

# Structured population dynamics – patches and networks

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## Motivation: Example 1. Transport on a network.

Let us consider a network represented by the directed graph

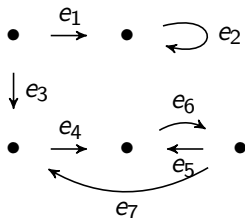


Figure: 1. A directed graph  $G$  representing the physical network considered in the example.

Many a dynamical model can be associated with this graph. The graph can represent a network of states (edges) containing some sub populations that can migrate through the nodes. If we count the total number of individuals on the edges, then the structured population can be described by a vector  $\mathbf{v} = (v_1, \dots, v_7)$  that satisfies

$$\mathbf{v}' = \mathcal{L}\mathbf{v}, \quad (1)$$

where  $\mathcal{L}$  is a matrix describing redistribution of the flow in the nodes (in fact, the adjacency matrix of the line graph of  $G$ ).

Models of this type are too crude for many purposes. They correspond to what is often referred to as lumped states – a macroscopic description of the system.

The macroscopic description usually is a resultant of many dynamical processes that take place at the nodes and along the edges of such a network. Including them in the description creates a micromodel whose analysis can provide a better insight into the dynamics of the process.

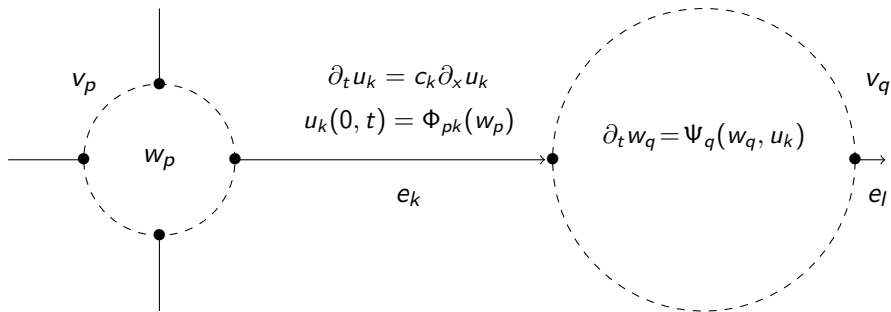


Figure: 2. A hypothetical micromodel of a network flow obeying first order equations along the edges with the boundary equation at the entry point determined by the state at the adjacent node. Inside the node the substance may undergo some chemical reaction.

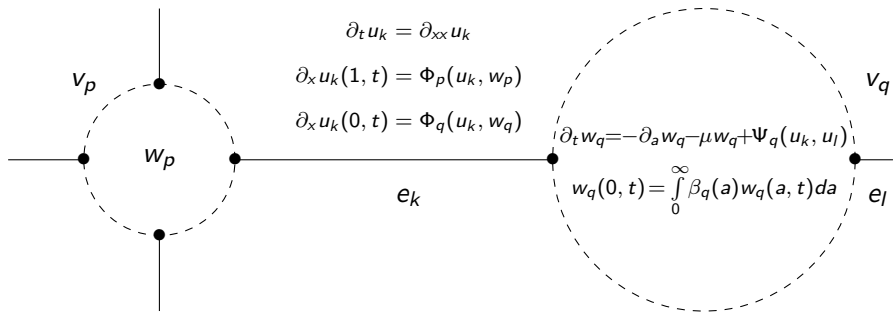


Figure: 3. A hypothetical micromodel related to a network in which the population in the node  $v_q$  evolves according to the McKendrick model and the exchange between the nodes occurs through diffusion along the edges.

It is important, however, to keep in mind that the procedure of enhancing the macromodel to a micromodel should be consistent in the sense that both should give (at least approximately) the same dynamics at the macroscale. In other words, macrovariables obtained from the micromodel (built either from first principles or by enhancing a macromodel) should have the same (approximately) the same dynamics as the macrovariables obtained from the macromodel.

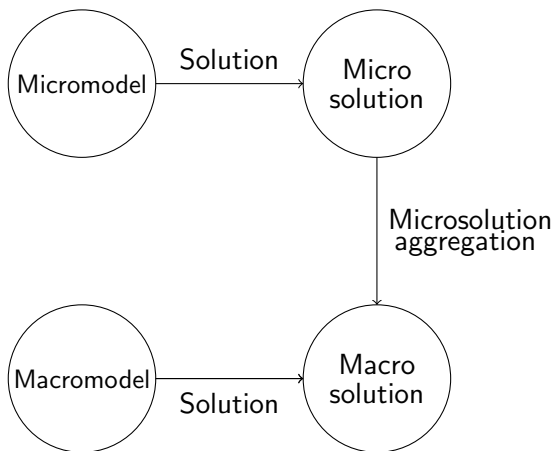


Figure: 4. A consistent micromodel



## Graph-theoretic notions and notations.

We consider a network represented by a simple (no loops or multiple edges) directed connected metric graph

$$G = (V(G), E(G)) = (\{v_1, \dots, v_r\}, \{e_1, \dots, e_m\})$$

and denote  $M = \{1, \dots, m\}$ .

By  $\mathbb{B}$  we denote the weighted adjacency matrix for the line graph of  $G$  whose coefficients are given by

$$b_{ij} = \begin{cases} w_{ki} & \text{if } \exists_k e_j \xrightarrow{v_k} e_i, \\ 0 & \text{otherwise.} \end{cases}$$

If there is an outgoing edge at each vertex, then  $\mathbb{B}$  is column stochastic.

## Flow on a network.

We parameterise the edges of  $G$ :

- $e_j \rightarrow [0, 1]$ , 0 is the tail and 1 is the head.
- a function on  $G$  is written as  $\mathbf{u}(x) = (u_j(x))_{j \in M}$ ,  $x \in [0, 1]$ .

The flow on  $G$  is described by  $\mathbf{u}(x, t) = (u_j(x, t))_{j \in M}$ , where  $u_j(x, t)$  is the density of particles at position  $x \in [0, 1]$  and time  $t \geq 0$ , moving along  $e_j$  from the tail 0 to the head 1 with a continuous velocity  $c_j(x) > 0$ .

If the mass conservation holds at each vertex then, denoting  $\mathbb{C}(x) = \text{diag}(c_j(x))_{j \in M}$  and  $\mathbb{K} = (k_{ij})_{i,j \in M} = \mathbb{C}^{-1}(0)\mathbb{B}\mathbb{C}(1)$ , the above transport problem can be written as

$$\begin{cases} \partial_t \mathbf{u}(x, t) + \partial_x (\mathbb{C}(x) \mathbf{u}(x, t)) = 0, & x \in (0, 1), \quad t \geq 0, \\ \mathbf{u}(0, t) = \mathbb{K} \mathbf{u}(1, t), \\ \mathbf{u}(x, 0) = \dot{\mathbf{u}}(x), \end{cases} \quad (2)$$

if (and only if)  $G$  does not contain a sink. Moreover, if  $G$  contains a sink, then the original transport problem is not solvable.

