The physics of boundary conditions in reaction–diffusion problems

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The use of fully or partially absorbing boundary conditions for diffusion-based problems has become paradigmatic in physical chemistry and biochemistry to describe reactions occurring in solutions or in living media. However, as chemical states may indeed disappear, particles cannot, unless such degradation happens physically and should thus be accounted for explicitly. Here, we introduce a simple, yet general idea that allows one to derive the appropriate boundary conditions self-consistently from the chemical reaction scheme and the geometry of the physical reaction boundaries. As an illustration, we consider two paradigmatic examples, where the known results are recovered by taking specific physical limits. More generally, we demonstrate that our mathematical analysis delivers physical insight that cannot be accessed through standard treatments.

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The work on diffusion-limited coagulation of colloidal particles of the Polish physicist Marian von Smoluchowski can be rightly considered as one of the fundamental pillars of modern molecular physical chemistry, and, as a matter of fact, of the entire biochemistry of living organisms. Smoluchowski’s demonstration of how a brilliant intuition was that, if diffusion is the rate-limiting step, i.e. the reaction that occurs upon contact proceeds much faster than the typical time of diffusive approach, then the problem can be reduced to that of a single A surrounded by a homogeneous fluid of Bs. Moreover, if the latter are themselves diluted enough to be considered non-interacting, the whole problem reduces further to a two-body problem. Smoluchowski’s brilliant intuition was that, if diffusion is the rate-limiting step, one may consider a steady non-equilibrium diffusive flux of particles disappearing instantly at the contact distance \( R = R_A + R_B \). Then, the total flux is the sought rate. Mathematically, one should solve the stationary diffusion equation for the concentration field of Bs around one A, \( c(r) \), with absorbing boundary conditions at \( r = R \) and constant bulk concentration at infinite \( A - B \) separation, that is,

\[
\nabla^2 c = 0, \quad \text{BC: } c(R) = 0, \lim_{r \to \infty} c(r) = c_\infty \quad (1)
\]

Integrating the current \( J = -D \nabla c (D = D_A + D_B) \) over the reaction sphere gives

\[
k = 4\pi DR^2 \left. \frac{dc}{dr} \right|_R = 4\pi DR c_\infty \quad (2)
\]

which is known as the Smoluchowski rate. This result is simple and elegant and, indeed, it conveys correctly the essential physics of diffusion-limited encounters in diluted solutions. A closer inspection, however, reveals some unsettling troubles.

An absorbing boundary condition is certainly a clever mathematical trick, but it implies nonetheless a somewhat mysterious mass annihilation. In fact, as pointed out by Collins and Kimball (CK) in 1949, the result cannot be correct if not every \( B \) particle that reaches the reaction radius eventually reacts. Based on this observation, CK surmised that a more physical boundary condition should be of the Robin (mixed) type, namely

\[
4\pi DR^2 \left. \frac{dc}{dr} \right|_R = k^* c(R) \quad (3)
\]

The rate constant \( k^* \) (units of inverse concentration times inverse time) somehow gauges the finite probability of a reaction indeed occurring and interpolates between reflecting (\( k^* = 0 \)) and absorbing (\( k^* \to \infty \)) BC. With the BC (3), the stationary solution yields a total flux

\[
k = 4\pi DR^2 \left. \frac{dc}{dr} \right|_R = k_S c_\infty \left( \frac{h}{1 + h} \right) \quad (4)
\]

where \( k_S = 4\pi DR \) and \( h = k^*/k_S \). This result has been famously employed by Shoup and Szabo to reinterpret the classical calculation by Berg and Purcell for the rate of irreversible binding of ligands to \( N \) receptors on a cell’s membrane. In this case, each receptor acts as an absorbing disk, so that \( k^* \propto N \). The point, however, is that fully or partially absorbing boundary conditions seem to be physically plausible only if particles do really disappear. For example, in a process of intake followed by degradation of some nutrient, say by a spherical colony of algae. By contrast, the use of fully or partially absorbing BCs to model binding appears more elusive.
The slight physical discomfort caused by the use of absorbing boundary conditions to model chemical transformations resides in the fact that, by doing this, particles cannot be properly distinguished from chemical states. A clear illustration of this ambiguity are so-called annihilation reactions, such as when a fluorescent molecule \( B^* \) relaxes upon collision with a quencher \( A \), i.e. \( B^* + A \rightarrow B + A^* \). In this case, the diffusing particles can exist in either the excited or relaxed state, with a transition in chemical space being promoted by a physical collision with the quencher. However, while the excited state disappears, the particle is never gone. It merely changes color, so to say.

