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ON THE THEORY OF REMEDIABILITY

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Abstract. Suppose $\{G_1(t)\}_{t\geq 0}$ and $\{G_2(t)\}_{t\geq 0}$ are two families of semigroups on a Banach space X (not necessarily of class C_0) such that for some initial datum u_0, $G_1(t)u_0$ tends towards an undesirable state u^*. After remedying by means of an operator $\boldsymbol{\rho}$ we continue the evolution of the state by applying $G_2(t)$ and after time $2t$ we retrieve a prosperous state u given by $u = G_2(t)\boldsymbol{\rho}G_1(t)u_0$. Here we are concerned with various properties of the semigroup $\mathcal{G}(t) : \boldsymbol{\rho} \to G_2(t)\boldsymbol{\rho}G_1(t)$. We define $\mathcal{R}(X)$ to be the space of remedial operators for $G_1(t)$ and $G_2(t)$, when the above map is well defined for all $\boldsymbol{\rho} \in \mathcal{R}(X)$ and satisfies the properties of a uniformly bounded semigroup on $\mathcal{R}(X)$. In this paper we study some properties of the space $\mathcal{R}(X)$ and we prove that when A_i generate a regularized semigroup for $i = 1, 2$, then the operator Δ defined on $\mathcal{L}(X)$ by $\Delta\boldsymbol{\rho} = A_2\boldsymbol{\rho}+\boldsymbol{\rho}A_1$ generates a tensor product regularized semigroup. Finally, we give two examples of remedial operators in radiotherapy and chemotherapy in proliferation of cancer cells.

1. Introduction. The theory of remediability describes mathematical models of biological states, which are represented by a dynamical system such that the solutions of the models stemming from such states tend inexorably towards undesirable states. We suppose that an undesirable state is remediable whether in the past or in the future. Think of the extinction of species or environmental degradation in ecology or a cohort of carcinogenic cells in the theory of proliferation of cell population, etc.

First let us suppose that such a phenomenon can be described by a linear or nonlinear dynamical system

$$\textbf{(DS)} \qquad \begin{cases} \frac{d}{dt}u(t) = Au(t), & t \in \mathbb{R}, \\ u(0) = u_0 \in X, \end{cases}$$

which has a global solution given by a group of operators $\{G(t)\}_{t\in\mathbb{R}}$.

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Suppose that at time $t = t_0$ we have at our disposal the initial datum u_0 and the trajectory coming from u_0 tends towards a disastrous state u^* which is to be avoided. A utopian strategy to alleviate the situation is to go back in time to instant $t_0 - t < 0$, when a remedy is plausible. After remedying by means of an operator $\boldsymbol{\rho}$ we go back to t_0 and we retrieve a prosperous state u given by

$$u = G(t - t_0)\boldsymbol{\rho}G(t_0 - t)u_0. \tag{1}$$

We are concerned more precisely with the properties of the map

$$\mathcal{L}(X) \ni \ \boldsymbol{\rho} \to G(t)\boldsymbol{\rho}G(-t) \in \mathcal{L}(X).$$

If $\{G(t)\}_{t\in\mathbf{R}}$ is a C_0-group on X, then this map defines a group $\mathcal{G}(t)$ on $\mathcal{L}(X)$ in the following sense:

(1) $\mathcal{G}(0)\boldsymbol{\rho} = \boldsymbol{\rho}$,
(2) $\mathcal{G}(t)\mathcal{G}(s)\boldsymbol{\rho} = \mathcal{G}(t)[G(s)\boldsymbol{\rho}G(-s)] = G(t)G(s)\boldsymbol{\rho}G(-s)G(-t) = G(t+s)\boldsymbol{\rho}G(-t-s) = \mathcal{G}(t+s)\boldsymbol{\rho}$,
(3) $\mathcal{G}(t)\boldsymbol{\rho}$ converges strongly to $\boldsymbol{\rho}$, for any $\boldsymbol{\rho} \in \mathcal{L}(X)$.

In general the convergence is not in the sense of uniform topology of $\mathcal{L}(X)$ unless X is a finite dimensional space or $\mathcal{G}(t)$ acts on the subalgebra $\mathcal{L}_c(X)$, the ideal of compact operators on X.

