

---

An averaging principle for fast diffusions in domains separated by  
semi-permeable membranes

Adam Bobrowski  
Bogdan Kazmierczak  
Markus Kunze

---

Konstanzer Schriften in Mathematik

Nr. 351, März 2016

ISSN 1430-3558

---

*Konstanzer Online-Publikations-System (KOPS)*  
URL: <http://nbn-resolving.de/urn:nbn:de:bsz:352-0-324467>



# AN AVERAGING PRINCIPLE FOR FAST DIFFUSIONS IN DOMAINS SEPARATED BY SEMI-PERMEABLE MEMBRANES

ADAM BOBROWSKI, BOGDAN KAZMIERCZAK, AND MARKUS KUNZE

ABSTRACT. We prove an averaging principle which asserts convergence of diffusions on domains separated by semi-permeable membranes, when the speed of diffusion tends to infinity while the flux through the membranes remains constant. In the limit, points in each domain are lumped into a single state of a limit Markov chain. The limit chain's intensities are proportional to membranes' permeability and inversely proportional to the domains' sizes. Analytically, the limit is an example of a singular perturbation in which boundary and transmission conditions play a crucial role. This averaging principle is strongly motivated by recent signaling pathways models of mathematical biology, which are discussed in the final section of the paper.

## 1. INTRODUCTION

The main aim of this article is to establish an averaging principle saying that fast diffusions on domains separated by semi-permeable domains may be approximated by certain Markov chains. More specifically, if diffusion's speed in each domain increases while the flux through the boundaries remains constant, in the limit, all points in each domain are lumped together to form a single state, and the limit process is a Markov chain with the state-space composed of these lumped states (Theorems 5.5 and 5.6). The jump intensities in the chain are in direct proportion to the total permeability of the membranes, and in inverse proportion to the sizes of the domains (see eq. (5.3)). We note that the principle just described is akin to the famous Freidlin–Wentzell averaging principle ([36, 38], see also [37]), though it is motivated by biological rather than physical models. Moreover, in contrast to Freidlin–Wentzell principle, in our case the crucial role is played by transmission conditions.

Predecessors of our principle have been studied in [19] and [14], see also [40]. In [19], in an attempt to reconcile two models of so-called neurotransmitters (a macroscopic one of Aristizabal and Glavinovič [6], and a microscopic one of Bielecki and Kalita [11]) it has been shown that fast diffusions in three domains, corresponding to the so-called large, small, and immediately available pools, may be approximated by a Markov chain with three states, see Figure 1. In fact, in [19] merely a one-dimensional variant of this limit theorem has been proved, in which the three 3-dimensional pools are replaced by three adjacent intervals. This result has later been generalized to the case of fast diffusions on arbitrary finite graphs in [14]; in both cases the limit theorems are stated as convergence theorems for semigroups in Banach spaces of continuous functions. In [40], a related result has been proved in a space of integrable functions. See also [7] for a generalization.

In this paper, we come back to the general,  $d$ -dimensional setting, and, in contrast to the previous papers, focus on the analysis in  $L^p$  spaces ( $p \geq 1$ ). To this end, we prove our main result in  $L^2$  first (Theorem 5.5), using convergence theorems

---

2010 *Mathematics Subject Classification.* 47A07, 47D07, 60J70, 92C45.

*Key words and phrases.* Convergence of sectorial forms and of semigroups of operators, diffusion processes, boundary and transmission conditions, Freidlin–Wentzell averaging principle, singular perturbations, signaling pathways, kinase activity, intracellular calcium dynamics, neurotransmitters.

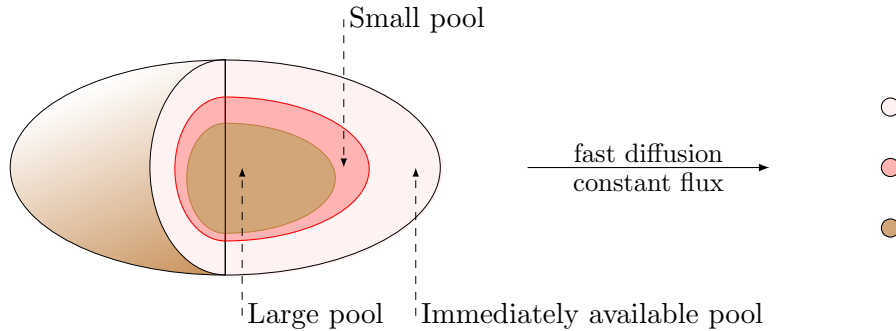


FIGURE 1. Averaging principle in two models of neurotransmitters

for quadratic forms, and then extend the analysis to other  $L^p$  (Theorem 5.6) by extrapolation and interpolation techniques – see Sections 4 and 5. In Section 6, three contemporary models of biology, including two recent signaling pathways models and the neurotransmitters model, are discussed as special cases of the principle so established.

As already mentioned, the key role in this analysis is played by transmission conditions (see (3.3)) describing permeability of membranes. In the context of heat flow, these conditions may be plausibly interpreted: according to Newton’s Law of Cooling, the temperature at the membrane changes at a rate proportional to the difference of temperatures on either sides of the membrane, see [21, p. 9]. In this context, J. Crank uses the term *radiation boundary condition*. (Although, strictly speaking, these are not *boundary*, but *transmission* conditions, see [25, 26, 27].)

In the context of passing or diffusing through membranes, analogous transmission conditions were introduced by J. E. Tanner [59, eq. (7)], who studied diffusion of particles through a sequence of permeable barriers (see also Powles et al. [56, eq. (1.4)], for a continuation of the subject). In [3] (see e.g. eq. (4) there) similar conditions are used in describing absorption and desorption phenomena. We refer also to [34], where a compartment model with permeable walls (representing e.g., cells, and axons in the white matter of the brain in particular) is analyzed, and to equation [42] there.

In the context of neurotransmitters, conditions of type (3.3) were (re)-invented in [19] and [14], interpreted in probabilistic terms, and linked with Feller–Wentzell’s boundary conditions [30, 31, 32, 33, 61] (see [47] for a more thorough stochastic analysis).

A systematic study of semigroups and cosine families related to such transmission conditions has been commenced in [15]. We note also the recent paper [9], where a heat problem for such transmission conditions is studied for quite irregular boundaries, and the monograph [1] in which related transmission conditions are analyzed.

## 2. PRELIMINARIES

The main tools to prove our averaging principle come from the theory of sectorial forms. In this section we briefly recall the relevant definitions and results. For more information we refer to the books by Kato [41] and Ouhabaz [55].

Let  $H$  be a Hilbert space. A *sesquilinear form* is a mapping  $\mathfrak{h} : D(\mathfrak{h}) \times D(\mathfrak{h}) \rightarrow \mathbb{C}$  which is linear in the first component and antilinear in the second component. Here  $D(\mathfrak{h})$  is a subspace of  $H$ . If  $D(\mathfrak{h})$  is dense in  $H$  we say that  $\mathfrak{h}$  is *densely defined*. We write  $\mathfrak{h}[u] := \mathfrak{h}[u, u]$  for the associated *quadratic form* at  $u \in D(\mathfrak{h})$ .

A sesquilinear form  $\mathfrak{h}$  is called *sectorial* if the *numerical range*

$$\Theta(\mathfrak{h}) := \{ \mathfrak{h}[u] : u \in D(\mathfrak{h}), \|u\|_H \leq 1 \}$$

is contained in some sector

$$\Sigma_\gamma(\theta) := \{z \in \mathbb{C} : |\arg(z - \gamma)| \leq \theta\}.$$

Here  $\theta \in [0, \frac{\pi}{2})$  is called the *angle* of the sector and  $\gamma \in \mathbb{R}$  is the *vertex* of the sector. To emphasize  $\theta$  we will say  $\mathfrak{h}$  is *sectorial of angle*  $\theta$ . If  $\operatorname{Re} \mathfrak{h}[u] \geq 0$  for all  $u \in D(\mathfrak{h})$  then  $\mathfrak{h}$  is called *accretive*. The numerical range of an accretive, sectorial form is always contained in a sector with vertex 0. We will mainly be interested in accretive forms. If the numerical range of a form is contained in  $\Sigma_\gamma(0)$ , the form is called *symmetric*.

The *adjoint form* of  $\mathfrak{h}$  is defined as  $\mathfrak{h}^* : D(\mathfrak{h}) \times D(\mathfrak{h}) \rightarrow \mathbb{C}$ ,  $\mathfrak{h}^*[u, v] := \overline{\mathfrak{h}[v, u]}$ . If  $\mathfrak{h}$  is sectorial (accretive, symmetric) then so is  $\mathfrak{h}^*$ . The *real* and *imaginary parts* of  $\mathfrak{h}$  are defined by  $\operatorname{Re} \mathfrak{h} := \frac{1}{2}(\mathfrak{h} + \mathfrak{h}^*)$  and  $\operatorname{Im} \mathfrak{h} := \frac{1}{2i}(\mathfrak{h} - \mathfrak{h}^*)$ , respectively. An easy computation shows that  $\operatorname{Re} \mathfrak{h}$  and  $\operatorname{Im} \mathfrak{h}$  are symmetric forms and that  $\mathfrak{h}[u, v] := \operatorname{Re} \mathfrak{h}[u, v] + i \operatorname{Im} \mathfrak{h}[u, v]$ . We point out that even if the quadratic forms associated with  $\operatorname{Re} \mathfrak{h}$  and  $\operatorname{Im} \mathfrak{h}$  take only values in the real numbers, the forms themselves may take values in the complex plane. It is easy to see that an accretive sesquilinear form is sectorial of angle  $\theta$  if and only if

$$|\operatorname{Im} \mathfrak{h}[u]| \leq \tan \theta \operatorname{Re} \mathfrak{h}[u].$$

In this case

$$\langle u, v \rangle_{\mathfrak{h}} := \operatorname{Re} \mathfrak{h}[u, v] + \langle u, v \rangle_H$$

defines an inner product on  $D(\mathfrak{h})$ . This is called the *associated inner product*. If this inner product turns  $D(\mathfrak{h})$  into a Hilbert space,  $\mathfrak{h}$  is called *closed*.

If  $\mathfrak{h}$  is a densely defined sesquilinear form, we define the *associated operator*  $\mathcal{L}$  by setting

$$D(\mathcal{L}) := \{u \in D(\mathfrak{h}) : \exists w \in H \text{ with } \mathfrak{h}[u, v] = \langle w, v \rangle \text{ for all } v \in D(\mathfrak{h})\}, \quad \mathcal{L}u = -w.$$

Note that by the density of  $D(\mathfrak{h})$  in  $H$  there exists at most one such  $w$ . We now have the following result, see [41, Theorem VI.2.1] or [55, Section 1.4]

**Theorem 2.1.** *Let  $\mathfrak{h}$  be an accretive, closed and densely defined sectorial form of angle  $\theta$ . Then the associated operator  $\mathcal{L}$  is closed and densely defined,  $\mathbb{C} \setminus \overline{\Sigma_0(\theta)}$  is contained in the resolvent set  $\rho(\mathcal{L})$  and*

$$\|R(\lambda, \mathcal{L})\| \leq \frac{1}{\operatorname{dist}(\lambda, \Sigma_0(\theta))} \quad \text{for all } \lambda \in \mathbb{C} \setminus \overline{\Sigma_0(\theta)}.$$

In particular,  $\mathcal{L}$  is sectorial of angle  $\frac{\pi}{2} - \theta$  in the sense of [28, Definition II.4.1] and thus generates a bounded, analytic semigroup of operators in  $H$  by [28, Theorem II.4.6]. This semigroup is contractive on  $[0, \infty)$ .

If the form  $\mathfrak{h}$  is closed and sectorial but not densely defined, there is no associated operator in  $H$ . However, we may associate an operator  $\mathcal{L}|_{H_0}$  on the Hilbert space  $H_0 := \overline{D(\mathfrak{h})}^H$ . We will also in this situation call  $\mathcal{L}|_{H_0}$  the operator associated with  $\mathfrak{h}$ . As a consequence of Theorem 2.1,  $\mathcal{L}|_{H_0}$  is a sectorial operator on  $H_0$  and thus generates a bounded, analytic semigroup  $e^{t\mathcal{L}|_{H_0}}$  on  $H_0$ . Following Simon [57], who treated the symmetric case, we extend each operator of the semigroup to  $H$  by setting it to 0 on  $H_0^\perp$ . In other words, for  $u = u_0 + u_1 \in H_0 \oplus H_0^\perp = H$  we define the (*degenerate*) semigroup  $e^{-z\mathfrak{h}}$  by setting

$$e^{-z\mathfrak{h}}u := e^{z\mathcal{L}|_{H_0}}u_0$$

and the pseudoresolvent  $(\lambda + \mathfrak{h})^{-1}$  by setting

$$(\lambda + \mathfrak{h})^{-1}u := R(\lambda, \mathcal{L}|_{H_0})u_0.$$

With slight abuse of notation, we write

$$(2.1) \quad e^{-z\mathfrak{h}} = e^{z\mathcal{L}|_{H_0}}P_{H_0} \quad \text{and} \quad (\lambda + \mathfrak{h})^{-1} = R(\lambda, \mathcal{L}|_{H_0})P_{H_0}$$

where  $P_{H_0}$  is the orthogonal projection onto  $H_0$ . Note that the relationship between  $e^{-z\mathfrak{h}}$  and  $(\lambda + \mathfrak{h})^{-1}$  is the same as in the case where  $\mathfrak{h}$  is densely defined. Namely,  $e^{-z\mathfrak{h}}$  can be computed from  $(\lambda + \mathfrak{h})^{-1}$  via an appropriate contour integral and, vice versa,  $(\lambda + \mathfrak{h})^{-1}$  is the Laplace transform of  $e^{-z\mathfrak{h}}$ .

As in [57] the main motivation to consider forms which are not densely defined are convergence results for sectorial forms, where non densely defined forms may appear naturally in the limit, even if we consider a sequence of densely defined sectorial forms. In fact, this is exactly what happens in our averaging principle. To prove it, we make use of the following convergence result due to Ouhabaz [54] which generalizes Simon's theorem [57] concerned with symmetric forms. See also the recent article [10] for related results.

**Theorem 2.2.** *Let  $\mathfrak{h}_n, n \geq 1$  be a sequence of accretive, closed and uniformly sectorial forms in a Hilbertspace  $H$ . The latter means that all the numerical ranges are contained in a common sector  $\Sigma_0(\theta)$ . Moreover, assume that*

- (a)  $\operatorname{Re} \mathfrak{h}_n \leq \operatorname{Re} \mathfrak{h}_{n+1}$ , i.e.  $D(\mathfrak{h}_{n+1}) \subset D(\mathfrak{h}_n)$  and  $\mathfrak{h}_n[u] \leq \mathfrak{h}_{n+1}[u]$  for all  $u \in D(\mathfrak{h}_{n+1})$ ;
- (b) we either have
  - (i)  $\operatorname{Im} \mathfrak{h}_n[u] \leq \operatorname{Im} \mathfrak{h}_{n+1}[u]$  for all  $u \in D(\mathfrak{h}_{n+1})$  or
  - (ii)  $\operatorname{Im} \mathfrak{h}_{n+1}[u] \leq \operatorname{Im} \mathfrak{h}_n[u]$  for all  $u \in D(\mathfrak{h}_{n+1})$ .

