Stochastic Resonance in a Bistable Chemical System: The Oxidation of Ascorbic Acid by Oxygen Catalyzed by Copper(II) Ions**

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The term "stochastic resonance" (SR) refers to the enhancement of a weak periodic signal by statistical perturbations (noise) in dynamic systems with a threshold value.[1] The threshold displayed by an autocatalytic (nonlinear) chemical reaction can be a complex function of several parameters that separate qualitatively different types of dynamic behavior (e.g., two stable steady states). If the threshold value of a suitable parameter is crossed by the combined amplitudes of the subthreshold periodic signal and the noise, the response of the weak signal is enhanced.[2] Despite an increasing number of publications dedicated to stochastic resonance in various fields of science,[1–3] there are only five publications concerning the experimental study of SR in chemical reactions in a continuous flow stirred tank reactor (CSTR).[4–8] Particularly, SR occurs in various nonlinear reactions if the unperturbed system is in a steady state close to a Hopf bifurcation, i.e. a control parameter is set close to the value at which oscillations appear. This has been revealed in CSTR studies for the Belousov–Zhabotinsky (BZ) reaction,[4] the minimal bromide oscillator,[5] the enzymatic peroxidase-oxidase reaction,[6, 7] and autooxidation of NADH catalyzed by copper(II) ions.[8] A positive effect of statistical fluctuations (noise) on wave propagation in a photosensitive BZ reaction has also been reported.[9]

The classical case of stochastic resonance concerns a perturbation of bistable systems, that is, systems that exhibit hysteresis as a result of the coexistence of two stable steady states.[1–3, 10] Herein we report the first experimental observation of SR in a bistable chemical system—the autooxidation of ascorbic acid by oxygen as catalyzed by copper(II) ions in a CSTR. The appearance of SR is confirmed by an analysis of probability distribution functions and power spectra; it is also supported by the singular-value decomposition method.

We have found that autooxidation of ascorbic acid by oxygen catalyzed by copper(II) ions in a CSTR exhibits hysteresis in response to a cyclic variation of the flow rate (k_f). (Figure 1). At low flow rates the system is in a steady state characterized by a low potential at the platinum electrode (Pt-potential). If we increase the flow rate the system response follows the low branch and finally reaches a second steady state characterized by high values of the Pt-potential. The transition from the lower to upper branch occurs at $k_f = 0.0037\ s^{-1}$. If k_f is reduced the system response follows the upper branch, and the reverse transition occurs at $k_f = 0.0023\ s^{-1}$. Therefore the system exhibits hysteresis in the range of $k_f = 0.0023 - 0.0037\ s^{-1}$, that is, a coexistence of two stable steady states is observed.

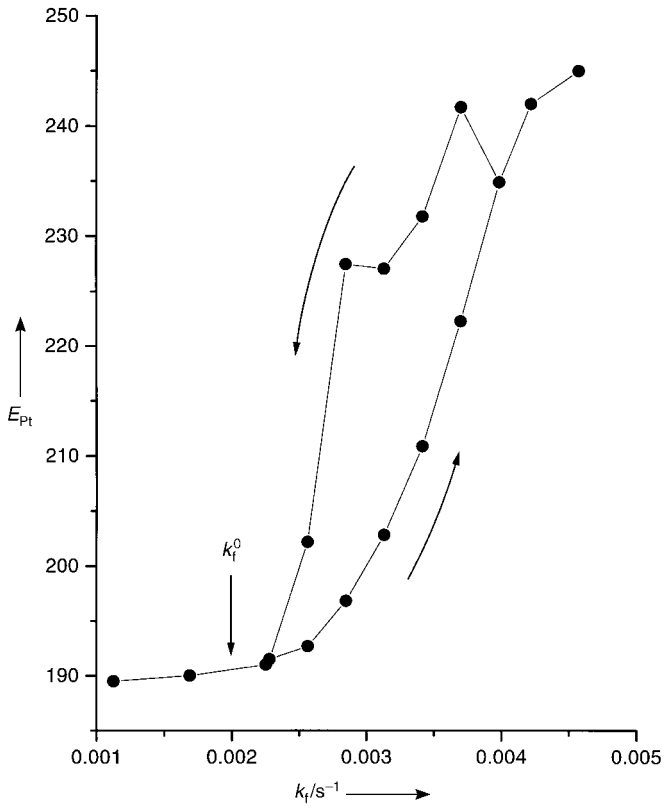

Figure 1. Dependence of the reaction on the flow rate k_f monitored by the Pt-electrode potential E_{Pt} (in arbitrary units) for the following reactor concentrations: $[H_2Asc]_0 = 5.0 \times 10^{-4}$ M; $[Cu^{2+}]_0 = 2.0 \times 10^{-6}$ M; $[H_2SO_4]_0 = 1.2 \times 10^{-4}$ M; $[Na_2SO_4]_0 = 0.08$ M.

