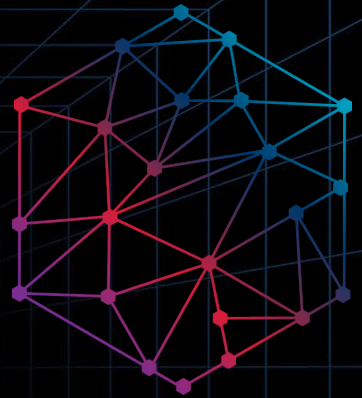
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Panel Discussion:
The Impact of Modeling in Drug Development

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Ascent of Model Informed Drug Development (MIDD)

We Stand on the Shoulders of Those Who Came Before Us

- There is a rich, long-standing history of science and mathematical modeling that set the table for the current, rich MIDD environment
- Technical advances have allowed PBPK, PopPK, PK-PD, QSP and other modeling disciplines to grow considerably over the years
- The development of software to facilitate the practice of developing and using models has proven to be a catalyst in adoption of modeling within drug development
- The establishment of academic programs to train students in modeling principles and practice have contributed to the ascent of MIDD

Early Examples of PBPK Modeling

STUDIES ON THE DIFFUSION EFFECT UPON IONIC DISTRIBUTION

II. Experiments on Ionic Accumulation

By TORSTEN TEORELL*

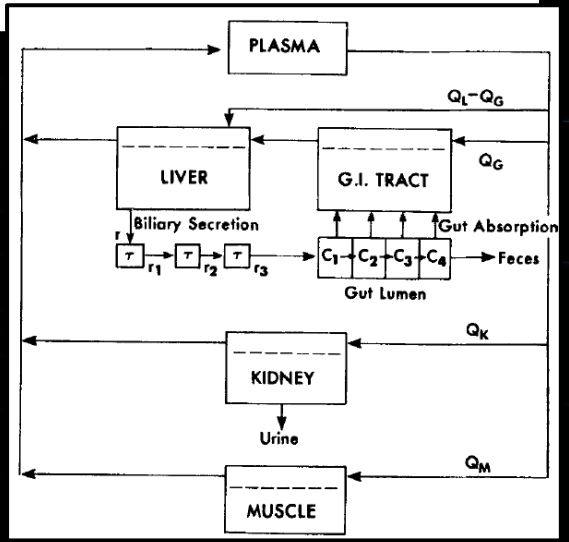
(From the Laboratories of The Rockefeller Institute for Medical Research, New York, and the Department of Medical Chemistry, University of Upsala, Upsala, Sweden)

(Accepted for publication, April 17, 1937)

RESEARCH ARTICLES

Methotrexate Pharmacokinetics

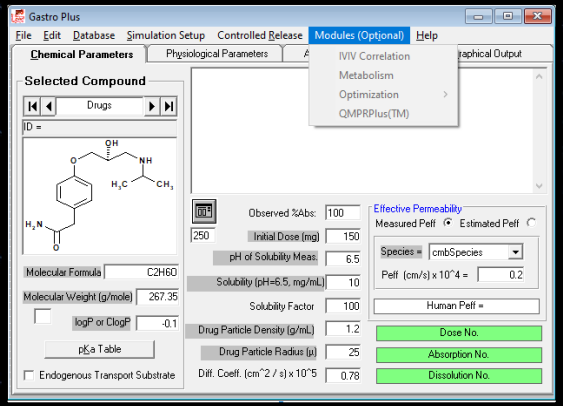
K. B. BISCHOFF*‡, R. L. DEDRICK*, D. S. ZAHARKO†, and J. A. LONGSTRETH*

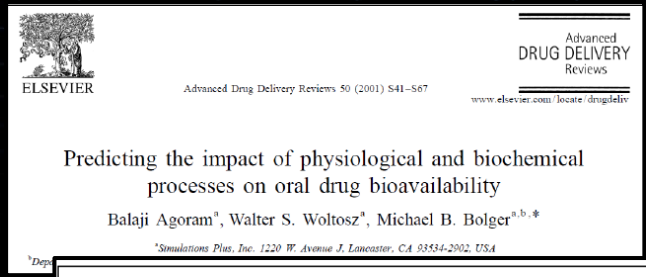


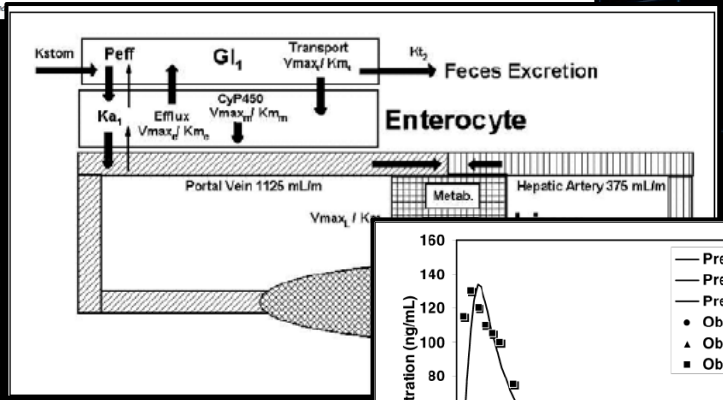
Scientific principles upon which PBPK modeling are based have very early origins