Define  $\mathfrak{h}[u] := \lim_{n \rightarrow \infty} \mathfrak{h}_n[u]$  with domain

$$D(\mathfrak{h}) := \left\{ u \in \bigcap_{n \in \mathbb{N}} D(\mathfrak{h}_n) : \sup_{n \in \mathbb{N}} \mathfrak{h}_n[u] < \infty \right\}.$$

Then  $\mathfrak{h}$  is an accretive, closed and sectorial form and  $\mathfrak{h}_n$  converges to  $\mathfrak{h}$  in the strong resolvent sense, i.e.

$$(\lambda + \mathfrak{h}_n)^{-1}u \rightarrow (\lambda + \mathfrak{h})^{-1}u \quad \text{as } n \rightarrow \infty,$$

for all  $u \in H$  and  $\lambda \in \mathbb{C} \setminus \overline{\Sigma_0(\theta)}$ .

Ouhabaz has proved this theorem only for densely defined forms but inspection of the proof shows that it generalizes also to non densely defined forms. Indeed, besides properties of analytic functions, the proof only makes use of Simon's monotone convergence theorem [57] which is valid also for non densely defined forms.

An important consequence of Theorem 2.2 is the following.

**Corollary 2.3.** *In the situation of Theorem 2.2 we have  $e^{-t\mathfrak{h}_n}u \rightarrow e^{-t\mathfrak{h}}u$  as  $n \rightarrow \infty$  for all  $u \in H$  and  $t \geq 0$ .*

*Proof.* To see this note that the degenerate semigroup  $e^{-t\mathfrak{h}_n}u$  can be computed from the pseudoresolvent  $(\lambda + \mathfrak{h}_n)^{-1}u$  via a contour integral. By the strong resolvent convergence the integrands converge pointwise on the contour to  $(\lambda + \mathfrak{h})^{-1}u$ . However, as our forms are uniformly sectorial, it follows from Theorem 2.1 that the associated operators are uniformly sectorial. From this, we obtain an integrable majorant for  $(\lambda + \mathfrak{h}_n)^{-1}u$ . The thesis now follows from the dominated convergence theorem. See e.g. [12, Proposition 4] for details.  $\square$

The situation where degenerate semigroups (or, equivalently, non densely defined operators) appear in convergence results is quite common in applications and can be studied in more generality in the framework of singular perturbation problems, see [8] and [17]. We would like to point out that the situation in Corollary 2.3 is rather special in that in general mere convergence of the resolvents does not imply convergence of the related semigroups (see examples in e.g. [12] or [13, Chapter 8]). What allows us to infer convergence of the semigroups from that of the resolvents is the fact that the related semigroups are uniformly holomorphic. That this is helpful in convergence results has been known for a time (see, e.g., [4, 12] and the seminal paper [23]).

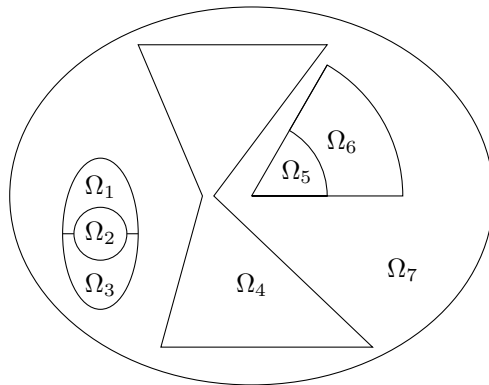


FIGURE 2. Partition of  $\Omega_0$  (here, an ellipse in  $\mathbb{R}^2$ ) into  $N = 7$  parts.

In the general situation where the semigroups considered are not uniformly holomorphic, more refined techniques are needed to establish convergence of the semigroups. It is worth noticing that many singular perturbation problems which not necessarily involve uniformly holomorphic semigroups, fall into an ingenious scheme devised by T. G. Kurtz [29, pp. 39-42][45, 46]. In fact, relatives of our averaging principle can also be deduced from Kurtz's theorem, see [17, Chapter 42]; the same is essentially true of the Freidlin–Wentzell principle [18].

### 3. NOTATION AND ASSUMPTIONS

**3.1. Domains and their boundaries.** We let  $\Omega_0 \subset \mathbb{R}^d$  be a connected, bounded open domain with Lipschitz boundary. Here, we say that an open set  $\Omega \subset \mathbb{R}^d$  has *Lipschitz boundary* if it is locally the epigraph of a Lipschitz function, see, e.g., [1, p. 111]. More precisely, given  $z \in \partial\Omega$  we may find an open neighborhood  $V$  of  $z$  in  $\partial\Omega$  such that there is (a) a cylinder  $C = B \times (a, b)$ , where  $B$  is an open ball in  $\mathbb{R}^{d-1}$  and  $(a, b)$  is an open subinterval of  $\mathbb{R}$ , and (b) an isomorphism  $J$  of  $\mathbb{R}^d$ , and (c) a Lipschitz continuous functions  $g : B \rightarrow \mathbb{R}$  such that defining  $\phi(w, t) = t - g(w)$  for  $(w, t) \in C$ , we have  $\Omega \cap C = J\{\phi < 0\}$ ,  $C \setminus \bar{\Omega} = J\{\phi > 0\}$ , and  $V = J\{\phi = 0\}$ . Our domain  $\Omega_0$  is further partitioned (see Figure 2), i.e., we consider subsets  $\Omega_1, \dots, \Omega_{N-1} \subset \Omega_0$  that are pairwise disjoint and open with Lipschitz boundary. We set

$$\Omega_N := \text{Int} \left( \Omega_0 \setminus \bigcup_{k=1}^{N-1} \bar{\Omega}_k \right).$$

We assume that also  $\Omega_N$  is a bounded open set with Lipschitz boundary. This assumption excludes certain configurations of the sets  $\Omega_1, \dots, \Omega_{N-1}$ . For example, it may not happen that we have two balls which touch in exactly one point. On the other hand, it is no restriction to assume that the sets  $\Omega_1, \dots, \Omega_N$  are connected, otherwise we consider the connected components of these sets.

The boundary of the set  $\Omega_k$  is denoted by  $\Gamma_k$  for  $k = 0, \dots, N$ . We write

$$\Gamma_{k,\ell} := \Gamma_k \cap \Gamma_\ell$$

for the common boundary of  $\Omega_k$  and  $\Omega_\ell$  ( $k, \ell = 0, \dots, N, k \neq \ell$ ). To simplify some formulas to be discussed later, we also agree that

$$\Gamma_{k,k} = \emptyset$$

for  $k = 1, \dots, n$ . Note that we may also well have that  $\Gamma_{k,\ell} = \emptyset$  for certain values of  $k \neq \ell$ . Below, we always endow the boundaries  $\Gamma_k$  with their natural surface measure  $\sigma_k$ . Actually  $\sigma_k$  coincides with  $(d-1)$ -dimensional Hausdorff measure  $\mathcal{H}^{d-1}$  since

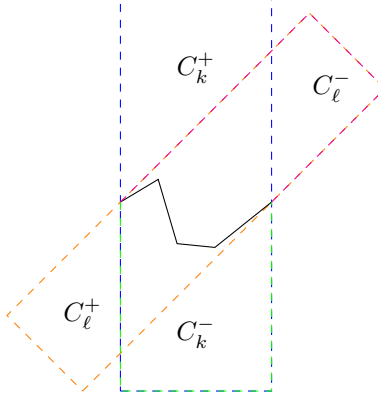


FIGURE 3. The set  $C_k^+ \cap C_l^+$  is empty:  $V_0$  is the graph drawn with solid line.

all appearing domains have a Lipschitz boundary. As there is no chance of confusion, we drop the index  $k$  and write  $\sigma$  for the surface measure on any of the  $\Gamma_k$ .

Below, we make use of the following observation.

**Lemma 3.1.** *If  $k, \ell, m$  are distinct numbers between 0 and  $N$ , then the  $(d - 1)$ -dimensional Hausdorff measure of  $\Gamma_k \cap \Gamma_\ell \cap \Gamma_m$  is zero.*

*Proof.* Since any set of non-zero Hausdorff measure contains a non-empty open set, it suffices to show that if there is a non-empty open set  $V \subset \Gamma_{k,\ell}$ , then there is a non-empty subset  $V_0$  of  $V$  which is open (in the relative topology) in  $\Gamma_{k,\ell}$  and an open subset  $U$  of  $\mathbb{R}^d$  such that

$$(3.1) \quad V_0 \subset U, \quad U \setminus V_0 \subset \Omega_k \cup \Omega_\ell.$$

To prove this claim, pick a point in  $V$ . Choosing a suitable coordinate system, we may assume without loss of generality that there exists an open neighborhood  $V_0 \subset V$  of this point such that the following conditions hold (see Figure 3):

1. There are two cylinders  $C_i = B_i \times (a_i, b_i)$ ,  $i = k, \ell$ , where  $B_i$ 's are open balls in  $\mathbb{R}^{d-1}$  and  $(a_i, b_i)$ 's are open subintervals of  $\mathbb{R}$ , and
2. there is an isomorphism  $J$  of  $\mathbb{R}^d$  and Lipschitz continuous functions  $g_i : B_i \rightarrow \mathbb{R}$  such that defining  $\phi_i(w, t) = t - g_i(w)$  for  $(w, t) \in C_i$ , we have
  - a.  $\Omega_k \cap C_k = \{\phi_k < 0\}$ ,  $C_k \setminus \overline{\Omega_k} = \{\phi_k > 0\}$ , and  $V_0 = \{\phi_k = 0\}$ ,
  - b.  $\Omega_\ell \cap C_\ell = J\{\phi_\ell < 0\}$ ,  $C_\ell \setminus \overline{\Omega_\ell} = J\{\phi_\ell > 0\}$ , and  $V_0 = J\{\phi_\ell = 0\}$ .

We note that continuity of  $g_i$ s implies continuity of  $\phi_i$ s as functions of two variables.

We claim that the neighborhood we look for is  $U = C_k \cap C_\ell$ . Since  $V_0 \subset C_k$  and  $V_0 \subset C_\ell$ , we clearly have  $V_0 \subset U$ . Let us show that  $U \setminus V_0 \subset \Omega_k \cup \Omega_\ell$ . To this end, we first simplify our notations by putting

$$\begin{aligned} C_k^+ &= \{\phi_k > 0\}, & C_k^- &= \{\phi_k < 0\}, \\ C_\ell^+ &= J\{\phi_\ell > 0\}, & C_\ell^- &= J\{\phi_\ell < 0\}, \end{aligned}$$

and then write  $U \setminus V_0 = (C_k^- \cup C_k^+) \cap (C_\ell^- \cup C_\ell^+)$  as the union of

$$C_k^- \cap (C_\ell^- \cup C_\ell^+) \subset C_k^- \subset \Omega_k$$

and

$$C_k^+ \cap (C_\ell^- \cup C_\ell^+) = (C_k^+ \cap C_\ell^-) \cup (C_k^+ \cap C_\ell^+).$$

Since  $C_k^+ \cap C_\ell^- \subset C_\ell^- \subset \Omega_\ell$ , it suffices to show that  $C_k^+ \cap C_\ell^+$  is empty (see again Figure 3).

Suppose that, contrary to our claim, there is  $(w_0, t_0) \in C_k$  that belongs to  $C_k^+ \cap C_\ell^+$ . Then, there is  $\varepsilon > 0$  such that  $(w, t_0) \in C_k^+ \cap C_\ell^+$  for all  $w \in B(w_0, \varepsilon)$ ,



where  $B(w_0, \varepsilon)$  denotes the ball in  $\mathbb{R}^{d-1}$  of radius  $\varepsilon$  centered at  $w_0$ . Fix such a  $w$ , and let  $I \subset C_k$  be the closed line segment with ends  $z_1 = (w, g_k(w))$  and  $z_2 = (w, t_0)$ . Then  $\tilde{I} := J^{-1}I$  is also a line segment (since  $J$  is an isometry) and it is contained in  $C_\ell$  (since  $C_\ell$  is a convex set containing  $J^{-1}(z_1)$  and  $J^{-1}(z_2)$ ). Moreover, we have  $\phi_\ell \circ J^{-1}(z_1) = 0$  and  $\phi_\ell \circ J^{-1}(z_2) > 0$ .

We note that,  $\phi_\ell$  is positive on  $\tilde{I} \setminus J\{z_1\}$ . Indeed, otherwise we would have  $\phi_\ell(z) = 0$  for some  $z$  in the interior of  $\tilde{I}$ . But this implies that  $J(z) \in I$  and, since  $JV_0 = V_0$ , also  $J(z) \in V_0$ . This is a contradiction to the fact that, by the definition of  $C_k$ , on  $I$  there is precisely one point, namely  $z_1$ , of  $V_0$ . Therefore,  $I$  does not contain points of  $\Omega_\ell$ . On the other hand, by the definition of  $C_k$ , the open line segment joining  $z_0 = (w, a_k)$  and  $z_1$  is contained in  $\Omega_k$  and thus cannot contain points of  $\Omega_\ell$ , either.

Altogether we have showed that the cylinder

$$C = B(w_0, \varepsilon) \times (a_k, t_0)$$

has empty intersection with  $\Omega_\ell$ . But  $C$  contains  $V_0$ . This clearly contradicts the fact that  $V_0$  is a part of boundary of  $\Gamma_\ell$ , and hence our assumption that  $C_k^+ \cap C_\ell^+$  is non-empty was false.  $\square$

We note that the argument presented above does not require the boundary to be Lipschitz: it suffices to assume that the boundary is continuous.

### 3.2. Diffusion and permeability of membranes. Let

$$\mathcal{N} = \{1, \dots, N\} \quad \text{and} \quad \mathcal{N}_0 = \{0, 1, \dots, N\}.$$

It is our aim to study diffusion on  $\Omega_0$  with the sets  $\Gamma_k$  (for  $k \in \mathcal{N}$ ) modeling semi-permeable membranes (see below). As far as our diffusion coefficients  $A = (a_{ij}) \in L^\infty(\Omega_0; \mathbb{R}^{d \times d})$  are concerned, we make the following assumptions.

- (i) They are symmetric, i.e.  $a_{ij} = a_{ji}$  for  $i, j = 1, \dots, d$ .
- (ii) They are uniformly elliptic, i.e. there exists a constant  $\gamma > 0$  such that for any vector  $\xi \in \mathbb{C}^d$  we have

$$\sum_{i,j=1}^d a_{ij}(x) \xi_i \bar{\xi}_j \geq \gamma \|\xi\|^2 = \gamma \sum_{j=1}^d |\xi_j|^2$$

for almost every  $x \in \Omega_0$ .

The differential operator we are interested in is formally given by

$$(3.2) \quad \mathcal{L}u = \sum_{i,j=1}^d \partial_i (a_{ij} \partial_j u) - cu = \operatorname{div}(A \nabla u) - cu,$$

where  $c \in L^\infty(\Omega_0)$  is a given non-negative function playing the role of a potential. To define a suitable realization of  $\mathcal{L}$  in  $L^2(\Omega_0)$  we use form methods. The related form is defined on the space  $\mathfrak{H} \subset L^2(\Omega_0)$ :

$$\mathfrak{H} := \{u \in L^2(\Omega_0) : u|_{\Omega_k} \in H^1(\Omega_k) \forall k = 1, \dots, N\}.$$

Obviously,  $\mathfrak{H}$  is a Hilbert space with respect to the inner product

$$\langle u, v \rangle_{\mathfrak{H}} := \int_{\Omega_0} u \bar{v} \, d\lambda + \sum_{k=1}^N \int_{\Omega_k} \nabla u \cdot \bar{\nabla} v \, d\lambda,$$

where  $\lambda$  denotes the  $d$ -dimensional Lebesgue measure, and  $\bar{z}$  is the conjugate of a complex number  $z$ .