The real problem seems that there is no general rigorous method at present to derive self-consistently the appropriate boundary conditions for mass diffusion coupled to chemical transformations among different states that may occur in the bulk and on some reactive manifold. Of course, the boundary conditions should ensure mass conservation if the chemistry at hand prescribes so.

In this paper, we introduce a simple, yet powerful idea that unveils a self-consistent method to solve this problem. In the following, we illustrate this method.

In order to determine the encounter rate, we can restrict to the stationary problem. The general solution of this takes the form

\[
\begin{align*}
\left( \frac{c}{c^*} \right) &= \left( \frac{c_\infty}{c^*_\infty} \right) + \frac{P}{r} \left( \frac{1}{k_{+1}} \right) + \frac{Q}{r} \left( \frac{1}{-1} \right) e^{-qr} \quad (9)
\end{align*}
\]

where \( q = \sqrt{(k_1 + k_{-1})/D} \). The constants \( P \) and \( Q \) are determined by the BCs (7) and (8), which gives the stationary profiles

\[
\begin{align*}
\frac{c(r)}{c_\infty} &= 1 - \frac{a}{r} \left( 1 - e^{\beta \epsilon} \right) \frac{k^* e^{-q(r-a)}}{k^* + k_{+1}^* + k_5 (1 + qa)} \quad (10)
\end{align*}
\]

\[
\begin{align*}
\frac{c^*(r)}{c^*_\infty} &= 1 - \frac{a}{r} \left( 1 - e^{-\beta \epsilon} \right) \frac{k^* e^{-q(r-a)}}{k^* + k_{+1}^* + k_5 (1 + qa)} \quad (11)
\end{align*}
\]

The exponential relaxation of the steady profiles conveys an important piece of physical information. As stated before, the whole theory rests on the hypothesis that \( A \) molecules be diluted enough. By contrast to the standard treatment, we now see clearly what enough means: the average \( A-A \) separation should be greater than the typical relaxation length of the profiles, \( q^{-1} \), i.e. \( q^{-1} \ll 1 \). This is tantamount to stating that the average time needed for a \( B \) molecule to diffuse over
the average A-A separation, \( \tau_A = D^{-1}a^{-2/3} \), should be longer than the average lifetime of the chemical states, \((k_1 + k_{-1})^{-1}\). In other words, demanding that particles be diluted in a reaction-diffusion system ought to involve a combination of diffusive relaxation time scales and lifetimes of chemical states.

As we are explicitly distinguishing particles from chemical states, the correct way to compute the overall reaction rate at the quenching surface is the following,

\[
k = J^* - J = k^* c^*(a) - k^* c(a)
\]

\[
= k_S(1 + qa) \frac{k^* c^* \kappa^* - k^* c^*}{k^* + k^* + k^* S}(1 + qa)
\]

(12)
The stationary profiles \( \{10\}, \{11\} \) and the rate \( \{12\} \) convey a wealth of physical insight. First and foremost, it is now clear that the rate should be measured as an excess flow in chemical space relative to equilibrium. However, the boundary condition \( \{7\} \) shows that this is nothing but the total flux of excited molecules over the reactive boundary according to the definition \( \{3\} \). Rather insightfully, our self-consistent theory reveals that the total particle flux equals the net current at the catalytic surface in chemical space. More generally, the sign of that current determines whether the catalyst acts as an active quencher or adds up to the excitation in a non-equilibrium steady state, i.e. when \( k^* / k_{-1} \neq k_{-1} / k_{1} \). Indeed, direct inspection of the profiles \( \{10\} \) and \( \{11\} \) shows that one may have enrichment of either species at the reaction surface, depending on the relative magnitudes of the relaxation-to-excitation rates ratio, or equivalently on the sign of \( c \).

