# Physiologically-based pharmacokinetic modeling for predicting caffeine/theophylline-ciprofloxacin interactions

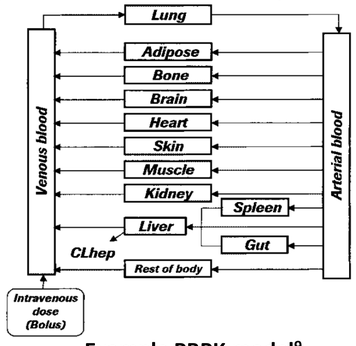
**David M. Ng, Ali Navid**

**Biosciences and Biotechnology Division, Lawrence Livermore National Laboratory, Livermore, CA**

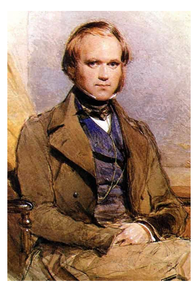
## Abstract

Dynamics of interactions between the drugs caffeine, theophylline, and ciprofloxacin are predicted using physiologically-based pharmacokinetic (PBPK) modeling. *Pharmacokinetic* means the model determines where the drugs are distributed in the body over time. *Physiologically-based* means the anatomy and physiology of the human body are reflected in the structure and functioning of the model. Multiple drugs can interact to increase or decrease their beneficial and/or undesired effects. This is important because some common substances, such as caffeine in coffee, soft drinks, and energy drinks, are actually drugs that affect the body. Ciprofloxacin is an inhibitor of caffeine and theophylline metabolism; such inhibition can lead to an overdose of caffeine and theophylline, and a reduced therapeutic effect for ciprofloxacin. PBPK modeling can be used by medical professionals to more precisely prescribe drug doses to achieve the desired therapeutic effects while minimizing the unwanted side effects by accounting for all drugs taken concurrently as well as lifestyle choices such as consumption of caffeinated beverages.

## Physiologically-based pharmacokinetic (PBPK) modeling[8]




Example PBPK model[9]



Example human (Charles Darwin)

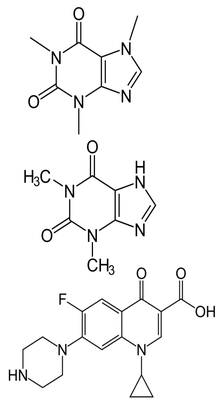
The block diagram (left) is an example of how a human (right) can be modeled:

- Organs appear as compartments (blocks) connected by blood flow (arrows).
- The model is described using differential equations.

Pharmacokinetics is divided into several processes:

- Absorption: Drugs can enter the body through various portals such as intravenous or oral routes.
- Distribution: Drugs circulate through the body via blood flow, or accumulate in tissue.
- Metabolism: Drugs may be changed or broken down into other substances by enzymes.
- Elimination: Drugs or their metabolic products are eliminated from the body through various routes including the kidney (urine), liver, or lungs.

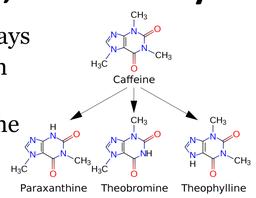
## Caffeine, theophylline, and ciprofloxacin



- Caffeine (top left) is a common psychoactive stimulant found in coffee, tea, soft drinks, and energy drinks.
- Theophylline (middle left) is used to treat respiratory conditions such as asthma, infant apnea, and chronic obstructive pulmonary disease (COPD).
- Ciprofloxacin (lower left) is an antimicrobial used to treat bacterial infections by inhibiting DNA and protein synthesis.[7] It is also used by the military to protect against anthrax, a biological weapon. Ciprofloxacin slows the rate at which the body eliminates caffeine and theophylline.[6]

## Metabolism, drug interactions, and toxicity

**Metabolism:** The diagram (right) shows pathways (arrows) by which caffeine, for example, is broken down in the liver by enzymes:




- Caffeine is broken down into theophylline by the enzyme CYP1A2.
- Theophylline is also broken down by CYP1A2.

### Drug Interactions

- A drug may affect the activity of another by altering its metabolism.
- Ciprofloxacin inhibits CYP1A2 by binding to it.[4]
- This slows down the metabolism of caffeine and theophylline which effectively increases their dose.
- The dose of ciprofloxacin is also effectively decreased.
- $K_I$ is the dissociation constant of the enzyme-inhibitor complex.

### Toxicity

- Theophylline intoxication occurs at a plasma level of 20 mg/L; toxicity occurs at 60 mg/L for chronic overdoses and at 100 mg/L for an acute overdose, and can result in seizures, arrhythmias, and death.[12, 16]
- For caffeine, 400 mg/day is a safe dose for healthy adults[11], 200 mg/day for pregnant women[15], and 2.5 mg/day per kg body mass for children [11] (e.g., 80 mg/day for an average 10 year old [17]).