For  $u \in \mathfrak{H}$  the function  $u|_{\Omega_k}$  has a trace in  $L^2(\Gamma_k)$  as  $\Omega_k$  has a Lipschitz boundary. We denote the trace of  $u|_{\Omega_k}$  by  $u|_k$ . Note that we can have  $u|_k \neq u|_\ell$  on  $\Gamma_{k,\ell}$ . Thus, we should interpret  $u|_k$  as ‘the values of  $u$  on the boundary  $\Gamma_{k,\ell}$  when approached

from within  $\Omega_k$ ', whereas  $u|_\ell$  are 'the values on the boundary when approached from within  $\Omega_\ell$ '.

We imagine that a diffusing particle in any subdomain  $\Omega_k$  may permeate through a semi-permeable membrane, i.e. through the boundary  $\Gamma_{k,\ell}$  separating this subdomain from the neighboring subdomain  $\Omega_\ell$ . The membrane's permeability may change along the boundary. In particular, the permeability may vary from  $\Gamma_{k,\ell}$  to  $\Gamma_{k,\ell'}$ . This is modeled by permeability functions  $\tau_k$  defined on  $\Gamma_k$ ; we assume  $\tau_k \in L^\infty(\Gamma_k; \mathbb{R})$  with  $\tau_k \geq 0$  almost everywhere. The value of  $\tau_k$  at a point  $x$  of the boundary should be thought of as the permeability coefficient of the membrane at this point, whose interpretation in probabilistic terms may be found in [14, 19, 47]. Roughly speaking, the larger  $\tau_k(x)$ , the less time it takes on average to permeate through the membrane at  $x$ , when approaching from within  $\Omega_k$  (see also the discussion after (3.3)). Note that by Lemma 3.1, up to a set of measure zero, there is only one adjacent set  $\Omega_\ell$  to which the particle may permeate.

Moreover, we are given measurable functions  $b_{k,\ell} : \Gamma_{k,\ell} \rightarrow [0, 1]$  for  $1 \leq k, \ell \leq N$ . The quantity  $b_{k,\ell}(x)$  describes the possibility that a particle right after filtering from  $\Omega_k$  through the membrane  $\Gamma_{k,\ell}$  at a point  $x$ , instead of starting diffusion in  $\Omega_\ell$ , will be immediately killed and removed from the state-space. For  $b_{k,\ell}(x) = 1$  all particles survive filtering through the membrane at this point, for  $b_{k,\ell}(x) = 0$  none of them does.

To formulate our transmission conditions, we need to define the conormal derivative associated with  $\mathcal{L}$  on the domain  $\Omega_k$ . We do this in a variational sense.

**Definition 3.2.** Let  $u \in \mathfrak{H}$  be such that  $\operatorname{div}(A\nabla u)|_{\Omega_k} \in L^2(\Omega_k)$ . Then there exists a unique function  $N_k(u) \in L^2(\Gamma_k, \sigma)$  such that

$$\int_{\Omega_k} \operatorname{div}(A\nabla u) \bar{v} \, d\lambda + \int_{\Omega_k} (A\nabla u) \cdot \overline{\nabla v} \, d\lambda = \int_{\Gamma_k} N_k(u) \bar{v}|_k \, d\sigma$$

for all  $v \in H^1(\Omega_k)$ . We call  $N_k(u)$  the *conormal derivative of  $u$  on  $\Omega_k$* .

To see that such a function  $N_k(u)$  exists, let  $\Phi : L^2(\Gamma_k) \rightarrow H^1(\Omega_k)$  be a continuous linear mapping such that  $\Phi(g)|_k = g$ . We can for example pick  $\Phi(g)$  as the unique solution of the Dirichlet problem

$$\begin{cases} \operatorname{div}(A\nabla u) &= 0 \\ u|_{\partial\Omega_k} &= g. \end{cases}$$

If  $u \in H^1(\Omega_k)$  is such that  $\operatorname{div}(A\nabla u) \in L^2(\Omega_k)$  we can consider the map  $\varphi_u : L^2(\Gamma_k) \rightarrow \mathbb{C}$  defined by

$$\varphi_u(g) := \int_{\Omega_k} \operatorname{div}(A\nabla u) \overline{\Phi(g)} \, d\lambda + \int_{\Omega_k} (A\nabla u) \overline{\nabla \Phi(g)} \, d\lambda.$$

Since  $\Phi$  is continuous  $\varphi_u$  is a continuous, antilinear functional on  $L^2(\Gamma_k)$ . Hence it follows from the theorem of Riesz–Fréchet that there exists a unique element  $N_k(u)$  such that

$$\varphi_u(v) = \int_{\Gamma_k} N_k(u) \bar{v} \, d\sigma.$$

In the situation where everything is smooth, it follows from the divergence theorem that

$$N_k(u) = \sum_{i,j=1}^d a_{ij} \partial_j u \nu_j$$

where  $\nu = (\nu_1, \dots, \nu_d)$  is the outer normal to  $\Omega_k$ .

Our transmission conditions are:

$$(3.3) \quad N_k(u) = -\tau_k(u|_k - b_{k,\ell} u|_\ell) \quad \text{on } \Gamma_{k,\ell} \quad \text{for all } k, \ell \in \mathcal{N}$$

(see also (3.6), further down). These conditions may be interpreted as follows: a particle diffusing in a region  $\Omega_k$  ‘bounces’ from the membrane separating it from  $\Omega_\ell$ , similarly to the reflected Brownian motion, but the time it spends ‘at the membrane’ is measured, and after an exponential time with respect to this reference measure elapses, the particle filters through to  $\Omega_\ell$ . The larger the  $\tau_k$  at an infinitely small part of the membrane the larger the parameter in the exponential time, and the shorter the time it takes to filter through that part of the membrane. Additionally, as described above, functions  $b_{k,\ell}$  describe the possibility that a particle will be killed after filtering through the membrane  $\Gamma_{k,\ell}$ .

For each  $k \in \mathcal{N}$ , on the part  $\Gamma_{k,0}$  of the outer boundary  $\Gamma_0$ , we impose the Robin boundary conditions

$$(3.4) \quad N_k(u) = -\tau_k u|_k,$$

and note that this reduces to (3.3) for  $\ell = 0$  when agreeing

$$b_{k,0} = 0,$$

i.e. that all particles filtering from  $\Omega_0$  to its complement are immediately killed, and removed from the state-space.

**3.3. The related quadratic form.** Let us assume that  $u \in \mathfrak{H}$  is such that  $\operatorname{div}(A\nabla u) \in L^2(\Omega_0)$  and such that the transmission conditions (3.3) and the boundary condition (3.4) are satisfied. Then for a function  $v \in \mathfrak{H}$  we have

$$\begin{aligned} - \int_{\Omega_0} \operatorname{div}(A\nabla u) \bar{v} \, d\lambda &= - \sum_{k \in \mathcal{N}} \int_{\Omega_k} \operatorname{div}(A\nabla u) \bar{v} \, d\lambda \\ &= \sum_{k \in \mathcal{N}} \left( \int_{\Omega_k} (A\nabla u) \cdot \bar{\nabla} v \, d\lambda - \int_{\Gamma_k} N_k(u) \bar{v}|_k \, d\sigma \right) \\ &= \int_{\Omega_0} (A\nabla u) \cdot \bar{\nabla} v \, d\lambda + \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} \int_{\Gamma_{k,\ell}} \tau_k (u|_k - b_{k,\ell} u|_\ell) \bar{v}|_k \, d\sigma. \end{aligned}$$

Here the first equality uses the fact that the  $d$ -dimensional Lebesgue measure of the set  $\Omega_0 \setminus \bigcup_{k=1}^N \Omega_k$  is zero, the second equality is the definition of the conormal derivative (or the divergence theorem in the smooth case), the third one follows from Lemma 3.1, the transmission conditions (3.3) and the boundary condition (3.4).

This calculation leads us to define the following forms on the Hilbert space  $L^2(\Omega_0)$ .

**Definition 3.3.** For a parameter  $\kappa \geq 0$ , we define the form  $\mathfrak{a}_\kappa$  by setting

$$\mathfrak{a}_\kappa[u, v] := \int_{\Omega_0} \kappa (A\nabla u) \cdot \bar{\nabla} v + cu \bar{v} \, d\lambda,$$

and the form  $\mathfrak{q}$  by

$$\mathfrak{q}[u, v] := \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} \int_{\Gamma_{k,\ell}} \tau_k (u|_k - b_{k,\ell} u|_\ell) \bar{v}|_k \, d\sigma$$

for  $u, v$  in the common domain  $D(\mathfrak{q}) = D(\mathfrak{a}) := \mathfrak{H}$ . We put  $\mathfrak{h}_\kappa := \mathfrak{a}_\kappa + \mathfrak{q}$ . The adjoint  $\mathfrak{q}^*$  of  $\mathfrak{q}$  is given by

$$(3.5) \quad \mathfrak{q}^*[u, v] = \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} \int_{\Gamma_{k,\ell}} \tau_k u|_k (\bar{v}|_k - b_{k,\ell} \bar{v}|_\ell) \, d\sigma.$$

Since  $\mathfrak{a}$  is symmetric we have  $\mathfrak{h}_\kappa^* = \mathfrak{a}_\kappa + \mathfrak{q}^*$ .

*Remark 3.4.* Rearranging the terms in (3.5), we see that

$$\mathfrak{q}^*[u, v] = \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} \int_{\Gamma_{k,\ell}} (\tau_k u|_k - \tau_\ell b_{k,\ell} u|_\ell) \bar{v}|_k \, d\sigma.$$

Repeating the computations from the beginning of this subsection, we conclude that functions in the domain of the adjoint operator satisfy the following transmission conditions:

$$(3.6) \quad N_k(u) = -(\tau_k u|_k - \tau_\ell b_{k,\ell} u|_\ell) \quad \text{on } \Gamma_{k,\ell} \quad \text{for all } k, \ell \in \mathcal{N}.$$

It should be noted, however, that in a sense both forms describe the same dynamics. More specifically, if  $S_2$  is the semigroup to be introduced in the next section, and ‘generated’ by  $\mathfrak{h}_\kappa^*$ , and if a non-negative  $u \in L^2(\Omega)$  is the initial distribution of the underlying stochastic process  $(X_t)_{t \geq 0}$  in  $\Omega_0$ , then  $S_2(t)u$  is the distribution of this process at time  $t \geq 0$ . On the other hand, the semigroup  $T_2$  of the next section, ‘generated’ by  $\mathfrak{h}_\kappa$ , speaks of the dynamics of expected values: for  $u \in L^2(\Omega_0)$ ,  $T_2(t)u(x)$  is the expected value of  $u(X_t)$  conditional on  $X_0 = x, x \in \Omega_0$ .

As we shall see in examples of Section 6, both (3.3) and (3.6) are used in practice, depending on what is the quantity modeled.

#### 4. GENERATION RESULTS

In this section, we prove that for  $\kappa \geq 1$  the operator associated with  $\mathfrak{h}_\kappa$  generates a strongly continuous, analytic and contractive semigroup on  $L^2(\Omega_0)$ . Afterwards, we extend these semigroups to the  $L^p$ -range. To simplify notation, we write  $\mathfrak{h} = \mathfrak{h}_1$  and  $\mathfrak{a} = \mathfrak{a}_1$  and prove the main results for this form. Note, however, that they also apply to  $\mathfrak{h}_\kappa$  for  $\kappa \geq 1$ , as is seen by changing the diffusion coefficients matrix  $A$ . The following proposition is the key step towards a generation result on  $L^2(\Omega_0)$ .

**Proposition 4.1.** *The forms  $\mathfrak{h}$  and  $\mathfrak{h}^*$  are closed, accretive and sectorial.*

*Proof.* Since  $A$  is symmetric and  $c$  is real valued with  $c \geq 0$ , the form  $\mathfrak{a}$  is symmetric and obviously we have  $\mathfrak{a}[u] \geq 0$  for all  $u \in \mathfrak{H}$ . Let  $M := \sup_{x \in \Omega_0} \|A(x)\| < \infty$ . We then have

$$\gamma |\nabla u|^2 \leq \langle A \nabla u, \nabla u \rangle \leq |A \nabla u| |\nabla u| \leq M |\nabla u|^2$$

almost everywhere. Integrating this inequality over  $\Omega_0$  and adding a suitable multiple of  $\|u\|_{L^2(\Omega_0)}^2$  we see that

$$\min\{1, \gamma\} \|u\|_{\mathfrak{H}}^2 \leq \mathfrak{a}[u] + \|u\|_{L^2(\Omega_0)}^2 \leq \max\{1 + \|c\|_{L^\infty(\Omega_0)}, M\} \|u\|_{\mathfrak{H}}^2.$$

Thus, the inner product  $\langle u, v \rangle_{\mathfrak{a}} := \mathfrak{a}[u, v] + \langle u, v \rangle_{L^2(\Omega)}$  is equivalent to the canonical inner product in  $\mathfrak{H}$ , i.e., the related norms are equivalent. This yields the closedness of  $\mathfrak{a}$ .

To prove that  $\mathfrak{h}$  is closed and sectorial we show that  $\mathfrak{q}$  is  $\mathfrak{a}$ -bounded with  $\mathfrak{a}$ -bound 0, i.e. for every  $\varepsilon > 0$  there exists a constant  $C(\varepsilon)$  such that

$$|\mathfrak{q}[u]| \leq \varepsilon \mathfrak{a}[u] + C(\varepsilon) \|u\|_{L^2(\Omega)}.$$

For the proof, let a sequence  $u_n$  be given with  $u_n \rightarrow 0$  in  $\mathfrak{H}$ . It follows from the compactness of the trace operator (which is a consequence of the Lipschitz nature of the boundary, see [53, Theorem 2.6.2]) that we have  $u_n|_k \rightarrow 0$  in  $L^2(\Gamma_k, \sigma)$  for  $k = 0, \dots, N$ . As the functions  $\tau_0, \dots, \tau_n$  and  $b_{k,\ell}$  ( $1 \leq k, \ell \leq N$ ) are bounded, it follows from the Cauchy-Schwarz inequality that  $\mathfrak{q}[u_n] \rightarrow 0$ . Since  $\mathfrak{q}$  is bounded on  $D(\mathfrak{a})$  (a consequence of the boundedness of the trace operator) it now follows from [24, Lemma 7.4] that  $\mathfrak{q}$  is  $\mathfrak{a}$ -bounded with  $\mathfrak{a}$ -bound 0.

A perturbation result for sectorial forms [41, Theorem VI.1.33] yields that  $\mathfrak{h}$  is a closed and sectorial form; moreover, the associated inner product is equivalent to that associated to  $\mathfrak{a}$  and thus it is equivalent to the canonical inner product in

$\mathfrak{H}$ , proving that  $\mathfrak{h}$  is closed. Finally, as the  $\mathfrak{a}$ -bound of  $\mathfrak{q}$  is 0, it follows that  $\mathfrak{h}$  is accretive as well.