Periodic and stochastic perturbations of the lower branch have been studied by perturbing the flow rate. A sinusoidal modulation is imposed on the flow rate at a given frequency and amplitude together with a statistical perturbation of variable amplitude as given in Equation 1:

$$k_f = k_f^0(1 + \alpha \sin(\omega t) + \beta R(\delta)) \quad (1)$$

where k_f^0 is the constant average flow rate in the steady state as marked in Figure 1, ω is the frequency of the sinusoidal perturbation, α is the amplitude of the sinusoidal perturbation, δ is the time interval of applied statistical fluctuations, and β is the amplitude of equally distributed stochastic noise. Typical time courses of the flow rate modulated by a simultaneously applied sinusoidal and stochastic perturbation have been shown in Figure 2 of ref [4] and Figures 3 and 6 of ref [5]. In our experiments we varied the value of β while all the other parameters were fixed: $k_f^0 = 0.0020\ s^{-1}$; $\alpha = 0.086$; $\omega = 0.024\ s^{-1}$; $\delta = 2.6$ s. The value of α has been chosen in such

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a way that a sinusoidal modulation does not force the system into the bistable region, that is, without applied stochastic perturbations ($\beta = 0$) the system always remains in its lower steady state.

Depending on the amplitude β, the system exhibits different dynamic behaviors. Figures 2 a,d,g,j give the time series obtained at increasing β. The middle panels represent a probability distribution function for Pt-potentials obtained from the time series. The right panels give the power spectra of the time series. The power P is given in dimensionless units as is usually done for the Fourier-transformed spectra of finite, discrete time series. At low noise amplitudes β the system remains in the same steady state and no transitions appear from the lower to the upper branch (Figure 2 a). The corresponding probability distribution function W (Figure 2 b) is a bell-shaped Gaussian distribution with a single maximum located at the position of the lower steady state. This indicates that the system remains in a single steady state.

