [31] at 20°C) we can numerically calculate the temperature-dependence of the period length in the Oregonator.

Table 3 shows how various activation energy combinations can influence the temperature behavior of the Oregonator. The fist six E_1–E_5 combinations show the Oregonator's behavior under antagonistic balance conditions, i.e., when $\Sigma^+ - \Sigma^- = 0$ (see Table 3). In these calculations the activations energies $E_2 - E_5$ have been varied randomly by a uniform random number generator (based on three linear congruential generators) [32] in the range 0–60 kJ/mol. Among a random list of E_i combinations six $E_2 - E_5$ combinations were arbitrarilly chosen which allowed to calculate six *positive* E_1 values which lead to antagonistic balance. The numerically calculated periods at different temperatures show that each activation energy combination that has antagonistic balance (in fact, there is an infinite number of such combinations) also leads to temperature-compensation.

The next row in Table 3 shows that when all E_i values are chosen to be 70 kJ/mol then the P-negative component processes have a major influence on the period and the period decreases with increasing temperature. In this case the calculated Q_{10} value is found to be 2.5, precisely as observed in our experiment (Fig. 1)! When only E_1 and E_5 are allowed to contribute with assumed realistic values [23,33–36] the temperature behavior of the Oregonator is practically the same.

When the P-positive reactions are allowed to dominate (increased E_2 and E_3 values) then the period increases with increasing temperature.

The last ten combinations of E_i values in Table 3 illustrate why the period in the BZ reaction decreases with increasing temperature. In this case 10 random activation energy combinations in the range 0–60 kJ/mol have been used. It is clearly seen that in all these cases the Oregonator's period decreases with increasing temperature. The reason for this is the rather high sensitivity of the period length on component process O5, which is expressed by the large value of the weighting factor a_5 (0.9417).

3. Relevance to the Belousov–Zhabotinsky reaction

However, the activation energies in the BZ reaction are not variables. They are fixed and reflect the qualitative nature of the substrates in the reaction. Although the temperature behavior of the classical (malonic acid) BZ reaction has been studied by several workers [23,33–39], only partial information about the temperature properties of the component processes is presently available.

Earlier emphasis in temperature studies has been put on the accumulation of bromo-malonic acid, the induction period, and the frequency [33]. An overall activation energy of about 70 kJ/mol in the oscillatory BZ reaction has been determined independently by Körös [34], Blandamer and Morris [35], and Yoshikawa [36]. These values are in fair agreement with our result (73 kJ/mol).

Blandamer and Morris note, in agreement with our calculations, that an increase in the rate of the autocatalytic process O3 leads to an *increase* in period length, contrary to what is observed in the overall system. As a consequence of this, Blandamer and Morris suggest that process O1 is the rate-determining step in the BZ reaction and should also determine the temperature behavior of the BZ reaction. It has, however, been noted by these authors [35] that the activation energy of process O1 is only 50 kJ/mol [23]. This indicates that O1 is probably not the rate-determining step.

On the basis of our determined a_i exponents (a_i can be considered as a measure for the period sensitivity of the BZ reaction towards the component process Oi) and the sensitvity analysis by

Table 3
Oregonator period as a function of temperature and activation energies of component processes O1–O5

E_1 (J/mol)	E_2 (J/mol)	E_3 (J/mol)	E_4 (J/mol)	E_5 (J/mol)	$\Sigma^+ - \Sigma^-$ [a] (J/mol)	Period				
						at 15°C	at 20°C	at 25°C	at 30°C	at 35°C
17848	46785	4691	6181	3903	0	356	354	354	353	352
36477	32867	59217	24424	875	0	353	355	358	363	368
25819	59088	56071	56764	2027	0	354	355	357	359	362
8717	38527	29507	42515	1317	0	355	355	355	356	357
1033	42946	44286	14315	9946	0	356	355	353	350	347
40943	35921	49142	17867	385	0	353	355	359	362	367
70000	70000	70000	70000	70000	−71435	585	355	219	138	87
50000	0	0	0	70000	−75739	605	355	213	130	82
40943	80000	80000	17867	385	10498	329	355	383	410	438
26487	59389	10186	36803	14252	−13477	391	355	323	296	271
27337	53948	31776	20429	7195	− 3062	362	355	347	341	334
51192	31300	30705	7055	55569	−55062	523	355	245	170	121
55745	47569	29048	56544	30476	−37416	458	355	277	217	172
38202	17177	47318	26272	30000	−31884	441	355	288	235	193
46122	39461	15733	27625	58358	−60116	543	355	235	159	109
30433	35003	36866	34186	54216	−52591	515	355	248	176	126
26098	4432	35971	3082	41158	−39767	469	355	271	209	163
9905	33336	46833	56558	47904	−45234	489	355	261	193	145
16440	13245	8106	4103	44278	−42523	482	355	265	200	153

[a] $\Sigma^+ - \Sigma^- = (0.1629E_2 + 0.1075E_3) - (0.1964E_1 + 0.1528E_4 + 0.9417E_5)$

Edelson and Thomas [40,41] we note that process O5, the regeneration of bromide ion by the interaction between oxidized catalyst and the organic compounds, has a major influence on the period length. Component processes O1, O4 and O5 decrease the period as the rate of these reactions is increased. As long as the a_i-weighted sum of these (P-negative) reactions dominate over the corresponding sum of the P-positive reactions (note the large influence of process O5), the Oregonator will show a decrease in period when temperature is increased.