With the same reasoning we can show that  $\mathfrak{h}^*$  is closed, sectorial and accretive.  $\square$

We denote by  $\mathcal{L}_2$  the associated operator of  $\mathfrak{h}$  in  $L^2(\Omega_0)$ . From Theorem 2.1 we obtain the following result.

**Corollary 4.2.** *The operator  $\mathcal{L}_2$  generates a strongly continuous, holomorphic and contractive semigroup  $T_2 = (T_2(t))_{t \geq 0}$  on  $L^2(\Omega)$ . The operator  $\mathcal{L}_2^*$  generates a strongly continuous, holomorphic and contractive semigroup  $S_2 = (S_2(t))_{t \geq 0}$  on  $L^2(\Omega_0)$ . We have  $S_2 = T_2^*$ .*

Next we establish additional properties of the semigroups  $T_2$  and  $S_2$ .

**Proposition 4.3.** *The semigroup  $T_2$  has the following properties.*

- (a)  $T_2$  is real, i.e. if  $u \in L^2(\Omega_0)$  is real-valued then so is  $T_2(t)u$  for all  $t \geq 0$ ;
- (b)  $T_2$  is positive, i.e. if  $u \geq 0$  almost everywhere then  $T_2(t)u \geq 0$  almost everywhere for all  $t \geq 0$ ;
- (c)  $T_2$  is  $L^\infty$ -contractive, i.e. if  $u \in L^\infty(\Omega_0)$  then for every  $t \geq 0$  we have  $T_2(t)u \in L^\infty(\Omega_0)$  and  $\|T_2 u\|_\infty \leq \|u\|_\infty$ .

The semigroup  $S_2$  is also real, positive and  $L^\infty$ -contractive.

*Proof.* The proof of all three parts is based on Ouhabaz' criterion [55, Theorem 2.2] and its corollaries. We do the necessary calculations for the form  $\mathfrak{h}$ . Similar calculations for  $\mathfrak{h}^*$  yield the corresponding properties for the semigroup  $S_2$ .

(a) Obviously, if  $u \in D(\mathfrak{h}) = \mathfrak{H}$  then also  $\operatorname{Re} u, \operatorname{Im} u \in D(\mathfrak{h})$ . As all the coefficients in  $A, c, \tau_0, \dots, \tau_n$  and  $b_{k,\ell}$  ( $1 \leq k, \ell \leq N$ ) are real-valued,  $\mathfrak{h}[\operatorname{Re} u, \operatorname{Im} u] \in \mathbb{R}$  for all  $u \in D(\mathfrak{h})$ . Now part (a) follows from [55, Proposition 2.5].

(b) Since  $\mathfrak{H}$  is a lattice with respect to the usual ordering, it follows that if  $u \in D(\mathfrak{h})$  is real-valued then also  $u^+ \in D(\mathfrak{h})$  and  $u^+ u^- = 0$  almost everywhere. Moreover, by Stampaccia's Lemma [39, Lemma 7.6] we have  $\partial_j u^+ = (\partial_j u) \mathbb{1}_{\{u > 0\}}$  so that, in particular, we have  $(A \nabla u^+) \cdot \overline{\nabla u^-} = 0$  almost everywhere. Note that we have  $(u|_k)^+ = (u^+)|_k$  for any  $k = 0, \dots, N$ , i.e. the trace of the positive part of  $u$  is the positive part of the trace of  $u$ . From this it follows that  $u|_k^+ u|_k^- = 0$  almost everywhere for  $k = 0, \dots, N$ . Using this we see that for a real-valued  $u \in D(\mathfrak{h})$  we have

$$\mathfrak{h}[u^+, u^-] = - \sum_{k, \ell \in \mathcal{N}} \int_{\Gamma_{k, \ell}} \tau_k b_{k, \ell} u|_\ell^+ u|_k^- \, d\sigma \leq 0$$

as  $\tau_k b_{k, \ell} \geq 0$  almost surely. It now follows from [55, Theorem 2.6] that  $T_2$  is positive.

(c) In view of [55, Theorem 2.13] for this part we have to show that if  $u \in D(\mathfrak{h})$  then we also have that  $(1 \wedge |u|) \operatorname{sgn} u \in D(\mathfrak{h})$  and that

$$(4.1) \quad \operatorname{Re} \mathfrak{h}[(1 \wedge |u|) \operatorname{sgn} u, (|u| - 1)^+ \operatorname{sgn} u] \geq 0.$$

Here we have  $\operatorname{sgn} z := \frac{z}{|z|}$  for a complex  $z \neq 0$  and  $\operatorname{sgn} 0 := 0$ . The condition that  $(1 \wedge |u|) \operatorname{sgn} u \in D(\mathfrak{h})$  follows from standard properties of  $H^1(\mathfrak{h})$ -functions, see e.g. the proof of [55, Theorem 4.6]. As in the proof of that result, we see that

$$\operatorname{Re} \mathfrak{a}[(1 \wedge |u|) \operatorname{sgn} u, (|u| - 1)^+ \operatorname{sgn} u] \geq 0.$$

Let us now take care of  $\mathfrak{q}$ . Writing

$$I_{k, \ell} := \int_{\Gamma_{k, \ell}} \tau_k ((1 \wedge |u|_k) \operatorname{sgn} u|_k - b_{k, \ell} (1 \wedge |u|_\ell) \operatorname{sgn} u|_\ell) (|u|_k - 1)^+ \overline{\operatorname{sgn} u|_k} \, d\sigma,$$

we have

$$\operatorname{Re} \mathfrak{q}[(1 \wedge |u|) \operatorname{sgn} u, (|u| - 1)^+ \operatorname{sgn} u] = \operatorname{Re} \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} I_{k,\ell}.$$

Since the integrand in  $I_{k,\ell}$  vanishes on the set  $\{|u|_k < 1\}$  we see that  $I_{k,\ell}$  equals

$$\begin{aligned} & \int_{\Gamma_{k,\ell} \cap \{|u|_k \geq 1\}} \tau_k [(1 \wedge |u|_k) \operatorname{sgn} u|_k - b_{k,\ell} (1 \wedge |u|_\ell) \operatorname{sgn} u|_\ell] (|u|_k - 1)^+ \overline{\operatorname{sgn} u|_k} \, d\sigma \\ &= \int_{\Gamma_{k,\ell} \cap \{|u|_k \geq 1\}} \tau_k [1 - b_{k,\ell} (1 \wedge |u|_\ell) \operatorname{sgn}(u|_\ell \overline{u|_k})] (|u|_k - 1)^+ \, d\sigma. \end{aligned}$$

Since  $\operatorname{Re} \operatorname{sgn}(u|_\ell \overline{u|_k}) \in [-1, 1]$  and  $0 \leq b_{k,\ell} \leq 1$ , it follows that  $\operatorname{Re} I_{k,\ell} \geq 0$  so that, altogether, we have proved (4.1). This finishes the proof.  $\square$

We now obtain:

**Corollary 4.4.** *There are consistent families  $T_p$  and  $S_p$  of contraction semigroups on  $L^p(\Omega_0)$  for  $1 \leq p \leq \infty$ . For  $1 \leq p < \infty$  these semigroups are strongly continuous whereas  $T_\infty$  and  $S_\infty$  are merely weak\*-continuous. Moreover, we have  $T_p^* = S_q$  where  $\frac{1}{p} + \frac{1}{q} = 1$  with the convention that  $\frac{1}{\infty} = 0$ .*

*Proof.* As we have seen,  $T_2$  is a contraction semigroup and it follows from Proposition 4.3 (c) that it restricts to a contraction semigroup  $T_\infty$  on  $L^\infty(\Omega_0)$ . As a consequence of the Riesz–Thorin interpolation theorem (see e.g. [35, Theorem 6.27]),  $T_2$  restricts to a contraction semigroup  $T_p$  on every  $L^p(\Omega_0)$  for  $2 < p < \infty$ .

Let us prove that  $T_\infty$  is weak\*-continuous. To that end, let  $u \in L^\infty(\Omega_0)$  and  $t_n \rightarrow 0+$ . Since  $T_2$  is strongly continuous we have  $T_2(t_n)u \rightarrow u$  in  $L^2(\Omega_0)$ . Passing to a subsequence, we may (and shall) assume that  $T_2(t_n)u \rightarrow u$  pointwise almost everywhere. Since the sequence  $(T_2(t_n)u)_{n \geq 1}$  is bounded in the  $\|\cdot\|_\infty$ -norm it follows from the dominated convergence theorem that

$$\int_{\Omega_0} (T_2(t_n)u) \bar{v} \, d\lambda \rightarrow \int_{\Omega_0} u \bar{v} \, d\lambda$$

for every  $v \in L^1(\Omega_0)$ . This proves that  $T_\infty(t_n)u = T_2(t_n)u$  converges in the weak\*-topology to  $u$ , so that  $T_\infty$  is weak\*-continuous. We note that  $T_\infty$  is never strongly continuous. Indeed, a general result due to Lotz [48] shows that every strongly continuous semigroup on  $L^\infty(\Omega_0)$  is automatically uniformly continuous and thus has a bounded generator. In our situation this would yield  $L^\infty(\Omega_0) \subset \mathfrak{H}$  which is absurd.

We now turn to continuity of the semigroups  $T_p$  for  $2 < p < \infty$ . Let  $q$  be the conjugate of  $p$ . Since  $L^q(\Omega_0) \subset L^1(\Omega_0)$ , and  $T_p u = T_\infty u$  for  $u \in L^p(\Omega_0) \cap L^\infty(\Omega_0)$  it follows from the above that  $T_p(t)u \rightarrow u$ , as  $t \rightarrow 0+$ , weakly in  $L^p(\Omega_0)$  for all  $u \in L^p(\Omega_0) \cap L^\infty(\Omega_0)$ . As is well known a weakly continuous semigroup is strongly continuous, see [28, Theorem I.5.8]. Actually, to use that theorem, we would need to prove that  $t \mapsto T_p(t)u$  is weakly continuous for every  $u \in L^p(\Omega)$ . However, inspection of the proof shows that for a bounded semigroup it actually suffices to prove weak continuity of the orbits for  $u$  in a dense subset. This shows that  $T_p$  is strongly continuous.

The same argument yields consistent semigroups  $S_p$  for  $2 \leq p \leq \infty$  where  $S_p$  is strongly continuous and  $S_\infty$  is weak\*-continuous.

We next prove that  $T_\infty$  is an adjoint semigroup. To that end, let  $u \in L^2(\Omega_0)$  and  $v \in L^\infty(\Omega_0)$ . Since  $S_2^* = T_2$  we find

$$\left| \int_{\Omega_0} (S_2(t)u) \bar{v} \, d\lambda \right| = \left| \int_{\Omega_0} u \overline{T_2(t)v} \, d\lambda \right| \leq \|u\|_1 \|T_2(t)v\|_\infty \leq \|u\|_1 \|v\|_\infty.$$

Taking the supremum over  $v \in L^\infty(\Omega_0)$  with  $\|v\|_\infty \leq 1$ , we see that  $S_2(t)u \in L^1(\Omega_0)$  and  $\|S_2(t)u\|_1 \leq 1$ . Thus,  $S_2(t)$  can be extended to a contraction  $S_1(t)$  on  $L^1(\Omega_0)$ . Clearly,  $[S_1(t)]^* = T_\infty(t)$  which proves that  $T_\infty$  consists of adjoint operators. It follows from the weak\*-continuity of  $T_\infty$  that the orbits of  $S_1$  are weakly continuous hence, by [28, Theorem I.5.8],  $S_1$  is a strongly continuous semigroup. Similarly,  $T_2$  extends to a strongly continuous contraction semigroup  $T_1$  on  $L^1(\Omega_0)$  with  $T_1^* = S_\infty$ .

Finally, in an analogous way we get  $S_p = T_q^*$  and  $T_p = S_q^*$  for  $1 < p < 2$  where  $q \in (2, \infty)$  is such that  $\frac{1}{p} + \frac{1}{q} = 1$ . It follows that all semigroups  $T_p$  (and  $S_p$ ),  $p \in (1, \infty)$  are weakly continuous, and hence also strongly continuous.  $\square$

## 5. CONVERGENCE RESULTS FOR FAST DIFFUSION

**5.1. Convergence in  $L^2$ .** In this section, we ‘speed up diffusion’ by considering the forms  $\mathfrak{h}_\kappa$  with index  $\kappa \geq 1$  again. Formally, this corresponds to replacing the diffusion matrix  $A$  with  $\kappa A$ . Applying the results of the previous section to  $\mathfrak{h}_\kappa$  and  $\mathfrak{h}_\kappa^*$ , we obtain consistent semigroups  $T_{p,\kappa}$  and  $S_{p,\kappa}$  for  $1 \leq p \leq \infty$ ; by  $\mathcal{L}_{p,\kappa}$  and  $\mathcal{L}_{p,\kappa}^*$  we denote their generators so that

$$e^{\mathcal{L}_{p,\kappa}t} = T_{p,\kappa}(t) \quad \text{and} \quad e^{\mathcal{L}_{p,\kappa}^*t} = S_{p,\kappa}(t).$$

We are interested in convergence of these semigroups as  $\kappa \rightarrow \infty$ .

Note that in changing the diffusion matrix  $A$  we are also changing the co-normal derivative which appears in our transmission conditions. Thus, such a change results in speeding up the diffusion while keeping the flux through the boundary constant. With the help of Theorem 2.2 we prove the following result. Note that the space  $H_0$  appearing in the following theorem is closed in  $L^2(\Omega_0)$ , so that  $H_0$  coincides with the closure of the form domain, considered in Section 2.

**Theorem 5.1.** *As  $\kappa \rightarrow \infty$  the form  $\mathfrak{h}_\kappa$  converges in the strong resolvent sense to the restriction of  $\mathfrak{a}_0 + \mathfrak{q}$  to the domain*

$$H_0 = \{u \in L^2(\Omega_0) : u|_{\Omega_k} \text{ is constant for } k = 1, \dots, N\}.$$

*Similarly,  $\mathfrak{h}_\kappa^*$  converges in the strong resolvent sense to  $\mathfrak{a}_0 + \mathfrak{q}^*$ . Moreover, we have strong convergence*

$$T_{2,\kappa}(t)u \rightarrow e^{-t(\mathfrak{a}_0 + \mathfrak{q})}u \quad \text{and} \quad S_{2,\kappa}(t)u \rightarrow e^{-t(\mathfrak{a}_0 + \mathfrak{q}^*)}u, \quad t > 0,$$

*in  $L^2(\Omega_0)$  as  $\kappa \rightarrow \infty$ .*

*Proof.* We have  $\text{Re } \mathfrak{h}_\kappa[u] = \mathfrak{a}_\kappa[u] + \text{Re } \mathfrak{q}[u]$  which is clearly increasing in  $\kappa$ . On the other hand,  $\text{Im } \mathfrak{h}_\kappa[u] = \text{Im } \mathfrak{q}[u]$  since  $\mathfrak{a}$  is symmetric. Thus  $\text{Im } \mathfrak{h}_\kappa[u]$  is independent of  $\kappa$  whence both conditions (b)(i) and (b)(ii) in Theorem 2.2 are satisfied. Next, since  $\mathfrak{h}_1$  is sectorial we find a constant  $C > 0$  such that

$$|\text{Im } \mathfrak{q}[u]| \leq C(\mathfrak{a}[u] + \text{Re } \mathfrak{q}[u]) \leq C(\kappa \mathfrak{a}[u] + \text{Re } \mathfrak{q}[u]) = C \text{Re } \mathfrak{h}_\kappa[u].$$

This shows that the forms  $\mathfrak{h}_\kappa$ ,  $\kappa \geq 1$  are indeed uniformly sectorial so that all assumptions of Theorem 2.2 are satisfied, implying the strong resolvent convergence of the forms and strong convergence of the semigroups.