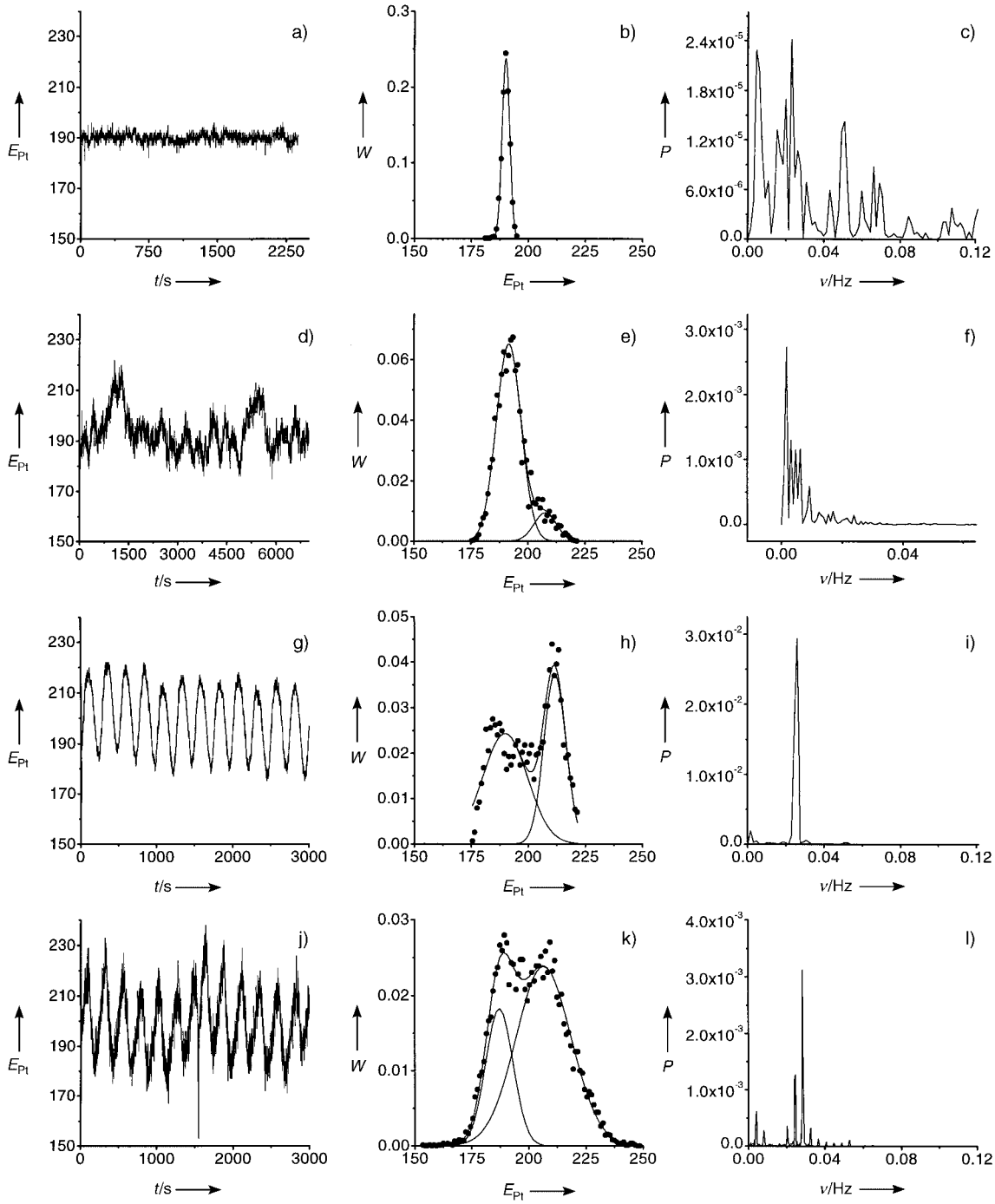

Figure 2. Time series, their probability distribution function and Fourier transformed power spectra at different levels of noise. In the figure E_{Pt} denotes the relative potential, t the time, W the probability and P the relative power. a,b,c) $\beta = 0.028$; d,e,f) $\beta = 0.057$; g,h,i) $\beta = 0.143$; j,k,l) $\beta = 0.257$. The system has been perturbed according to Equation (1) with the following parameters: $k_f^0 = 0.0020\ s^{-1}$; $\alpha = 0.086$; $\omega = 0.024\ s^{-1}$; $\delta = 2.6$ s. Other conditions are the same as in Figure 1. The solid curves show the fitted total probability function and the probability distribution of the two steady states.

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The power spectrum of the time series in Figure 2c shows no significant maximum, that is, the system varies statistically around the steady state. An increase of the noise amplitude β produces bursts into the higher steady state as illustrated in Figure 2d. The corresponding probability distribution function shown in Figure 2e becomes wider and it is characterized by an appearance of a second maximum; the power spectrum of which is shown in Figure 2f. However, for this value of β the system is still governed by statistical noise. This behavior changes at the "optimal" value of β (= 0.143) where the stochastic resonance appears. Figure 2g shows a time series of the Pt-potential under the SR conditions. The oscillations are almost sinusoidal and the frequency matches that of the sinusoidal modulation of the flow rate. Two well-resolved maximums appear in the probability distribution function (Figure 2h). The power spectrum is characterized by a single sharp maximum at ω, the frequency of the periodic perturbation. Therefore, the system response is synchronized with the frequency of the small amplitude periodic modulation of the flow rate.