Consequently, the simplest way to explain the temperature behavior of the BZ reaction with the Oregonator is that all component processes O1–O5 follow Van't Hoffs rule with process O5 as the period-determining step and a activation energy of about 70 kJ/mol. Besides component process O1, whose activation energy has been determined and verified [23] to about 50 kJ/mol, processes O2–O4 will have little influence on the period, as shown in Table 3 when $E_2 = E_3 = E_4 = 0$. Their activation energies are therefore difficult to estimate from these calculations.

4. Temperature-compensation in chemical oscillations and biological rhythms

4.1. Chemical Oscillators

From the above analysis it is clear why the BZ reaction is not temperature-compensated: the contribution from the P-negative component process O5 is completely dominating over the P-positive reactions. On the other hand, the BZ reaction is expected to get "more temperature-compensated" when E_5 is reduced. The use of alternate organic substates that ease the liberation of bromide ion and allow more rapid oxidation by the oxidized form of the catalyst may be one step in this directon.

Similar dominance of P-negative reactions in other oscillatory systems in solution phase seems operative, because all show generally an increase in frequency as temperature is increased.

For membrane oscillators [8] the situation appears somewhat different but nevertheless interesting. Urabe and Sakaguchi [43,43] recently investigated the temperature behavior of a membrane oscillator in the range −4.8°C to 45°C. Interestingly, the increase in frequency shows saturation behavior as temperature increases. Thus, at higher temperatures, the types of membrane oscillators studied by Urabe and Sakaguchi seem to go to a temperature-compensated limit.

It appears most interesting that biologists twenty years ago [27] have proposed the involvement of membranes as the reponsible components that may lead to temperature-compensation in circadian rhythms. It has to be seen whether similar temperature-insensitivities can be found in other membrane oscillators, and whether there is a possible relevance to temperature-compensation in circadian rhythms.

4.2. Circadian Rhythms

Temperature-compensation is one of *the* characteristic properties of circadian rhythms: its presence ensures that important physiological processes are induced at correct times independent of environmental (temperature) fluctuations. The precision of the compensating mechanism is generally high: Q_{10} values of 1.1 or even closer to one are often found [9–18,44]. It is now generally accepted that in biological rhythms a true compensating mechanism is operative; the system is not merely temperature-insensitive.

The question of how temperature-compensation is achieved in biological systems is still not understood, but it must be closely related to the physiology of the clock mechanism itself. For example, temperature-compensation in the CO_2 exchange rhythm in *Bryophyllum* appears to be regulated by malate due to the allosteric properties of the enzyme phosphoenolpyruvate carboxylase [45], while for *Neurospora*, regulation occurs also at the nucleic acid level [46].

With the development of techniques within molecular biology it has become possible to track the biochemical reactions at the nucleic acid level and to identify different gene loci, like the *per* gene in *Drosophila* [7] or the *frq* gene in *Neurospora* [7,46], that have influence on the performance of the biological clock. With the introduction of mutant organisms where certain gene loci has been altered by (point) mutations, it has been observed that the temperature-compensation (and other characteristics) of the circadian rhythm can be destroyed [47,7].

Using the Brusselator as a caricature of the oscillatory clock physiology of a model organism, it has been shown how temperature-compensated forms/mutants can arise when the organism is coupled to the environment via a simple evolutionary (random walk) process [29]. Subsequent mutations acting on the temperature-compensated forms destroy the antagonistic balance, which results in a loss of temperature-compensation, a change in period length, or even in the loss of the oscillatory behavior.

The work of Pittendrigh and coworkers [48] has indicated that temperature-compensation is a special case of a more general homeostatic mechanism that keeps the period of a circadian oscillator constant when certain environmental properties such as pH, temperature, food supply, etc. are changed. Within the framework of *antagonistic balance* [29] it has now been shown how general homeostasis in period may become possible: for each physico-chemical property a "balance equation" analogous to Eq. (2) can be formulated and the simultaneous satisfaction of these equations results in homeostasis in period when these physico-chemical properties are varied [29].

It appears most interesting to study along these lines circadian oscillations in (mutant) organisms that have lost their homeostasis regulating mechanism. At the same time it is a challenge to find/design chemical oscillators that can be studied experimentally as simple model systems for temperature-compensation or homeostasis in period.

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