The problem can be converted into a constant speed problem by a change of variables and from now on we assume that  $c_j$  does not depend on  $x$  for  $j \in M$ .

## Generalization: Example 2. Kimmel–Stivers model.

Consider the gene amplification; that is, an increase or decrease of numbers of drug resistant gene copies observed in tumor cells and associated with resistance to certain drugs. In this model the population is divided into a denumerable quantity of types according to the number of drug resistant genes,  $(V_n(t))_{n \in \mathbb{N}_0}$  and its evolution is modelled by a branching random walk. We assume that at death any cell (apart from class 0) produces two offspring that only can belong to classes  $j + 1$ ,  $j$ , or  $j - 1$ . Then the expectations of the random variables  $(V_n(t))_{n \in \mathbb{N}_0}$ , denoted by  $(v_n(t))_{n \in \mathbb{N}_0}$ , satisfy the birth-and-death system with proliferation,

$$\begin{aligned}v_0' &= a_0 v_0 + d_1 v_1, \\v_1' &= a_1 v_1 + d_2 v_2, \\v_n' &= a_n v_n + b_{n-1} v_{n-1} + d_{n+1} v_{n+1}, \quad n \geq 2, \quad (3)\end{aligned}$$

where  $d_{n+1}$ ,  $b_{n-1}$  are the rates of recruitment from the populations  $n + 1$  and  $n - 1$  into the population  $n$ , and  $a_n$  is the net growth rate of the population  $n$  that incorporates birth, death and loss to other populations of cells of type  $n$ .

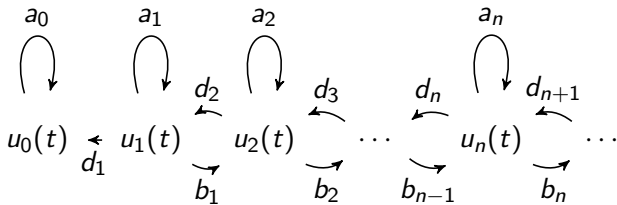


Figure: 6. Graphical representation of the Kimmel–Stivers model.

However, the cells have their own vital dynamics:

- they age till they die or divide;
- they could have different lifespans  $\tau_n$ .

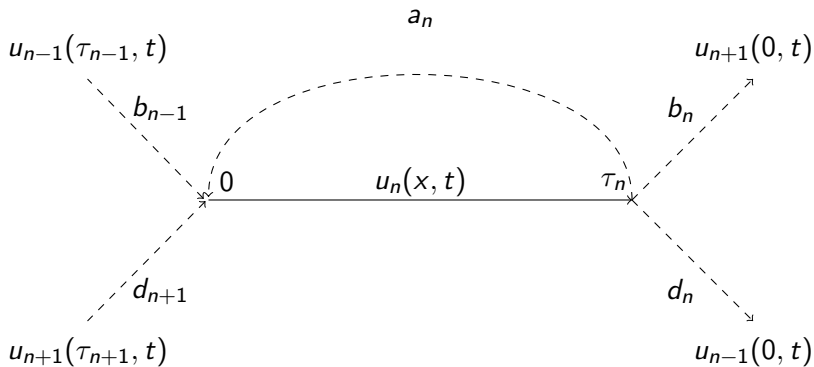


Figure: 7. Kimmel–Stievers model with vital dynamics



Also, in principle, the mutations can change the number of the resistant genes in an arbitrary way and cells can die at any time for various reasons (at the rate  $\mu_n$ ,  $n \in \mathbb{N}$ ). Further, the mutations can be divided into various groups:

- due to the replication errors occurring when the cell divides (at the rates  $(k_{ij})_{i,j \in \mathbb{N}}$ );
- due to external factors (mutagenes) that may happen at any moment of the cell's life cycle (at the rates  $(r_{ij})_{i,j \in \mathbb{N}}$ ).

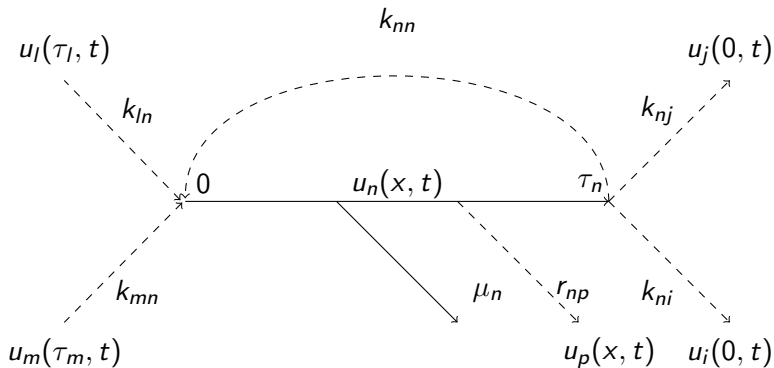


Figure: 8. Discrete Lebowitz–Rubinov–Rotenberg model.

Thus

$$\begin{aligned}\partial_t u_n + \partial_x u_n &= -\mu_n u_n + \sum_j r_{nj} u_j, & x \in (0, \tau_n), \\ u_n(0, t) &= \sum_j k_{nj} u_j(\tau_j, t),\end{aligned}\tag{4}$$

$n \geq 1$ , where the summation is extended over all states  $j$  that, by mutation, can change the number of genes to  $n$ .

**Problem:** Different domains.

**Solution:** Rescaling; for each  $n$ ,

$$\tau_n^{-1} x \rightarrow x.$$

Then  $c_n = \tau_n^{-1}$  can be considered as the speed of maturation in class  $n$ .

This allows for writing (4) in the form (2):

$$\partial_t \mathbf{u} + \mathbb{C} \partial_x \mathbf{u} = -\mathbb{M} \mathbf{u} + \mathbb{R} \mathbf{u}, \quad x \in (0, 1), \quad (5)$$

$$\mathbf{u}(0, t) = \mathbb{K} \mathbf{u}(1, t), \quad (6)$$

$$\mathbf{u}(x, 0) = \dot{\mathbf{u}}(x), \quad (7)$$

where  $\mathbb{C} = \text{diag}(c_j)_{j \in \mathbb{N}}$ ,  $\mathbb{M} = \text{diag}(\mu_j)_{j \in \mathbb{N}}$ ,  $\mathbb{R} = (r_{ij})_{i, j \in \mathbb{N}}$  and  $\mathbb{K} = (k_{ij})_{i, j \in \mathbb{N}}$ . We assume

$$0 < c_{\min} \leq c_n \leq c_{\max} < \infty, \quad n \in \mathbb{N}.$$

and  $\mathbb{K}, \mathbb{R}, \mathbb{M}$  are bounded operators.

