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Review Article

The difference bidirectionality makes to the kinetic modeling of molecular catalysis

Andrea Fasano, Vincent Fourmond and Christophe Léger

Abstract

The quantitative modeling of voltammograms obtained with molecular redox catalysts is important for mechanistic studies and benchmarking. Most kinetic models developed for that purpose were based on unidirectional reaction mechanisms, but many redox enzymes work in both directions of the reaction, and chemists have recently successfully designed bidirectional, synthetic, molecular catalysts. An important conclusion from recent work is that unidirectional kinetic models should not be used to interpret bidirectional electrochemical responses. Understanding the latter will require much more work than simply adapting unidirectional models.

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Keywords

Kinetic modeling, Molecular catalysis, Redox enzymes

Bidirectionality versus reversibility

The term “reversibility” is sometimes used in chemistry as a synonym for “bidirectional,” as in “the reversible Michaelis—Menten equation” [1] or when one refers to a particular chemical step being reversible. In thermodynamics, reversibility refers instead to a quasistatic transformation, where the system remains so close to equilibrium that no entropy is created. By analogy, we use the expression “catalytic reversibility” to describe the subset of bidirectional catalysts that can function with minimal overpotential and energy dissipation. In Figure 1, the catalytic cyclic voltammograms (CVs) J and K are irreversible according to this definition, and the rightmost column shows unidirectional CVs.

Many redox enzymes that have been wired to electrodes are efficient catalysts in both directions of the reaction they catalyze. This is, for example, the case of certain enzymes that convert H^+ and H_2 [3,4] (Figure 2a—d), succinate/fumarate [5,6], CO_2/CO [7], CO_2/formate [8], $NADH/NAD^+$ [9], or tetrathionate/thiosulfate [10]. The vast majority of synthetic molecular redox catalysts studied in the literature are unidirectional, but various groups of chemists recently designed bidirectional molecular catalysts for the conversion between H^+ and H_2 [11—13] (Figure 2e), CO_2/formate [14—16], CO_2/CO [17], and O_2/H_2O (9), and a subset of these bidirectional catalysts function in either direction of the reaction in response to a small departure from equilibrium [18,19].