Let us check that the limiting form is as claimed. Obviously,  $\sup_\kappa \text{Re } \mathfrak{h}_\kappa[u] < \infty$  if and only if

$$(5.1) \quad \int_{\Omega_0} (A \nabla u) \cdot \overline{\nabla u} \, d\lambda = 0$$

and in this case  $\lim_{\kappa \rightarrow \infty} \mathfrak{h}_\kappa[u] = \mathfrak{a}_0[u] + \mathfrak{q}[u]$ . Since the matrix  $A$  is uniformly elliptic (as assumed throughout) Equation (5.1) implies that  $\nabla u = 0$  on  $\Omega_k$  for  $k = 1, \dots, N$ . As each  $\Omega_k$  was assumed to be connected,  $u$  is constant on each of these sets. Since, conversely,  $u \in H_0$  implies (5.1), we are done.  $\square$

*Remark 5.2.* We can actually ‘speed up’ diffusion in a much more general way and obtain the same convergence result. Indeed, let  $A_\kappa = (a_{ij}^{(\kappa)}) \in L^\infty(\Omega_0, \mathbb{R}^{d \times d})$  be such that

$$\gamma \|\xi\|^2 \leq \sum_{i,j=1}^d a_{ij}^{(\kappa)}(x) \xi_i \bar{\xi}_j \leq \sum_{i,j=1}^d a_{ij}^{(\kappa+1)}(x) \xi_i \bar{\xi}_j$$

for every  $\kappa \geq 1$ , every  $\xi \in \mathbb{C}^d$  and almost all  $x \in \Omega_0$  and such that

$$\sup_{\kappa} \sum_{i,j=1}^d a_{ij}^{(\kappa)}(x) \xi_i \bar{\xi}_j = \infty$$

for almost all  $x \in \Omega_0$  and all  $\xi \in \mathbb{C}^d \setminus \{0\}$ . If we define the form  $\mathfrak{a}_\kappa$  as in Definition 3.3 with  $\kappa A$  replaced with  $A_\kappa$ , then  $\mathfrak{a}_\kappa$  is an increasing sequence of symmetric forms and  $\sup \mathfrak{a}_\kappa[u] < \infty$  if and only if  $\mathfrak{a}[u] = 0$ , and the conclusion in Theorem 5.5 remains valid.

**5.2. Interpretation of the result.** In this section, we describe in more detail the limiting form and the limit semigroup, and provide a probabilistic interpretation of Theorem 5.5. As we have seen in Section 2, the limit semigroup basically operates on the space  $H_0$ , whereas everything in  $H_0^\perp$  is immediately mapped to 0. The orthogonal projection onto  $H_0$  is given by

$$(5.2) \quad P_{H_0} u := \sum_{k \in \mathcal{N}} \frac{1}{\lambda(\Omega_k)} \int_{\Omega_k} u \, d\lambda \cdot \mathbf{1}_{\Omega_k}, \quad u \in L^2(\Omega_0).$$

Let  $\mu$  be the measure on  $\mathcal{N}$  defined by

$$\mu(S) = \sum_{k \in S} \lambda(\Omega_k), \quad \text{for } S \subset \mathcal{N}.$$

We denote the associated  $L^p$  spaces by  $\ell_\mu^p := L^p(\mathcal{N}, 2^\mathcal{N}, \mu)$ . Clearly,  $\ell_\mu^p$  can be identified with  $\mathbb{C}^{\mathcal{N}}$  equipped with the norm

$$\|x\|_{\ell^p} := \left( \sum_{k \in \mathcal{N}} |x_k|^p \lambda(\Omega_k) \right)^{\frac{1}{p}} \quad \text{for } x = (x_1, \dots, x_N) \in \mathbb{C}^{\mathcal{N}}.$$

In particular,  $\ell_\mu^2$  is a Hilbert space with respect to the scalar product

$$\langle x, y \rangle_{\ell_\mu^2} = \sum_{k \in \mathcal{N}} x_k \bar{y}_k \lambda(\Omega_k).$$

We note that the norm  $\|\cdot\|_{\ell_\mu^p}$  is chosen in such a way that  $\ell_\mu^p$  is isometrically isomorphic to  $H_0$  viewed as a subspace of  $L^p(\Omega_0)$  via the isomorphism

$$\Phi : x \mapsto \sum_{k \in \mathcal{N}} x_k \mathbf{1}_{\Omega_k}.$$

Our goal is to identify the operator associated with the limiting form, or – more specifically – its isomorphic image in  $\ell_\mu^2$ . To this end, for  $k \in \mathcal{N}$ ,  $\ell \in \mathcal{N}_0$ ,  $\ell \neq k$ , let

$$\rho_{k,\ell} = \int_{\Gamma_{k,\ell}} \tau_k \, d\sigma.$$

For  $\ell \neq 0$  this is the total permeability of the membrane  $\Gamma_{k,\ell}$  separating  $\Omega_k$  from  $\Omega_\ell$  when approached from within  $\Omega_k$ . It may also be thought of as the average number of particles that filter through  $\Gamma_{k,\ell}$  in a unit of time. Next, for  $k \in \mathcal{N}$ ,

$$\varrho_{k,k} = - \sum_{\ell \in \mathcal{N}_0, \ell \neq k} \rho_{k,\ell}$$



is (minus) the average number of particles that filter from  $\Omega_k$  to an adjacent  $\Omega_\ell$  in a unit of time, i.e. the number of particles lost by  $\Omega_k$ . Finally, the quantity

$$\varrho_{k,\ell} = \int_{\Gamma_{k,\ell}} b_{k,\ell} \tau_k \, d\sigma \quad k, \ell \in \mathcal{N},$$

may be thought of as the average number of particles that after filtering from  $\Omega_k$  to  $\Omega_\ell$  in a unit of time survive to continue their chaotic movement in  $\Gamma_\ell$ , i.e. the number of particles gained by  $\Omega_\ell$  from  $\Omega_k$ . Finally, we define

$$(5.3) \quad q_{k,\ell} = \frac{\varrho_{k,\ell}}{\lambda(\Omega_k)}, \quad k, \ell \in \mathcal{N}$$

and let  $Q$  be the real  $n \times n$  matrix of the coefficients  $q_{k,\ell}$ ,  $k, \ell \in \mathcal{N}$ .

In the case where  $\tau_{k,0} = 0$  for all  $k \in \mathcal{N}$ , i.e. when we impose Neumann boundary conditions on the boundary of  $\Omega_0$  and, additionally,  $b_{k,\ell} = 1$  so that  $\varrho_{k,\ell} = \rho_{k,\ell}$  for all  $k, \ell \in \mathcal{N}$ , i.e. when no loss of particles is possible in the process of filtering through the inward membranes, the diagonal entries in  $Q$  are non positive, the off-diagonal entries are non negative and the row sums  $\sum_{\ell \in \mathcal{N}} q_{k,\ell}$  are zero for every  $k \in \mathcal{N}$ . This shows that  $Q$  is the intensity matrix of a continuous time (honest) Markov chain with  $N$  states. In general, however, a loss of probability mass is possible – this corresponds to the possibility for a particle to be killed after filtering through the inward or outward membrane in the approximating process. Hence, in general the chain described by  $Q$  is not honest.

**Proposition 5.3.** *The operator associated with  $\mathfrak{q}$  restricted to  $H_0$  is*

$$\Phi Q \Phi^{-1}.$$

*Proof.* Let  $u = \Phi(x), v = \Phi(y) \in H_0$ . Then

$$\begin{aligned} \mathfrak{q}[u, v] &= \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} \int_{\Gamma_{k,\ell}} \tau_k (x_k - b_{k,\ell} x_\ell) \bar{y}_k \, d\sigma \\ &= \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} x_k \bar{y}_k \int_{\Gamma_{k,\ell}} \tau_k \, d\sigma - \sum_{\substack{k \in \mathcal{N} \\ \ell \in \mathcal{N}_0}} x_\ell \bar{y}_k \int_{\Gamma_{k,\ell}} \tau_k b_{k,\ell} \, d\sigma \\ &= - \sum_{k \in \mathcal{N}} \varrho_{k,k} x_k \bar{y}_k - \sum_{\substack{k, \ell \in \mathcal{N} \\ k \neq \ell}} \varrho_{k,\ell} x_\ell \bar{y}_k \quad (\text{recall } b_{k,0} = 0 \text{ and } \Gamma_{k,k} = \emptyset) \\ &= - \sum_{k, \ell \in \mathcal{N}} q_{k,\ell} x_\ell \bar{y}_k \lambda(\Omega_k) = - \langle Qx, y \rangle_{\ell_\mu^2} \end{aligned}$$

where  $Qx$  is the matrix product. It follows that

$$\mathfrak{q}[u, v] = - \langle Q \Phi^{-1} u, \Phi^{-1} v \rangle_{\ell^2} = - \langle \Phi Q \Phi^{-1} u, v \rangle_{H_\tau},$$

where the last scalar product in  $H_\tau$  is that inherited from  $L^2(\Omega_0)$ . This completes the proof.  $\square$

Let  $C := \text{diag}(\Phi^{-1} P c)$ , where  $P$  is defined by (5.2). In other words,  $C$  is the diagonal matrix whose entries are the average values of  $c$  on the sets  $\Omega_k$  ( $1 \leq k \leq N$ ). A straightforward computation shows that the operator related to  $\mathfrak{a}_0$  restricted to  $H_0$  is  $-\Phi C \Phi^{-1}$ . Combining this with Proposition 5.3, we obtain the following corollary.

**Corollary 5.4.** *The operator associated with the limiting form is*

$$\Phi(Q - C)\Phi^{-1}.$$

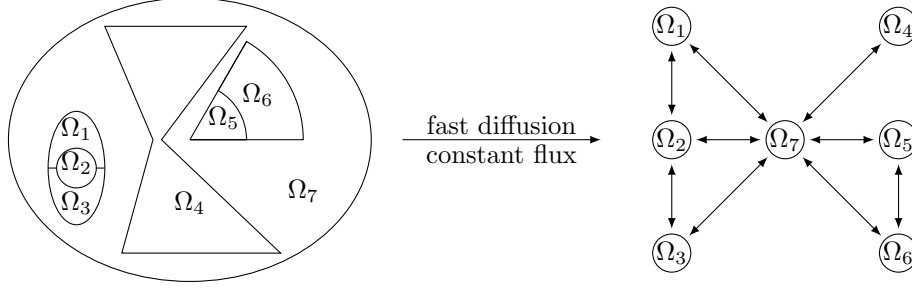


FIGURE 4. State-space collapse as fast diffusions on domains separated by semi-permeable domains converge to a Markov chain. Intensity of jump between aggregated states  $\Omega_k$  and  $\Omega_\ell$  is  $q_{k,\ell} = \frac{\varrho_{k,\ell}}{\lambda(\Omega_k)}$ .

From now on, we no longer distinguish between  $\ell_\mu^2$  and its isometric image  $H_0 = \Phi(\ell^2)$ . Thus, with slight abuse of notation, we will consider the (matrix) semigroups  $e^{t(Q-C)}$  and  $e^{t(Q-C)^*}$  as semigroups on the space  $H_0$ . With this convention, we can now reformulate Theorem 5.1 as follows (see (2.1) and (5.2)).

**Theorem 5.5.** *With the notation introduced above, we have for every  $u \in L^2(\Omega_0)$  and  $t > 0$*

$$\lim_{\kappa \rightarrow \infty} T_{2,\kappa}(t)u = e^{t(Q-C)}P_{H_0}u \quad \text{and}$$

$$\lim_{\kappa \rightarrow \infty} S_{2,\kappa}(t)u = e^{t(Q^*-C)}P_{H_0}u.$$

To summarize: in probabilistic terms discussed in this subsection, Theorem 5.5 with  $c = 0$  asserts that our diffusion processes converge to a continuous time Markov chain with state space  $\mathcal{N}$  which may be thought of as being composed of  $N$  aggregated states, each of them corresponding to one domain of diffusion (see Figure 4);  $c \neq 0$  plays the role of a potential term. As advertised in the introduction, the jump intensities in this chain (given by (5.3)) are in direct proportion to the total permeability of the membranes, and in inverse proportion to the sizes of the domains.

**5.3. Convergence in  $L^p$ .** The space  $H_0$  is contained in  $L^p(\Omega_0)$  for every  $1 \leq p \leq \infty$ . Moreover, the right hand side of (5.2) is well defined also for  $u$  in  $L^p(\Omega_0)$  and defines a projection on  $L^p(\Omega_0)$  with range  $H_0$ . By slight abuse of notation, we denote that projection still by  $P_{H_0}$ . Thus, we may view  $e^{t(Q-C)}P_{H_0}$  and  $e^{t(Q^*-C)}P_{H_0}$  as degenerate semigroups on  $L^p(\Omega)$ . The main result of this section (which, along with Theorem 5.5, is the main result of the paper as well) extends Theorem 5.5 to the setting of  $L^p$  spaces.

