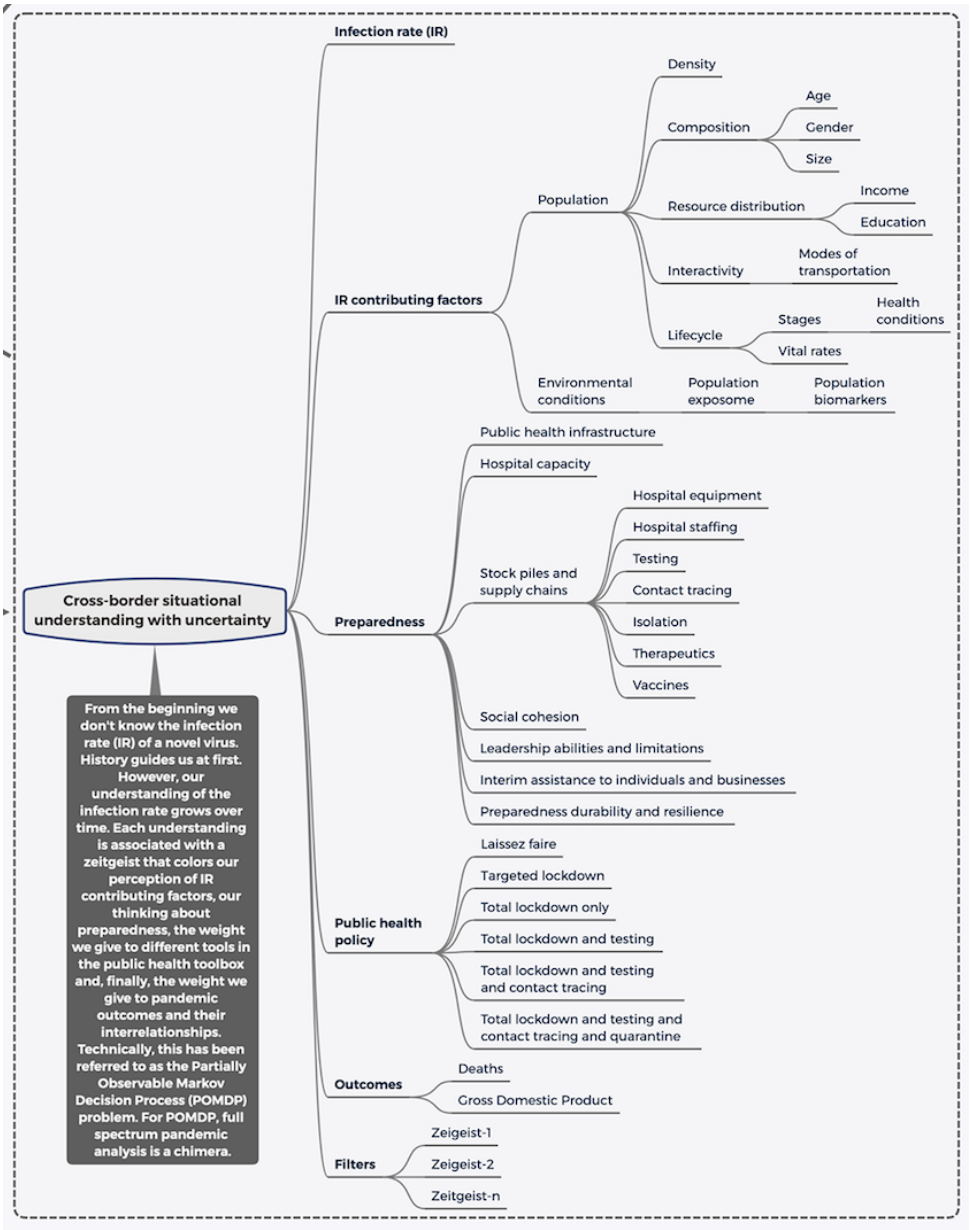
# Exposome

- The Exposome in an Epidemiological Context [15]




- Concept
  - Birth [16]
    - The term exposome was coined by Dr Christopher Wild (Cancer Epidemiologist) in 2005. Exposome is a linguistic blend of Exposure + Genome. [16]
  - Definition [1]
    - "The cumulative measure of environmental influence and associated biological response  throughout the lifespan of an individual including exposures from the environment, behavior, diet and endogenous processes."
    - Simplified

- Total exposure (endogenous and exogenous) of an individual from conception till death.

