UNIT 1
HISTORY OF COMPUTERS IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT

1. HISTORY OF COMPUTERS IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT

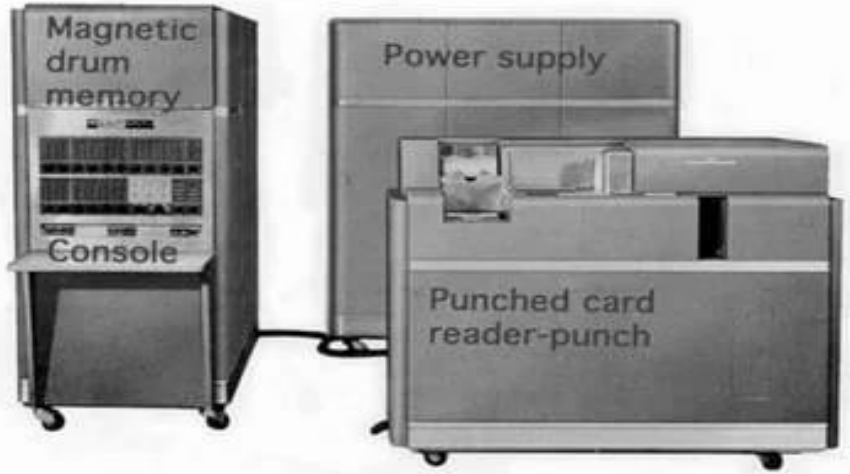
- Today computers are seen everywhere in **Pharmaceutical research and development** that it may be hard to imagine a time when there were no computers to assist the medicinal chemist or biologist.
- Computers began to be utilized at pharmaceutical companies as early as the **1940s**.
- There were several scientific and engineering advances that made possible a computational approach to **design** and **develop** a molecule.
- One fundamental concept understood by chemists was that **chemical structure** is related to **molecular properties** including **biological activity**.

- A quarter-century ago, the notion of a computer on the desk of every scientist and company manager was not even contemplated.
- Now, computers are absolutely essential for **generating, managing**, and **transmitting information**.

BRIEF ACCOUNT ON HISTORIC DEVELOPMENT :

- In the late 1950's or early 1960'S, the **first computers** to have stored programs of scientific interest were acquired.
- One of these was an **IBM 650**, it had a rotating magnetic drum memory consisting of 2000 accessible registers.
- The programs, the data input, and the output were all in the form of **IBM punched cards**.

IBM 650 :



IBM 650 CONSOLE PANEL

MEMORY DRUM FROM AN IBM 650

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EVOLUTION OF DIGITAL SYSTEM IN HEALTHCARE SYSTEM

- Let's review health information system trends, decade by decade,

1. 1960s :

- The main healthcare drivers in this era were Medicare and Medicaid.
- The IT drivers were expensive mainframes and storage.
- Because computers and storage were so large and expensive, hospitals typically shared a **Mainframe**.
- The principal applications emerging in this environment were shared hospital accounting systems.

2.1970s :

- One of the main healthcare drivers in this era was the need to do a better job communicating between departments (ADT, order communications, and results review) and the need for discrete departmental systems (e.g., clinical lab, pharmacy).
- Computers are now small enough to be installed in a single department without environmental controls.
- As a result, departmental systems proliferated.
- Unfortunately, these transactional systems, embedded in individual departments, were typically islands unto themselves.

3. 1980s

- Healthcare drivers were heavily tied to DRG's and reimbursement.
- For the first time, hospitals needed to pull significant information from both clinical and financial systems in order to be reimbursed.
- At the same time, personal computers, widespread, non-traditional software applications, and networking solutions entered the market.
- As a result, hospitals began integrating applications so financial and clinical systems could talk to each other in a limited way.

4.1990s :

- In this decade, competition and consolidation drove healthcare, along with the need to integrate hospitals, providers, and managed care.

- From an IT perspective, hospitals now had access to broad, distributed computing systems and robust networks.

- Therefore, creation of Integrated delivery network (IDN)- like integration, including the impetus to integrate data and reporting.

5.2000s :

- The main healthcare drivers were increased integration and the beginnings of outcomes-based reimbursement.
- We now had enough technology and bedside clinical applications installed to make a serious run at commercial, real-time clinical decision support.

2. PHARMACOINFORMATICS :

- It is the **new** originating information technology.
- It includes neuroinformatics, bioinformatics, immunoinformatics, genoinformatics, metaboloinformatics, healthinformatics which are used as a base for the discovery of drugs.
- The computers are needed to **spread** this pharmacoinformatics, i.e., transferring the data/information and knowledge to the public. This evolving or emerging technology is becoming a **fundamental component** to pharmaceutical sciences.
- Medical informatics focuses on using information processing with in the clinical setting for medical billing, patient and resource scheduling, and patient care.