In quantum mechanics we can find such a formalism in which $\mathcal{G}(t)$ is called a quantum dynamical semigroup in the theory of open systems (see [7]). In this theory $G(t)$ appears as a unitary group generated by a skew-adjoint operator $-iH$, where H is the Hamiltonian of the system. In this formalism the dynamical semigroup $\mathcal{G}(t)$ acts on the state space V, which is the trace class operators on a Hilbert space $\mathcal{H}$ and for the trace norm topology we have $\lim_{t\to 0} \|\mathcal{G}(t)\boldsymbol{\rho} - \boldsymbol{\rho}\|_{tr} = 0$. However, the use of such theory presents several difficulties.

First, in the practical cases the evolution dynamics is in general irreversible in time. For example in population dynamics the individuals cannot become less mature in time. This irreversibility forces us to redefine the generalized dynamical semigroup $\mathcal{G}(t)$ and to replace $G(t)\boldsymbol{\rho}G(-t)$ by $G(t)\boldsymbol{\rho}G(t)$ or more generally by $G_2(t)\boldsymbol{\rho}G_1(t)$. This type of semigroup have been also studied in the literature (see [1], [5], [8], [12], [13], [14] and [15]). It is formally clear that if the C_0-semigroups $G_1(t)$ and $G_2(t)$ are generated by the operators A_1 and A_2 on the Banach spaces X, then the semigroup $\mathcal{G}(t)$ has Δ as its infinitesimal generator where

$$\Delta\boldsymbol{\rho} = A_2\boldsymbol{\rho} + \boldsymbol{\rho}A_1. \tag{2}$$

This is strictly true when the generators A_1 and A_2 are bounded. That is why this semigroup intervenes for studying the operator equation $A_2\boldsymbol{\rho} + \boldsymbol{\rho}A_1 = Q$ in the scattering theory (see [9] and [10]).

By applying $\mathcal{G}(t) = G_2(t) \otimes G_1(t)^*$ to operators of rank one, $u \otimes v^* = \langle ., v^*\rangle u$ ($u \in X, v^* \in X^*$), it turns out that

$$\begin{aligned}[G_2(t) \otimes G_1^*(t)]\,(u \otimes v^*) &= G_2(t)u \otimes G_1^*(t)v^* = \langle \cdot, G_1^*(t)v^*\rangle G_2(t)u \\ &= G_2(t)(u \otimes v^*)G_1(t).\end{aligned}$$

Hence, $\mathcal{G}(t)$ is an extension to $\mathcal{L}(X)$ of the tensor product $G_2(t) \otimes G_1(t)^*$ acting on the space of operators of finite rank, $X \otimes X^*$. Therefore $\mathcal{G}(t)$ is referred to as a *tensor product semigroup*. In the following proposition we gather the essential properties of a tensor product semigroup $\mathcal{G}(t)$.

PROPOSITION 1 (see [8]).

(1) *If* $G_1(t)$ *and* $G_2(t)$ *are two* C_0*-semigroups on a Banach space* X*, then for any* $\boldsymbol{\rho} \in \mathcal{L}(X)$, $\mathcal{G}(t)\boldsymbol{\rho} = G_2(t)\boldsymbol{\rho}G_1(t)$ *is continuous in* $t \in [0, \infty)$ *relative to the strong operator topology;*
(2) *Let* $\mathcal{D}(\Delta) := \{\boldsymbol{\rho} \in \mathcal{L}(X)$ *such that* $\boldsymbol{\rho}\mathcal{D}(A_1) \subset \mathcal{D}(A_2)$ *and the operator* $\Delta\boldsymbol{\rho}$ *has a bounded extension on* X *defined by* (2)$\}$. *Then* Δ *is closed for weak operator topology and*

$$\Delta\boldsymbol{\rho} = s - \lim_{t\to 0} \frac{\mathcal{G}(t)\boldsymbol{\rho} - \boldsymbol{\rho}}{t}.$$

Furthermore, if $G_1(t)$ and $G_2(t)$ are defined on two different Banach spaces X and Y, then we can also define the family $\{\mathcal{G}(t) \ : \ t \geq 0\}$ on the Banach algebra $\mathcal{L}(Y, X)$ (see [12]).

The second difficulty is related to the ill-posedness of the dynamics $G_1(t)$. Even in the linear case, if we assume that X is the space of prosperious states and if for some initial datum $u_0 \in X$, $G_1(t)u_0$ tends towards an undesirable state $u^* \notin X$, such a semigroup cannot be strongly continuous and needs to be regularized or to be extended in a larger space. This situation requires the theory of C-regularized semigroups and C-existence families which is extensively studied in [6].

DEFINITION 1. For a bounded injective operator C, the strongly continuous family $\{W(t)\}_{t\geq 0}$ in $\mathcal{L}(X)$ is a *C-regularized semigroup* if

(1) $W(0) = C$;
(2) $W(t)W(s) = CW(t+s)$ for all $s, t \geq 0$.