**Theorem 5.6.** *For  $1 \leq p < \infty$ ,  $t > 0$  and  $u \in L^p(\Omega_0)$  we have*

$$\lim_{\kappa \rightarrow \infty} T_{p,\kappa}(t)u = e^{t(Q-C)}P_{H_0}u \quad \text{and} \quad \lim_{\kappa \rightarrow \infty} S_{p,\kappa}(t)u = e^{t(Q^*-C)}P_{H_0}u$$

*in the  $L^p(\Omega)$  norm. Moreover, for  $u \in L^\infty(\Omega_0)$  we have*

$$\lim_{\kappa \rightarrow \infty} T_{\infty,\kappa}(t)u = e^{t(Q-C)}P_{H_0}u \quad \text{and} \quad \lim_{\kappa \rightarrow \infty} S_{\infty,\kappa}(t)u = e^{t(Q^*-C)}P_{H_0}u$$

*in the weak\* topology of  $L^\infty(\Omega_0)$ .*

*Proof.* Let  $u \in L^\infty(\Omega_0)$ . By the previous theorem,  $T_{2,\kappa}(t)u$  converges to  $e^{t(Q-C)}P_{H_0}u$  in the norm of  $L^2(\Omega_0)$ . Passing to a subsequence, we may and shall assume that we have almost sure convergence. Since the sequence  $T_{2,\kappa}(t)u$  is uniformly bounded (by

$\|u\|_\infty$ ) it follows from the dominated convergence theorem that  $T_{2,\kappa}(t)u$  converges to  $e^{t(Q-C)}P_{H_0}u$  weak\* in  $L^\infty(\Omega_0)$ . Another consequence of the dominated convergence theorem is that  $T_{2,\kappa}(t)u = T_{p,\kappa}(t)u \rightarrow e^{t(Q-C)}P_{H_0}u$  in  $L^p(\Omega_0)$  for every  $1 \leq p < \infty$ . Since  $L^\infty(\Omega_0)$  is dense in  $L^p(\Omega_0)$  for  $1 \leq p < \infty$  and since the operators  $T_{p,\kappa}(t)$ ,  $\kappa > 0$  are uniformly bounded, a  $3\varepsilon$  argument yields that  $T_{p,\kappa}(t)u \rightarrow e^{t(Q-C)}P_{H_0}f$  in  $L^p(\Omega_0)$  for every  $u \in L^p(\Omega_0)$ . The corresponding statements for  $S_{p,\kappa}$  are obtained similarly.  $\square$

*Remark 5.7.* We stress again that the limit dynamics in Theorem 5.6 is that in  $\ell_\mu^p$ , which is a natural choice for the semigroups  $T_{p,\kappa}$ . In describing the limits of densities of approximating processes (dynamics of densities of these processes are governed by the semigroups  $S_{1,\kappa}$ ), it is often more natural to consider  $\mathbb{C}^N$  equipped with the standard norm:

$$\|x\|_{\ell^1} := \sum_{k \in \mathcal{N}} |x_k| \quad \text{for } x = (x_1, \dots, x_N) \in \mathbb{C}^N;$$

the latter space will be denoted  $\ell^1$ . Clearly,  $\ell^1$  and  $\ell_\mu^1$  are isometrically isomorphic, with the isomorphism, say  $\Phi_1$ , mapping  $x \in \ell^1$  to

$$\Phi_1 x = \left( \frac{x_1}{\lambda(\Omega_1)}, \dots, \frac{x_N}{\lambda(\Omega_N)} \right) \in \ell_\mu^1.$$

As a bit of linear algebra shows, in the context of  $\ell^1$  the limit dynamics is governed by  $\tilde{Q} = \Phi_1^{-1}Q\Phi_1$ , i.e. the matrix obtained from  $Q$  by first multiplying the  $i$ th row of  $Q$  by  $\lambda(\Omega_i)$  and then dividing its  $i$ th column by  $\lambda(\Omega_i)$  for each  $i \in \mathcal{N}$ . In other words, the entries of  $\tilde{Q}$  are given by (compare (5.3))

$$(5.4) \quad \tilde{q}_{k,\ell} = \frac{\varrho_{k,\ell}}{\lambda(\Omega_\ell)}, \quad k, \ell \in \mathcal{N};$$

see Section 6.3 for an example.  $\square$

In our examples in the following section, we will also consider *inhomogeneous equations*, i.e. equations of the form

$$z'(t) = Az(t) + f(t), \quad u(0) = u_0$$

where  $A$  is the generator of a strongly continuous semigroup  $T$  on a Banach space  $X$  and  $f \in L^1((0, t_0); X)$ , for some  $t_0 > 0$ . Most often, one uses the concept of a *mild solution* for such equations. By [5, Proposition 3.1.6], the mild solution is given through the *variation of constants formula*

$$(5.5) \quad z(t) = T(t)u_0 + \int_0^t T(t-s)f(s) \, ds$$

for  $t \in [0, t_0]$ .

We now obtain the following corollary to Theorem 5.6.

**Corollary 5.8.** *Fix  $p \in [0, \infty)$  and  $t_0 > 0$ . Let  $[0, t_0] \ni t \mapsto f(t) \in L^p(\Omega_0)$  be a Bochner integrable function, and  $u_0$  be a fixed element of  $L^p(\Omega_0)$ . Then, as  $\kappa \rightarrow \infty$ , the mild solutions  $[0, t_0] \ni t \mapsto z_\kappa(t) \in L^p(\Omega_0)$  of the Cauchy problems*

$$z'_\kappa(t) = \mathcal{L}_{p,\kappa}u_\kappa(t) + f(t), \quad t \in [0, t_0], \quad z_\kappa(0) = u_0,$$

*converge in  $L^p(\Omega_0)$  and pointwise on  $(0, t_0]$  to the function*

$$e^{t(Q-C)}P_{H_0}u_0 + \int_0^t e^{(t-s)(Q-C)}P_{H_0}f(s) \, ds,$$

*the solution of the Cauchy problem*

$$z'(t) = (Q - C)z(t) + P_{H_0}f(t) \quad t \in [0, t_0], \quad z(0) = P_{H_0}u_0$$

*on the space  $H_0$ . An analogous result holds for  $\mathcal{L}_{p,\kappa}^*$ .*

*Proof.* This is immediate from Theorem 5.6, formula (5.5) and the dominated convergence theorem.  $\square$

*Remark 5.9.* A related convergence result also holds for  $p = \infty$ . However, the situation is slightly more complicated as we are dealing with a semigroup which is not strongly continuous. However, if we interpret the integral in (5.5) as a weak\*-integral, then the integral is well-defined whenever  $f$  is weak\* measurable and  $\|f\|$  is integrable. If we accept (5.5) as definition of a mild solution in the case of  $p = \infty$ , then, in the situation of Corollary 5.8 we easily obtain pointwise weak\*-convergence of mild solutions.

## 6. EXAMPLES

**6.1. Kinase activity.** Fast diffusion is a rich source of interesting singular perturbations, see e.g. [16]. This is the case, for example, in the following model of kinase activity from [42] (see also [22]). Let us recall that kinases are enzymes that transport phosphate groups. In doing this, protein kinases transmit signals and control complex processes in cells. In [42], following [20], a cell is modeled as a unit  $3d$  ball. All kinases, whether active (i.e. phosphorylated) or inactive, are diffusing inside the ball. Binding a receptor located at the cell membrane (the sphere) by an extracellular ligand is a signal which is to be conveyed to the cell. This is done by the kinases which, when touching the boundary (the sphere) become activated by their interaction with the ligand-bound receptors; such active kinases diffuse freely into the interior of the cell. Simultaneously, they are randomly inactivated when meeting phosphatases which are uniformly distributed over the cell.

In the no feedback case, where all receptors at the membrane are ligand-bound almost simultaneously, reaching a uniform stable concentration  $C > 0$ , the master equation for the concentration  $K^*$  of active kinases (after suitable rescaling) is a diffusion-degradation equation

$$(6.1) \quad \frac{\partial K^*}{\partial t} = \kappa \Delta K^* - K^*, \quad t \geq 0,$$

with boundary condition

$$(6.2) \quad aC(1 - K^*|_0) = \kappa \frac{\partial K^*}{\partial \nu}.$$

Here,  $\kappa > 0$  is a diffusion coefficient and  $a > 0$  is a reaction coefficient.  $K^*|_0$  is the value of  $K^*$  at the boundary,  $\frac{\partial K^*}{\partial \nu}$  is the usual normal derivative at the boundary and the term  $-K^*$  describes random dephosphorylation of active kinases. We note that condition (6.2) describes an inflow of active kinases from the boundary (this b.c. is missing in [20] and was introduced in [42]).

One of the aims of both [20] and [42] is to show that (perhaps somewhat surprisingly) *slow* diffusion may facilitate signal transmission more effectively than fast diffusion. To show this, the authors of [42] study the case of infinitely fast diffusion and compare the properties of solutions of the limit equation with those of the original one, showing that the infinite diffusion case leads to less-effective signal transmission. To do this, they assume spherical symmetry and argue that the limit equation has to be of the form

$$(6.3) \quad \frac{dK^*}{dt} = 3aC(1 - K^*) - K^*, \quad t \geq 0.$$

This is interpreted as follows: As diffusion coefficients increase to infinity, the active kinases' distribution becomes uniform over the ball and may be identified with a real function of time, whose dynamics is then described by (6.3). Nevertheless, the form of the limit equation is quite curious, with particularly intriguing factor 3.

In [16] a convergence theorem for semigroups on continuous functions has been proved asserting that, if spherical symmetry suggested in [42] is granted, the solutions

of (6.1)–(6.2) indeed converge to those to (6.3) equipped with appropriate initial condition. Here we will show that this convergence for  $\kappa \rightarrow \infty$  is a special case of our averaging principle. In fact, we can also prove convergence in more general situations, where the ball is replaced by an arbitrary bounded domain, the Laplacian is replaced by a more general diffusion operator and we can consider more general Robin boundary conditions. Note, however, that in our context we obtain convergence in the sense of  $L^p$  spaces, and not in a space of continuous functions, thus we do not obtain uniform convergence.

To fit the above example into our framework, we only need the simplest situation where  $\Omega_0$  is not partitioned into subregions. Thus, we have  $N = 1$  and  $\Omega_N = \Omega_0$ . Strictly speaking, therefore, in this case we are not dealing with transmission conditions, but merely with (Robin) boundary conditions. On the other hand, boundary conditions may be seen as particular instances of transmission conditions. In other words, the outer boundary of  $\Omega_0$ , i.e. the boundary of  $\Omega_0$  with its complement, may be thought of as a membrane that is permeable only in one direction.

Thus, let  $\Omega_0$  be a bounded domain in  $\mathbb{R}^3$  with Lipschitz boundary  $\Gamma_0$ . We replace the operator  $\kappa\Delta - I$  with  $\mathcal{L}_{p,\kappa}$ , the  $L^p(\Omega_0)$  version of the elliptic operator (3.2) with diffusion matrix  $A$  replaced by  $\kappa A$ . Moreover, instead of the constant  $aC$  in the boundary condition, we consider a non-negative function  $\tau \in L^\infty(\Gamma_0; \mathbb{R})$  (playing the role of  $\tau_0$  of Section 3.2). With these generalizations, equations (6.1)–(6.2) become

$$(6.4) \quad \frac{\partial K^*}{\partial t} = \mathcal{L}_{p,\kappa} K^*, \quad t \geq 0,$$

and

$$(6.5) \quad \tau(1 - K|_{\Gamma_0}^*) = N_0(K^*).$$

Note that  $N_0$  is now the conormal derivative with respect to the matrix  $\kappa A$ , and so the constant  $\kappa$  is no longer visible on the right-hand side of the boundary condition. As in [42], we are interested in the limit as  $\kappa \rightarrow \infty$ .

To transform this system to a form suitable for application of Theorem 5.5 we consider  $K^\diamond$ , the concentration of inactive kinases, defined as

$$K^\diamond = \mathbf{1}_{\Omega_0} - K^*.$$

A straightforward calculation shows that  $K^\diamond$  satisfies:

$$\frac{\partial K^\diamond}{\partial t} = \mathcal{L}_{p,\kappa} K^\diamond + \mathbf{1}_{\Omega_0}, \quad t \geq 0,$$

and

$$-\tau K|_{\Gamma_0}^\diamond = N_0(K^\diamond),$$

i.e., an equation of the type Corollary 5.8 is devoted to (with  $K^\diamond$  playing the role of  $z_\kappa$ ).

Since in this case  $N = 1$ , the orthogonal projection onto  $H_0$  is just the orthogonal projection onto the constant functions given by  $Pu = \frac{1}{\lambda(\Omega_0)} \int_{\Omega_0} u \, d\lambda$ . Also, the matrices  $Q$  and  $C$  are real numbers given by

$$(6.6) \quad -q := q_{1,1} = -\frac{1}{\lambda(\Omega_0)} \int_{\Gamma_0} \tau_0 \, d\sigma \quad \text{and} \quad c_{1,1} = 1,$$

respectively. Thus,  $Q - C = -(q + 1)$  and, as a consequence of Corollary 5.8, in the limit as  $\kappa \rightarrow \infty$ ,  $K^\diamond(t)$  converges (strongly or in the weak\* topology, depending on the choice of  $p$ ) to  $k^\diamond(t)\mathbf{1}_{\Omega_0}$  where  $k^\diamond$  is the solution of

$$\frac{dk^\diamond}{dt} = -(q + 1)k^\diamond + 1, \quad t \geq 0,$$

with initial condition  $k^\diamond(0) = P(\mathbf{1}_{\Omega_0} - K_0^*) = 1 - PK_0^*$ , where  $K_0^*$  is the initial concentration of  $K^*$ . Therefore,  $K^*(t)$  converges to  $k^*(t)\mathbf{1}_{\Omega_0}$  where  $k^*$  is the solution

of

$$\frac{dk^*}{dt} = q(1 - k^*) - k^*, \quad t \geq 0, \quad k^*(0) = PK_0^*.$$

This indeed generalizes the results from [42] and [16] as in the case where  $\Omega_0$  is the  $3d$  unit ball and  $\tau_0$  is the constant function equal to  $aC$ , we have by (6.6):

$$q = aC \frac{\text{unit ball's surface area}}{\text{unit ball's volume}} = 3aC.$$

**6.2. Neurotransmitters.** In modeling dynamics of synaptic depression, one often adopts a widely accepted, if simplified, view that a secretory cell is divided into three subregions,  $\Omega_1, \Omega_2$  and  $\Omega_3$  corresponding to the so-called immediately available, small and large pools, where neurotransmitters are located. This is also the case in the model of Bielecki and Kalita [11], in which a terminal bouton, playing the role of our  $\Omega_0$ , is modeled as a  $3d$  region (see Figure 1) and the concentration of (vesicles with) neurotransmitters is described by functions on those subregions. However, no clear distinction between the subregions is made; in particular, no transmission conditions on the borders between pools are imposed, and it appears as if diffusing vesicles with neurotransmitter may freely cross from one pool to the other. For reasons explained in [19], such a model cannot be easily connected with the older, and apparently better known model of Aristizabal and Glavinović [6] where the situation is described by three scalars, evolving with time, i.e. by the levels  $U_i, i = 1, 2, 3$  of neurotransmitters in the pools  $\Omega_1, \Omega_2$  and  $\Omega_3$  respectively. Arguably, to draw such a connection, specifying the way the particles may filter from one region to the other is necessary, and it transpires that the appropriate transmission conditions are of the form (3.3) with  $b_{k,\ell} \equiv 1$ . (One should note here, however, that no physical membranes separating pools exist in the secretory cells, and the interpretation similar to the Newton's Law of Cooling seems to be more suitable, for example the one provided by Fick's law.)

To see that the connection in question is a particular case of our averaging principle, we fix  $p \geq 0$  and write the governing equation for the neurotransmitter level  $u$  in  $L^p(\Omega_0)$  in the form (compare [11, eq. (1)]):

$$(6.7) \quad \frac{\partial u}{\partial t} = \mathcal{L}_{p,\kappa} u + \beta u^\sharp, \quad t \geq 0,$$

where  $\beta$  is a measurable, bounded and non-negative function which vanishes everywhere but on  $\Omega_3$ , and is interpreted as neurotransmitter's production rate (varying in  $\Omega_3$ ),  $\mathcal{L}_{p,\kappa}$  is the  $L^p(\Omega_0)$  version of the elliptic operator (3.2) with  $c = \beta$  and diffusion matrix  $\kappa A$ , and  $u^\sharp \in L^p(\Omega_0)$  is a given function interpreted as a balance concentration of vesicles.

