Fractional-Order Pharmacokinetics and Control

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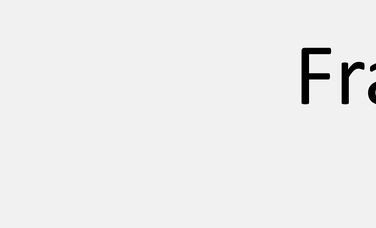
Abstract: Amiodarone is an antiarrhythmic drug that exhibits highly complex and non- exponential dynamics whose controlled administration has important implications for its clinical use especially for long-term therapies. Its pharmacokinetics has been accurately modelled using a fractional-order compartmental model. In this paper we design a fractional-order PID controller and we evaluate its dynamical characteristics in terms of the stability margins of the closed loop and the ability of the controlled system to attenuate various sources of noise and uncertainty.



Fractional Dynamics: One of the most exotic properties of non-integer order derivatives is that they are non-local operators. They come as generalisations of classical operators. For instance, using the Cauchy formula for the definite integral operator:

$$(I^n f)(t) = \frac{1}{(n-1)!}\int_0^t (t-\tau)^{n-1} f(\tau)\mathrm{d}\tau,\ t \geq 0.$$

Using the fact that the Gamma function intercepts the factorial on the set of natural numbers, we extend the above integral to introduce the *Riemann-Liouville fractional-order integral*:

$$n! = \Gamma(n+1),\ \forall n \in \mathbb{N}$$

$$(I^\alpha f)(t) = \frac{1}{\Gamma(\alpha)}\int_0^t (t-\tau)^{\alpha-1} f(\tau)\mathrm{d}\tau,\ t \geq 0.$$

We now define the *Caputo fractional-order derivative* as follows:

$$(D^\alpha f)(t) = I^{m-\alpha}\frac{\mathrm{d}^m f(t)}{\mathrm{d}t^m},\ \text{where } m = \lceil \alpha \rceil$$

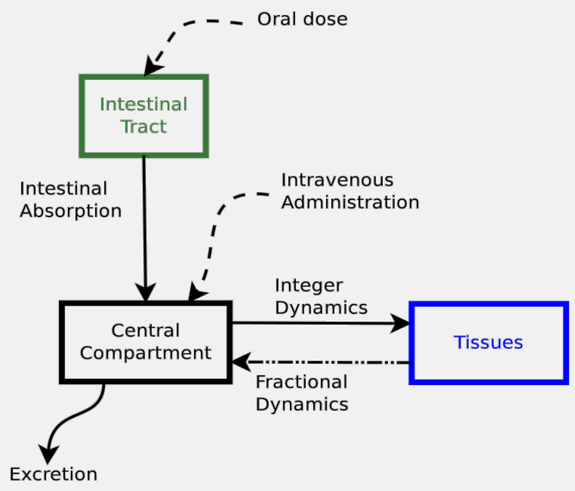
It is of fundamental importance that it is possible to have an analytical expression for the Laplace transformation of the Caputo fractional-order derivative:

$$\mathcal{L}\left[D^\alpha f\right](s) = s^\alpha F(s) - \sum_{k=0}^{m-1} s^{\alpha-k-1}\left.\frac{\mathrm{d}^k f}{\mathrm{d}t^k}\right|_0,$$

$$\text{where } F(s) = (\mathcal{L}f)(s)$$

This enables us to represent fractional-order dynamical systems in the Laplace domain using transfer functions and design controllers using frequency criteria (such as the Bode stability criterion).

In this study we consider the compartmental pharmacokinetic model for the distribution of Amiodarone, an antiarrhythmic agent. The compartmental topology is shown in the figure below [1]:



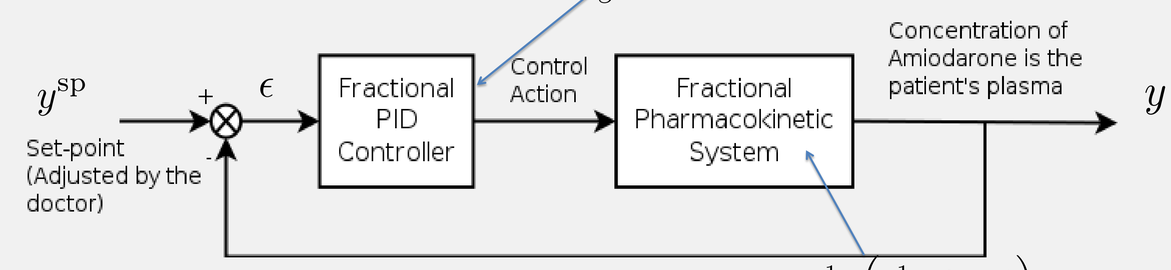
The fractional pharmacokinetic model reads as follows:

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = -(k_{12}+k_{10})A_1 + k_{21}\cdot D^{1-a}A_2 + u,$$
$$\frac{\mathrm{d}A_2}{\mathrm{d}t} = k_{12}A_1 - k_{21}\cdot D^{1-a}A_2,$$

where A1 and A2 are the amounts of Amiodarone (in ng) in the plasma and the tissues respectively and u be the administration rate (in ng/day). The parameter values are as follows: α=-0.587, k_{10}=1.4913day^{-1}, k_{12}=2.9522day^{-1} , k_{21}=0.4854day$^{-\alpha}$