An operator A is the *generator* of the semigroup $\{W(t)\}_{t\geq 0}$ if

$$Ax = C^{-1}\left[\lim_{t\to 0} \frac{1}{t}(W(t)x - Cx)\right]$$

with

$$D(A) := \{x \mid \text{the limit exists and is in } \mathrm{Im}(C)\}.$$

Note that when $C = I, \{W(t)\}_{t\geq 0}$ is a C_0-semigroup generated by A. When A generates a C-regularized semigroup $\{W(t)\}_{t\geq 0}$, then we can define the semigroup $\{e^{tA}\}_{t\geq 0}$ of (possibly unbounded) operators by

$$e^{tA} := C^{-1}W(t), \quad t \geq 0 \tag{3}$$

with domain

$$D(e^{tA}) := \{x \in X \mid W(t)x \in \mathrm{Im}(C)\}.$$

If the operator C does not satisfy the commutation relation $CG_1(t) = G_1(t)C$, then one can even so use the theory of C-existence family in such a manner that $W(t) = CG_1(t)$ becomes a linear bounded operator.

In the next section we will define the space of remedial operators $\boldsymbol{\rho}$ for which $\mathcal{G}(t)\boldsymbol{\rho} := G_2(t)\boldsymbol{\rho}G_1(t)$ is well defined and we will indicate some properties of this space. In the third section we suppose that the operator A_1 and A_2 are the generators of C_1 and C_2-regularized semigroups. We show that Δ is also the generator of some regularized semigroup. A similar result is already proved in [5], when A_i generates exponentially bounded n-times integrated semigroups, for $i = 1, 2$. In the last section we give two examples of remedial operators in radiotherapy and chemotherapy in proliferation of cancer cells.

2. Space of remedial operators

DEFINITION 2. Let $\{G_1(t)\}_{t\geq 0}$ and $\{G_2(t)\}_{t\geq 0}$ be two families of semigroups in $\mathcal{L}(X)$ (not necessarily of class C_0). We say that $\mathcal{R}(X) \subset \mathcal{L}(X)$ is the set of *remedial operators for $G_1(t)$ and $G_2(t)$* if $\mathcal{G}(t)\boldsymbol{\rho} := G_2(t)\boldsymbol{\rho}G_1(t)$ is well defined for all $\boldsymbol{\rho} \in \mathcal{R}(X)$ and we have

(i) $\mathcal{G}(0)\boldsymbol{\rho} = \boldsymbol{\rho}$ for all $\boldsymbol{\rho} \in \mathcal{R}(X)$;
(ii) $\mathcal{G}(t)\mathcal{G}(s)\boldsymbol{\rho} = \mathcal{G}(t+s)\boldsymbol{\rho}$ for all $\boldsymbol{\rho} \in \mathcal{R}(X)$ and all $t, s \geq 0$;
(iii) $\mathcal{G}(t)\boldsymbol{\rho}$ converges strongly to $\boldsymbol{\rho}$, for any $\boldsymbol{\rho} \in \mathcal{R}(X)$, as $t \to 0$;
(iv) For any $\boldsymbol{\rho} \in \mathcal{R}(X)$, there exists $M > 0$ such that $\sup_{t\geq 0} \|\mathcal{G}(t)\boldsymbol{\rho}\| \leq M$.

It is clear that $\mathcal{R}(X)$ is a subspace of $\mathcal{L}(X)$ and the condition (iv) implies that $\mathcal{R}(X)$ can be endowed with the norm

$$|\!|\!|\boldsymbol{\rho}|\!|\!| := \sup_{t\geq 0} \|\mathcal{G}(t)\boldsymbol{\rho}\|.$$

Let us denote once more by $\mathcal{R}(X)$ the completion of $\mathcal{R}(X)$ for this norm.

