DoseMeRx | Precision dosing
Every patient, every dose, every time.

An Introduction to DoseMeRx and Precision Dosing

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An Introduction to Precision Dosing and Bayesian Dose Individualization

DoseMeRx is a precision dosing software designed for clinicians, built on the principles of Bayesian statistics to predict the optimal dose of drugs monitored by Therapeutic Drug Monitoring. Its simplicity and portability means precision dosing and the benefits of Bayesian statistics can be brought to every bedside.

Bayesian statistics is a branch of statistics where the probability of an event happening is described by the past history of that and/or similar events. To compare this to frequentist statistics, we can consider a hypothetical, standard coin toss.

The frequentist statistics (i.e. the statistics/probability taught at high-school) will teach that in the event of flipping a normal coin the likelihood of it coming up heads in any given toss is 50% (regardless of how many heads have come up previously), and that the percentage of heads tossed will approach 50% as the number of tosses approaches infinity.

In contrast, should a coin come up heads ten times in a row, Bayesian statistics would suggest that the coin is biased.

Should a coin come up heads ten times in a row, Bayesian statistics would ask:

- What do we believe that the coin should have a probability of before we start?

- How can we integrate the new information with our old beliefs?

If we were to previously assume that the coin was unbiased (e.g. between 45% and 55% fair), and yet it came up heads 10 times in a row, we can trivially calculate that:

$$\Pr(0.45 < r < 0.55) = \int_{0.45}^{0.55} \frac{(10+1)!}{10!\ 0!}\, r^{10}\,(1-r)^{0}$$

When solved, this shows that the likelihood of the coin being unbiased is 0.12%. We can then use this model further to predict the next toss of the coin (e.g. not very likely to be tails).

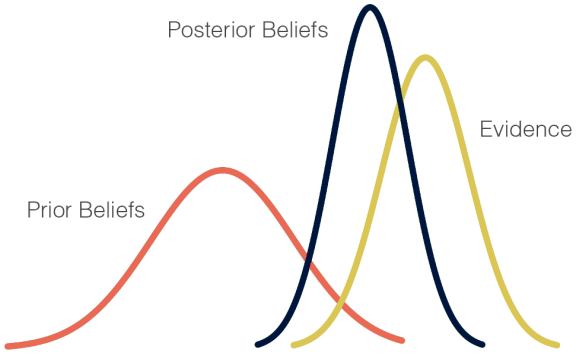
The key part to note here is the terminology. We have the **prior probability** of a coin toss coming up heads (45-55%), and the **posterior probability** after we have integrated the new information.

This applies to drug models. We know the mean and standard deviation of a drug metabolism rate from the literature, allowing us to calculate the **prior probability** that any given patient has a certain metabolic rate. We can then take data from an individual patient, and calculate the **posterior probability** that the metabolic rate that we measure in an individual patient is real, or if the data was recorded incorrectly, for example.

While this may sound and look a little complex here, it's basically the process of:

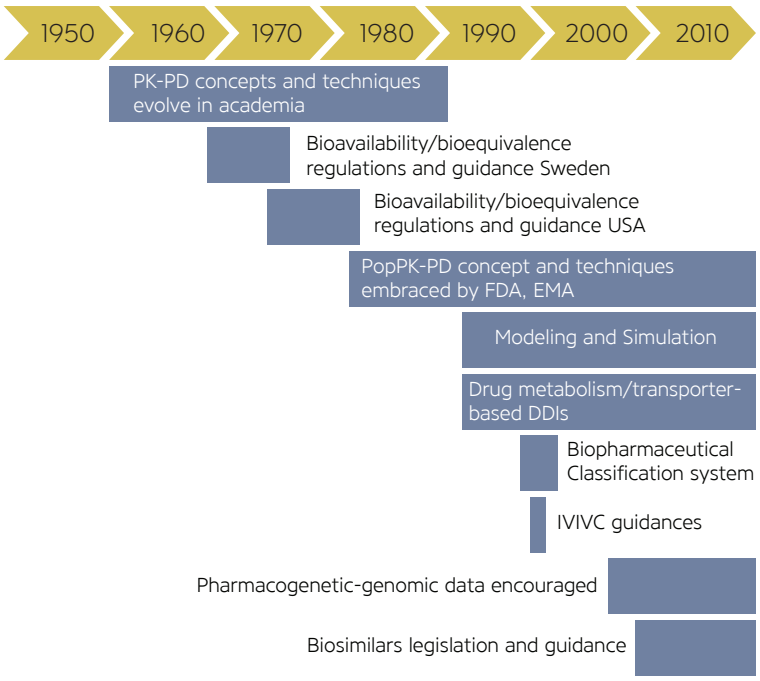
1. Fit a curve to data

2. Ask "is this curve reasonable given how the previous data (drawn from a previous model/population) describes it?"



Precision Dosing - A History of Bayesian Dose Individualization

The idea of modeling the overall dose-to-effect relationship across a population and determining what features are individually significant in varying that dose (e.g. weight) is not only well accepted by the FDA, but also mandated for new drug applications. In essence, this approach is conceptually very similar to that of Google Maps above. We don't need to know and model each cytochrome p450 enzyme used in drug metabolism, but rather develop a model that describes the overall effect and overall dose to response relationship instead and describe major impacts instead.



Rowland M *et al.* (J. Pharm. Sci. 2012.) present an overview publication, from which we reproduce Figure 1 (right). From this figure, we can see that from the 1980s onwards, these models and more generic drug modeling has been embraced by regulatory authorities. For additional information on how these models are used at the FDA, please refer to http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm167032.htm .

Today, these drug models are used to establish label based dosing, by integrating data from the most recent clinical trial with that of previous clinical trials, using the same Bayesian approach described above. These models are then used to establish which dose is most effective and safe (for most people), and drive the creation of the drug labeling.

Individualized dosing tools that use these models, however, have been available for significantly longer than the use of these models for regulatory purposes. In 1969, Lewis B. Sheiner published a paper, "Computer-Aided Long-Term Anticoagulation Therapy", which was the first application of Bayesian statistics to dosing pharmaceuticals. It outperformed 2 of 3 cardiologists using the same mathematical approach that we have in DoseMeRx (but a different underlying pharmacokinetic model).

Since the initial publication of Bayesian dosing, Bayesian dosing has been used widely clinical, using a wide range of models. These models are specific to individual drugs (often with many models for the one drug), and are published widely in the scientific literature.

How DoseMeRx Works

DoseMeRx leverages clinically validated pharmacokinetic models, patient characteristics, drug concentrations and genotype to guide dose optimization. By incorporating patient characteristics and utilizing Bayesian statistics, DoseMeRx can support clinicians in calculating a precise dose to achieve the desired clinical target.

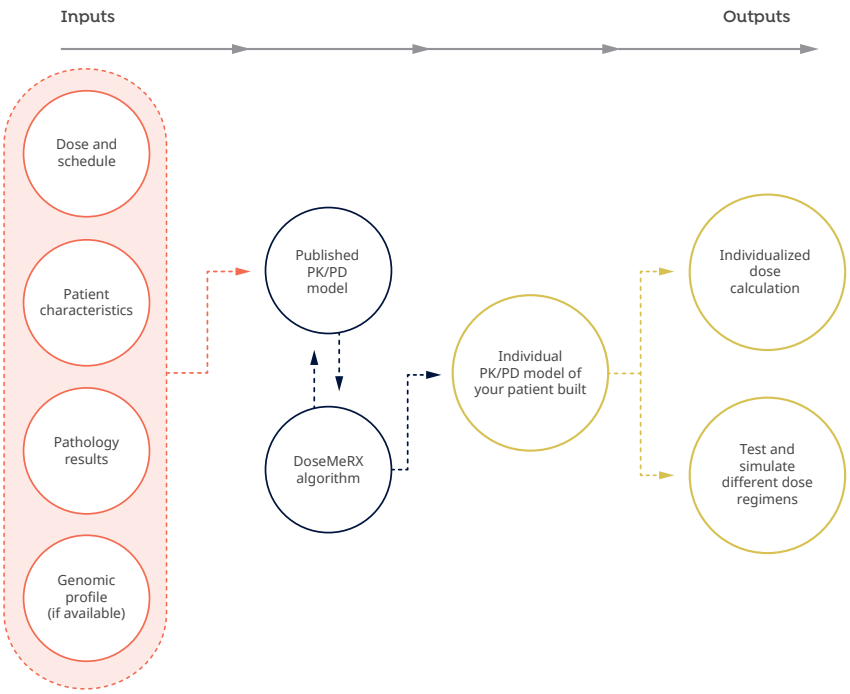
Inputs

Doses and schedule - The dose administered (e.g. 100mg), and the time/date.