A further increase of the noise amplitude β reduces SR and the response of the reaction becomes increasingly noisy (Figure 2j,k,l). The two maximums in the total probability distribution function become less resolved and overlap, and various harmonics (lines) appear in the power spectrum. At the highest values of β (not shown) the system behavior is totally governed by noise (the sinusoidal perturbation is totally obscured by noise), that is, the probability distribution function has a single maximum located at the position of the upper steady state, and there are no significant peaks in the power spectrum; the noise obscures the weak sinusoidal signal. The data in Figure 2g,h,i give a semiquantitative illustration for the appearance of SR at $\beta = 0.143$. Typically, a description of SR is based on the power spectrum.[1–10] Under the SR condition a peak appears at the frequency of the weak periodic signal. In Figure 3a the intensity of the first harmonic ($|C_1|^2$) is shown as a function of noise amplitude. The value of $|C_1|^2$ has been calculated as the squared value of the dimensionless coefficient in the Fourier spectrum of the time series at the frequency ω. In Figure 3a the intensity of the first harmonic rises with the amplitude of the noise to a maximum and then decreases for $\beta > 0.2$. Therefore, the stochastic resonance appears in the range $\beta = 0.143 - 0.20$. The value of β where SR occurs may be located by an analysis of the third harmonic in the Fourier spectrum as well. In Figure 3b the intensity of the third harmonic ($|C_3|^2$) is shown as a function of noise, under SR conditions the third harmonic is depressed[11] (see arrow). Stochastic resonance appears at $\beta =$ 0.143, at this value the third harmonic shows a minimum (Figure 3b). In Figure 3c the number of degrees of freedom (N) computed from the singular value decomposition (SVD)[12] is shown as a function of β. The dependence is characterized by a minimum at $\beta = 0.143$, that is, at the same noise amplitude where in the Fourier spectrum the amplitude of the first harmonic rises and the amplitude of the third harmonic is depressed.

The data presented in Figure 3 illustrate that stochastic resonance can be quantified by methods other than an analysis of the first harmonic of the power spectrum. It is also worth noting that an analysis of the signal-to-noise ratio is of limited value for the system studied here, since the amplitude of the signal (the measured Pt-potential) grows with an increase of flow rate (see Figure 1). Therefore, it may happen that the signal-to-noise ratio grows even if the system is far from SR. Stochastic resonance is well pronounced in an analysis of the amplitude of the third harmonic (Figure 3b) or by the number of SVD modes which are reduced to a single mode $N = 1$ under SR conditions (Figure 3c).

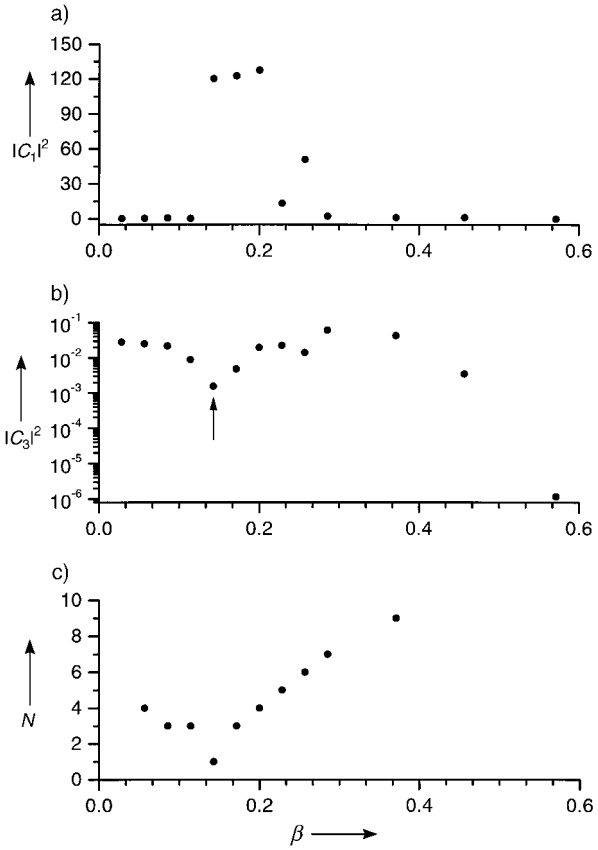

Figure 3. Quantitative characteristics illustrating the appearance of stochastic resonance at $\beta = 0.143$: a) dependence of the amplitude of the first harmonic $\omega = 0.024\ s^{-1}$ and b) third harmonic in the Fourier analysis, c) dependence of the degrees of freedom of the system on the noise amplitude β.

The system studied is a typical example for the oxidation of an organic substrate by molecular oxygen catalyzed by a coordinated metal ion. Similar reactions are widely used in industrial processes. This allows us to predict that stochastic resonance may be observed in various chemical systems. Chemical reactions may be conducted in batch, semibatch, or in flow reactors and their dynamic behavior is usually affected by various types of interfering noise which can be reduced by an appropriate design of the system but may never be eliminated.[13] Noise, or stochastic perturbations of a chemical reaction, is usually considered as a disturbing factor that should be eliminated. However, our experimental studies indicate that noise may play a positive role through stochastic resonance. Particularly, to achieve a high signal-to-noise ratio one may *increase* the noise amplitude instead of decreasing it.