THEOREM 2. *On the Banach space $\mathcal{R}(X)$, $\mathcal{G}(t)$ is a family of contractions in $\mathcal{L}(\mathcal{L}(X))$.*

Proof. It is not hard to verify that all the conditions of Definition 2 are true (by passing to limits of Cauchy sequences) for all $\boldsymbol{\rho} \in \mathcal{R}(X)$. Hence $\mathcal{G}(t)$ defines a generalized tensor product semigroup on $\mathcal{R}(X)$ and we have

$$|\!|\!|\mathcal{G}(s)\boldsymbol{\rho}|\!|\!| = \sup_{t\geq 0} \|\mathcal{G}(t+s)\boldsymbol{\rho}\| \leq |\!|\!|\boldsymbol{\rho}|\!|\!|.$$

This implies that

$$|\!|\!|\mathcal{G}(t)|\!|\!|_{\mathcal{L}(\mathcal{L}(X))} := \sup\{|\!|\!|\mathcal{G}(t)\boldsymbol{\rho}|\!|\!| \ : \ |\!|\!|\boldsymbol{\rho}|\!|\!| \leq 1\} \leq 1. \ \blacksquare$$

Since, in general, $G_1(t)$ and $G_2(t)$ are not continuous in the norm operator topology $\mathcal{G}(t)$ is not strongly continuous on $\mathcal{R}(X)$. However, in the next section we construct a C-regularized semigroup which is generated by an extension of some restriction of the generator Δ defined by $\Delta\boldsymbol{\rho} = A_2\boldsymbol{\rho} + \boldsymbol{\rho}A_1$.

3. Tensor product regularized semigroup. For $i = 1, 2$, let A_i generate a C_i-regularized semigroup $W_i(t)$ and let A_1 be densely defined. Let $\mathcal{D}(\Delta)$ be domain of Δ defined as in Proposition 1(2), with $\Delta\boldsymbol{\rho} = A_2\boldsymbol{\rho} + \boldsymbol{\rho}A_1$. We suppose that $\rho(A_i)$ is the resolvent set of A_i and $\rho(A_1) \cap \rho(A_2)$ is not empty. For $r \in \rho(A_1) \cap \rho(A_2)$, we define Λ_r by $\Lambda_r\boldsymbol{\rho} := (r - A_2)^{-1}\boldsymbol{\rho}(r - A_1)^{-1}$ on $\mathcal{L}(X)$.

LEMMA 1. *Under the above assumptions* Δ *is a closed operator on* $\mathcal{L}(X)$ *and if we denote by* $\widetilde{\Delta}$ *the restriction of* Δ *to*

$$\mathcal{L}_{A_2,A_1}(X) := \{\boldsymbol{\rho} \in \mathcal{L}(X)\ ;\ \boldsymbol{\rho}(X) \subset \mathcal{D}(A_2)\ \text{ and }\ A_2\boldsymbol{\rho}A_1 \text{ is bounded on } \mathcal{D}(A_1)\},$$

then we have

$$\operatorname{Im}(\Lambda_r) = \mathcal{D}(\widetilde{\Delta}) := \mathcal{D}(\Delta) \cap \mathcal{L}_{A_2,A_1}(X).$$

Proof. Let $\boldsymbol{\rho}_n$ be a sequence in $\mathcal{D}(\Delta)$ which converges to $\boldsymbol{\rho}$ and $\Delta\boldsymbol{\rho}_n$ to B in $\mathcal{L}(X)$. Hence for any $x \in \mathcal{D}(A_1)$, $\boldsymbol{\rho}_n x$ converges to $\boldsymbol{\rho}x$ and $\boldsymbol{\rho}_n A_1 x$ converges to $\boldsymbol{\rho}A_1x$. This implies that $A_2\boldsymbol{\rho}_n x$ converges also to $Bx - \boldsymbol{\rho}A_1x$. Now, since any generator of a regularized semigroup is closed (see [6, Theorem 3.4]), thus A_2 is closed and consequently $\boldsymbol{\rho}x \in \mathcal{D}(A_2)$ and $A_2\boldsymbol{\rho}x = Bx - \boldsymbol{\rho}A_1x$, which implies the closedness of Δ.

If $\boldsymbol{\rho} \in \operatorname{Im}(\Lambda_r)$, then there exists $\boldsymbol{\sigma} \in \mathcal{L}(X)$ such that $\boldsymbol{\rho} = (r - A_2)^{-1}\boldsymbol{\sigma}(r - A_1)^{-1}$. Hence on $\mathcal{D}(A_1)$ we have

$$\Delta\boldsymbol{\rho} = (r(r - A_2)^{-1} - I)\boldsymbol{\sigma}(r - A_1)^{-1} + (r - A_2)^{-1}\boldsymbol{\sigma}(r(r - A_1)^{-1} - I),$$

which has a bounded extension

$$B = -[\boldsymbol{\sigma}(r - A_1)^{-1} + (r - A_2)^{-1}\boldsymbol{\sigma}] + 2r\boldsymbol{\rho}$$

that implies $\operatorname{Im}(\Lambda_r) \subset \mathcal{D}(\Delta)$. Furthermore, for any $x \in X, \boldsymbol{\rho}x \in \mathcal{D}(A_2)$ and for $\boldsymbol{\sigma} = (r - A_2)\boldsymbol{\rho}(r - A_1)$ on $\mathcal{D}(A_1)$, $\boldsymbol{\sigma} - r^2\boldsymbol{\rho} + rB$ is a bounded extension of $A_2\boldsymbol{\rho}A_1$ from $\mathcal{D}(A_1)$. This implies also that $\operatorname{Im}(\Lambda_r) \subset \mathcal{L}_{A_2,A_1}(X)$.