## Solvability

Consider in  $\mathbf{X} = L_1([0, 1], l_1^{|\mathbf{M}|})$  the abstract Cauchy problem

$$\mathbf{u}_t = A\mathbf{u}, \quad \mathbf{u}(0) = \mathbb{K}\mathbf{u}(1), \quad \mathbf{u}(0) = \mathbf{f}, \quad (8)$$

where  $A$  is the realization of the expression

$$A\mathbf{u} = A_0\mathbf{u} + Q\mathbf{u} = \text{diag}(-c_j \partial_x u_j)_{j \in \mathbf{M}} - M\mathbf{u} + R\mathbf{u}$$

on the domain  $D(A) = \{\mathbf{u} \in W_1^1([0, 1], l_1^{|\mathbf{M}|}); \mathbf{u}(0) = \mathbb{K}\mathbf{u}(1)\}$ .

## Theorem

*Let  $\mathbb{K}$  be an arbitrary matrix. Then  $(A_0, D(A))$  generates a  $C_0$ -semigroup. This semigroup is positive if and only if  $\mathbb{K}$  is nonnegative and it is stochastic if and only if  $\mathbb{K} = \mathbb{C}^{-1}\mathbb{B}\mathbb{C}$ , where  $\mathbb{B}$  is a stochastic matrix.*

$A$  generates a semigroup by the Bounded Perturbation Theorem.

## A representation formula.

Many results can be proven under an additional assumption that  $c_j = 1$  for  $j \in M$ . The general problem

$$\mathbf{u}_t = -\mathbb{C}\partial_x \mathbf{u}, \quad \mathbf{u}(0) = \mathbb{K}\mathbf{u}(1), \quad \mathbf{u}(0) = \mathbf{f}, \quad (9)$$

can be converted to such a one, provided

$$\exists c \in \mathbb{R} \forall j=1, \dots, m \frac{c}{c_j} = l_j \in \mathbb{N}. \quad (10)$$

Since  $\tau_j = 1/c_j$  is the time taken to traverse  $e_j$ , the above condition can be expressed by saying that all traverse times are natural multiples of a reference time  $\tau_0 = 1/c$ .

Then

$$(e^{tA}\mathbf{u})(x) = [\mathbb{K}^r \mathbf{u}](t+x-r), \quad r \in \mathbb{N}_0, \quad 0 \leq t+x-r \leq 1. \quad (11)$$

Thus the representation (11) reduces the analysis of  $(e^{tA})_{t \geq 0}$  to that of the iterates of  $\mathbb{K}$ .



## **Asymptotic state lumping.**

At the same time, micromodels, both built from first principles and as extending macromodels, tend to be exceedingly complex, often to the extent of not allowing for any robust analysis. Moreover, while being important from theoretical point of view, the full information they yield often is redundant for many applications. Thus, there is a tendency to use in practice macromodels that are backed by more detailed micromodels should a need for a more precise description arise.

As mentioned earlier, the micromodel should be consistent with the original macromodel in the sense that both should give the same macroscopic description of the process they model. Hence, here we ask a reverse question – how to construct a consistent macromodel from a given micromodel.

Thus we aim at completing the diagram in Fig. 4 in such a way that it commutes (at least approximately).

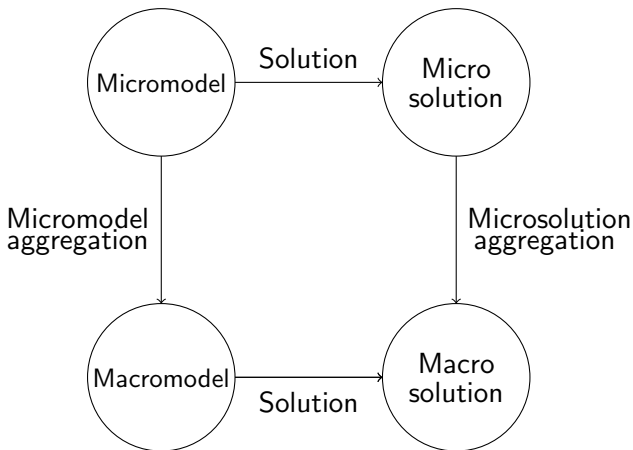


Figure: 9. Commutativity of the aggregation diagram

## Some mathematical tidbits.

As we shall see, the aggregation problems discussed above can be cast into the form of a singularly perturbed Cauchy problem

$$\partial_t u_\epsilon = K_\epsilon u_\epsilon, \quad t > 0, \quad u_\epsilon(0) = \overset{\circ}{u} \in X, \quad (12)$$

where  $\{K_\epsilon\}_{\epsilon>0}$  is a family of generators of  $C_0$ -semigroups  $(e^{tK_\epsilon})_{t\geq 0}$  in a Banach space  $X$ , that correspond to the micromodels. The problem is to determine the limit equation, corresponding to the macromodel, satisfied by  $u = \lim_{\epsilon\rightarrow 0} u_\epsilon$ .

Often the convergence of  $(e^{tK_\epsilon})_{t \geq 0}$  (almost uniformly) for  $t \geq 0$  occurs for initial values  $\overset{\circ}{u}$  from a subspace  $X_0 \neq X$  of the original space; such a convergence is called *regular convergence*. This space is uniquely determined as the closure of the range of the limit of the resolvents. For initial conditions  $\overset{\circ}{u} \notin X_0$ ,  $e^{tK_\epsilon} \overset{\circ}{u}$  may or may not converge. If it does, the convergence occurs (almost uniformly) for  $t > 0$ . Such a convergence is called *degenerate convergence*. The degenerate convergence often can be handled by a lemma by T. Kurtz.

We consider a family of equibounded semigroups  $(e^{tK_\epsilon})_{t \geq 0}$  and the generator  $V$  of a  $C_0$ -semigroup  $(e^{tV})_{t \geq 0}$  which is assumed to satisfy

$$\lim_{t \rightarrow \infty} e^{tV} f =: Pf, \quad f \in X; \quad (13)$$

$P$  is a projection onto the kernel  $\text{Ker}V$  of  $V$  along the closure of the range of  $V$ . Then

$$\lim_{\epsilon \rightarrow 0} e^{t\epsilon K_\epsilon} f = e^{tV} f \quad (14)$$

implies

$$\lim_{\epsilon \rightarrow 0} e^{t\epsilon K_\epsilon} f = 0, \quad f \in \text{Ker}P, t > 0.$$

The regular convergence that occurs on  $\text{Ker}V = \text{Im}P$  must be handled separately.

In many applications we have

$$K_\epsilon = S + \frac{1}{\epsilon}C,$$

then  $\epsilon K_\epsilon = \epsilon S + C$  and there exists

$$\lim_{t \rightarrow \infty} e^{tC} f = Pf$$

then  $X_0 = \text{Im}P$  is the space of regular convergence and if there exists a semigroup  $(e^{tK})_{t \geq 0}$  on  $X_0$  such that

$$\lim_{\epsilon \rightarrow 0} e^{tK_\epsilon} f = e^{tK} Pf,$$

almost uniformly on each  $[t_0, \infty)$ ,  $t_0 > 0$ .