Clearly this governing equation is of the form considered in Corollary 5.8 with  $f(t) = \beta u^\sharp$  independent of  $t$ . In this case, the space  $H_0$  is composed of functions that are constant on each of the three pools (separately), and the projection on this space is a particular case of (5.2) with  $\mathcal{N} = \{1, 2, 3\}$ . As explained in Section 5.2,  $H_0$  is isometrically isomorphic to  $\mathbb{C}^3$  with suitable norm. In particular, since  $\beta$  vanishes on  $\Omega_1$  and  $\Omega_2$ , the function  $P\beta u^\sharp$  may be identified with the vector  $e = (0, 0, e_3) \in \mathbb{C}^3$  where

$$e_3 = \frac{1}{\lambda(\Omega_3)} \int_{\Omega_3} \beta u^\sharp \, d\lambda.$$

Hence, identifying isomorphic objects, we see that Corollary 5.8 establishes convergence of solutions of (6.7) to a  $\mathbb{C}^3$ -valued function  $u$  solving the equation:

$$u'(t) = (Q - C)u(t) + e.$$

In order to find a more explicit form of the limit matrix  $Q$  we note that, because of the special arrangement of pools,  $\Omega_3$  borders only with  $\Omega_2$ , and  $\Omega_1$  is the only

region having common border with the complement of  $\Omega_0$ . As a result (see (5.3) and recall that we agreed on  $b_{k,\ell} \equiv 1$ )

$$Q = \begin{pmatrix} -q_{10} - q_{12} & q_{12} & 0 \\ q_{21} & -q_{21} - q_{23} & q_{23} \\ 0 & q_{32} & -q_{32} \end{pmatrix}, \quad q_{k,\ell} = \frac{\int_{\Gamma_{k,\ell}} \tau_k \, d\sigma}{\lambda(\Omega_k)}.$$

Also, the matrix  $C$  has, as diagonal entries, the values of  $P\beta$  on the sets  $\Omega_1, \Omega_2$  and  $\Omega_3$  respectively, and since  $\beta$  vanishes on  $\Omega_1$  and  $\Omega_2$ , it follows that  $C$  acts on a vector in  $\mathbb{C}^3$  as coordinate-wise multiplication with the vector  $(0, 0, c)^\top$ , where  $c = \frac{1}{\lambda(\Omega_3)} \int_{\Omega_3} \beta \, d\lambda$ .

So, the limit equation is precisely of the form considered by Aristizabal and Glavinovič for the levels  $U_i, i = 1, 2, 3$  (which now may be thought of as coordinates of  $u$ ). Comparing the entries of the matrix  $Q - C$  with the coefficients used by Aristizabal and Glavinovič, we may interpret the latter in new terms, see the discussion given in [19] and compare with eq. (7) there. (The apparent discrepancy between our  $Q$  and that given in the cited equation (7) is that the latter involves diffusion coefficients. To explain this, we note that transmission conditions in [19] are devised in a slightly different way than here. In particular, in [19] it is not the flux but the ratio flux/diffusion coefficient that is preserved.)

**6.3. Intracellular calcium dynamics.** The last example concerns calcium dynamics in eukaryotic cells. Calcium plays a crucial role in mediating and recognizing signals from the extracellular space into various parts of the cell, in particular to the nucleus. On the other hand, an elevated concentration of calcium ions inside the cytosol is harmful and may induce the cell's apoptosis. For that reason it is stored also in intracellular compartments, like endoplasmic reticulum or mitochondria. (A large amount of calcium is also bound to, so called, buffer protein molecules.) The average concentration of free calcium inside the cytosol does not exceed  $1 \, \mu M$ , while the average concentration of calcium inside endoplasmic reticulum and mitochondria may be two orders of magnitude bigger [43]. This is possible due to the action of special pumps, which by using different forms of energy can push free calcium into the regions of higher concentration, e.g. SERCA pumps (reticulum) or mitochondrial sodium-calcium exchangers (MNCX). In this way, cells can transport calcium against the diffusional flux.

In some circumstances, oscillations of calcium concentration between the internal stores and cytosol are observed. Such oscillations are usually described by means of systems of ordinary differential equations (see e.g., [43, 52, 58]). In these descriptions, inhomogeneities in the spatial distribution of calcium inside the regions corresponding to different cell compartments are neglected. As we will argue, our Theorem 5.6 justifies such a simplified description, provided diffusion in the cell is fast.

To begin with, we assume that the processes of binding and unbinding of calcium ions by buffer molecules, characterized by certain parameters  $k_+ > 0$  and  $k_- > 0$ , respectively, are very fast. This allows applying the reduction method of Wagner and Keizer [60], so that equations for buffer molecules are neglected. Moreover, for further simplicity, we assume that the buffers are immobile, that is to say their diffusion coefficients are negligible and that they are uniformly distributed in the space.

Let  $\Omega_0 \subset \mathbb{R}^3$  model the spatial region occupied by the cell, with the exception of its nucleus. Let  $\Omega_1 \subset \Omega_0$  correspond to the region occupied by the endoplasmic reticulum of the cell, and let  $\Omega_2 \subset \Omega_0$ , disjoint from  $\Omega_1$ , correspond to the mitochondria inside the cell. (Usually, there is a number of mitochondria, but to simplify the model we combine the regions occupied by them into a single region.) Finally, let  $\Omega_3 := \text{Int}(\Omega_0 \setminus \bigcup_{k=1}^2 \bar{\Omega}_k)$ , correspond to the cytosolic region of the cell.

The concentration  $U$  of free calcium in  $\Omega_0$  is governed by the following equation [60]:

$$(6.8) \quad \frac{\partial U}{\partial t} = a(x) \frac{1}{1 + \alpha(x, U)} \Delta U$$

where the positive function  $a \in L^\infty(\Omega_0)$  describes the diffusivity of the free calcium ions, i.e. of the ions which are not bound to buffer molecules. Since diffusivity does not change within each region, we assume that  $a = \sum_{i=1}^3 a_i \mathbb{1}_{\Omega_i}$  for some positive  $a_i, i = 1, 2, 3$ .

In (6.8), the factor  $\eta(x, U) = \frac{1}{1 + \alpha(x, U)}$  where  $\alpha$  is a non-negative function, describing the effect of calcium buffering for sufficiently large binding and unbinding coefficients  $k_+$  and  $k_-$ , coming into play as a result of the Wagner and Keizer reduction method. Let us also note that due to the fact that the buffer molecules are assumed to be immobile, the gradient quadratic term in equation (2.5a) in [60] vanishes. For simplicity we confine ourselves to the case of one representative kind of buffers in each of the regions  $\Omega_1, \Omega_2$  and  $\Omega_3$ . We allow the coefficients  $k_+$  and  $k_-$  to differ in the subregions of the cell, i.e. for them to be functions of  $x$ . We set  $K = k_-/k_+$ . Then,  $\alpha$  is given by

$$\alpha(x) = b_{\text{tot}}(x)K(x)(K(x) + U)^{-1},$$

where  $b_{\text{tot}}$  denotes the total concentration of buffering molecules. In general, also  $b_{\text{tot}}$  depends on  $x$ . In some situations, however, it may be assumed that  $\alpha$  does not depend on  $U$ , and depends on  $x$  only via  $\Omega_i$ . Such an approximation can be justified in the cytosolic region by the fact that for typical endogeneous buffers we have  $k_+ \approx 50 \mu M^{-1} s^{-1}$ ,  $k_- \approx 500 s^{-1}$ , so that  $K \approx 10 \mu M$ , and the maximal value of  $U$  of the order of  $1 \mu M$ . On the other hand, the calcium capacity of reticular and mitochondrial subregions is very large, so the concentration of calcium  $U$  does not change significantly in these compartments in the non-apoptotic state of the cell. To be able apply the theory developed in this paper, we further simplify the model and assume that  $\eta < 1$  is a constant.

We are thus lead to the following, reduced form of equation (6.8):

$$(6.9) \quad \frac{\partial U}{\partial t} = \eta a \Delta U;$$

in particular, the diffusion matrix  $A(x)$  is a  $3 \times 3$  diagonal matrix with all entries on the diagonal equal  $\eta a_i$  in  $\Omega_i$ .

Turning to transmission conditions, we assume – in accordance with biological reality – that neither the reticulum nor the mitochondria have common points with the cell's membrane  $\Gamma_0$ , and that they do not communicate each other directly, either. As a result, calcium may only permeate from the cytosol to reticulum or mitochondria and back to cytosol, or from the cytosol to the extracellular matrix. Secondly, we suppose that the functions describing the flows through the separating membranes are *linear*. (We note, however, that the process of calcium transmission through the cell membrane, as well as that through the reticular and mitochondrial boundaries is rather complicated and these functions are, in general, nonlinear. A possible form of the functions modulo constant factors can be deduced from [52], where a three-compartmental non-spatial model of calcium dynamics is proposed. An extension of the main theorem of our paper to the case of nonlinear transmission conditions is a very interesting topic for future research.) We thus suppose that the transport of calcium through the membranes separating the reticular and mitochondrial



subregions from the cytosol is governed by the transmission conditions:

$$(6.10) \quad \begin{aligned} \tau_3 u|_3 - \tau_1 u|_1 &= a_1 \frac{\partial u}{\partial \nu}, & \tau_3 u|_3 - \tau_1 u|_1 &= a_3 \frac{\partial u}{\partial \nu}, & \text{on } \Gamma_1 = \Gamma_{1,3} & \text{ and} \\ \tau_3 u|_3 - \tau_2 u|_2 &= a_2 \frac{\partial u}{\partial \nu}, & \tau_3 u|_3 - \tau_2 u|_2 &= a_3 \frac{\partial u}{\partial \nu}, & \text{on } \Gamma_2 = \Gamma_{2,3} \end{aligned}$$

respectively, where  $\tau$ 's are permeability functions, as in (3.6). Recall that  $\tau$ 's in general depend on  $x$ .

Several remarks are here in order. First of all, we note that since (6.9) is to describe distribution of calcium ions, we use transmission conditions akin to (3.6) and not (3.3) (see Remark 3.4). Secondly, the first of the equations in the first line describes the flux of calcium from the cytosol to the reticulum, while the second describes the flux of calcium from the cytosol to the cytosol. Thirdly, in the first of these equations,  $\frac{\partial u}{\partial \nu}$  refers to the derivative of  $u$  in direction of the outer normal of  $\Omega_1$ , whereas in the second it refers to the derivative of  $u$  in direction of the inner normal of  $\Omega_1$ . Note that the inner normal of  $\Omega_1$  is the outer normal of  $\Omega_3$ . The other two equations are interpreted in the same way.

Additionally, we have the equation

$$(6.11) \quad -\tau_3 u|_3 = a_3 \frac{\partial u}{\partial \nu} \quad \text{on } \Gamma_0 = \Gamma_{0,3},$$

governing the outflow of free calcium ions through the outer boundary of the cell and through the membrane separating the cytosol from the cell's nucleus. Since the latter part of  $\Omega_0$  is impermeable for the ions, we assume that  $\tau_3$  vanishes there. We note that condition (6.11) implies that we assume either that the local free calcium concentration in the extracellular space is zero or the influx of calcium from outside the cell is blocked.

We stress that transmission conditions (6.10) are not yet of the form (3.6), because the right-hand sides are not yet the conormal derivatives for the operator  $\eta a \Delta$  appearing in (6.9). Biologically, this is a reflection of the fact that only free calcium ions can pass through the separating boundaries – the buffer molecules (either free or with bound calcium ions) cannot do that. Mathematically, to make (6.10) compatible with (3.3) we need to multiply all equations by  $\eta < 1$ . This amounts to introducing new permeability functions, equal to the old ones multiplied by  $\eta$ , and so the intensity matrix  $Q$  of (5.3) becomes:

$$Q = \eta \begin{pmatrix} -\frac{\int_{\Gamma_1} \tau_1 d\sigma}{\lambda(\Omega_1)} & 0 & \frac{\int_{\Gamma_1} \tau_1 d\sigma}{\lambda(\Omega_1)} \\ 0 & -\frac{\int_{\Gamma_2} \tau_2 d\sigma}{\lambda(\Omega_2)} & \frac{\int_{\Gamma_2} \tau_2 d\sigma}{\lambda(\Omega_2)} \\ \frac{\int_{\Gamma_1} \tau_3 d\sigma}{\lambda(\Omega_3)} & \frac{\int_{\Gamma_2} \tau_3 d\sigma}{\lambda(\Omega_3)} & -\frac{\sum_{i=0}^2 \int_{\Gamma_i} \tau_3 d\sigma}{\lambda(\Omega_3)} \end{pmatrix}.$$

This means that in this approximation, buffer molecules' influence reduces to slowing down the process of communication between reticulum, mitochondria and cytosol. Remarkably, more interesting phenomena are observed even for  $\eta$  dependent on  $x$  merely via  $\Omega_i$ .

To proceed, we must take into account that the natural space for dynamics of densities  $u_i$  is not  $\ell_\mu^1$  but  $\ell^1$ . Consequently, according to Remark 5.7, working in the latter space, we should replace the matrix  $Q$  by the matrix  $\tilde{Q}$  defined as

$$\tilde{Q} = \eta \begin{pmatrix} -\frac{\int_{\Gamma_1} \tau_1 d\sigma}{\lambda(\Omega_1)} & 0 & \frac{\int_{\Gamma_1} \tau_1 d\sigma}{\lambda(\Omega_3)} \\ 0 & -\frac{\int_{\Gamma_2} \tau_2 d\sigma}{\lambda(\Omega_2)} & \frac{\int_{\Gamma_2} \tau_2 d\sigma}{\lambda(\Omega_3)} \\ \frac{\int_{\Gamma_1} \tau_3 d\sigma}{\lambda(\Omega_1)} & \frac{\int_{\Gamma_2} \tau_3 d\sigma}{\lambda(\Omega_2)} & -\frac{\sum_{i=0}^2 \int_{\Gamma_i} \tau_3 d\sigma}{\lambda(\Omega_3)} \end{pmatrix}.$$

Theorem 5.5 (formulated in the  $\ell^1$  space) asserts that if  $a$  is replaced by  $\kappa a$  or if (see Remark 5.2)  $a^{(\kappa)}$  is a family of functions indexed by  $\kappa$  such that  $\sup_\kappa a^{(\kappa)}(x) = \infty$

for almost all  $x \in \Omega_0$ , then as  $\kappa \rightarrow \infty$  solutions to (6.12) become more and more uniform, i.e. ‘flat’, in each of the regions  $\Omega_1, \Omega_2, \Omega_3$ . Moreover, if  $u_i(t)$  denotes the common value of the limit function at time  $t$  in  $\Omega_i$  then for the column vector  $u(t)$  with coordinates  $u_i(t)$  we have

$$(6.12) \quad u'(t) = \tilde{Q}^* u(t).$$

The form of the limit system (6.12) agrees with the following heuristic reasoning. Suppose that  $u(t) = \sum_{i=1}^3 u_i(t) \mathbf{1}_{\Omega_i}$  is a solution to (6.9) with transmission conditions (6.10) and (6.11) and  $a$  replaced by  $\kappa a$ . Then, using the Gauss theorem, we see that

$$\lambda(\Omega_1)u_1'(t) = - \int_{\Gamma_1} \eta\tau_1 d\sigma u_1(t) + \int_{\Gamma_1} \eta\tau_3 d\sigma u_3(t),$$

and dividing by  $\lambda(\Omega_1)$  leads to the first equation in (6.12). Similarly, we check that the second and third equations of (6.12) agree with the result of formal integration based on the Gauss theorem.