Conversely if $\boldsymbol{\rho} \in \mathcal{D}(\widetilde{\Delta})$, then there exists a bounded operator B such that for any $x \in \mathcal{D}(A_1)$, $(A_2\boldsymbol{\rho} + \boldsymbol{\rho}A_1)x = Bx$. With the bounded operator $\boldsymbol{\sigma} = r\boldsymbol{\rho} - rB + A_2\boldsymbol{\rho}A_1$ we retrieve $\boldsymbol{\rho} = (r - A_2)^{-1}\boldsymbol{\sigma}(r - A_1)^{-1}$ and $\mathcal{D}(\widetilde{\Delta}) \subset \operatorname{Im}(\Lambda_r)$. ∎

Let us denote by Γ the operator $\Gamma\boldsymbol{\rho} = C_2\boldsymbol{\rho}C_1$ on $\mathcal{L}(X)$.

THEOREM 3. *Under the above assumptions, suppose there exists a real* r *such that for any* $t \geq 0$, $W_i(t)$ *commutes with* $(r - A_i)^{-1}$, *for* $i = 1, 2$. *Then an extension of* $\widetilde{\Delta}$ *generates a* $\Lambda_r\Gamma$*-regularized semigroup* $\mathcal{W}(t)$, *which is continuous in the uniform operator topology of* $\mathcal{L}(\mathcal{L}(X))$, *that leaves* $D(\widetilde{\Delta})$ *invariant.*

Proof. Define $\mathcal{W}(t)$ on $\mathcal{L}(X)$ by

$$\mathcal{W}(t)\boldsymbol{\rho} := (r - A_2)^{-1}W_2(t)\boldsymbol{\rho}W_1(t)(r - A_1)^{-1}.$$

For any $x \in X$ and $i = 1, 2$,

$$\frac{d}{d\tau}W_i(\tau)(r - A_i)^{-1}x = W_i(\tau)A_i(r - A_i)^{-1}x.$$

Since $W_i(t)$ is a strongly continuous family in $\mathcal{L}(X)$, $W_i(\tau)A_i(r - A_i)^{-1}x$ is uniformly bounded on $[s, t]$ by the mean value theorem in the Banach space X, there exists $\tau_0 \in [s, t]$, such that

$$\big(W_i(t) - W_i(s)\big)(r - A_i)^{-1}x = (t - s)W_i(\tau_0)A_i(r - A_i)^{-1}x$$

and by the uniform boundedness principle $\|W_i(\tau)A_i(r - A_i)^{-1}\|$ is bounded in a closed neighborhood of τ_0. Thus, $W_i(t)(r - A_i)^{-1}$ is continuous in the operator norm topology of $\mathcal{L}(X)$. Since

$$\begin{aligned}\|\mathcal{W}(t)\boldsymbol{\rho} - \Lambda_r\Gamma\boldsymbol{\rho}\| &= \|(r-A_2)^{-1}(W_2(t)-C_2)\boldsymbol{\rho}W_1(t)(r-A_1)^{-1} \\ &\qquad + (r-A_2)^{-1}C_2\boldsymbol{\rho}(W_1(t)-C_1)(r-A_1)^{-1}\| \\ &\le (\|(r-A_2)^{-1}W_2(t)-(r-A_2)^{-1}C_2\|.\|W_1(t)(r-A_1)^{-1}\| \\ &\qquad + \|(r-A_2)^{-1}C_2\|.\|(W_1(t)(r-A_1)^{-1} - C_1(r-A_1)^{-1}\|)\|\boldsymbol{\rho}\|\end{aligned}$$

and since $W_i(t)(r-A_i)^{-1} = (r-A_i)^{-1}W_i(t)$ converges uniformly to $C_i(r-A_i)^{-1} = (r-A_i)^{-1}C_i$, as $t \to 0$, this implies the continuity of $\mathcal{W}(t)$ in the uniform operator topology of $\mathcal{L}(\mathcal{L}(X))$.