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$$\lim_{\epsilon \rightarrow 0} e^{tK_\epsilon} f = e^{tK} Pf,$$

almost uniformly on each  $[t_0, \infty)$ ,  $t_0 > 0$ . In most relevant cases,  $P$  is the spectral projection onto the null space of  $C$ . Thus, in particular, for a nontrivial limit dynamics  $Cx = 0$  must have non-trivial solutions.



**Example 1.** Consider the two models for the spread of the genotype in a population: the Kimmel-Stivers macromodel without vital dynamics,

$$\mathbf{v}' = \mathcal{K}\mathbf{v}, \quad (15)$$

where  $\mathbf{v} = (v_i)_{i \in \mathbb{N}}$  describes the genotype distribution, and the LRR micromodel with cells' vital dynamics,

$$\begin{aligned} \partial_t \mathbf{u}(x, t) + \mathbb{C} \partial_x \mathbf{u}(x, t) &= 0, \\ \mathbf{u}(x, 0) &= \mathbf{u}(x), \quad \mathbf{u}(0, t) = \mathbb{K} \mathbf{u}(1, t), \end{aligned} \quad (16)$$

where  $\mathbf{u}(x) = (u_i(x))_{i \in \mathbb{M}}$  is the density of cells with genotype  $i$  at age  $x$ .

Since (16) and (15) describe the same phenomenon, the solutions should give the same answer at the level at which they are comparable. Here,  $\mathbf{v}(t)$  gives the total amount of cells in each class, hence we compare it with the 'aggregated', or 'lumped', solution to (16)

$$[\mathbf{P}_M \mathbf{u}](t) = \int_0^1 \mathbf{u}(x, t) ds = \left( \int_0^1 u_1(x, t) ds, \dots, \int_0^1 u_n(x, t) ds, \dots \right). \quad (17)$$

It turns out that for the Kimmel–Stivers model asymptotic state lumping can be done if we assume that the cells divide many times in the chosen reference unit of time. To balance this, we assume that the daughter cells have a tendency to be of the same genotype as the mother:

$$\begin{aligned}\partial_t \mathbf{u}_\epsilon(x, t) + \epsilon^{-1} \mathbb{C} \partial_x \mathbf{u}_\epsilon(x, t) &= 0, \\ \mathbf{u}_\epsilon(x, 0) &= \mathbf{u}(x), \quad \mathbf{u}_\epsilon(0, t) = (\mathbb{I} + \epsilon \mathbb{B}) \mathbf{u}_\epsilon(1, t),\end{aligned}\quad (18)$$

As before, for any fixed  $\epsilon > 0$  there is a strongly continuous semigroup  $(e^{tA_\epsilon})_{t \geq 0}$  solving (18).

## Theorem

(i)  $(e^{tA_\epsilon})_{t \geq 0}$  is equibounded;

(ii) if  $\lambda > c_{\min} \|\mathbb{B}\|$ , then

$$\lim_{\epsilon \rightarrow 0^+} R(\lambda, A_\epsilon) = R(\lambda, \mathbb{C}\mathbb{B})\mathbf{P}_M;$$

(iii) If  $\hat{\mathbf{u}} \in l_1^{|\mathbf{M}|}$  (that is, the initial condition is independent of  $x$ ), then

$$\lim_{\epsilon \rightarrow 0^+} e^{tA_\epsilon} \hat{\mathbf{u}} = e^{t\mathbb{C}\mathbb{B}} \hat{\mathbf{u}} \quad \text{in } L_1([0, 1], l_1^{|\mathbf{M}|}).$$

In general,  $(e^{tA_\epsilon})_{t \geq 0}$  do not converge on  $x$ -dependent initial values.

However, if the average lifespans  $\tau_n$  are integer multiples of some  $\tau(= 1)$ , then we can prove a stronger version of this result.

### Theorem

For any  $\dot{\mathbf{u}} \in L_1([0, 1], l_1^{|\mathbf{M}|})$  we have

$$\lim_{\epsilon \rightarrow 0^+} \mathbf{P}_M e^{tA_\epsilon} \dot{\mathbf{u}} = e^{t\mathbf{CB}} \mathbf{P}_M \dot{\mathbf{u}}. \quad (19)$$

Applying this result to the Kimmel–Stivers model we see that if

$\mathbf{u}_\epsilon(x, t) = (u_{0,\epsilon}(x, t), \dots, u_{n,\epsilon}(x, t), \dots)$  is the solution to

$$\partial_t u_n + \epsilon^{-1} \partial_x u_n = 0, \quad x \in (0, 1), \quad t > 0,$$

$$u_n(x, 0) = \dot{u}_n(x)$$

and

$$u_0(0, t) = u_0(1, t) + \epsilon(a_0 u_0(1, t) + d_1 u_1(1, t)),$$

$$u_1(0, t) = u_1(1, t) + \epsilon(a_1 u_1(1, t) + d_2 u_2(1, t)),$$

$$u_n(0, t) = u_n(1, t) + \epsilon(a_n u_n(1, t) + c_{n-1} u_{n-1}(1, t) + d_{n+1} u_{n+1}(1, t)),$$

$$n \geq 2,$$

then  $\int_0^1 \mathbf{u}_\epsilon(x, t) dx$  converges to the solution of (4) (with the initial condition  $\mathring{\mathbf{v}} = \int_0^1 \mathring{\mathbf{u}}(x) dx$ ). The interpretation of the boundary operator  $\mathcal{B} = \mathcal{I} + \epsilon\mathcal{C}$  is that at the mitosis one daughter cell always has the genotype of its mother, while the probability of mutations described in the Kimmel–Stivers model is very low.

