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Mean Residence Times in Linear Compartmental Systems. Symbolic Formulae for their Direct Evaluation

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A complete analysis has been performed of the mean residence times in linear compartmental systems, closed or open, with or without traps and with zero input. This analysis allows the derivation of explicit and simple general symbolic formulae to obtain the mean residence time in any compartment of any linear compartmental system, closed or open, with or without traps, as well as formulae to evaluate the mean residence time in the entire system like the above situations. The formulae are given as functions of the fractional transfer coefficients between the compartments and, in the case of open systems, they also include the excretion coefficients to the environment from the different compartments. The relationship between the formulae derived and the particular connection properties of the compartments is discussed. Finally, some examples have been solved.

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1. INTRODUCTION

The global analysis of the compartmental models in applications, in which the models are applicable, requires the evaluation of mean parameters and of particular interest, the mean residence times, because they are often treated in the literature on compartmental systems. In addition to their usefulness in pharmacokinetics (Veng-Pedersen, 1989; Zimmermann *et al.*, 1999; Isoherranen *et al.*, 2000), the evaluation of the residence times in compartmental models is related with other interesting areas. Some of these are enzyme kinetics (Schuster and Heinrich, 1987; Sines and Hackney, 1987), the study of basic nutritional processes, e.g., digestion, absorption and metabolism of nutrients (Green, 1992; Wilson and Dainty, 1999; Wastney *et al.*, 2000), aspects of cellular growth (Jacquez, 1985) and of pathological processes, such as tumourigenesis (Moolvakar and Luebeck, 1990; Cremonesi *et al.*, 1999) and atherosclerosis (Tozer and Carew, 1997).

Conceptually, the mean residence time of a particle in a compartment of a compartmental system after its injection at $t = 0$ in any compartment of the system, is defined as the mean time that the particle spends in the compartment, in which the residence time is to be determined, before leaving this compartment definitively. Analogously, the mean residence time in the entire compartmental system of a particle injected at $t = 0$ in any of its compartments is defined as the mean time that the particle spends in the compartmental system before leaving it definitively. This mean residence time can be evaluated as the sum of the mean residence times in each of the compartments of the system (Anderson, 1983).

Operationally, the general definitions about the residence times are based either on the matrix associated with the compartmental system (Anderson, 1983; Jacquez, 1985) or on the theory of statistical moments theory (Hearon, 1972; Rescigno and Gurpide, 1973; Cutler, 1987; Veng-Pedersen, 1989; Gibaldi, 1991; Rescigno, 1999). These definitions have been applied to studies of certain models consisting of a few compartments, e.g., the mammalian model of two compartments with excretion from the central compartment only (Kong and Jusko, 1988), catenary models (Cheng, 1991) and drugs with multicompartmental distribution and a reversible metabolism (Cheng and Jusko, 1990).

As far as we know, the analysis of the mean residence times has been performed only for open systems in which the substance is totally eliminated from the system, i.e., open systems without traps (Anderson, 1983; Cutler, 1987; Cheng, 1991; Gibaldi, 1991; Rescigno, 1999), but the corresponding analysis has not been carried out yet, neither for the open systems with traps, nor for any closed system. This may be due to the fact that the methods used require the inversion of matrices, which is not feasible because the matrices corresponding to both the open compartmental systems with traps and any closed compartmental system are singular, i.e., noninvertible. Moreover, even for the systems already studied, which are open without traps, the procedures used so far are arduous,