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, Fréderic 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

ESF REACTOR Workshop, 24-27 January, 2003, Budapest

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).

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

Formal definitions

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

How to find M?

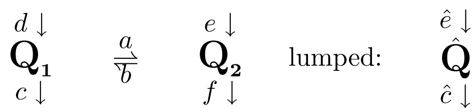
And if some rows (new, lumped variables) are prescribed? (See Li, Rabitz, 1991)

Symbolic and numerical relationships between old and new parameters?

Symbolic functional relationships

Small models (2–3 compartments)

Exact lumping



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

(Constrained lumping)

Simple models (of symmetric structure)

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

Exact lumping of the mamillary model

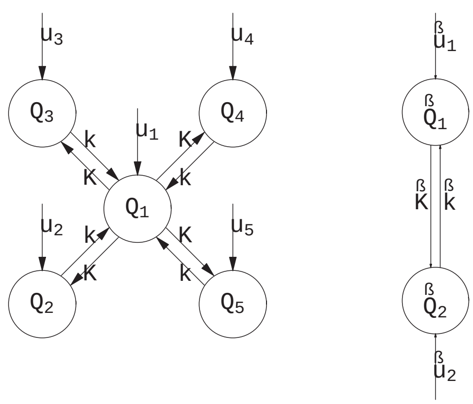


Figure 1: Five compartment mamillary model and lumped version

$$\hat{q}_1 = -\frac{\sqrt{5}+1}{2} q_1 + \frac{\sqrt{5}+1}{2} q_2 - q_3 + q_5$$

$$\hat{q}_2 = -q_1 + \frac{\sqrt{5}+1}{2} q_2 - \frac{\sqrt{5}+1}{2} q_3 + q_4$$

$$\hat{u}_1 = -\frac{\sqrt{5}+1}{2}u_1 + \frac{\sqrt{5}+1}{2}u_2 - u_3 + u_5$$

$$\hat{u}_2 = -u_1 + \frac{\sqrt{5}+1}{2}u_2 - \frac{\sqrt{5}+1}{2}u_3 + u_4$$

$$\hat{K} = \frac{5+\sqrt{5}}{2}k \quad \hat{k} = \frac{5+\sqrt{5}}{2}k$$

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

Exact lumping of a reversible circular model

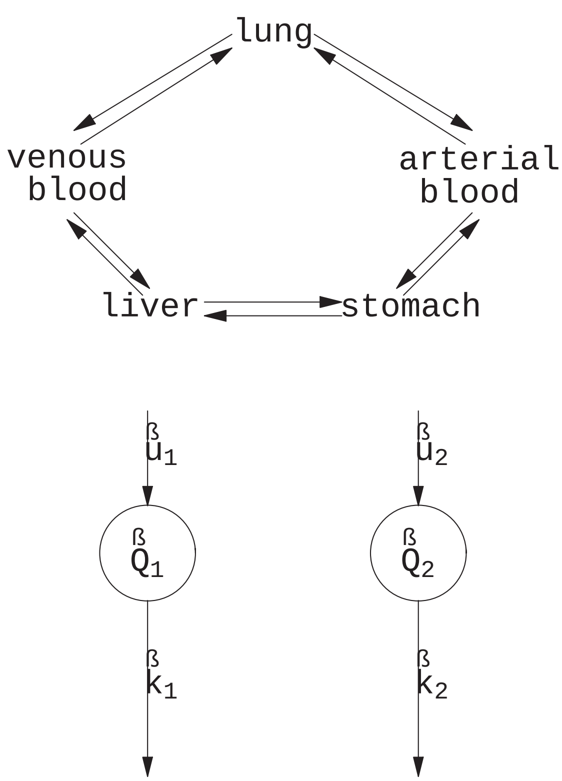


Figure 2: Five compartment circular model and lumped version

$$\hat{q}_1 = q_1 + q_3 + q_4 + 2q_5$$

$$\hat{q}_2 = q_1 + 2q_2 + q_3 + q_4$$

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

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

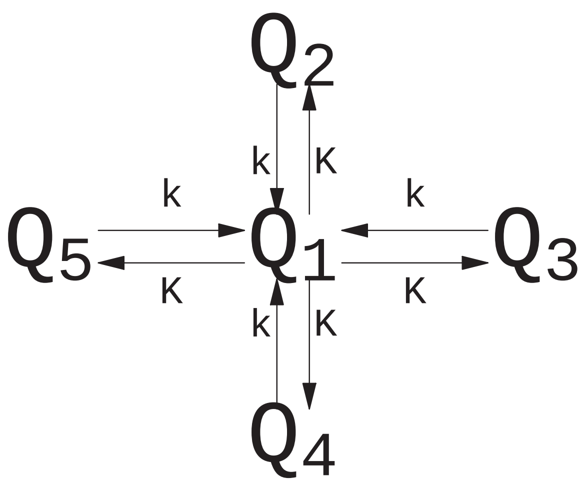


Figure 3: Five compartment mamillary model, $K = 2, k = 1$

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

$$\begin{aligned}\hat{N} &= 3 && (1)\\ \hat{q}_1 &= 0.94q_1 - 0.24q_2 - 0.24q_3 && (2)\\ \hat{q}_2 &= 0.27q_1 + 0.53q_2 + 0.53q_3 - 0.43q_4 - 0.43q_5 && (3)\\ \hat{q}_3 &= 0.20q_1 + 0.40q_2 + 0.40q_3 + 0.56q_4 + 0.56q_5 && (4)\\ & && (5)\end{aligned}$$