Patient characteristics - Weight, Height, Sex, and Age.

Pathology results - A measurement of the drug concentration in the blood and for some drug models, serum creatinine.

Genomic Profile - While applicable for some drug models, DoseMeRx does not require it.



Pharmacokinetic/Pharmacodynamic (PK/PD) Model

PK/PD models are published in the literature, describing the patient population from which they have been developed. An example model is shown below.

Volume and Clearance can be considered as parameters in this model. This model can be expressed mathematically as:

$$k = \frac{CL}{V}$$

$$C(t) = \frac{D}{V} e^{-k(t-t_D)}$$

Where CL is the clearance, V is the volume of distribution, and C(t) is the concentration in the blood of the patient at a time.

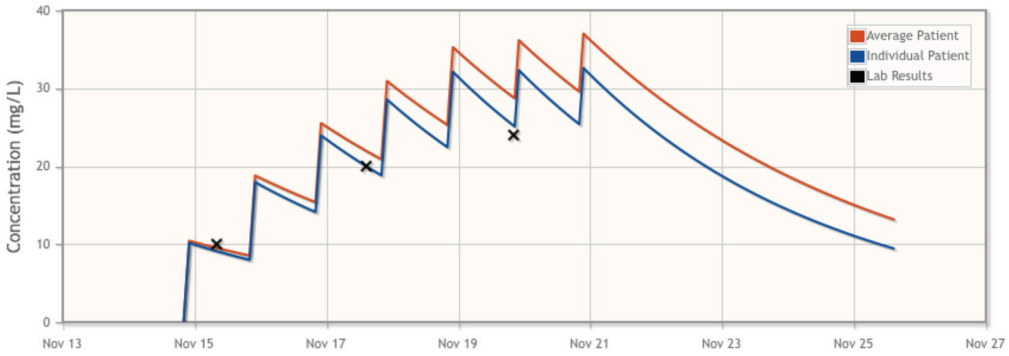
For a population pharmacokinetic model, we not only have the mean parameter reported, but also the standard deviation. In other words, we know the prior probability that a patient has a certain rate of drug clearance from the published trial. We then can measure their **actual** rate of clearance from the doses, schedule and observed drug responses given as input to DoseMeRx. Weighing up these parameters, we then adjust the parameters of the model to fit the doses and observed responses provided by the clinician.

While this cannot feasibly be done on paper with a pen, a clinician who desired to check this could do it in Excel, or on a graphics calculator. Within DoseMeRx, we provide links behind (?) icons that provide a reference to the specific calculations required for a given step in using DoseMeRx.

DoseMeRx in Practice

Visually, using the vancomycin model as an example (which is structurally the same as the above example but with different parameters for clearance and volume), DoseMeRx can produce the following plot (using a generalized version of the equation above).

This image represents a course of vancomycin in a single patient, who has been given seven doses, and had three concentrations measured.



On the plot above, we have three pieces of information:

Red line

The 'average' patient. In this case, it's the population pharmacokinetic model. It's how you would expect the average person to respond to the drug. In this case, it takes into account that patient's weight and renal function as well, since these are included in the published model.

Black Crosses

The black crosses are recorded observations of the concentration of vancomycin in a patient's blood at that point in time. Note that two of the three are not lying on the red/average patient line but rather show a difference.

Blue Line

The blue line takes the population model/equation, and adjusts the parameters that are described in the population model as varying between patients (i.e. those parameters that have a between-subject variability term in the population model).

DoseMeRx adjusts the population model until it fits the actual recorded doses and recorded drug concentration results - the actual course of treatment recorded for this patient. It works very similarly to the goal-seek function in Excel.

Note: DoseMeRx hasn't actually fit to the right-most observation all the way. This is where the prior and posterior probability comes into play. Bayesian dosing considers how likely it is that an observation is 'real' - i.e. that when we adjust the parameters of the population model to describe an individual datapoint, is it likely that the adjusted parameter (and therefore the datapoint) came from a real population (based on the population models mean and standard deviation of each parameter), or is it a mistake in data entry.