The familiar Smoluchowski setting is approached in the catalytic limit, i.e. when the relaxation rate at the surface is much greater than in the bulk. In the limit \( k^* \rightarrow \infty \) one has

\[
k \rightarrow k^* S \equiv k_S c^*_\infty (1 + qa) = k_S c^*_\infty (1 + \sqrt{Da})
\]

(13)
where \( Da = (qa)^2 \) is the appropriate Damköhler number for this problem. We discover that this is greater than the expected Smoluchowski limit, \( k_S c^*_\infty \). In the conventional picture of particles pouring diffusively from infinity and vanishing into a sink, this may be interpreted as an extra accumulation of particles in the bulk, where reactions are not infinitely slow with respect to the typical diffusion limit, \( \tau_D = a^2 / D \). Indeed, the Smoluchowski rate is recovered in the infinite-diffusion limit, i.e. \( qa \rightarrow 0, Da \rightarrow 0 \), or, equivalently, \( k_{1} + k_{-1} \ll \tau_D^{-1} \). The expression \( \{12\} \) also yields the physically sensible result if the infinite-diffusion limit \( qa \rightarrow 0 \) is taken at finite surface quenching rate, \( k^* \). In this case one has

\[
k = c_0 (k^* k_{1} - k^* k_{-1})
\]

(14)
which correctly only accounts for relative flow in chemical space.

Let us now turn to another well-known problem, that of binding of a ligand molecule to \( N \) receptors of size \( b \) at the surface of a cell. The well-known Berg and Purcell (BP) formula has the form of eq. \( \{1\} \) and thus can be derived by solving a stationary diffusion problem subject to mixed BC, provided \( k^* = 4DbN_b^2 \). In other words, the surface reaction rate should correspond to as many fully absorbing disks of radius \( b \) as there are receptors on the cell’s surface. Unfortunately, despite the correction worked out by Zwanzig through an elegant effective-medium argument, the BP formula still suffers from the same ambiguity connected to the use of sinks to describe binding reactions. Following our method, this problem can be cast in a form that is more physically and biologically transparent and that reduces to a BP-like formula in the appropriate physical limit.

Let a cell of radius \( a \) be covered with \( N \) receptors that can exist in their free form or in complex with some ligand. We consider the following scheme of reactions

\[
\begin{align*}
L + R & \rightarrow \frac{k_1}{k_{-1}} C, \\
C & \rightarrow k_{d} R, \\
L & \rightarrow k_{d} \emptyset
\end{align*}
\]

(15)
These correspond to complex formation/dissociation at the cell’s surface and complex internalization followed by receptor recycling and ligand degradation, occurring with the same rate \( k_{d} \). Taking into account the diffusion of ligand molecules in the bulk, we can write the following set of equations,

\[
\begin{align*}
\frac{\partial \rho}{\partial t} &= D \nabla^2 \rho + \frac{\delta(r - a)}{4\pi r^2} (k_{-1} N_C - k_{1} \rho N_R) \\
\frac{dN_C}{dt} &= k_{d} \rho(a, t) N_R - (k_{-1} + k_{d}) N_C \\
\lim_{r \rightarrow \infty} \rho(r) &= \rho_0
\end{align*}
\]

(16)
where \( \rho(r, t) \) is the ligand concentration field, \( \rho_0 \) its bulk concentration and \( N_R, N_C \) are the numbers of free receptors and complexes at the surface of a single cell, respectively. Combining eq. \( \{16\} \) with the conservation law \( N_R + N_C = N \), one easily obtains the number of complexes in the stationary state, that is,

\[
N_C = \frac{N \rho(a)}{\mathcal{K} + \rho(a)}
\]

(17)
where \( \mathcal{K} = (k_{-1} + k_{d}) / k_{1} \) is the complex dissociation constant (units of concentration). The appropriate boundary condition for the diffusion equation can be obtained again by integrating eq. \( \{16a\} \) from \( r = a - \delta a \) to \( r = a + \delta a \) and then taking the limit \( \delta a \rightarrow 0 \). Taking into account eq. \( \{17\} \), this yields the appropriate self-consistent BC, that is,

\[
4\pi Da^2 \frac{d\rho}{dr} \bigg|_{a} - k_{d} \left( \frac{N \rho(a)}{\mathcal{K} + \rho(a)} \right) = 0
\]