Numerical relationships

Six compartment model for a contrast agent

Exact lumping

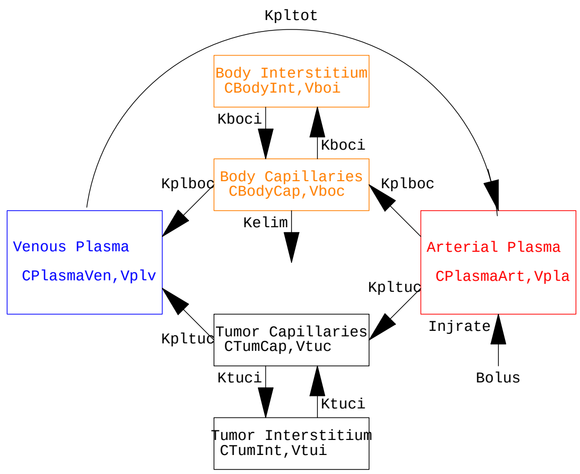


Figure 4: Realistic model for a contrast material

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

Acknowledgements

The present work has been supported by the French Ministry of the Environment and Sustainable Development (BCRD-DRC-07-AP-2001) and by the Hungarian National Science Foundation (T037491).

References

[1] Bois, F. Y.; Smith, Th. J.; Gelman, A.; Chang, H-Y.; and Smith, A.: Optimal design for a study of butadiene toxicokinetics in humans, *Toxicol. Sci.* **49**:213–224 (1999).

[2] Érdi, P. and Tóth, J.: *Mathematical Models of Chemical Reactions*, Princeton University Press, Princeton, 1989.

[3] Farkas, Gy.: Kinetic lumping schemes, *Chem. Engng. Sci.* **54**:3909–3915 (1999).

[4] Horváth, Zs.: Effect of lumping on controllability and observability, 2002.

[5] Jacquez, J. A.: *Compartmental Analysis in Biology and Medicine* (Third ed.), Biomedware, Ann Arbor, MI, 1996.

[6] Jacquez, J. A.: *Modeling with Compartments*, Biomedware, Ann Arbor, MI, 1999.

[7] Li, G.; and Rabitz, H.: New approaches to determination of constrained lumping schemes for a reaction system in the whole composition space, *Chem. Engng. Sci.* **46**:95–111 (1991).

[8] Nestorov, I. A.; Aarons, L. J.; Arundel, Ph. A.; and Roland, M.: Lumping of whole-body physiologically based pharmacokinetic models, *J. Pharmacokin. Biopharm.* **26**:21–46 (1998).

[9] Ollivier, F.; and Sedoglavic, A.: Algorithmes efficaces pour tester l'identifiabilité locale, *Proceedings of CIFA'2002* (Nantes, France, 8–10 juillet 2002), IEEE, pp. 811–816. (http://medicis.polytechnique.fr/ sedoglav/papiers.html)

[10] Tomlin, A. S.; Turányi, T.; and Pilling, M. J.: Mathematical tools for the construction, investigation and reduction of combustion mechanisms, In: M. J. Pilling (ed.) *Low-temperature Combustion and Autoignition*, Volume **35** of series *Comprehensive Chemical Kinetics*, Elsevier, Amsterdam, 1997, pp. 293–437.

[11] Tóth, J.: Formal kinetics with applications. In: N. Callaos, M. Margenstern, and B. Sanchez (eds.), *Proc. 6th World Multiconference on Systemics, Cybernetics and Informatics*, Vol. **XI**, Orlando, Florida, USA, 2002, pp. 573–576.

[12] Tóth, J.; Li, G.; Rabitz, H.; and Tomlin, A. S.: The effect of lumping and expanding on kinetic differential equations, *SIAM J. Appl. Math.* **57**:1531–1556 (1997).

[13] Tóth, J.; Rospars, J.-P.: Dynamic modeling of biochemical reactions with applications to signal transduction: principles and tools (submitted).

[14] Van den Hof, J. M.: Positive linear observers for linear compartmental systems, *SIAM J. Control Optim.* **36**:590–608 (1998).

[15] Wolfram, S.: *The Mathematica Book* (4th ed.), Cambridge University Press, Cambridge, 2002.