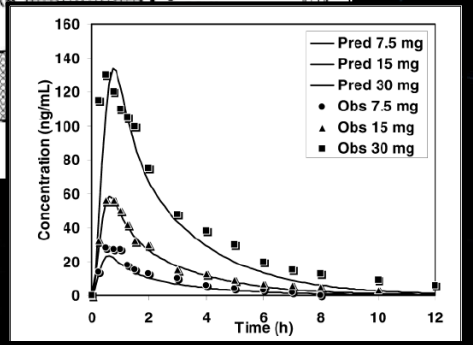
- Teorell 1937 is perhaps first example of PBPK-type approach
- Bischoff 1971 a nice early example of PBPK modeling

Early Examples of PBPK Modeling: GastroPlus





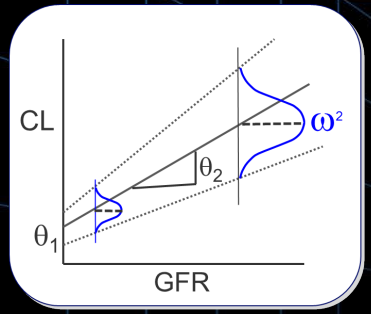




Commercially available PBPK models and software accelerated the adoption of this approach within pharma and biotech

- Initially made available in the 1990's
- Industry and regulators make wide use of PBPK models and simulation results today

NONMEM Development Encouraged PopPK and PK-PD Modeling Use



Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data

Lewis B. Sheiner,[1,4] Barr Rosenberg,[2] and Vinay V. Marathe[2,3]

Received December 3, 197

The Pharmacokinetic Model

The basic pharmacokinetic model used is the one-compartment open model. The model is cast in a recursive form so that the "state" of the model at time t_n is calculated from the time difference ($t_n - t_{n-1}$, where $t_n > t_{n-1}$) and the previously calculated "state" of the model at time t_{n-1} (1). From the "state" of the model at any time, the plasma concentration or the average urine concentration in a specified collection period can be calculated. The model applies to a given individual, but subscripts denoting the individual are suppressed. The subscripts used below (1 and 2) refer to times t_{n-1} and t_n, respectively.

The formal statement of the model is

$$A_2^0 = A_1^0 \exp(-k_e \Delta t) + f^0 d_2^0 + \frac{k^0}{k_e}[1 - \exp(-k_e \Delta t)] + \sum_{r=1}^{2} \frac{A_1^r k_a^r}{k_a^r - k_e}[\exp(-k_e \Delta t) - \exp(-k_a^r \Delta t)] \quad \text{(A1)}$$

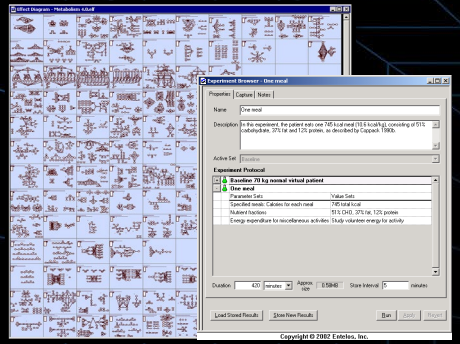
$$A_2^r = A_1^r \exp(-k_a^r \Delta t) + f^r d_2^r; \qquad r = 1, 2 \quad \text{(A2)}$$

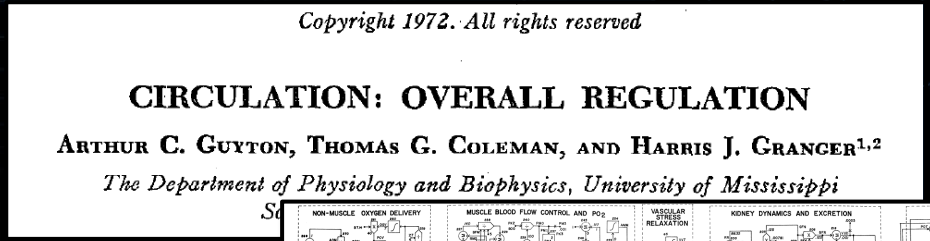
$$A_2^u = \frac{k_u}{k_e}\left(\sum_{r=0}^{2} A_1^r - \sum_{r=0}^{2} A_2^r + \sum_{r=0}^{2} f^r d_2^r + k^0 \Delta t\right) + A_1^u \quad \text{(A3)}$$