It is clear that $\mathcal{W}(0)$ equals $\Lambda_r\Gamma$ and

$$\begin{aligned}\mathcal{W}(t)\mathcal{W}(s)\boldsymbol{\rho} &= (r-A_2)^{-1}W_2(t)(r-A_2)^{-1}W_2(s)\boldsymbol{\rho}W_1(s)(r-A_1)^{-1}W_1(t)(r-A_1)^{-1} \\ &= (r-A_2)^{-2}C_2W_2(t+s)\boldsymbol{\rho}W_1(t+s)C_1(r-A_1)^{-2} \\ &= \Lambda_r\Gamma\mathcal{W}(t+s)\boldsymbol{\rho}.\end{aligned}$$

Hence, $\mathcal{W}(t)$ is a $\Lambda_r\Gamma$-regularized semigroup.

Now, by taking $\boldsymbol{\rho} \in D(\widetilde{\Delta}) = \mathrm{Im}(\Lambda_r)$, we can write $\mathcal{W}(t)$ as

$$\mathcal{W}(t)\boldsymbol{\rho} = (r-A_2)^{-2}W_2(t)(\Lambda_r^{-1}\boldsymbol{\rho})W_1(t)(r-A_1)^{-2}.$$

Again using the mean value theorem, one may show that $(r-A_i)^{-2}W_i(t)$ is a differentiable function of t, in the operator norm topology of $\mathcal{L}(X)$, for $i=1,2$. Thus $\mathcal{W}(t)\boldsymbol{\rho}$ is differentiable, with

$$\begin{aligned}\frac{d}{dt}\mathcal{W}(t)\boldsymbol{\rho} &= \left[\frac{d}{dt}(r-A_2)^{-2}W_2(t)\right](\Lambda_r^{-1}\boldsymbol{\rho})W_1(t)(r-A_1)^{-2} \\ &\qquad + (r-A_2)^{-2}W_2(t)(\Lambda_r^{-1}\boldsymbol{\rho})\left[\frac{d}{dt}(r-A_1)^{-2}W_1(t)\right] \\ &= (r-A_2)^{-1}W_2(t)A_2(r-A_2)^{-1}(\Lambda_r^{-1}\boldsymbol{\rho})(r-A_1)^{-1}W_1(t)(r-A_1)^{-1} \\ &\qquad + (r-A_2)^{-1}W_2(t)(r-A_2)^{-1}(\Lambda_r^{-1}\boldsymbol{\rho})(r-A_1)^{-1}A_1W_1(t)(r-A_1)^{-1} \\ &= (r-A_2)^{-1}W_2(t)(A_2\boldsymbol{\rho})W_1(t)(r-A_1)^{-1} \\ &\qquad + (r-A_2)^{-1}W_2(t)(\boldsymbol{\rho}A_1)W_1(t)(r-A_1)^{-1} \\ &= \mathcal{W}(t)\Delta\boldsymbol{\rho}.\end{aligned}$$

This implies that an extension of $\widetilde{\Delta}$ generates $\mathcal{W}(t)$. Since $\mathcal{W}(t)$ commutes with Λ_r, $\mathcal{W}(t)$ leaves $D(\widetilde{\Delta}) = \mathrm{Im}(\Lambda_r)$ invariant. ∎

The following definition is a natural consequence of the preceding theorem.

DEFINITION 3. Whenever A_1 and A_2 generate two regularized semigroups, then the regularized semigroup generated by an extension of the operator $\widetilde{\Delta}$ on $\mathcal{L}(X)$ is called *a tensor product regularized semigroup.*

COROLLARY 1. *Let $W_1(t)$ be an exponentially bounded C-regularized semigroup of the type ω generated by A_1 and let $G_2(t)$ be a C_0-semigroup of the type $-\omega$ generated by A_2. Then all the elements of*

$$\mathcal{I}_C := \{\boldsymbol{\rho} \in \mathcal{L}(X)\ ;\ \boldsymbol{\rho} = BC \text{ with } B \in \mathcal{L}(X)\},$$

the right ideal generated by C, are remedial operators for $e^{tA_1} = C^{-1}W_1(t)$ and $G_2(t)$.

Proof. Since $G_2(t)BCe^{tA_1} = G_2(t)BW_1(t)$ all the properties of Definition 2 are readily satisfied for $\boldsymbol{\rho} \in \mathcal{I}_C$. ■

In the following section we give an application of the above Corollary.