In practice, precision dosing software using Bayesian statistical methods calculate the parameters to describe the doses and observations recorded and calculate the probability that the parameters are 'real' in one step for efficiency.

The Mathematics behind DoseMeRx

The formulae behind DoseMeRx and Bayesian dose individualization are well accepted and in fact are critical to dose selection for clinical trials based upon the results of previous clinical or animal studies. These methods are used for approval of clinical trial protocols by regulators.

For those who want further information, we suggest reviewing the paper by Burton, ME. *et al.* titled, A Bayesian feedback method of aminoglycoside dosing (Clinical pharmacology and therapeutics. 1985:37, 349-357.) - describing the approach used in DoseMeRx.

In brief, the approach can be described mathematically as:

$$\mathrm{Obj} = \sum \frac{(P_n' - P_n)^2}{(SD_n)^2} + \sum \frac{(C_{\mathrm{pred}} - C_{\mathrm{obs}})^2}{(SE_m)^2}$$

Where:

- **P'_n** is a revised parameter (that fits the individual's recorded doses and observations),
- **P_n** is the model population parameter,
- **C_{pred}** is the predicted concentration (given the new parameters),
- **C_{obs}** is the recorded concentration/observation, and
- **SE_m** is an adjusted standard error.

Bayesian dosing minimizes the above equation, attempting to make **Obj** as small as possible. On the left is a penalty term, which (as previously described) implicitly calculates the posterior probability that the parameter that describes the recorded observations is 'real' (i.e. drawn from the population of the publish PK/PD model).

On the right of the equation is a sum-of-squares minimization to calculate the new parameters based on how well the adjusted model fits the recorded observations. It seeks to minimize the difference between the concentration that the model we're evaluating predicts and each real measured concentration.

By having both terms, in a single step, we simultaneously find parameters (e.g. volume and clearance). These best describe an individual patient's pharmacokinetics for a drug, and calculate if they're likely given the probability that the 'new' parameter for our individual course came from the population. The denominator on the right term balances this with the overall known unexplained variance in the assay and model. This is why DoseMeRx applies criteria when adding models to our library - to have not only individual parameters being identifiable but also the unexplained variance being minimal.

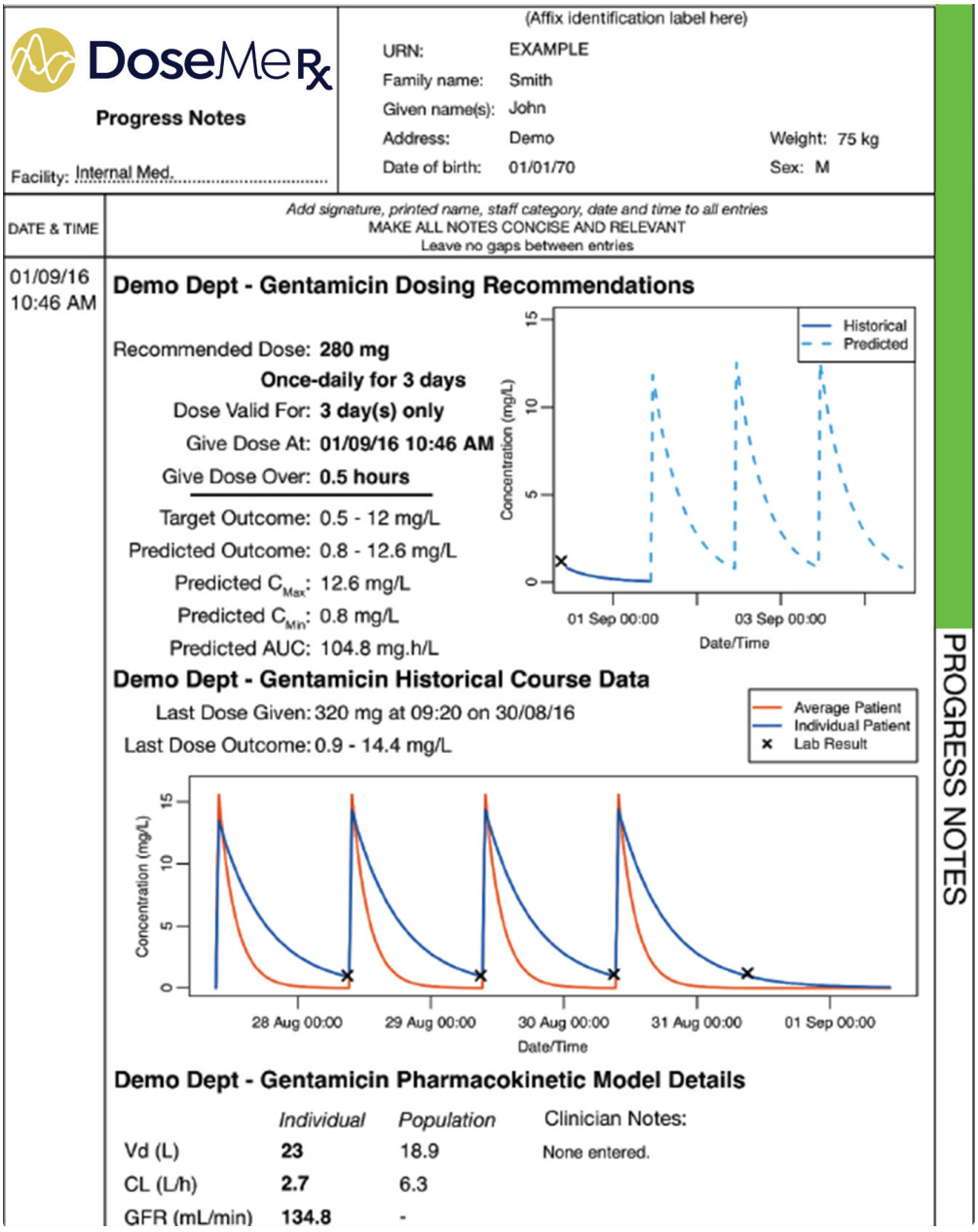
What's next?