The above result can be extended to more general boundary conditions, namely, to problems

$$\begin{cases} \partial_t \mathbf{u}(x, t) = -\frac{1}{\epsilon} \partial_x \mathbf{u}(x, t) + \mathcal{M} \mathbf{u}(x, t), & x \in (0, 1), \quad t > 0, \\ \mathbf{u}(x, 0) = \dot{\mathbf{u}}(x), & x \in [0, 1], \\ \mathbf{u}(0, t) = (\mathcal{K} + \epsilon \mathcal{C}(\epsilon)) \mathbf{u}(1, t), & t \geq 0, \end{cases} \quad (20)$$

in  $\mathbf{X} = L_1([0, 1], l_1^{|M|})$ , with continuous  $\mathcal{C}(\epsilon)$  satisfying  $\mathcal{C}(0) = \mathcal{C}$  and

$\mathcal{K}$  is contractive and 1 is an isolated and semisimple eigenvalue of  $\mathcal{K}$ .

$$(21)$$



To provide some insight into the following result, let us consider a simplified model

$$\begin{cases} \partial_t \mathbf{u}(x, t) = -\frac{1}{\epsilon} \partial_x \mathbf{u}(x, t), & x \in (0, 1), & t > 0, \\ \mathbf{u}(x, 0) = \dot{\mathbf{u}}(x), & x \in [0, 1], \\ \mathbf{u}(0, t) = (\mathcal{K} + \epsilon \mathcal{C}) \mathbf{u}(1, t), & t \geq 0, \end{cases} \quad (22)$$

Then the solution is given by

$$(e^{tA_\epsilon} \dot{\mathbf{u}})(x) = (\mathcal{K} + \epsilon \mathcal{C})^n \dot{\mathbf{u}} \left( n + x - \frac{t}{\epsilon} \right), \quad n \in \mathbb{N}, \quad 0 \leq n + x - \frac{t}{\epsilon} < 1.$$

Then formula (14) gives

$$\lim_{\epsilon \rightarrow 0} [e^{tA_\epsilon} \dot{\mathbf{u}}](x) = \mathcal{K}^n \dot{\mathbf{u}}(n + x - t) = [e^{tA} \dot{\mathbf{u}}](x),$$

for  $n \in \mathbb{N}, 0 \leq n + x - t < 1$ ;

that is the semigroup  $(e^{tA})_{t \geq 0}$  is solving

$$\begin{cases} \partial_t \mathbf{u}(x, t) = -\partial_x \mathbf{u}(x, t), & x \in (0, 1), & t > 0, \\ \mathbf{u}(x, 0) = \dot{\mathbf{u}}(x), & x \in [0, 1], \\ \mathbf{u}(0, t) = \mathcal{K} \mathbf{u}(1, t), & t \geq 0. \end{cases} \quad (23)$$

The projection  $P$  of the Kurtz result is then given by

$$\lim_{t \rightarrow \infty} e^{tA} = P, \quad (24)$$

provided it does exist. Let us consider this question.

$$\begin{aligned}
[e^{tA}\hat{\mathbf{u}}](x) &= \sum_{j, \lambda_j \in \sigma_{per}(\mathcal{K})} \lambda_j^n (\mathbf{W}_j \cdot \hat{\mathbf{u}}(n+x-t)) \mathbf{V}_j + O(\alpha^t) \quad (25) \\
&= \sum_{j, \lambda_j=1} (\mathbf{W}_j \cdot \hat{\mathbf{u}}(n+x-t)) \mathbf{V}_j \\
&+ \sum_{j, \lambda_j \in \sigma_{per}(\mathcal{K}) \setminus \{1\}} \lambda_j^n (\mathbf{W}_j \cdot \hat{\mathbf{u}}(n+x-t)) \mathbf{V}_j + O(\alpha^t) \\
&= [\Pi_1 e^{tA} \hat{\mathbf{u}}](x) \\
&+ \sum_{j, \lambda_j \in \sigma_{per}(\mathcal{K}) \setminus \{1\}} \lambda_j^n (\mathbf{W}_j \cdot \hat{\mathbf{u}}(n+x-t)) \mathbf{V}_j + O(\alpha^t),
\end{aligned}$$

$0 \leq n+x-t < 1$ ,  $n \in \mathbb{N}_0$ ,  $\alpha < 1$ ,  $\mathbf{W}_j$  and  $\mathbf{V}_j$  are, respectively, left and right eigenvectors belonging to eigenvalues from the peripheral spectrum of  $\mathcal{K}$ .

Hence, the long time behaviour of  $(e^{tA})_{t \geq 0}$  is not independent of  $t$  and thus it is not a projection, as required by the Kurtz lemma.

Let  $\Pi_1$  be the spectral projection onto the eigenspace of  $\mathcal{K}$  belonging to 1 and  $(e^{t\mathcal{A}_\epsilon})_{t \geq 0}$  be the solution semigroup to (20).

Further, for any operator  $\mathcal{O}$ , let  $\mathcal{O}_{11} = \Pi_1 \mathcal{O} \Pi_1$ .

## Theorem

a) Let (21) be satisfied. Then

$$\lim_{\epsilon \rightarrow 0^+} e^{t\mathcal{A}_\epsilon} \mathbf{u} = e^{t(\mathcal{C}_{11} + \mathcal{M}_{11})} \mathbf{u} \quad (26)$$

for any  $\mathbf{u} \in \Pi_1 \mathbf{P}_M \mathbf{X}$ . Moreover

$$\lim_{\epsilon \rightarrow 0^+} \Pi_1 \mathbf{P}_M e^{t\mathcal{A}_\epsilon} \mathbf{u} = e^{t(\mathcal{C}_{11} + \mathcal{M}_{11})} \Pi_1 \mathbf{P}_M \mathbf{u} \quad (27)$$

for any  $\mathbf{u} \in \mathbf{X}$ . In both cases the convergence is almost uniform on  $[0, \infty)$ .

## Theorem

b) If, additionally,  $\sup\{|\lambda| : \lambda \in \sigma(\mathcal{K}), \lambda \neq 1\} < 1$ , then

$$\lim_{\epsilon \rightarrow 0^+} e^{tA_\epsilon} \hat{\mathbf{u}} = e^{t(C_{11} + \mathcal{M}_{11})} \Pi_1 \hat{\mathbf{u}} \quad (28)$$

for any  $\hat{\mathbf{u}} \in \mathbf{P}_M \mathbf{X}$  and  $t > 0$  and the convergence is almost uniform on  $(0, \infty)$ .

So, if each ergodic state of  $\mathcal{K}_i$  is primitive,  $\Pi_1 \mathbf{P}_M \hat{\mathbf{u}}$  can be interpreted as the effective initial condition in that state(s) consisting of all individuals originally present there as well as all individuals that would reach the ergodic states at some moment in time. Thus, in the limit (28)

$$\lim_{\epsilon \rightarrow 0^+} e^{t\mathcal{A}_\epsilon} \hat{\mathbf{u}} = e^{tC_{11}} \Pi_1 \hat{\mathbf{u}},$$

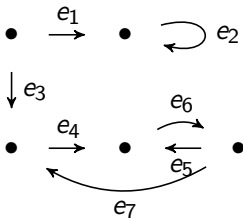
for  $\hat{\mathbf{u}}$  that is constant on each edge, we see that for the approximation we need to consider the ODE

$$\mathbf{v}' = C_{11} \mathbf{v}$$

with the effective initial condition  $\hat{\mathbf{v}} = \Pi_1 \hat{\mathbf{u}}$ .