## References

[1] Azad, M. A. K., Ullah, A., Latif, A. H. M. M., & Hasnat, A. (2007). Bioequivalence and pharmacokinetic study of two oral formulations of ciprofloxacin tablets in healthy male volunteers. *The Journal of Applied Research*, 7(2).
[2] Bergan, T., Thorsteinsson, S. B., Kolstad, I. M., & Johnsen, S. (1986). Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses. *European journal of clinical microbiology*, 5(2), 187–92.
[3] Crump, B., Wise, R., & Dent, J. (1983). Pharmacokinetics and tissue penetration of ciprofloxacin. *Antimicrobial agents and chemotherapy*, 24(5), 784–6.
[4] Fuhr, U., Wolff, T., Harder, S., Schymanski, P., & Staib, A. H. (1990). Quinolone inhibition of cytochrome P-450-dependent caffeine metabolism in human liver microsomes. *Drug metabolism and disposition: the biological fate of chemicals*, 18(6), 1005–10.
[5] Ginsberg, G., Hattis, D., Russ, A., & Sonawane, B. (2004). Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: implications for assessing children's risks from environmental agents. *Journal of toxicology and environmental health. Part A*, 67(4), 297–329.
[6] Healy, D. P., Polk, R. E., Kanawati, L., Rock, D. T., & Mooney, M. L. (1989). Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrobial agents and chemotherapy*, 33(4), 474–8.
[7] LeBel, M. (1988). Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. *Pharmacotherapy*, 8(1), 3–33.
[8] Lüpfert, C., & Reichel, A. (2005). Development and application of physiologically based pharmacokinetic-modeling tools to support drug discovery. *Chemistry & biodiversity*, 2(11), 1462-86.
[9] Luttringer, O., Theil, F.-P., Poulin, P., Schmitt-Hoffmann, A. H., Guentert, T. W., & Lavé, T. (2003). Physiologically based pharmacokinetic (PBPK) modeling of disposition of epiprofen in humans. *Journal of pharmaceutical sciences*, 92(10), 1990-2007.
[10] Mahr, G., Sörgel, F., Granneman, G. R., Kinzig, M., Muth, P., Patterson, K., ... Stephan, U. (1992). Effects of temafloxacin and ciprofloxacin on the pharmacokinetics of caffeine. *Clinical pharmacokinetics*, 22 Suppl 1, 90–7.
[11] Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., & Feeley, M. (2003). Effects of caffeine on human health. *Food additives and contaminants*, 20(1), 1–30.
[12] Olson, K. R., Benowitz, N. L., Woo, O. F., & Pond, S. M. (1985). Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *The American journal of emergency medicine*, 3(5), 386–94.
[13] *Physicians' desk reference*. (2004) (58th ed.). Thomson PDR.
[14] Rovei, V., Chanoine, F., & Strolin Benedetti, M. (1982). Pharmacokinetics of theophylline: a dose-range study. *British journal of clinical pharmacology*, 14(6), 769–78.
[15] Sengpiel, V., Elind, E., Bacelis, J., Nilsson, S., Grove, J., Myhre, R., ... Brantsaeter, A.-L. (2013). Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. *BMC medicine*, 11(1), 42.
[16] Shannon, M. (1993). Predictors of Major Toxicity after Theophylline Overdose. *Annals of Internal Medicine*, 119(12), 1161.
[17] Wolf, L. (2013). Caffeine Jitters. *Chemical and Engineering News*, (Feb 04), 9–12.

Image sources: • Caffeine structural formula and metabolism diagram: http://en.wikipedia.org/wiki/Caffeine • Ciprofloxacin structural formula: http://en.wikipedia.org/wiki/Ciprofloxacin • Darwin, Charles portrait: http://en.wikipedia.org/wiki/Charles_Darwin • PBPK block diagram: Luttringer (2003) • Theophylline structural formula: http://en.wikipedia.org/wiki/Theophylline

## Results

- A PBPK model for caffeine, theophylline, and ciprofloxacin was implemented using the *Mathematica* program.[5, 9]
- Figures 1 and 2 show good correspondence between the model's predictions (curves) with experimental data (points) for theophylline[14] and ciprofloxacin[1, 2, 3].
- Many common beverages contain caffeine at relatively high doses.[17] Figure 3 shows predicted plasma caffeine concentrations six hours after consuming a single serving of various beverages.