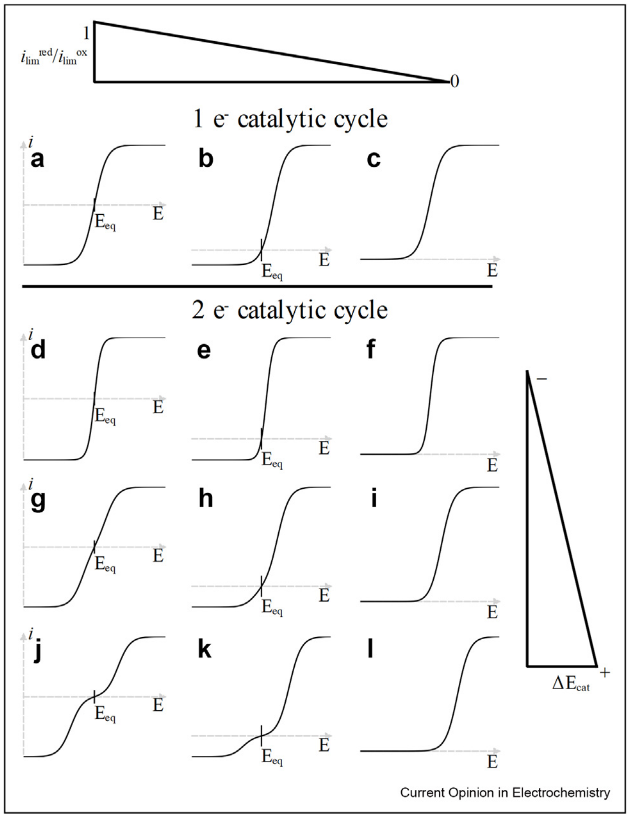
The definition of overpotential

In electrochemical studies of unidirectional reactions, the difference between the standard reduction potential of the reaction to be catalyzed (oxidized substrate S + ne^- ⇔ reduced product P) and that of the catalyst (E^0_{cat}, the redox couple that triggers catalysis) is related to the standard free energy of the homogeneous reaction between the catalyst and the substrate [22]. This thermodynamic descriptor may correlate with the maximal turnover frequency (TOF_{max}) [23]. Any reference to the equilibrium (Nernst) potential of the S/P couple under the conditions of the experiment (E_{eq}) is meaningless because E_{eq} depends on the concentration of the product of the irreversible reaction, which is unreactive and often not even present in the bulk solution [22].

Only when the catalyst is bidirectional does it make sense to consider the traditional definition of the overpotential η as the “additional potential (beyond the thermodynamic requirement) applied to drive the reaction” [24,25]. This overpotential η equates to $E\text{-}E_{eq}$, and the current is zero when $\eta = 0$.

Molecular catalysts usually switch on and off over a narrow potential range. In the simplest case, where the catalytic response is S-shaped, the catalytic potential E_{cat} is easily defined as the mid-point potential of the catalytic wave. Unlike the onset potential widely used in the benchmarking of electrocatalytic surfaces, this catalytic potential is independent of the magnitude of the current and thus, on the concentration of the catalyst in

Figure 1



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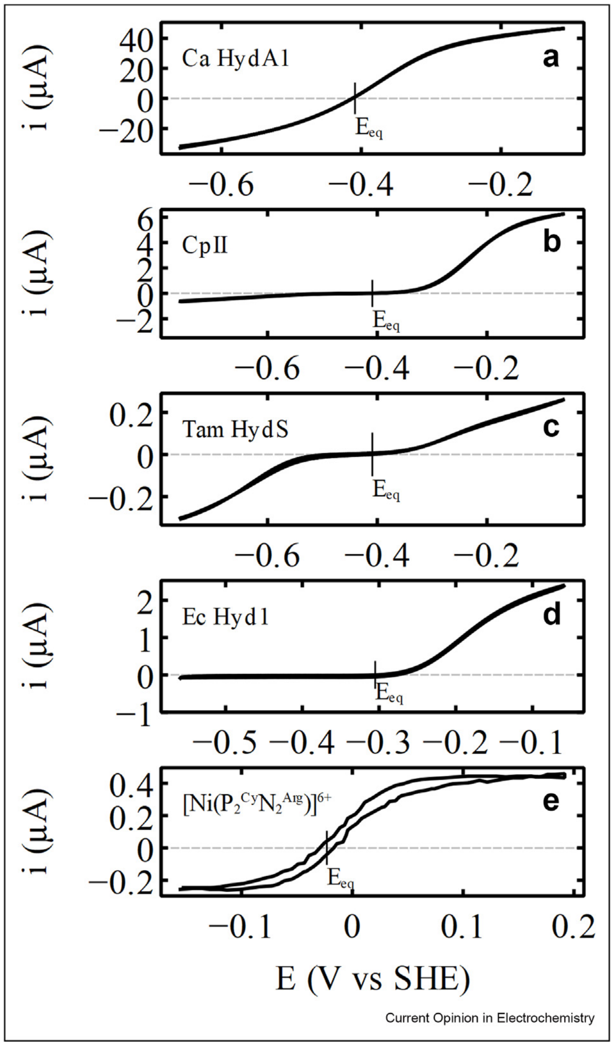
Simulated voltammograms for 1-electron **(a–c)** and 2-electron **(d–l)** catalytic cycles. The leftmost column shows voltammograms with equal limiting currents in the two directions. The rightmost column shows unidirectional voltammograms in the direction of oxidation. The middle column illustrates intermediate situations. For the 2-electron catalytic cycle, the uppermost row (d–f) shows voltammograms simulated with a negative (–100 mV) difference between the two catalytic potentials (ΔE_{cat}), while the middle (g–i) and lowermost (j–l) rows show voltammograms with more positive ΔE_{cat}, +100 and +200 mV, respectively. The effect of slow interfacial electron transfer and the distribution thereof is described in fig. 1 of Ref. [2].

