

# LUMPING IN TOXICOKINETICS\*

János TÓTH

Department of Mathematical Analysis, Faculty of Sciences  
Budapest University of Technology and Economics  
Budapest, HUNGARY, jtoth@math.bme.hu

Céline BROCHOT, Frédéric BOIS

Unité de Toxicologie Expérimentale, Direction Risques Chroniques  
Institut National de l'Environnement Industriel et des Risques  
Verneuil-en-Halatte, FRANCE; F-60550  
Celine.Brochot@ineris.fr, Frederic.Bois@ineris.fr

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## Dimension reduction methods (Tomlin et al. 1997)

- chemical or natural lumping
- quasi steady state hypothesis (singular perturbation)
- analysis of the Jacobian (time scale separation, principal component analysis)
- etc.
- **lumping**

How to simplify models with known structure and with unknown parameters?

Only functions of the original parameters are identifiable - which ones and how many? (Ollivier and Sedoglavic, 2002)

## Lumping is physical, it produces chemically interpretable simplifications:

- an ODE closed in the new variables
- a kinetic ODE (Farkas, 1999)
- an ODE of a compartmental system

Qualitative properties are (partially) kept (Horváth Zs., 2002; Tóth et al. 1997).

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\*Full text and programs: <http://www.math.bme.hu/~jtoth>

**Formal definitions**

Original ODE:  $\dot{y} = Ky + u \quad (y(t) \in \mathbf{R}^N)$   
 New variables:  $\hat{y} := My \quad (\hat{y}(t) \in \mathbf{R}^{\hat{N}}; \hat{N} \leq N)$   
 New inflow:  $\hat{u} := Mu$   
 New coefficients:  $\hat{K} := MK\bar{M}; \quad M\bar{M} = I_{\hat{N}}$   
 New ODE:  $\dot{\hat{y}} = \hat{K}\hat{y} + \hat{u}$

**How to find  $M$ ?**

And if some rows (new, lumped variables) are prescribed? (See Li, Rabitz, 1991)

Symbolic and numerical relationships between old and new parameters?

**Symbolic functional relationships**

Small models (2–3 compartments)

Exact lumping

$$\begin{array}{ccc} \begin{array}{c} d \downarrow \\ \mathbf{Q}_1 \\ c \downarrow \end{array} & \frac{a}{b} & \begin{array}{c} e \downarrow \\ \mathbf{Q}_2 \\ f \downarrow \end{array} \end{array} \quad \text{lumped:} \quad \begin{array}{c} \hat{e} \downarrow \\ \hat{\mathbf{Q}} \\ \hat{c} \downarrow \end{array}$$

$$\hat{c} = c \quad \hat{q} = 2b(q_1 + q_2) \quad \hat{u} = 2b(d + e)$$

(Constrained lumping)

Simple models (of symmetric structure)

(e.g. Mamillary models, catenary models, circular model)

Exact lumping of the mamillary model

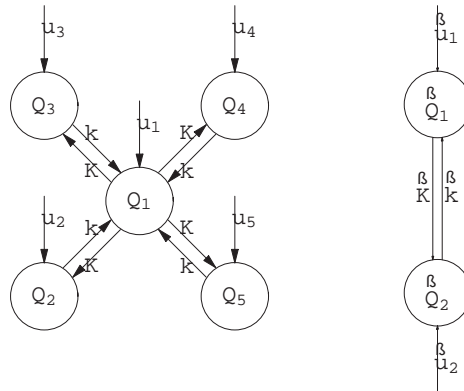


Figure 1: Five compartment mamillary model and lumped version

$$\begin{aligned} \hat{q}_1 &= -\frac{\sqrt{5}+1}{2}q_1 + \frac{\sqrt{5}+1}{2}q_2 - q_3 + q_5 \\ \hat{q}_2 &= -q_1 + \frac{\sqrt{5}+1}{2}q_2 - \frac{\sqrt{5}+1}{2}q_3 + q_4 \end{aligned}$$

$$\begin{aligned}\hat{u}_1 &= -\frac{\sqrt{5}+1}{2}u_1 + \frac{\sqrt{5}+1}{2}u_2 - u_3 + u_5 \\ \hat{u}_2 &= -u_1 + \frac{\sqrt{5}+1}{2}u_2 - \frac{\sqrt{5}+1}{2}u_3 + u_4 \\ \hat{K} &= \frac{5+\sqrt{5}}{2}k \quad \hat{k} = \frac{5+\sqrt{5}}{2}k\end{aligned}$$

Three functions of the original seven parameters can be estimated from the new model.