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3. CURRENT APPLICATIONS OF COMPUTERS IN PHARMACY

1. Usage of computers in the **Retail pharmacy**
2. Computer aided design of drugs (**CADD**)
3. Use of Computers **in Hospital Pharmacy**
4. **Data storage** and retrieval
5. **Information system** in Pharmaceutical Industry
6. **Diagnostic** laboratories
7. Computer aided **learning**
8. **Clinical trial** management
9. **Adverse drug events** control
10. Computers in **pharmaceutical formulations**
11. Computers in **Toxicology and Risk Assessment**
12. Computational **modeling of drug disposition**
13. Recent development in bio computation of drug development
14. In **Research Publication**
15. **Digital Libraries**

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4. STATISTICAL MODELING IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT

What is Statistics?

- Statistics is a **scientific study of numerical data** based on natural phenomena.

- It is also the **science of collecting, organizing, interpreting and reporting data.**

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PHARMACEUTICAL STATISTICS

Pharmaceutical statistics is the application of statistics to matters concerning the pharmaceutical industry. This can be from issues of **design** of experiments, to analysis of drug trials, to issues of commercialization of a medicine.

- Evaluate the **activity of a drug**; e.g. effect of caffeine on attention; compare the analgesic effect of a plant extract and NSAID.
- To explore **whether the changes produced by the drug are due to the action of drug or by chance.**
- To **compare the action of two or more different drugs or different dosages of the same drug** are studied using statistical methods.
- To find an **association between disease and risk factors** such as Coronary artery disease and smoking.

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- The new major challenge that the pharmaceutical industry is facing in the discovery and development of new drugs is to **reduce costs** and **time needed** from **discovery to market**, while at the same time raising standards of quality.

- The development of **models** in the pharmaceutical industry is certainly one of the significant breakthroughs proposed to face the challenges of cost, speed, and quality, somewhat imitating what happens in the aeronautics industry.

- The concept, however, is that of adopting just another new technology , known as "**modeling**".

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- The purpose of the model is essentially for that of translating the known properties as well as some new hypotheses into a mathematical representation.
- In this way, a **model** is a **simplifying representation of the data-generating mechanism under investigation**.
- The identification of an appropriate model is **often not easy** and may **require thorough investigation**.

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DESCRIPTIVE VERSUS MECHANISTIC MODELLING

1.DESCRIPTIVE MODELLING :

- If the purpose is just to provide a **reasonable description** of the data in some appropriate way without any attempt at understanding the underlying phenomenon, that is, the data-generating mechanism, then the family of models is selected based on its adequacy to represent the data structure.
- The net result in this case is only a descriptive model of the phenomenon.
- These models are very **useful for discriminating between alternative hypotheses** but are totally useless for capturing the fundamental characteristics of a mechanism.

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2.MECHANISTIC MODELLING :

- Whenever the interest lies in the understanding of the mechanisms of action, it is critical to be able to count on a strong collaboration between scientists, specialists in the field, and statisticians or mathematicians.

- The former must provide updated, rich, and reliable information about the problem.

- Whereas the latter are trained for translating **scientific information in mathematical models.**

EXAMPLE :

- A first evaluation of the data can be done by running non-parametric statistical estimation techniques like, for example, the **Nadaraya–Watson kernel regression estimate**.

- These techniques have the advantage of being **relatively cost-free in terms of assumptions**, but they **do not provide any possibility of interpreting the outcome** and are **not at all reliable when extrapolating**.

- The fact that these techniques **do not require a lot of assumptions** makes them **relatively close to what algorithm-oriented people try to do**.

5. STATISTICAL PARAMETERS

A **statistical parameter** or **population parameter** is a quantity entering into the probability distribution of a statistic or a random variable.

- **Dispersion (also called Variability, Scatter, Spread)**
- **Coefficient of Dispersion (COD)**
- **Variance**
- **Standard Deviation (SD) σ**
- **Root Mean Squared Error (RMSE)**
- **Absolute Error (AE)**
- **Mean Absolute Error (MAE)**
- **Percentage Error of Estimate (PE)**
- **Mean Square Error (MSE)**
- **Mean Absolute Percentage Error (MAPE) Mean Absolute Deviation (MAD)/ Mean Ratio Residuals**
- **Sum of Squares of Error (SSE)**
- **Factor Analysis**
- **Eigen Value (λ)**
- **Eigen Vector**