Once an individualized model is built based upon the data a clinician has available and the selection of an appropriate model, two main questions can be asked:

"Given what I know, what are the most likely future outcomes (e.g. concentrations) of a set of doses?"

"Given a goal concentration, for this patient, what dose is most likely to achieve it?"

DoseMeRx can then generate a report with this information (see below), which clinicians can use as part of their decision making in conjunction with label information.



DoseMeRx

Progress Notes

Facility: Internal Med.

(Affix identification label here)

URN: EXAMPLE
Family name: Smith
Given name(s): John
Address: Demo
Weight: 75 kg
Date of birth: 01/01/70
Sex: M

DATE & TIME

Add signature, printed name, staff category, date and time to all entries
MAKE ALL NOTES CONCISE AND RELEVANT
Leave no gaps between entries

01/09/16 10:46 AM

Demo Dept - Gentamicin Dosing Recommendations

Recommended Dose: **280 mg**
Once-daily for 3 days
Dose Valid For: **3 day(s) only**
Give Dose At: **01/09/16 10:46 AM**
Give Dose Over: **0.5 hours**
Target Outcome: 0.5 - 12 mg/L
Predicted Outcome: 0.8 - 12.6 mg/L
Predicted C_{Max}: 12.6 mg/L
Predicted C_{Min}: 0.8 mg/L
Predicted AUC: 104.8 mg.h/L

Demo Dept - Gentamicin Historical Course Data

Last Dose Given: 320 mg at 09:20 on 30/08/16
Last Dose Outcome: 0.9 - 14.4 mg/L

Demo Dept - Gentamicin Pharmacokinetic Model Details

	Individual	*Population*
Vd (L)	**23**	18.9
CL (L/h)	**2.7**	6.3
GFR (mL/min)	**134.8**	-

Clinician Notes:
None entered.

PROGRESS NOTES

References

1. Rowland M et al. “Impact of the Pharmaceutical Sciences on Health Care: A Reflection over the Past 50 Years” J. Pharm. Sci. 2012.

2. “Computer-Aided Long-Term Anticoagulation Therapy”, Comput Biomed Res. 1969 Dec;2(6):507-18.

3. Burton, ME. et al. “A Bayesian Feedback Method of Aminoglycoside Dosing”, Clinical Pharmacology and Therapeutics. 1985:37, 349-357.

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