We consider that Amiodarone is administered to the patient intravenously and continuously, the controller has access to plasma measurements of the concentration of Amiodarone and that the administration rate can be adjusted in real time by the controller. We use a fractional-PID feedback controller to control the concentration of Amiodarone in the patient's plasma. The treating doctor can modify the set point in real time to achieve the desired therapeutic effect. The controller's dynamics is given by the following transfer function:

$$G_c(s) = K_p + \frac{K_i}{s^\lambda} + K_d s^\mu$$



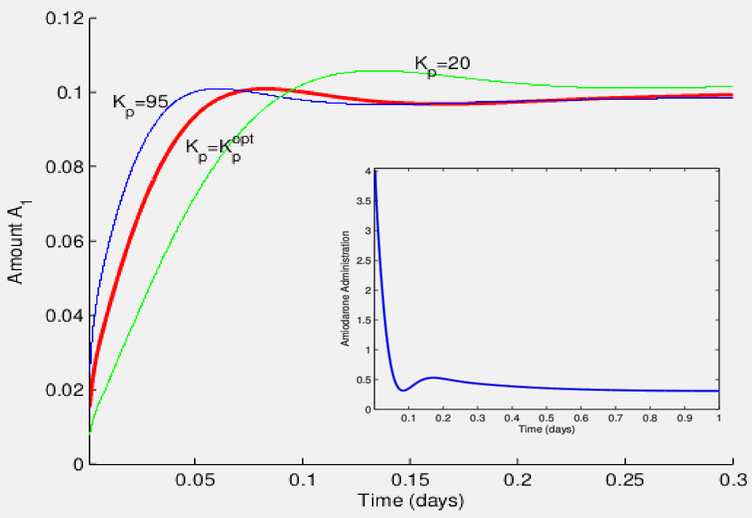
$$G_{ol}(s) = G(s)G_c(s) \text{ and } G_{cl}(s) = \frac{G_{ol}(s)}{1+G_{ol}(s)} \qquad G(s) = \frac{\frac{1}{k_{10}}\left(\frac{1}{k_{21}}s^a + 1\right)}{\frac{1}{k_{10}k_{21}}s^{a+1} + \frac{1}{k_{10}}s + \frac{k_{10}+k_{12}}{k_{10}k_{21}}s^a + 1}$$

In order to tune the controller we selected those parameters that minimise the Integral Time Absolute Error (ITAE) index following the excitation of the closed-loop system with a step pulse. → $J_{\text{itae}} = \int_0^\infty \tau\epsilon(\tau)\mathrm{d}\tau$

The optimal tuning parameters are given in the table below. The phase margin of the system was found to be 98deg and its gain margin is 43.9db! The closed-loop is therefore stable and can attenuate delays as high as 3.3 days. In the figure below we see how the system responds to a change of its set-point.

Tuning Parameter	Value
Kp	50.52
Ki	151.05
Kd	0.0756
λ	0.917
μ	0.759

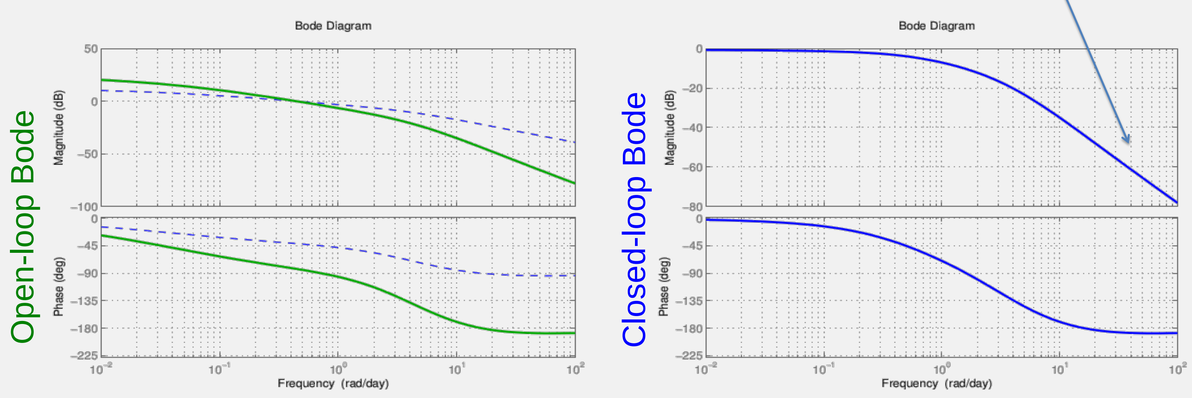
Stability Margin	Value
Phase Margin	98deg
Gain Margin	43.9db



The controller needs to compensate parametric uncertainties and fluctuations and modelling errors or time-varying dynamics. A measure for the resilience of the closed-loop under such uncertain conditions is quantified by the slope of the argument of the open-loop function at the cross-over frequency of the system, i.e.,

$$M_z = \left.\frac{\mathrm{d}}{\mathrm{d}\omega}\arg\left(G_{\text{ol}}(\imath\omega)\right)\right|_{\omega=\omega_{\text{co}}} = 0.5\text{deg}\cdot\text{rad}^{-1}\cdot\text{day}$$

The gain of the closed-loop transfer function at high frequencies is less than -60db which suggests that the controller can reject high-frequency noise in the closed loop.



References

[1] A. Dokoumetzidis, R. Magin, and P. Macheras. Fractional kinetics in multi-compartmental systems. Journal of Pharmacokinetics and Pharmacodynamics, 37:507–524, 2010a.