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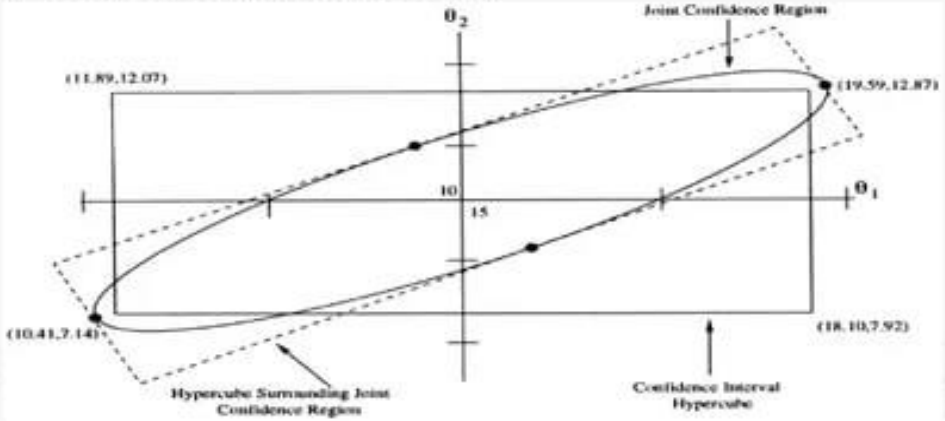
6. CONFIDENCE REGION

- In statistics, a **confidence region** is a multi-dimensional generalization of a confidence interval. It is a set of points in an ***n*-dimensional space**, often represented as an ellipsoid around a point which is an estimated solution to a problem, although other shapes can occur.



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- The confidence region is calculated in such a way that if a set of measurements were repeated many times and a confidence region calculated in the same way on each set of measurements, then a certain percentage of the time (e.g. 95%) the confidence region would include the point representing the "**true**" values of the set of variables being estimated.

- However, unless certain assumptions about prior probabilities are made, it does **not** mean, when one confidence region has been calculated, that there is a 95% probability that the "true" values lie inside the region, since we do not assume any particular probability distribution of the "true" values and we may or may not have other information about where they are likely to lie.

7. NONLINEARITY AT OPTIMUM

- Confidence regions can be defined for any probability distribution. The experimenter can choose the significance level and the shape of the region, and then the **size** of the region is determined by the **probability distribution**. A natural choice is to use as a boundary a set of points constant chi-squared values.

- One approach is to use a **linear approximation to the nonlinear model**, which may be a close approximation in the vicinity of the solution, and then apply the analysis for a linear problem to find an approximate confidence region. This may be a reasonable approach if the **confidence region is not very large and the second derivatives of the model are also not very large**.

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8. SENSITIVITY ANALYSIS

- A technique used to determine how different values of an independent variable will impact a particular dependent variable under a given set of assumptions.

- **Sensitivity analysis** is a way to predict the outcome of a decision if a situation turns out to be different compared to the key prediction(s).

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- **Sensitivity analysis answers the question?**

"If these **variables deviate from expectations, what will the effect on** (model, system, or whatever is being analyzed), and **which variables are causing the largest deviations**"

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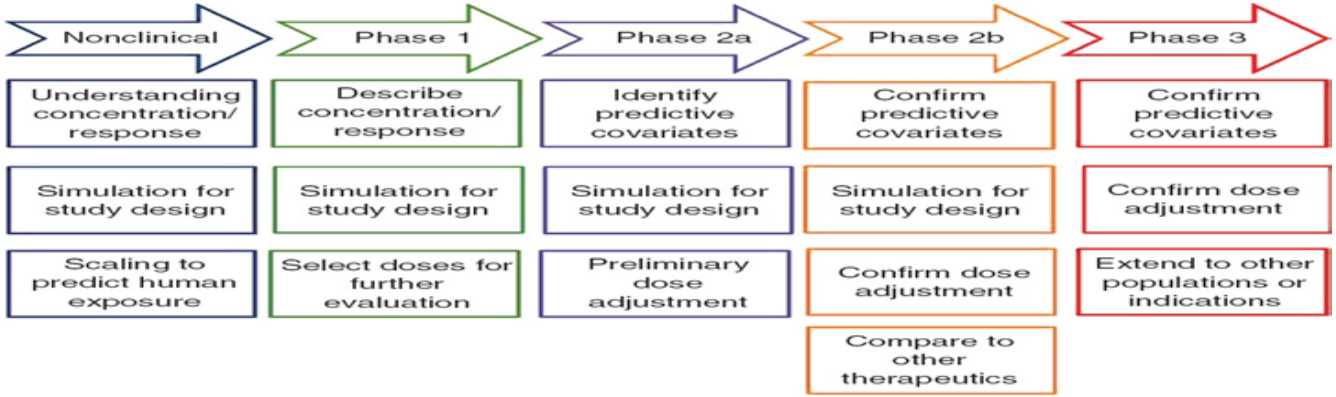
GOALS OF SENSITIVITY ANALYSIS :

- Better **understanding** of the model and its mechanisms
- **Sanity check**: does the model behave as expected
- **Identification** of influential and **non-influential** model parameters.

The model is investigated, not the underlying system!

9. POPULATION MODELING

- **Population modeling is a tool to identify and describe relationships between a subject's physiological characteristics and observed drug exposure or response.**



TYPES OF MODELS :

1. **PK models** - Describe the relationship between drug concentration(s) and time. The building block of many PK models is a "**compartment**"

2. **PK/PD Model** - Measure of drug effect (PD) & PK information.

3. **Disease progression models –** The time course of a disease metric.


Thank you!