## Worked example.

Consider the flow on the graph from Fig. 1,





given by (22) with

$$\mathcal{K} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{2} & 0 & 0 \end{pmatrix} \quad \mathcal{C} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix} .$$

The eigenvalues of  $\mathcal{K}$  are  $\lambda_1 = 1$ ,  $\lambda_2 = 0$ ,  $\lambda_3 = \frac{-1+i}{2}$ ,  $\lambda_4 = \frac{-1-i}{2}$ , where  $\lambda_1$  is a double and  $\lambda_2$  is a triple eigenvalue. The normalized left and right eigenvectors of  $\mathcal{K}$  associated with 1, respectively  $\mathbf{e}_l^i$  and  $\mathbf{e}_r^i$ ,  $i = 1, 2$ , are

$$\begin{aligned} \mathbf{e}_l^1 &= \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} & \mathbf{e}_r^1 &= \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \\ \mathbf{e}_l^2 &= \begin{pmatrix} 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 \end{pmatrix} & \mathbf{e}_r^2 &= \frac{1}{5} \begin{pmatrix} 0 & 0 & 0 & 1 & 2 & 1 & 1 & 1 \end{pmatrix} \end{aligned}$$

The dimension of the eigenspace belonging to the eigenvalue 1 of  $\mathcal{K}$  equals the number of terminal strong components of  $G$ . Since  $|\lambda_i| < 1$  for  $i = 2, 3, 4$ , the assumptions of Theorem 5 are satisfied. Furthermore, since 1 is a semisimple eigenvalue, then  $\dim X_1 = n = 2$  and the limiting system of ordinary differential equations consists of 2 differential equations describing the evolution of the material trapped in each terminal component:

$$\begin{aligned} \lim_{\epsilon \rightarrow 0^+} e^{tA_\epsilon} \hat{\mathbf{u}} &= e^{tC_{11}} \Pi_1 \hat{\mathbf{u}} = e^t \left( \sum_{i=1}^2 \hat{u}_i \right) \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 2 & 1 & 1 \end{pmatrix} \\ &+ \frac{1}{5} e^{\frac{7}{5}t} \left( \sum_{i=3}^7 \hat{u}_i \right) \begin{pmatrix} 0 & 0 & 0 & 1 & 2 & 1 & 1 \end{pmatrix}. \end{aligned}$$

for any  $t > 0$  and  $\hat{\mathbf{u}} \in \mathbb{R}^7$ .

Analogously, if for an arbitrary  $\mathbf{\hat{u}} = (\hat{u}_i(x))_{i=1,2,\dots,7} \in L_1([0, 1], \mathbb{R}^7)$  we write  $(u_{1,\epsilon}(x, t), \dots, u_{7,\epsilon}(x, t)) = e^{tA_\epsilon} \mathbf{\hat{u}}$ , then

$$\begin{aligned} \Pi_1 \mathbf{P}_M e^{tA_\epsilon} \mathbf{\hat{u}} &= \left( \sum_{i=1}^2 \int_0^1 u_{i,\epsilon}(x, t) \right) \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \\ &+ \frac{1}{5} \left( \sum_{i=3}^7 \int_0^1 u_{i,\epsilon}(x, t) \right) \begin{pmatrix} 0 & 0 & 0 & 1 & 2 & 1 & 1 \end{pmatrix} \end{aligned}$$

and we have

$$\begin{aligned} \lim_{\epsilon \rightarrow 0^+} \Pi_1 \mathbf{P}_M e^{tA_\epsilon} \mathbf{\hat{u}} &= e^t \left( \sum_{i=1}^2 \int_0^1 \hat{u}_i(x) dx \right) \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \\ &+ \frac{e^{7t}}{5} \left( \sum_{i=3}^7 \int_0^1 \hat{u}_i(x) dx \right) \begin{pmatrix} 0 & 0 & 0 & 1 & 2 & 1 & 1 \end{pmatrix}. \end{aligned}$$

We observe that the dynamics of the macro-model, obtained as the limit solution, is given by two equations

$$v_1'(t) = v_1(t), \quad v_2'(t) = \frac{7}{5}v_2(t),$$

instead of the postulated system (1) of the same dimension as the adjacency matrix of the line graph of  $G$ . Moreover, the solution of the above equation approximates the total mass of the system at terminal strong components instead of the masses on each edge of  $G$ . Note that  $\mathcal{K}$  is column stochastic and hence there is conservation of mass, so that the whole initial mass is eventually distributed according to the Perron eigenvector of  $\mathcal{K}$ .

## **Population equation with age and space structure.**

In the next example we illustrate the micromodel shown in Fig. 3 where, however, we ignore the dynamics occurring along the pathways connecting the states. Namely, we consider an age-structured population of individuals, divided into  $N$  patches. We denote by  $n_i$  the population density in patch  $i$  and  $a$  is the age.

By  $c_{ij}$  we denote the migration rate from patch  $j$  to patch  $i$ ,  $j \neq i$ . The transition matrix  $\mathcal{C}(a) = \{c_{ij}(a)\}_{1 \leq i, j \leq N}$  is a typical transition matrix (of a time-continuous process); that is the off-diagonal entries are positive and columns sum up to 0.



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$-\mathcal{M}(a) = \{-\mu_{ij}(a)\}_{1 \leq i, j \leq N}$  is a sub-Kolmogorov matrix which describes mortality and additional intercohort phenomena.

Since the migration process is conservative with respect to the life dynamics, we have assumption

$$c_{ii}(a) = - \sum_{\substack{j=1 \\ j \neq i}}^N c_{ji}(a).$$

The matrix  $-\mathcal{M}(a)$ , being sub-Kolmogorov, satisfies

$$- \sum_{j=1}^N \mu_{ji}(a) =: -\mu_i(a) \leq 0, \quad (29)$$

where  $\mu_i(a)$  is the age specific death rate in the patch  $i$ .

Thus, the vector  $\mathbf{n}(t, a) = (n_1(t, a), \dots, n_N(t, a))$  satisfies

$$\begin{aligned}\partial_t n_1(t, a) &= -\partial_a n_1(t, a) - \sum_{i=1}^N \mu_{1i}(a) n_i(t, a) \\ &\quad + (c_{11}(a) n_1(t, a) + \dots + c_{1N}(a) n_N(t, a)), \\ &\quad \vdots \quad \vdots \quad \vdots, \end{aligned} \tag{30}$$

$$\begin{aligned}\partial_t n_N(t, a) &= -\partial_a n_N(t, a) - \sum_{i=1}^N \mu_{Ni}(a) n_i(t, a) \\ &\quad + (c_{N1}(a) n_1(t, a) + \dots + c_{NN}(a) n_N(t, a)).\end{aligned}$$

Further, we introduce the McKendrick-Von Foerster boundary conditions:

$$n_j(t, 0) = \int_0^{\infty} \sum_{i=1}^N \beta_{ji}(a) n_i(t, a) da, \quad 1 \leq j \leq N, \quad (31)$$

where  $B(a) = \{\beta_{ij}(a)\}_{1 \leq i, j \leq N}$  describes the age and patch specific fertility rates, and the initial distribution of the population

$$n_1(0, a) = \overset{\circ}{n}_1(a), \dots, \quad n_N(0, a) = \overset{\circ}{n}_N(a). \quad (32)$$

## Solvability

Let  $\mathbf{X} := L^1(\mathbb{R}^+, l_1^n)$ . The entries in  $\mathcal{M}(a), \mathcal{C}(a)$  and  $B(a)$  satisfy  $\mu_{ij}, c_{ij}$  and  $\beta_{ij} \in L^\infty(\mathbb{R}^+)$ ,  $\beta_{ij}(a) \geq 0$ . Denote  $\bar{b} := \operatorname{ess\,sup}_{a \in \mathbb{R}_+} \|B(a)\|$ .