Figure 2



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Experimental catalytic voltammograms showing H_2 oxidation and evolution (positive and negative current, respectively) and recorded with different hydrogenases adsorbed onto a rotating disc electrode or an inorganic catalyst diffusing in solution: the FeFe hydrogenases from *Clostridium acetobutilicum*, HydA1 [20] **(a)**, *Clostridium pasteurianum* hydrogenase II **(b)**, *Thermoanaerobacter marthranii*, HydS [21] **(c)**; the NiFe hydrogenase 1 from *E. coli* [21] **(d)**; the “Dubois” catalyst $[Ni(P_2^{Cy}N_2^{Arg})]^{6+}$ in **(e)** [13]. Conditions: 30 °C, pH 7, 100% H_2 in (a–c); 40 °C, pH 6, 0.3% H_2 in (d); 40 °C, pH 1, 12.5% H_2 in (e).

solution or adsorbed on the electrode. We have called “catalytic overpotential,” η_{cat}, the difference E_{cat}-E_{eq}.

For a two-electron bidirectional catalyst, two catalytic potentials must be defined, one for each direction (E_{cat}^{ox} and E_{cat}^{red}) [26,27].

Electrochemical models of bidirectional molecular catalysis

Table 1 lists the models that have theoretically described the voltammetry of bidirectional catalysts that are either adsorbed onto an electrode or that diffuse in solution. They differ by the sequence of redox (E) and chemical (C) steps in the catalytic cycle. We assume that the rate constants of the latter are first-order or pseudo-first-order, so that concentrations of reactants are considered only implicitly.

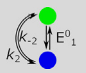
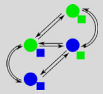
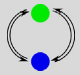
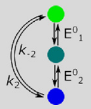
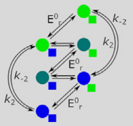
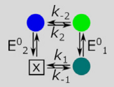
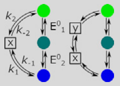
In the Nernstian limit, on the condition that the catalytic cycle is “ordered” (meaning that the cycle is the same for the two directions of the reaction [19]), irrespective of the number and order of the steps in the catalytic cycle and whether the catalyst is attached or diffuses, the steady-state catalytic response is [22,26,27]:

$$i = \frac{i_{\mathrm{lim}}^{\mathrm{ox}}\, e^{F\left(E-E_{\mathrm{cat}}^{\mathrm{ox}}\right)/RT}\, e^{F\left(E-E_{\mathrm{cat}}^{\mathrm{red}}\right)/RT} - i_{\mathrm{lim}}^{\mathrm{red}}}{1 + e^{F\left(E-E_{\mathrm{cat}}^{\mathrm{red}}\right)/RT}\left(1 + e^{F\left(E-E_{\mathrm{cat}}^{\mathrm{ox}}\right)/RT}\right)} \qquad (1)$$

The current tends to $-i_{\mathrm{lim}}^{\mathrm{red}}$ at low potential and to $i_{\mathrm{lim}}^{\mathrm{ox}}$ at high potential. The shape of the signal depends on the difference between the values of the two catalytic potentials (top to bottom in Figure 1). Note that irreversibility

Table 1

The bidirectional kinetic cycles considered for the modeling of the voltammetry of bidirectional molecular catalysts.

	Mechanism (a)	Kinetic scheme	Diffusing catalyst	Adsorbed catalyst	Comment
One-electron models	ECr		[28,29]	[2,30,31]	(b,c)
	ECr + relay			[32]	(d)
Two-electron models	EE			[33]	(e)
	EEC$_r$		[22,26,27,29]	[26,27,2]	(b,c)
	EEC$_r$ + relay			[26]	(d)
	EC$_r$EC$_r$		[13,27]	[27,21]	
	EEC$_r$C$_r$, EEC$_r$C$_r$C$_r$		[27]	[27,34,21]	