4. Application to transport theory for growing cell populations. One of the most appealing applications of this theory can be found in the modelling of a carcinogenic cell population. Since this kind of cells has a high proliferating rate, we can associate with them an abnormally large maturation velocity. In 1983, Rotenberg [11] presented a model for growing cell populations. In his model cells are distinguished by their degree of maturity $\mu \in I = (0, 1)$ and their maturation velocity $v(= \frac{d\mu}{dt})$ which is considered as an independent variable within $J = (a, b)$ $(0 \leq a < b \leq \infty)$. The positivity of velocities comes from the fact that a cell cannot become less mature with time and adds to the irreversible character of the problem. The density of the population $f = f(\mu, v, t)$ is described by the following partial differential equation of transport type:

$$\frac{\partial f}{\partial t} = -v\frac{\partial f}{\partial \mu} - \sigma(\mu, v)f + \int_a^b r(\mu, v, v')f(\mu, v', t)dv' = Tf, \tag{4}$$

where $\sigma(\mu, v) = \int_a^b s(\mu, v', v)dv'$ and $s(\mu, v', v)$ is the *sinking rate* at which cells drop out of the cohort characterized by v to join those of v'. The kernel $r(\mu, v, v')$ is the *transition rate* at which cells change their velocities from v' to v. The reproduction rule are given by the following boundary condition, so called *Lebowitz–Rubinow boundary condition*:

$$vf(0, v, t) = p\int_a^b k(v, v')v'f(1, v', t)dv' \tag{5}$$

where $p \geq 0$ is the average number of viable daughters per mitosis. This rule allows a choice in the degree of positive correlation k between velocities of mother and daughter cells.

For a mathematical study of this problem, let us denote $\Omega = (0, 1) \times (a, b) = I \times J$, $L^1(\Omega)$ the Lebesgue's space with its natural norm $\|\cdot\|_1$ and the partial Sobolev space $W^1(\Omega) = \{\varphi \in L^1(\Omega) \mid v\frac{\partial\varphi}{\partial\mu} \in L^1(\Omega)\}$ endowed with the norm $\|\varphi\|_{W^1(\Omega)} = \|\varphi\|_1 + \|v\frac{\partial\varphi}{\partial\mu}\|_1$. In [3], we studied the well-posedness of this model under the condition that the maturation velocity v belongs to $J = (a, b)$ with $0 < a < b < \infty$ and we proved that the operator A_2 with domain $D(T) := \{f \in W^1(\Omega) \mid (5) \text{ holds}\}$ generates a C_0-semigroup. We have also showed the positivity, irreducibility of the generated semigroup which converges asymptotically to a projection of rank one. In [4], in contrast with [3], we allow that the maturation velocity for any cell can become null. This implies that the cell population never leaves completely its initial distribution, because at every time we can find some cells of the initial cell population that are not divided. In this case, in spite of the fact that we lose the weak compact character of the generated semigroup, we have calculated explicitly its essential type and we have showed the asymptotic convergence of the generated semigroup to a projection of rank one. Finally, the case $0 \leq a < b = \infty$ is a pathological case. In fact, M. Boulanouar in [2] showed that even with a simplest reproduction rule, which is called by M. Rotenberg [11] a *perfect memory reproduction* *rule*, if $b = \infty$ and $p > 1$ then the problem (4) is ill-posed and he introduced a regularized operator C with which A_2 generates a C-regularized semigroup in the sense of deLaubenfels [6]. This perfect memory kind of reproduction rule is one in which the maturation velocity of a parent cell at mitosis is transmitted to the daughter cells. This gives the following boundary condition:

$$f(0, v, t) = pf(1, v, t). \tag{6}$$

This identity asserts that the last velocity the parent happened to have just before mitosis would be the initial velocity assumed by the daughters. Hence, this kind of reproduction rule produces a population at the maximum rate and can be simulated as a cohort of the cancer cells. If we take $\sigma = r = 0$ in (4), then A_2 with boundary condition (6) generates a semigroup $T(t)$ which has an explicit form

$$T(t)\varphi(\mu, v) = p^{[tv-\mu]}\varphi(\mu + [tv - \mu] - tv, v). \tag{7}$$

where $[tv - \mu] = n + 1$ if $n < tv - \mu \leq n + 1$. This semigroup is not strongly continuous for $p > 1$. In fact

$$\begin{aligned} \|T(t)f\| &= \int_0^\infty \int_0^1 |T(t)f(\mu, v)| d\mu dv \\ &= \sum_{n\geq 0} \int_{\frac{n}{t}}^{\frac{n+1}{t}} \Big[\int_0^{tv-n} p^{n+1}|f(\mu + n + 1 - tv, v)| d\mu \\ &\qquad + \int_{tv-n}^1 p^n |f(\mu + n - tv, v)| d\mu \Big] dv. \end{aligned}$$

Hence, the series diverges for $p > 1$ and for some $f \in L^1((0, 1) \times (a, \infty))$. This implies that $T(t)$ is an unbounded semigroup and consequently, is not strongly continuous.