The matrix  $-\mathcal{M}$  can be decomposed into the Kolmogorov part and the diagonal part  $\operatorname{diag}(-\mu_j)_{1 \leq j \leq n}$ , where

$\mu_j(a) = \mu_{jj}(a) + \sum_{\substack{i=1 \\ i \neq j}}^n \mu_{ij}(a)$ ; these are the 'true' death rates, see

(29). We denote  $\underline{m} := \inf_{1 \leq j \leq n, a \in \mathbb{R}_+} \mu_j(a)$ . Then we have

### Theorem

*There is a strongly continuous semigroup  $(e^{tA})_{t \geq 0}$  solving (30)–(32) which satisfies  $\|e^{tA}\| \leq \exp(\bar{b} - \underline{m})t$ .*

We note that, in particular,  $\|e^{tA}\|$  is independent of  $\mathcal{C}$ .

## Singularly perturbed problem (30)–(32)

In the structured population theory, the inter-patch migration often happens on a much faster time scale than the demographic processes such as ageing and death. This leads to the scaling

$$\begin{aligned} \partial_t \mathbf{n}_\epsilon &= \mathcal{S} \mathbf{n}_\epsilon + \mathcal{M} \mathbf{n}_\epsilon + \frac{1}{\epsilon} \mathcal{C} \mathbf{n}_\epsilon, \\ \mathbf{n}_\epsilon(0, t) &= \mathcal{B}[\mathbf{n}_\epsilon(\cdot, t)] := \int_0^\infty B(a) n_\epsilon(a, t) da, \quad \mathbf{n}_\epsilon(a, 0) = \mathring{\mathbf{n}}(a). \end{aligned} \quad (33)$$

The operator  $\mathcal{A}_\epsilon$ , which is the expression  $A_\epsilon = \mathcal{S} + \mathcal{M} + \frac{1}{\epsilon} \mathcal{C}$  restricted to  $(W_1^1(\mathbf{R}_+))^n$ –functions satisfying the boundary conditions, is the generator of an equibounded semigroup  $(e^{t \cdot \mathcal{A}_\epsilon})_{t \geq 0}$ .

Biological heuristics suggests that the macro model should not depend on the parameters related to the geographical structure as we consider a very large interpatch transition rates.

By the Kurtz approach, we need to understand the long term behaviour of solutions to the problem

$$\partial_t \mathbf{u} = \mathcal{C} \mathbf{u}, \quad \mathbf{u}(0) = \mathbf{u}_0, \quad (34)$$

where  $\mathbf{u} = (u_1, \dots, u_n) \in \mathbb{R}^n$  and  $\mathbf{u}_0$  is an initial condition, which describes the so-called fast dynamics of (33). This requires spectral analysis of  $\mathcal{C}$ . The precise result depends on the structure of the network of migrations described by the matrix  $\mathcal{C}$ .

In particular, if  $\mathcal{C}$  is irreducible,

$\mathcal{M} = \text{diag}(\mu_j)_{1 \leq j \leq n}$ ,  $B = \text{diag}(\beta_j)_{1 \leq j \leq n}$  then, subject to some technical assumptions, the solution  $\mathbf{n}_\epsilon$  converges, as  $\epsilon$  goes to 0, to  $n\mathbf{N}$ , where  $u$  is the solution of the following scalar equation

$$\partial_t n = -\partial_x n - \mu^* n, \quad n(t, 0) = \int_0^\infty \beta^* n(t, x) dx, \quad n(0, x) = \sum_{i=1}^m \dot{n}_i(x), \quad (35)$$

where  $\mu^* = \sum_{i=1}^n \mu_i N_i$ ,  $\beta^* = \sum_{i=1}^n \beta_i N_i$



and  $\mathbf{N} = (N_1, N_2, \dots, N_n)$  gives the stable population distribution; that is, the asymptotic fractions of the total population residing in different patches,  $\mu^*$  and  $\beta^*$  are the death and birth rates averaged with weights corresponding to the relative size of each patch.

In contrast to the Lebovitz–Rubinov–Rotenberg model, here we can also prove the convergence of the solutions to  $n(t)\mathbf{N}$  in the norm of  $L_1([0, \infty))^m$  for any initial condition from the state space and for any  $t > 0$ .

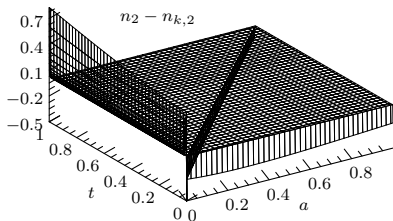


Figure: The error of approximation for arbitrary initial data

We see that, indeed, the approximation is bad close to  $t = 0$  (initial layer effect), close to  $a = 0$  (boundary layer effect) and at  $a = t = 0$  (corner layer effect). It is possible to construct corrections in a systematic and algorithmic way to get the error looking like

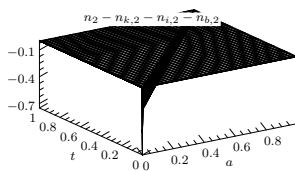
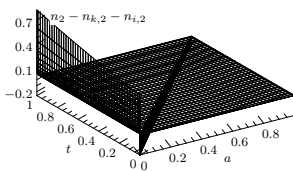


Figure: Reducing the error of approximation. From the left: bulk approximation, bulk and initial layer approximation and bulk, initial and boundary layer approximation.

## A worked example.

In this section we will illustrate the asymptotic procedure as applied to the McKendrick models with 5 patches. To make calculations simple, we consider age independent matrices  $\mathcal{M}$ ,  $\mathcal{B}$  and  $\mathcal{C}$  with

$$\mathcal{C} := \begin{bmatrix} -2 & 0 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 \\ 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 1 & 0 & 0 & 1 & -1 \end{bmatrix}. \quad (36)$$

The matrix  $\mathcal{C}$  is reducible, with  $\sigma(\mathcal{C}) = \{0, -2\}$ . The eigenvalue  $\lambda = 0$  is dominant, semisimple with multiplicity 2, while  $\lambda = -2$  is of algebraic multiplicity 3 and geometric multiplicity 2.

Accordingly, the null space of  $\mathcal{C}$  is also two dimensional.