## 7. DISCUSSION

In modeling biological processes one often needs to take into account different time-scales of the processes involved [8, 17]. This is in particular the case when one of the components of the model is diffusion which in certain circumstances may transpire to be much faster than other processes. For example, in the Alt and Lauffenberger’s [2] model of leucocytes reacting to a bacterial invasion by moving up a gradient of some chemical attractant produced by the bacteria (see Section 13.4.2 in [44]) a system of three PDEs is reduced to one equation provided bacterial diffusion is much smaller than the diffusion of leukocytes or of chemoattractants (which is typically the case). Similarly, in the early carcinogenesis model of Marcinak–Czochra and Kimmel [16, 49, 50, 51], a system of two ODEs coupled with a single diffusion equation (involving Neumann boundary conditions) is replaced by a so-called shadow system of integro-differential equations with ordinary differentiation, provided diffusion may be assumed fast.

In this context it is worth recalling that one of the fundamental properties of diffusion in a bounded domain is that it ‘averages’ solutions (of the heat equation with Neumann boundary condition) over the domain. As it transpires, it is this homogenization effect of diffusion, when coupled with other physical or biological forces that leads to intriguing singular perturbations; this is exemplified by a more careful analysis of the models mentioned above (see also [16]).

In this paper we describe the situation in which fast diffusion in several bounded domains separated by semi-permeable membranes is accompanied by low permeability of the membranes. Assuming that the flux through the membranes is of moderate value, we show that such models are well-approximated by those based on Markov chains. More specifically, because of the homogenization effect, all points in each domain of diffusion are lumped into a single state, and the non-negligible flux forces so-formed new states to communicate as the states of a Markov chain (eq. (5.3) provides the entries in its intensity matrix).

Certainly, applicability of the theorem depends in a crucial way on whether and to what extent diffusion involved in the model is faster than other processes. Nevertheless, the literature of the subject provides numerous examples of such situations. Two of them: the model of intracellular dynamics and that of neurotransmitters are discussed in detail above. Our third example is of slightly different type: its main purpose is to show that diffusion of kinases in a cell cannot be too fast for signaling pathways to work properly.

From the mathematical viewpoint, the established principle is a close relative of the famous Freidlin–Wentzell averaging principle ([36, 38], see also [37]), but it differs from its more noble cousin in the crucial role played by transmission conditions,

which are of marginal or no importance in the latter. These conditions, sometimes referred to as radiation boundary conditions, describe in probabilistic and analytic terms the way particles permeate through the membranes, and thus, indirectly, the flux, which influences the model in a critical way (see eq. (5.3) again).

## REFERENCES

- [1] M. S. AGRANOVICH, *Sobolev Spaces, Their Generalizations and Elliptic problems in Smooth and Lipschitz Domains*, Springer Monographs in Mathematics, Springer, Cham, 2015. Revised translation of the 2013 Russian original.
- [2] W. ALT AND D. A. LAUFFENBURGER, *Transient behavior of a chemotaxis system modelling certain types of tissue inflammation*, J. Math. Biol, 24 (1987), pp. 691–722.
- [3] S. S. ANDREWS, *Accurate particle-based simulation of adsorption, desorption and partial transmission*, Phys. Biol., (2010), p. 046015.
- [4] W. ARENDT, *Approximation of degenerate semigroups*, Taiwanese J. Math., 5 (2001), pp. 279–295.
- [5] W. ARENDT, C. J. K. BATTY, M. HIEBER, AND F. NEUBRANDER, *Vector-valued Laplace transforms and Cauchy problems*, vol. 96 of Monographs in Mathematics, Birkhäuser/Springer Basel AG, Basel, second ed., 2011.
- [6] F. ARISTIZABAL AND M. I. GLAVINOVIC, *Simulation and parameter estimation of dynamics of synaptic depression*, Biol. Cybern., 90 (2004), pp. 3–18.
- [7] J. BANASIAK, A. FALKIEWICZ, AND P. NAMAYANJA, *Asymptotic state lumping in transport and diffusion problems on networks with applications to population problems*, Mathematical Models and Methods in Applied Sciences, 26 (2016), pp. 215–247.
- [8] J. BANASIAK AND M. LACHOWICZ, *Methods of Small Parameter in Mathematical Biology*, Modeling and Simulation in Science, Engineering and Technology, Birkhäuser, 2014.
- [9] C. BARDOS, D. GREBENKOV, AND A. ROZANOVA-PIERRAT, *Short-time heat diffusion in compact domains with discontinuous transmission boundary conditions*, Mathematical Models and Methods in Applied Sciences, 26 (2016), pp. 59–110.
- [10] C. J. K. BATTY AND A. F. M. TER ELST, *On series of sectorial forms*, J. Evol. Equ., 14 (2014), pp. 29–47.
- [11] A. BIELECKI AND P. KALITA, *Model of neurotransmitter fast transport in axon terminal of presynaptic neuron*, J. Math. Biol, 56 (2008), pp. 559–576.
- [12] A. BOBROWSKI, *Degenerate convergence of semigroups*, Semigroup Forum, 49 (1994), pp. 303–327.
- [13] ———, *Functional Analysis for Probability and Stochastic Processes. An introduction*, Cambridge University Press, Cambridge, 2005.
- [14] ———, *From diffusions on graphs to Markov chains via asymptotic state lumping*, Ann. Henri Poincaré, 13 (2012), pp. 1501–1510.
- [15] ———, *Families of operators describing diffusion through permeable membranes*, in Operator Semigroups Meet Complex Analysis, Harmonic Analysis and Mathematical Physics, Arendt, W., Chill, R., Tomilov, Y., eds., vol. 250 of Operator Theory, Advances and Applications, Birkhäuser, 2015, pp. 87–105.
- [16] ———, *Singular perturbations involving fast diffusion*, J. Math. Anal. Appl., 427 (2015), pp. 1004–1026.
- [17] ———, *Convergence of One-Parameter Operator Semigroups. In Models of Mathematical Biology and Elsewhere*, Cambridge University Press, Cambridge, 2016.
- [18] ———, *Emergence of Freidlin–Wentzell’s transmission conditions as a result of a singular perturbation of a semigroup*, Semigroup Forum, 92 (2016), pp. 1–22.
- [19] A. BOBROWSKI AND K. MORAWSKA, *From a PDE model to an ODE model of dynamics of synaptic depression*, Discr. Cont. Dyn. Syst. B, 17 (2012), pp. 2313–2327.
- [20] G. C. BROWN AND B. N. KHOLODENKO, *Spatial gradients of cellular phospho-proteins*, FEBS Letters, 457 (1999), pp. 452–454.
- [21] J. CRANK, *The mathematics of diffusion*, Clarendon Press, Oxford, second ed., 1975.
- [22] E. CROOKS, B. KĄZMIERCZAK, AND T. LIPNIACKI, *A spatially extended model of kinase-receptor interaction*, SIAM J. Appl. Math., 73 (2013), pp. 374–400.
- [23] G. DA PRATO AND E. SINISTRARI, *Differential operators with nondense domain*, Ann. Scuola Norm. Sup. Pisa Cl. Sci. (4), 14 (1987), pp. 285–344.
- [24] D. DANERS, *Principal eigenvalues for generalised indefinite Robin problems*, Potential Anal., 38 (2013), pp. 1047–1069.
- [25] R. DAUTRAY AND J.-L. LIONS, *Mathematical Analysis and Numerical Methods for Science and Technology. Vol. 2*, Springer-Verlag, Berlin, 1988. Functional and variational methods, With the collaboration of Michel Artola, Marc Authier, Philippe Bénilan, Michel Cessenat, Jean

- Michel Combes, Hélène Lanchon, Bertrand Mercier, Claude Wild and Claude Zuily, Translated from the French by Ian N. Sneddon.
- [26] ———, *Mathematical Analysis and Numerical Methods for Science and Technology. Vol. 1*, Springer-Verlag, Berlin, 1990. Physical origins and classical methods, With the collaboration of Philippe Bénilan, Michel Cessenat, André Gervat, Alain Kavenoky and Hélène Lanchon, Translated from the French by Ian N. Sneddon, With a preface by Jean Teillac.
- [27] ———, *Mathematical Analysis and Numerical Methods for Science and Technology. Vol. 3*, Springer-Verlag, Berlin, 1990. Spectral theory and applications, With the collaboration of Michel Artola and Michel Cessenat, Translated from the French by John C. Amson.
- [28] K.-J. ENGEL AND R. NAGEL, *One-parameter semigroups for linear evolution equations*, vol. 194 of Graduate Texts in Mathematics, Springer-Verlag, New York, 2000. With contributions by S. Brendle, M. Campiti, T. Hahn, G. Metafuno, G. Nickel, D. Pallara, C. Perazzoli, A. Rhandi, S. Romanelli and R. Schnaubelt.
- [29] S. N. ETHIER AND T. G. KURTZ, *Markov Processes. Characterization and Convergence*, Wiley, New York, 1986.
- [30] W. FELLER, *Diffusion processes in genetics*, in Proceedings of the Second Berkeley Symposium on Mathematical Statistics and Probability, 1950, Berkeley and Los Angeles, 1951, University of California Press, pp. 227–246.
- [31] ———, *Two singular diffusion problems*, Ann. Math., 54 (1951), pp. 173–182.
- [32] ———, *Diffusion processes in one dimension*, Trans. Amer. Math. Soc., 77 (1952), pp. 468–519.
- [33] ———, *The parabolic differential equations and the associated semi-groups of transformations*, Ann. Math., 55 (1952), pp. 468–519.
- [34] E. FIEREMANS, D. S. NOVIKOV, J. H. JENSEN, AND J. A. HELPERN, *Monte Carlo study of a two-compartment exchange model of diffusion*, NMR in Biomedicine, (2010), pp. 711–724.
- [35] G. B. FOLLAND, *Real analysis*, Pure and Applied Mathematics (New York), John Wiley & Sons, Inc., New York, second ed., 1999. Modern techniques and their applications, A Wiley-Interscience Publication.
- [36] M. I. FREIDLIN AND A. D. WENTZELL, *Diffusion processes on graphs and the averaging principle*, Ann. Math., 21 (1993), pp. 2215–2245.
- [37] ———, *Diffusion processes on an open book and the averaging principle*, Stochastic Processes and their Applications, 113 (2004), pp. 101–126.
- [38] ———, *Random Perturbations of Dynamical Systems*, vol. 260 of Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences], Springer, Heidelberg, third ed., 2012. Translated from the 1979 Russian original by Joseph Szücs.
- [39] D. GILBARG AND N. S. TRUDINGER, *Elliptic partial differential equations of second order*, Classics in Mathematics, Springer-Verlag, Berlin, 2001. Reprint of the 1998 edition.
- [40] A. GREGOSIEWICZ, *Asymptotic behaviour of diffusions on graphs*, in Probability in Action, Banek, T., Kozłowski, E., eds., Lublin University of Technology, 2014, pp. 83–96.
- [41] T. KATO, *Perturbation theory for linear operators*, Classics in Mathematics, Springer-Verlag, Berlin, 1995. Reprint of the 1980 edition.
- [42] B. KAZMIERCZAK AND T. LIPNACKI, *Regulation of kinase activity by diffusion and feedback*, J. Theor. Biol., 259 (2009), pp. 291–296.
- [43] J. KEENER AND J. SNEYD, *Mathematical Physiology*, vol. 8 of Interdisciplinary Applied Mathematics, Springer, New York, second ed., 2009.
- [44] ———, *Mathematical Physiology. Vol. II: Systems Physiology*, vol. 8 of Interdisciplinary Applied Mathematics, Springer, New York, second ed., 2009.
- [45] T. G. KURTZ, *A limit theorem for perturbed operator semigroups with applications to random evolutions*, J. Functional Analysis, 12 (1973), pp. 55–67.
- [46] ———, *Applications of an abstract perturbation theorem to ordinary differential equations*, Houston J. Math., 3 (1977), pp. 67–82.
- [47] A. LEJAY, *The snapping out Brownian motion*. hal-00781447, Dec. 2013.
- [48] H. P. LOTZ, *Uniform convergence of operators on  $L^\infty$  and similar spaces*, Math. Z., 190 (1985), pp. 207–220.
- [49] A. MARCINIAK-CZOCHRA, S. HARTING, G. KARCH, AND K. SUZUKI, *Dynamical spike solutions in a nonlocal model of pattern formation*. arXiv:1307.6236, 2013.
- [50] A. MARCINIAK-CZOCHRA AND M. KIMMEL, *Modelling of early lung cancer progression: influence of growth factor production and cooperation between partially transformed cells*, Math. Mod. Meth. Appl. Sci., 17 (2007), pp. 1693–1719.
- [51] ———, *Reaction-diffusion model of early carcinogenesis: the effects of influx of mutated cells*, Math. Model. Nat. Phenom., 3 (2008), pp. 90–114.
- [52] M. MARHL, T. HABERICHTER, M. BRUMEN, AND R. HEINRICH, *Complex calcium oscillations and the role of mitochondria and cytosolic proteins*, Biosystems, 57 (2000), pp. 75–86.
- [53] J. NEČAS, *Direct methods in the theory of elliptic equations*, Springer Monographs in Mathematics, Springer, Heidelberg, 2012. Translated from the 1967 French original by Gerard Tronel

- and Alois Kufner, Editorial coordination and preface by Šárka Nečasová and a contribution by Christian G. Simader.
- [54] E. M. OUHABAZ, *Second order elliptic operators with essential spectrum  $[0, \infty)$  on  $L^p$* , Comm. Partial Differential Equations, 20 (1995), pp. 763–773.
  - [55] ———, *Analysis of heat equations on domains*, vol. 31 of London Mathematical Society Monographs Series, Princeton University Press, Princeton, NJ, 2005.
  - [56] J. G. POWLES, M. J. D. MALLETT, G. RICKAYZEN, AND W. A. B. EVANS, *Exact analytic solutions for diffusion impeded by an infinite array of partially permeable barriers*, Proc. Roy. Soc. London Ser. A, 436 (1992), pp. 391–403.
  - [57] B. SIMON, *A canonical decomposition for quadratic forms with applications to monotone convergence theorems*, J. Funct. Anal., 28 (1978), pp. 377–385.
  - [58] P. SZOPA, M. DYZMA, AND B. KAŹMIERCZAK, *Membrane associated complexes in calcium dynamics modelling*, Physical Biology, 10(3) (2013), pp. 35004–35016.
  - [59] J. E. TANNER, *Transient diffusion in a system partitioned by permeable barriers. Application to NMR measurements with a pulsed field gradient*, The Journal of Chemical Physics, 69 (1978), pp. 1748–1754.
  - [60] J.-C. TSAI AND J. SNEYD, *Traveling waves in the buffered FitzHugh-Nagumo model*, SIAM J. Appl. Math., 71 (2011), pp. 1606–1636.
  - [61] A. D. WENTZELL, *On lateral conditions for multidimensional diffusion processes*, Teor. Veroyatnost. i Primenen., 4 (1959), pp. 172–185. English translation: Theory Prob. and its Appl. 4, 164–177 (1959).

*E-mail address:* a.bobrowski@pollub.pl

LUBLIN UNIVERSITY OF TECHNOLOGY, NADBYSTRZYCKA 38A, 20-618 LUBLIN, POLAND

*E-mail address:* bkazmier@ippt.pan.pl

INSTITUTE OF FUNDAMENTAL TECHNOLOGICAL RESEARCH, PAS, PAWINSKIEGO 5B, 02-106 WARSAW, POLAND

*E-mail address:* markus.kunze@uni-konstanz.de

UNIVERSITÄT KONSTANZ, FACHBEREICH MATHEMATIK UND STATISTIK, 78467 KONSTANZ, GERMANY