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Experimental Section

All reagents were analytical grade. Stock solutions of ascorbic acid (H_2Asc, 1.0×10^{-3} M) and copper(II) sulfate (4.0×10^{-6} M), each containing H_2SO_4 (1.2×10^{-4} M) and Na_2SO_4 (0.08 M), were prepared using doubly distilled water. Solutions containing ascorbic acid were prepared immediately before use.

All studies were conducted in a CSTR thermostatically controlled at (298.0 ± 0.1) K. Details of the experimental setup are presented elsewhere.[4–7] The state of the system was monitored by measuring the platinum-electrode potential; a Ag/AgCl electrode was used as the reference electrode. Signals were amplified electronically and recorded by a desk computer as a function of time with time steps of 0.1 s. As a consequence of the amplification of the signal the potential is given in arbitrary units.

CSTR experiments have been performed at different flow rates and noise intensities. Solutions of inflow reagents were pumped into the reactor by a precise two-channel piston pump. Syringe 1 contained H_2Asc (1.0×10^{-3} M), H_2SO_4 (1.2×10^{-4} M), and Na_2SO_4 (0.08 M); syringe 2 contained copper(II) sulfate (4.0×10^{-6} M), H_2SO_4 (1.2×10^{-4} M), and Na_2SO_4 (0.08 M). Correspondingly, the reactor concentrations after mixing but before any reaction were: $[H_2Asc]_0 = 5.0 \times 10^{-4}$ M; $[Cu^{2+}]_0 = 2.0 \times 10^{-6}$ M; $[H_2SO_4]_0 = 1.2 \times 10^{-4}$ M; $[Na_2SO_4]_0 = 0.08$ M.

Perturbation of the reaction has been performed according to Equation (1) by using a 16 bit D/A (digital/analogue) converter.

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Enantioselective Ribozyme Catalysis of a Bimolecular Cycloaddition Reaction**

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There is currently a wide-spread interest in the development of new catalytic methods for regio- and stereoselective syntheses. Various approaches aim at the utilization and improvement of synthetic compounds, surfaces, and biomolecules as stereoselective catalysts or synthetic auxiliaries.[1–4] Combinatorial strategies have developed into powerful tools in catalysis research, allowing the isolation of potential catalysts from vast libraries by either screening or iterative deconvolution.[5, 6]

Ribozymes are RNA molecules with catalytic properties. While the chemistry of the naturally occurring ribozymes is restricted to cleavage and joining reactions at internucleotide bonds, artificial ribozymes isolated from synthetic combinatorial libraries have been shown to accelerate the chemical steps in a broad range of reactions, including carbon–carbon and peptide bond formation.[7–10] These ribozymes, however, behave unlike typical chemical catalysts or protein enzymes in that they require at least one of the reactants to be RNA or to be covalently tethered to RNA. Except for the formation of dinucleotides from activated mononucleotides,[11] there is no example of ribozymes accelerating bond-forming reactions between two small organic substrates, a central reaction type in organic synthesis and the basis of all anabolic biochemical pathways. Also, although RNA molecules can exquisitely distinguish between enantiomers when binding target molecules,[12, 13] enantioselective bond formation by ribozymes has not yet been described.

The Diels–Alder reaction is one of the most important carbon–carbon bond-forming processes available to organic chemists. The reaction creates two carbon–carbon bonds and up to four new stereocenters. There is currently much interest in developing catalytic methods for improving its rate and selectivity because, for many applications, the synthetic value of the Diels–Alder reaction relies on the degree of stereocontrol that can be exercised.[14–16]

We have recently described the isolation of Diels-Alderase ribozymes from a combinatorial RNA library that accelerate up to 20000-fold the carbon–carbon bond formation between anthracene, which is covalently tethered to the ribozyme, and a biotinylated maleimide (Scheme 1A).[17] 90% of the active sequences contained a small common structural motif (Scheme 1B), and a synthetic 49-mer oligoribonucleotide containing all elements of this motif was shown to be catalytically

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