(a) The catalytic cycles considered in the papers listed here consist of an ordered series of redox steps (“E”), whose rate constants depend exponentially on electrode potential, and reversible chemical steps (“C$_r$”), whose rate constants are independent of potential. The cycles are drawn using the following symbols: light green, dark green, and blue circles for the oxidized, one-electron reduced, and two-electron reduced catalysts. The redox relay, oxidized (green) or reduced (blue), is shown as a square. “X” and “Y” are other catalytic intermediates. Note that irreversibility does not require that distinct catalytic cycles operate in each direction of the reaction [19,27,35]. (b) Molina et al. considered the EC$_r$ and EEC$_r$ catalytic responses of a diffusing catalyst beyond the steady-state regime [29]. (c) Slow interfacial electron transfer (iET) and the possibility that the rate constants of iET are distributed are considered in Refs. [26,2,29,30,31]. (d) The models in Refs. [26,32] explicitly consider intramolecular electron transfer between a one-electron relay and either a one- or a two-electron active site. In contrast, the models in Refs. [30,31] consider a one-electron relay and no other redox site. (e) This model is applied in the context of electrocatalysis, but the equations are the same for a molecular catalyst adsorbed onto an electrode.

can be observed even in this situation, where interfacial ET is assumed to be infinitely fast [27].

The simpler equation below is obtained when a single redox step is considered in the bidirectional catalytic cycle [28].

$$i = \frac{i_{\text{lim}}^{\text{ox}} e^{F(E-E_{\text{cat}})/RT} - i_{\text{lim}}^{\text{red}}}{1 + e^{F(E-E_{\text{cat}})/RT}} \tag{2}$$

predicts shapes that are very different from those of eq. (1) (Figure 1), and in most cases, it does not apply to two-electron reactions. Therefore, the models of bidirectional two-electron reactions have to explicitly include the two redox transitions of the active site. This contrasts with the case of unidirectional catalysis, where many multistep multielectron catalytic cycles can be described by the "EC$_i$" model [36].

Another difference between uni and bi-directional catalytic cycles is that the rate constants of any bidirectional catalytic cycle are related by a Haldane equation [37], obtained by equating the net current to zero when $E = E_{\text{eq}}$. As a consequence, if one wants to consider the free energy of any step of the bidirectional catalytic cycle as a thermodynamic descriptor, it is not possible to examine the effect of changing it independently of the other steps.

Measuring the reversibility

Higher reversibility corresponds to a higher slope of the current versus potential response at $E = E_{\text{eq}}$, but this slope cannot be used for measuring the reversibility because it is proportional to the magnitude of the current response, and therefore it is dependent on how much catalyst is in solution or on the electrode.

When the response is so irreversible that distinct oxidative and reductive waves are observed, a better measure of the (ir)reversibility is the difference between the catalytic potentials defined in eq. (1). These can be determined by visual inspection if the S-shaped oxidative and reductive waves are sufficiently separated from one another or obtained by fitting [2]. The more positive $E_{\text{cat}}^{\text{ox}} - E_{\text{cat}}^{\text{red}}$, the more irreversible the response. When $E_{\text{cat}}^{\text{ox}} - E_{\text{cat}}^{\text{red}}$ is small or even negative, the signal consists of a single, sharp sigmoid (Figure 1d), and the two catalytic potentials cannot be measured (just like in noncatalytic two-electron redox systems, only the average two-electron standard potential can be measured when potential inversion occurs [38]).

The foot of the wave analysis is not useful for bidirectional responses

The popular foot of the wave analysis (FOWA) is used to extrapolate the value of the limiting current when catalysis is unidirectional [39]. It assumes that the steady-state current response that would be obtained in the "pure kinetic region" without substrate depletion [40] is a one-electron sigmoid centered on the potential of the catalyst ($E_{\text{cat}} = E_{\text{cat}}^0$). From the signal at the onset of the current, where the current increases exponentially and interfacial electron transfer is not limiting, it is possible to reconstruct this sigmoidal response to obtain the limiting current. Interpreting the foot of the wave is not trivial for multielectronic unidirectional reactions [41,29], and even less so for bidirectional voltammetry.