Here, we are going to give two concrete examples of remedial operators in this situation.

A remedial operator in radiotherapy. Current radiotherapy techniques fire radiation beams into the body to kill cancer cells. This treatment reduces spontaneously the amount of cancer cell population and can be modelled by a multiplicative operator. In [2], Boulanouar has taken $\boldsymbol{\rho} f(\mu, v) := p^{-v^2} f(\mu, v)$ for regularizing the ill-posed semigroup. In spite of the fact that this operator reduces considerably those cells which have large maturation velocities, but the resulting $\boldsymbol{\rho}$-regularized semigroup $W(t) = \boldsymbol{\rho}T(t)$ has a behavior as $p^{\frac{t^2}{4}+1}$ (see [2, Lemme 2.3]). So it seems hard to find a C_0-semigroup $S(t)$ such that $S(t)\boldsymbol{\rho}T(t)$ remains bounded for all $t > 0$, unless taking $S(t)$ as a superstable semigroup, that become zero after finite time. This choice of semigroup would be another strategy of remedying, which consists of shifting the emphasis from the remedial operator $\boldsymbol{\rho}$ to the semigroup $S(t)$. This sort of strategy is far from our primary objective.

Thus, such a remedial operator does not belong to any space $\mathcal{R}(X)$ for any C_0-semigroup $S(t)$. Experimentally one knows that after radiotherapy remediation the residual cells can generate an amount of cancer cells of exponential growth.

A remedial operator in chemotherapy. During chemotherapy treatment a hostile biophysical environment is created in order to stop the proliferation of the cancer cells.

This treatment reduces the population distribution by a kind of two compartmental actions; annihilation of the cohort with the large maturation velocities, while maintaining the colony with small maturation velocities, for a long period to render them inoffensive. This can be done be introducing a time dependent integral operator $[\boldsymbol{\rho}(t)f](\mu,v) = \int_0^\infty r(v,v',t)f(\mu,v')dv'$, with a bounded positive kernel $r(v,v',t)$ such that the support of r is in $[0,\alpha]\times[0,\beta]\times[0,\infty)$ with α and β relatively small. Such integral operator annihilates the cells which have a large maturation velocity and also any function in its image has a small maturation velocities. For simplicity we take a time independent kernel $r(v,v')$, with $\sup_{(v,v')\in[0,\alpha]\times[0,\beta]}|r(v,v')| \le M$. From (7) it follows that for any $f \in L^1(\Omega)$, if $N-1 < t\beta \le N$, the $\boldsymbol{\rho}$-regularized semigroup $W(t) = \boldsymbol{\rho}T(t)$ can be estimated by

$$\begin{aligned}
\|W(t)f\| &= \int_0^\infty \int_0^1 \int_0^\infty r(v,v')|T(t)f(\mu,v')|dv'd\mu dv \\
&\le M\alpha \int_0^\beta \int_0^1 |T(t)f(\mu,v)|d\mu dv \\
&\le M\alpha \sum_{0\le n\le N} \int_{\frac{n}{t}}^{\frac{n+1}{t}} \Big[\int_0^{tv-n} p^{n+1}|f(\mu+n+1-tv,v)|d\mu \\
&\qquad + \int_{tv-n}^1 p^n|f(\mu+n-tv,v)|d\mu\Big] dv \\
&= M\alpha \sum_{0\le n\le N} \int_{\frac{n}{t}}^{\frac{n+1}{t}} \Big[\int_0^{n+1-tv} p^{n+1}|f(\mu,v)|d\mu + \int_0^{n+1-tv} p^n|f(\mu,v)|d\mu\Big] dv \\
&\le M\alpha p^{t\beta+1}\|f\|.
\end{aligned}$$

Thus, by taking a C_0-semigroup $S(t)$ of type $\omega = -\beta\ln p$, $\|S(t)\boldsymbol{\rho}T(t)\|$ would be bounded and $\boldsymbol{\rho}$ is a remedial operator in the sense of Definition 2.

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