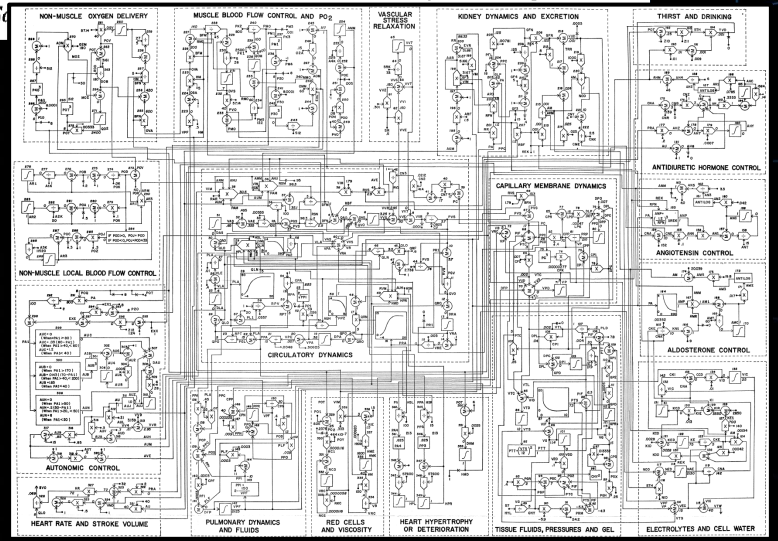
Sheiner, Beal, and Boeckmann developed NONMEM in late 1970's to enable curve-fitting applications with sparsely collected PK data

- Provided ability to estimate inter-individual variability in key parameters and explore the sources of variability
- Accelerated application of PopPK modeling
- Accelerated application of PK-PD modeling

QSP Modeling Utilizes Long-Standing Approaches That Have Been Advanced Over Time



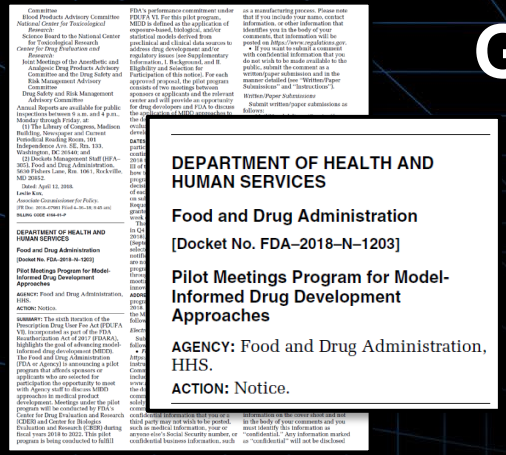




Mechanistic, mathematical models of biochemistry and physiology have long been in use

- Guyton 1972 is an early example of the mathematically integrating numerous layers of physiologic systems to generate an increased understanding of the overall system
- The application of QSP modeling to drug development took major steps forward in late 1990's. Entelos PhysioLabs are good examples of this application

Great Future for MIDD



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

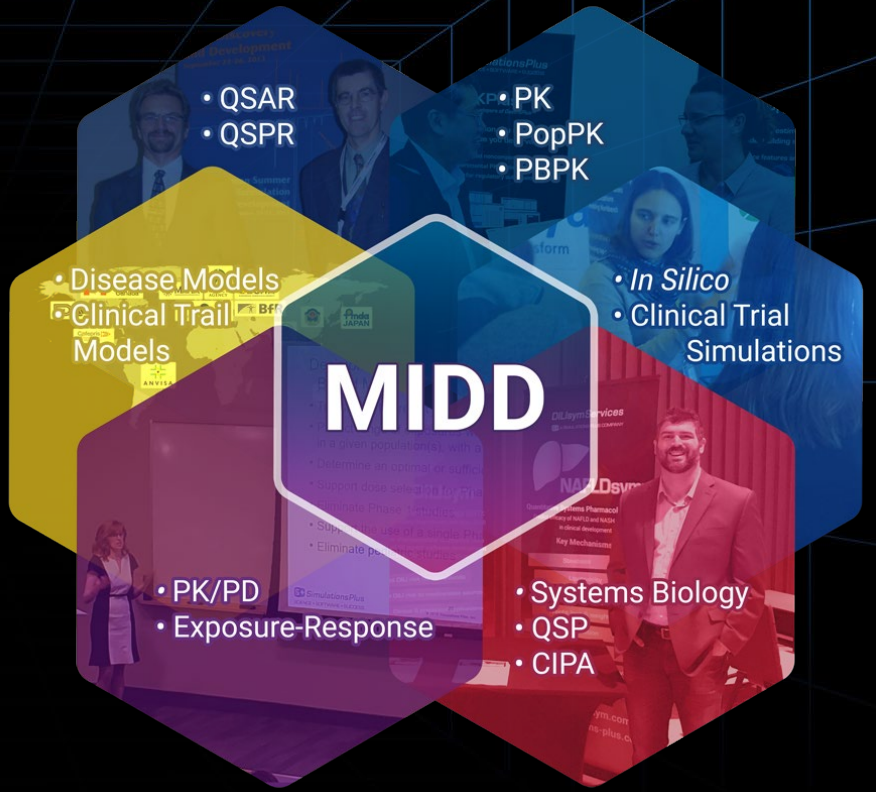
[Docket No. FDA–2018–N–1203]

Pilot Meetings Program for Model-Informed Drug Development Approaches

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

- MIDD continues to grow, with the intent to contribute to getting safe and effective treatments to patients as soon as possible
- Modeling methodologies continue to advance
- Computational capabilities expanding
- Increasing number of trained modelers available to practice the art of modeling



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Q&A

Questions & Answers

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