Indeed, when reversibility is approached, the two catalytic waves merge, and the onset of current at $E \approx E_{\text{eq}}$ is linear, not exponential. Therefore, the FOWA can only be carried out in situations where the response is very irreversible [29].

The second problem arises even in the irreversible situation: if the catalytic scheme includes successive reversible steps, the catalytic potentials depart from the E^0 of the catalyst measured in the absence of catalysis [27,34], whereas directly extrapolating the current plateau from the onset potential requires that this catalytic potential be known *a priori*.

And last, when catalysis is bidirectional, the plateau current that may be observed with diffusing catalysts is not simply related to TOF$_{\text{max}}$, as explained below.

Measuring maximal turnover frequency in each direction

The turnover frequency (TOF) is the ratio of the number of moles of the product generated per unit of time divided by the number of moles of the active form of the catalyst involved in the reaction (adsorbed onto the electrode or contained in the reaction-diffusion layer) [22]. The TOF depends on the electrode potential and tends to a maximal value at large overpotentials, TOF$_{\text{max}}$, which is achieved when the redox steps in the catalytic cycle are infinitely fast in one direction or the other.

For adsorbed catalysts, if there is no complication by the mass transport of the substrate or a dispersion of interfacial electron transfer rate constants, the current tends towards a plateau value at high or low potential (i_{lim}), which is simply proportional to TOF$_{\text{max}}$, irrespective of the kinetic mechanism [26,27].

$$i_{\text{lim}} = nFA\Gamma \times \text{TOF}_{\text{max}} \tag{3}$$

(A is the electrode surface, and Γ is the electroactive surface coverage).

For diffusing catalysts, the current also tends to plateau under certain conditions (called pure kinetic conditions, in the absence of complications by the diffusion of the substrate [29]). According to the popular Nicholson and Shain equation, the plateau current is related to the square root of $\mathrm{TOF_{max}}$ [42]

$$i_{\mathrm{lim}} = nFAC_{\mathrm{cat}}\sqrt{D \times \mathrm{TOF_{max}}} \tag{4}$$

where C_{cat} is the concentration of catalyst in solution and D is its diffusion coefficient. However, this equation is not always applicable.

Equation (4) is exact only for very simple kinetic schemes (e.g. $\mathrm{EC_i}$, $\mathrm{EEC_i}$, $\mathrm{EC_iEC_i}$, where subscript i means "irreversible" [43]). It may still be useful for other mechanisms; for example, the rate equation of the $\mathrm{EC_iC_i}$ mechanism reduces to that of the $\mathrm{EC_i}$ mechanism if one of the two chemical reactions is much faster than the other (table 2 in Ref. [43]). With schemes that consist of only irreversible chemical steps, eq. (4) seems to never be *very* wrong. Considering the $\mathrm{EC_iC_i}$ scheme, for example, in the worst case where $k_1 = k_2$, $\mathrm{TOF_{max}} = k_1k_2/(k_1 + k_2) = k_1/2$ and $i_{\mathrm{lim}} = 2FAC_{\mathrm{cat}}\sqrt{D}\sqrt{(4k_1/9)}$, so the maximal error on the value of $\mathrm{TOF_{max}}$ that is made by interpreting the limiting current with eq. (4) is only 10%.

However, the situation is much less favorable when the chemical steps are reversible: equation (4) is not correct, and using it may lead to a significant error. We take two examples.