Exact lumping of a reversible circular model

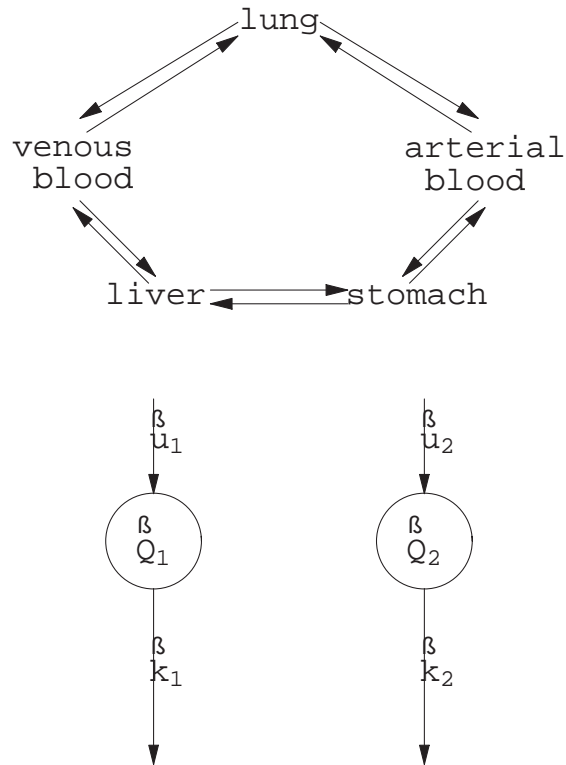


Figure 2: Five compartment circular model and lumped version

$$\begin{aligned}\hat{q}_1 &= q_1 + q_3 + q_4 + 2q_5 \\ \hat{q}_2 &= q_1 + 2q_2 + q_3 + q_4\end{aligned}$$

$$\begin{aligned}
\hat{u}_1 &= u_1 + u_3 + u_4 + 2u_5 \\
\hat{u}_2 &= u_1 + 2u_2 + u_3 + u_4 \\
\hat{K} &= k/2 \\
\hat{k} &= k/2
\end{aligned}$$

Constrained lumping of a mamillary model  
Constraints to be fulfilled as closely as possible:

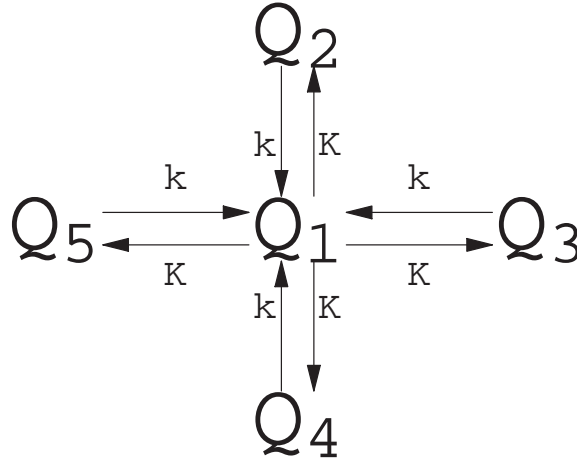


Figure 3: Five compartment mamillary model,  $K = 2, k = 1$

$$\hat{q}_1 = q_1 \quad \hat{q}_2 = \frac{q_2 + q_3}{\sqrt{2}}$$

$$\hat{N} = 3 \tag{1}$$

$$\hat{q}_1 = 0.94q_1 - 0.24q_2 - 0.24q_3 \tag{2}$$

$$\hat{q}_2 = 0.27q_1 + 0.53q_2 + 0.53q_3 - 0.43q_4 - 0.43q_5 \tag{3}$$

$$\hat{q}_3 = 0.20q_1 + 0.40q_2 + 0.40q_3 + 0.56q_4 + 0.56q_5 \tag{4}$$

$$\tag{5}$$

### Numerical relationships

Six compartment model for a contrast agent

Exact lumping

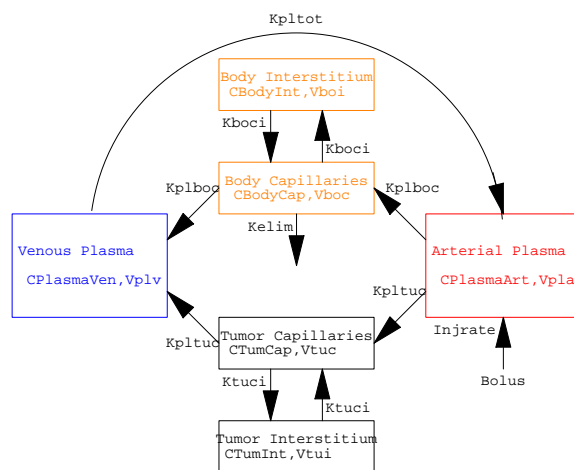


Figure 4: Realistic model for a contrast material

Preliminary results show good agreements between the original and the lumped model.

Constrained lumping

Linearized model of butadiene transport and metabolism

Exact lumping

Constrained lumping

On the programs

Model generation is a separate problem

By hand

From reaction steps

Lumping linear models

Linear lumping without constraints

Linear lumping with constraints

Lumping polynomial models with and without constraints

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