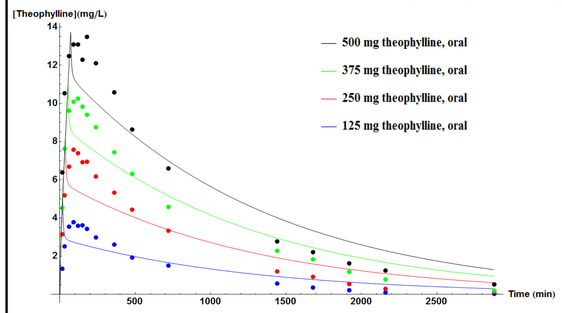



**Figure 1: Concentration of theophylline in the venous system: model prediction (curve) and experimental data (points) for the same theophylline dose have the same color.**

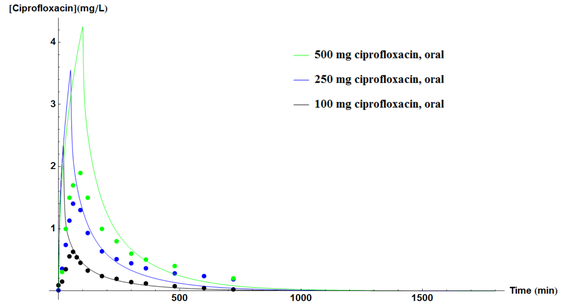



**Figure 2: Concentration of ciprofloxacin in the venous system: model prediction (curve) and experimental data (points) for the same ciprofloxacin dose have the same color.**

- Ciprofloxacin inhibits CYP1A2. Mahr et al. provide experimental results for caffeine plasma levels when coadministered with ciprofloxacin.[10] Fuhr et al. provide a value for $K_I$ : 0.18 mM.[4] The model predicts a poor match with experiment given this value for $K_I$ , and predicts a value of 1.4 μM for $K_I$ (data not shown).
- Figure 4 shows the serum concentration of theophylline when administered alone (blue), and that theophylline administered with ciprofloxacin (red) leads to theophylline intoxication[12] (exceeds black line) due to ciprofloxacin's inhibition of CYP1A2, even when the doses of both drugs are consistent with therapeutic guidelines[13].

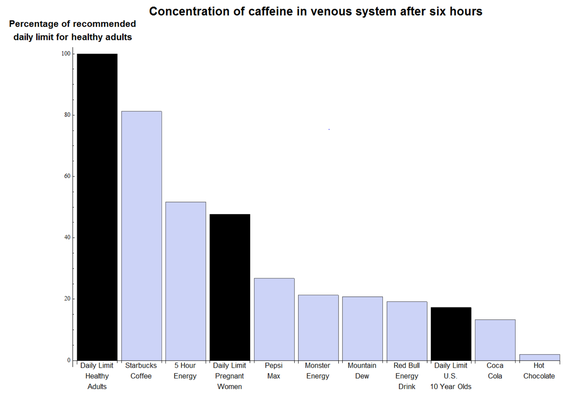



**Figure 3: Predicted plasma concentrations of caffeine six hours after ingesting a single serving of various beverages (as a percentage of the recommended daily limit for healthy adults). Black bars denote recommended daily limits; blue bars denote beverages.**

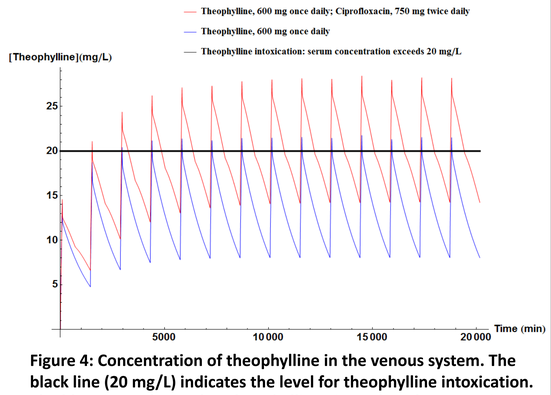



**Figure 4: Concentration of theophylline in the venous system. The black line (20 mg/L) indicates the level for theophylline intoxication. The blue curve shows that theophylline given alone has a maximum concentration near the intoxication level, but given in combination with ciprofloxacin will exceed the intoxication level (both drugs given within dosage guidelines).**

## Conclusion and future work

- Theophylline and ciprofloxacin, both prescribed within therapeutic guidelines, can, in combination, lead to theophylline intoxication due to ciprofloxacin's inhibitory effect on theophylline metabolism.
- The model predicts a value for $K_I$ for ciprofloxacin-CYP1A2 significantly different from the *in vitro* value determined by Fuhr et al.
- Model development will continue with the inclusion of ciprofloxacin metabolism, leading to publication.

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. This material is based upon work supported by the S.D. Bechtel, Jr. Foundation, National Marine Sanctuary Foundation, Carnegie Corporation of New York, and/or National Science Foundation under Grant Nos. 0952013 and 0833353. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the funders. The STAR program is administered by the Cal Poly Center for Excellence in Science and Mathematics Education (CESaME) on behalf of the California State University. This work was funded by the Laboratory Directed Research and Development Program at LLNL under project tracking code 12-SI-004. LLNL-POST-641787.