For the $\mathrm{EC_r}$ model [28] (the subscript r indicates a reversible step), the values of $\mathrm{TOF_{max}}$ in the two directions are k_2 and k_{-2}, but the expressions of the limiting currents are

$$i^{\mathrm{ox}}_{\mathrm{lim}} = 2FA\sqrt{D}C_{\mathrm{cat}}\sqrt{\frac{k_2^2}{k_2 + k_{-2}}} \tag{5}$$

$$i^{\mathrm{red}}_{\mathrm{lim}} = 2FA\sqrt{D}C_{\mathrm{cat}}\sqrt{\frac{k_{-2}^2}{k_2 + k_{-2}}} \tag{6}$$

The $\mathrm{TOF_{max}}$ in the faster direction that is measured using eq. (4) is only slightly underestimated, but in the slower direction, the $\mathrm{TOF_{max}}$ is underestimated by a factor equal to the ratio of the two $\mathrm{TOF_{max}}$. The reason the current in the "+" direction at very high overpotential depends on both k_2 and k_{-2}, when the catalyst diffuses in solution, is that the steady-state current depends on the compensation between the diffusion of the catalyst and its reaction in the diffusion layer, and the latter is bidirectional, so that the catalyst equilibrates with the substrate/product in the solution [22]. All things being equal, at high overpotential, where the catalyst is entirely oxidized near the electrode, increasing the backward rate constant k_{-2} (for the homogeneous reoxidation of the catalyst) decreases the size of the diffusion layer, hence the number of catalyst molecules that participate in the reaction.

Last, we emphasize that for multistep mechanisms, there is no simple relationship between i_{lim} and $\mathrm{TOF_{max}}$ when the catalyst diffuses. For example, in the $\mathrm{EEC_rC_r}$ mechanism, the limiting current of the *adsorbed* catalyst is simply proportional to $\mathrm{TOF_{max}}$

$$i^{\mathrm{red}}_{\mathrm{lim}} = 2FA\Gamma\frac{k_1k_2}{k_1 + k_2 + k_{-1}}$$

but the limiting current calculated for a diffusing catalyst is a very complex combination of the same rate constants [27]:

$$\begin{aligned} i^{\mathrm{red}}_{\mathrm{lim}} = {} & \left[\frac{1}{2}FA\sqrt{D}\ k_2k_1(\alpha_1(\beta_1 + \alpha_3\beta_2) + \alpha_2(\beta_1 - \alpha_3\beta_2))\right] \\ & \times \Big/ \end{aligned}$$

$$\begin{aligned} & \Big[(-k_1 + k_{-2})(k_2 + k_1 + k_{-2}k_{-1} + k_{-2}k_1)\sqrt{\kappa} \\ & + k_{-1}k_{-2}(k_1 + k_2 + k_{-1})^2 + k_1k_2(k_2 + k_{-2})^2 \\ & + k_2k_{-1}\left(k_{-2}{}^2 + 2k_1k_2 + k_1k_{-1} + k_1{}^2\right)\Big] \end{aligned}$$

where

$$\kappa = k_2k_1 + k_{-2}k_1 + k_{-2}k_{-1}$$

$$\alpha_1^2 = 2[k_1 + k_2 + k_{-1} + k_{-2} - \alpha_3]$$

$$\alpha_2^2 = 2[k_1 + k_2 + k_{-1} + k_{-2} + \alpha_3]$$

$$\alpha_3^2 = (k_1 + k_2 + k_{-1} + k_{-2})^2 - 4\kappa$$

$$\beta_1 = (k_1 + k_{-2})^2 - k_2k_1 + k_1k_{-1} + k_{-2}{}^2 + 2k_2k_{-2} - k_1k_{-2}$$

$$\beta_2 = k_{-1} + k_2 + k_{-2}$$

It may be possible to extract the values of some of the rate constants in the catalytic cycle from a thorough inspection of the voltammetry [13], but clearly, the actual value of the limiting current has no simple meaning.

Conclusion

Recent results regarding the modeling of the bidirectional response of two-electron molecular redox catalysts show that the electrochemical literature on unidirectional reactions cannot be used to interpret bidirectional systems. This is because, in contrast to unidirectional catalysis, the onset of current is not exponential, the two redox transitions of the catalyst must be explicitly included in the model, the Nernst potential of the reaction to be catalyzed in a relevant parameter, thermodynamics constrains the rate constants of the catalytic cycle, and the different forms of the catalyst equilibrate in the diffusion layer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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