The nonnegative basis of (normalized) vectors for the null space of  $\mathcal{C}$  is given by

$$\mathbf{e}_4 = \left( 0, \frac{1}{2}, \frac{1}{2}, 0, 0 \right),$$

$$\mathbf{e}_5 = \left( 0, 0, 0, \frac{1}{2}, \frac{1}{2} \right),$$

while in the complementary space we can select the basis

$$\mathbf{e}_1 = (0, 1, -1, 0, 0),$$

$$\mathbf{e}_2 = (0, 0, 0, 1, -1),$$

$$\mathbf{e}_3 = \left( 1, 0, -\frac{1}{2}, 0, -\frac{1}{2} \right),$$

where  $\mathbf{e}_3$  is an associated eigenvector.

Similarly, the bi-orthogonal basis of the left null space is

$$\mathbf{x}_4 = \left( \frac{1}{2}, 1, 1, 0, 0 \right),$$

$$\mathbf{x}_5 = \left( \frac{1}{2}, 0, 0, 1, 1 \right)$$

while in  $\mathbf{W}$  we can select the basis

$$\mathbf{x}_1 = \left( -\frac{1}{4}, \frac{1}{2}, -\frac{1}{2}, 0, 0 \right),$$

$$\mathbf{x}_2 = \left( -\frac{1}{4}, 0, 0, \frac{1}{2}, -\frac{1}{2} \right),$$

$$\mathbf{x}_3 = (1, 0, 0, 0, 0).$$

The approximating system takes the following form,

$$\begin{aligned}\partial_t \bar{u}_t^4 &= -\partial_a \bar{u}^4 - \mu_{44}^* \bar{u}^4 - \mu_{45}^* \bar{u}^5, \\ \partial_t \bar{u}_t^5 &= -\partial_a \bar{u}^5 - \mu_{54}^* \bar{u}^4 - \mu_{55}^* \bar{u}^5, \\ \bar{u}^4(0, t) &= \int_0^\infty (\beta_{44}^* \bar{u}^4(a, t) + \beta_{45}^* \bar{u}^5(a, t)) da, \\ \bar{u}^5(0, t) &= \int_0^\infty (\beta_{54}^* \bar{u}^4(a, t) + \beta_{55}^* \bar{u}^5(a, t)) da, \\ \bar{u}^4(a, 0) &= \frac{1}{2} \dot{u}_1(a) + \dot{u}_2(a) + \dot{u}_3(a), \\ \bar{u}^5(a, 0) &= +\frac{1}{2} \dot{u}_1(a) + \dot{u}_4(a) + \dot{u}_5(a),\end{aligned}\tag{37}$$

where



$$\mu_{44}^* = \frac{1}{2} \left( \mu_{22} + \mu_{23} + \mu_{32} + \mu_{33} + \frac{1}{2}\mu_{12} + \frac{1}{2}\mu_{13} \right),$$

$$\mu_{45}^* = \frac{1}{2} \left( \mu_{24} + \mu_{25} + \mu_{34} + \mu_{35} + \frac{1}{2}\mu_{14} + \frac{1}{2}\mu_{15} \right).$$

Similarly

$$\mu_{54}^* = \frac{1}{2} \left( \mu_{42} + \mu_{43} + \mu_{52} + \mu_{53} + \frac{1}{2}\mu_{12} + \frac{1}{2}\mu_{13} \right),$$

$$\mu_{55}^* = \frac{1}{2} \left( \mu_{44} + \mu_{45} + \mu_{54} + \mu_{55} + \frac{1}{2}\mu_{14} + \frac{1}{2}\mu_{15} \right).$$

and  $(\beta_{ij}^*)_{1 \leq i \leq 2, 1 \leq j \leq 2}$  is given by analogous formulae.

Thus, using  $\tau = t/\epsilon$ , we can write

$$\begin{aligned}\mathbf{u}_\epsilon(t) &= \mathbf{u}(t) + \tilde{\mathbf{u}}(\tau) + O(\epsilon) = \bar{u}^4(t)\mathbf{e}_4 + \bar{u}^5(t)\mathbf{e}_5 \\ &+ e^{-2\tau} \left( \frac{\tau^2 \circ^3}{8} \bar{w} - \frac{\tau \circ^2}{2} \bar{w} + \bar{w}^{\circ 1} \right) \mathbf{e}_1 + e^{-2\tau} \left( -\frac{\tau \circ^3}{2} \bar{w} + \bar{w}^{\circ 2} \right) \mathbf{e}_2 + e^{-2\tau} \bar{w}^{\circ 3} \mathbf{e}_3 \\ &+ O(\epsilon)\end{aligned}$$

in  $\mathbf{X}_5 = (L_1(\mathbb{R}_+))^5$  norm, uniformly in  $t$  on  $[0, T]$ .

Using the expression for  $\mathbf{e}_j$ ,  $1 \leq j \leq 5$ , we can write the approximation in the component form as

$$\begin{aligned} \left\| u_1(t) - e^{-2\tau} \overset{\circ}{w}^3 \right\|_{L_1(\mathbb{R}_+)} &= O(\epsilon), \\ \left\| u_2(t) - \frac{1}{2} \bar{u}^4(t) - e^{-2\tau} \left( \frac{\tau^2}{8} \overset{\circ}{w}^3 - \frac{\tau}{2} \overset{\circ}{w}^2 + \overset{\circ}{w}^1 \right) \right\|_{L_1(\mathbb{R}_+)} &= O(\epsilon), \\ \left\| u_3(t) - \frac{1}{2} \bar{u}^4(t) + e^{-2\tau} \left( \frac{\tau^2}{8} \overset{\circ}{w}^3 - \frac{\tau}{2} \overset{\circ}{w}^2 + \overset{\circ}{w}^1 \right) + \frac{1}{2} e^{-2\tau} \overset{\circ}{w}^3 \right\|_{L_1(\mathbb{R}_+)} &= O(\epsilon), \\ \left\| u_4(t) - \frac{1}{2} \bar{u}^5(t) - e^{-2\tau} \left( -\frac{\tau}{2} \overset{\circ}{w}^3 + \overset{\circ}{w}^2 \right) \right\|_{L_1(\mathbb{R}_+)} &= O(\epsilon), \\ \left\| u_5(t) - \frac{1}{2} \bar{u}^5(t) + e^{-2\tau} \left( -\frac{\tau}{2} \overset{\circ}{w}^3 + \overset{\circ}{w}^2 \right) + \frac{1}{2} e^{-2\tau} \overset{\circ}{w}^3 \right\|_{L_1(\mathbb{R}_+)} &= O(\epsilon), \end{aligned}$$

where  $\bar{u}^i$ ,  $i = 1, 2$ , solve (37) and  $\overset{\circ}{w}^j$ ,  $j = 3, 4, 5$ , are projections of  $\bar{\mathbf{u}}$  onto the complementary space.