(18)
The stationary ligand profile outside the cell has the form \( \rho(r) = \rho_0 (1 - \mu R/r) \), where \( \mu \) is fixed by the BC \( \{15\} \).
\[ \mu = \frac{1}{2} \left( \frac{K_d + \rho_0}{\rho_0} - \sqrt{\left( \frac{K_d + \rho_0}{\rho_0} \right)^2 - \frac{4k_dN}{K_S\rho_0}} \right) \]  

(19)

with \( K_d = K + k_dN/k_s \). In this case, the setting is intrinsically a non-equilibrium one as in the standard Smoluchowski formulation, with the important difference that the present approach allows one to build in ligand binding and degradation in a physically and biologically transparent manner. The overall ligand intake rate follows immediately as \( k_i = 4\pi Da^2(d\rho(a)/dr) = \mu k_S \rho_0 \).

This result should be considered as the minimal extension of the Berg-Purcell formula in the direction of physical transparency of the underlying biochemical process. Once more, taking specific limits turns out to be insightful.

At first glance, one may expect that the Smoluchowski rate \( k_S \rho_0 \) should be recovered in the limit of infinite degradation, \( k_d \to \infty \). In fact, the math reveals a slightly different physical picture, that is,

\[ \lim_{k_d \to \infty} k_i = k_S \rho_0 \left( \frac{\kappa^*}{\kappa^* + k_S} \right) \]

(20)

where \( \kappa^* = NK_1 \). We thus learn that the BP formula corresponds to the limit of infinite internal degradation of ligand molecules when the kinetics of complex formation at the membrane is properly accounted for. Moreover, the intuitive prescription \( \kappa^* \propto N \) posited by Shoup and Szabo\(^1\) is recovered here self-consistently. Interestingly, our calculation unveils the correct interpretation of the intrinsic reaction rate \( \kappa^* \), beyond the physical ambiguity of circular sinks. Not surprisingly, in this minimal model it is the ligand-receptor association rate constant, \( k_1 \), that determines how effective a ligand absorber is a receptor-covered cell. Of course, if the kinetics of ligand binding and the degradation chain were described in more detail, the calculation would provide more insight into how the inner workings of the whole biochemical pathway should enter the overall intake rate.

In summary, in this paper we have introduced a simple, yet powerful, idea that allows one to address problems in molecular kinetics in solution on totally new grounds. Instead of relying on the old idea of supplementing the diffusion equation with empirical fully or partially absorbing boundary conditions, we have shown that it is possible to derive the appropriate BCs self-consistently from the geometry of the reaction boundary and the details of the chemical reaction network. In our scheme, this can comprise reactions occurring in the bulk and at the reaction surface alike. The extent of the proposed change of perspective can be readily appreciated from the potential applications of our idea. For example, with reference to ligand binding at a cell’s membrane, the biochemical kinetic network considered may be enriched by including different receptors, other surface proteins that activate/inhibit them, more complex steps associated with internalization and recycling and a more detailed description of the degradation chain. In principle, our method should provide a rigorous microscopic strategy to investigate how combined ligand diffusion and binding regulate any signaling pathways. These include signaling cascades related to the emergence of polarisation in cells steered by non-equilibrium self-generated gradients\(^10\) created close to their plasma membrane through mechanisms such as the scheme \( \text{(1)} \). These gradients can in principle be measured experimentally and compared with our predictions based on detailed models of the underlying biochemical networks.

More generally, our idea may be readily employed to investigate time-dependent reaction diffusion problems too, as well as complex non-spherical reaction boundaries or even multiple disconnected boundaries arranged according to some pattern\(^11\). The latter perspective appears especially intriguing, as our method would allow one to explore how neighbouring reaction surfaces, e.g. clusters of cells, influence each other with respect to a given microscopic kinetic (signaling) scheme within a physically and biologically transparent model.

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