Optimal designs for compartmental models with unknown/non-constant transfer coefficients

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SUMMARY
Numerical procedures for obtaining optimal designs for compartmental models when there is not an analytical solution are proposed. The ideas can be extended to other (non-compartmental) ordinary-differential-equation systems without analytical solutions.

Optimal designs for compartmental models and ordinary-differential-equation systems
- Known set of techniques for obtaining optimal designs when the model is linear in the parameters.
- For non-linear models (but given by an analytical expression) the usual approach is to linearize it. In this case initial values are needed for the non-linear parameters (locally optimal designs)
- Problems when it is not possible to obtain an analytical expression for the model. Example: model described by a system of ordinary differential equations (ODE) without a general solution. In this situation, the techniques used routinely by the optimal design theory cannot be employed.

Method 1
- Virtual model
- Numerical derivatives

Method 2
- Extended systems

Method 3
Compartmental-like models
- Models given by Equation (1)

$$\begin{cases} x(t) = Ax + b(t), t \geq 0 \\ x(0) = x_0 \end{cases}$$

(for instance compartmental models), where $x_i(t)$ denotes the amount or content of species in compartment $i$ at a time $t$. $A$ is the $m \times m$ system matrix given by $a_{ij} = g(k_{ij})$, where $k_{ij}$ are the transfer constants. $b_i(t)$ is the input rate into compartment $i$ from the environment.

- The solution of Equation (1) when the coefficients $a_{ij}$ are constants is

$$x(t) = x_0 \exp(At) + \exp(At)\ast b(t)$$

(see Bates and Watts, 1988), where “$\ast$” denotes convolution,

$$\exp(At) \ast b(t) = \int_0^t \exp([t-\tau]A)b(\tau)d\tau$$

Then, if $b(t)$ and $x_0$ are not dependent on $\theta_j$,

$$\dot{x}_{ij}(t) = A \dot{x}_{ij}(t) + A_{ij} x(t)$$

Now, mimicking Equation (2) $\dot{x}_{ij}(t) = \exp(At) \ast [A_{ij}]x_{ij}(t)$, and substituting $x(t)$ from (2)

$$\dot{x}_{ij}(t) = \exp(At) \ast [A_{ij}] x_{ij}(t) + \exp(At) \ast A_{ij} \exp(At) x(t)$$

that is the derivative function

- In particular, if the input occurs for $t = 0, x(0) = x_0$ and $b(t) = 0$ for $t > 0$, and then $\dot{x}_{ij}(t) = \exp(At) \ast A_{ij} \exp(At) x_0$

Example: Biokinetic model of Ciprofloxacin and Ofloxacin
It is a physiological (non-compartmental) model that produces the following differential-equation system (Sánchez Navarro et al, 1999):

$$\begin{align*}
\dot{c}_1(t) &= -5.87256c_1(t) + 2.7893c_2(t) + 3.08325c_{init}(t) \\
\dot{c}_2(t) &= 0.423335c_1(t) + (-0.423335) c_2(t) + 0.15598k_{off}x_3(t) \\
\dot{x}_3(t) &= 6.411k_{con}x_2(t) - k_{off}x_3(t)
\end{align*}$$

with $x_1(0) = x_2(0) = x_3(0) = 0$ and $t$ in days. According to Sánchez (2007), $c_{in}(t) = 13610.1t e^{-11.216t}$ will be used.

Optimal designs

Optimal times when using exponential covariance

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Efficiency study:
- D-opt: 2-point design is the best (then 3-point)
- A-opt: 3-point design is the best (then 4-point)

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References