- Utility
  - Information gathered can indicate not only the link between an exposure and a disease but also provide insights into the mechanisms by which an exposure might be exerting its effects.  Such insights may contribute to the weight of evidence in assigning causality to an exposure–disease association and open up avenues to prevention through modulation of specific identified biological pathways. [3]
  - Exposomic data may contribute to determining why some people will develop a disease while other with the same or greater amount of exposure will not. [1]
- Composition [3]

  There is overlap in the three domains described above and sometimes difficulty in placing a particular exposure in one domain or another; for example, one can debate whether physical activity should be in the internal or specific external domains. Furthermore, the domains not only overlap but also may be considered as intertwined, in that the internal may at least partially be a response to the external. Measures in one domain or another may reflect to differing degrees one component of the exposome.

  - Internal  [1]
    - Internal factors are those that are specific to the individual such as age, body morphology, genome, metabolism, gut microflora, oxidative stress and aging (...)
  - Specific External [1]
    - Specific External factors include diet, occupational and environmental exposures (radiation, infectious agents, chemical contaminants) as well as physical (occupations), biological and physiological exposures (...)
  - General External [1]
    - General external factors include broader social constructs such as home location (climate, urban vs rural) education level and socioeconomic status, Psychological and mental stress (...)

- Strategies
  - Facilitating Interdisciplinary connections [3]

    The exposome implies the need for inter-disciplinary research. The juxtaposition of omics, Human Biomarkers, Molecular Epidemiology, Geographic Information Systems, Reality mining, epidemiology and Exposure Science research requires collaboration across disciplines that currently use different paradigms, tools and even language.

    Training researchers to have the linguistic skills to order more than a beer outside their discipline of origin is an important goal. Like the transcripts in cells transcribe DNA into RNA, we need more transcripts that connects fields together at a mid-point and facilitate communication.

- Stages of the Exposome [3]

  Because of the intrinsic dynamicity of the exposome, we can only take snapshots of the exposome at a certain moment in time. A number of key stages of life where cross-sectional measures of the exposome could be made, including gestation, early childhood, puberty and the reproductive years, as these stages are likely to exhibit significant differences in exposure patterns for a given individual.

- Identifying Common compounds in the Exposome [2]

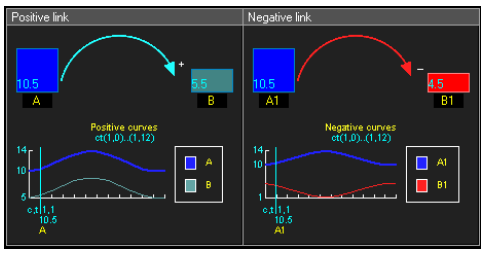
  Developing an idea of what is normal in the exposome for as many chemicals as possible; based on various factor such as age, gender, ethnicity, geography (...)

- Identification Analysis of the Exposome [20]

  Identification Analysis or causal inference is a the process of drawing a conclusion about a causal connection based on the condition of the occurrence of an effect. There are different way of visualizing causal relationships : causal looping, structural equations, Markov chains (...) which can give us another perspective in the quest of understanding and quantifying the exposome.

  PS : I will not get into Structural equations and Markov chains but I will leave some sources on them in the Source page.

  - Structural Equations [18]
  - Markov Chains [19]
  - Causal Looping [17]

    Causal loops or feedback loops focus away from linear cause effect to circular cause effect and explains the behavior of a system by showing a collection of connected nodes and the feedback loops created by the connections. This approach could be used as a tool to visualize how different parts of the exposome interact with each other.

    There are two foundational type of loops :

    The reinforcing loop or Positive feedback (on the left of the Gif above) and the Balancing loop or Negative feedback (on the right of the Gif above).

- Reinforcing Loop (positive feedback)

  A reinforcing loop is one in which an action produces a result which influences more of the same action thus resulting in growth or decline.
  The bigger the initial push, the bigger the consequential push.

  Examples: When consumers adopt a hot new product, more potential consumers encounter the product and are likely to purchase it themselves strengthening the word of mouth advertisement and leading to more adopters in the future.

  When immigrants settle in a particular part of a foreign land, they build infrastructure and provide services, creating an environment that in turn attracts more people like them. This leads to the formation of large homogenous ethnic neighborhoods like China town in San Francisco.

- Balancing loops (Negative feedback)

  Balancing loops are circles of cause and effect that counter a change with a push in the opposite direction. The harder the push, the harder the system pushes back. Balancing feedback loops bring stability or a certain stubbornness to a system.

  Example : When the internal temperature of your body increases, you sweat, and as that sweat evaporates from the warm surface of your body, you cool down: balancing the initial increase. When you are cool, you sweat less, so there is less sweat to evaporate and it drains less heat allowing your body temperature to rise. At the same time, if your body temperature drops you may start shivering, releasing more heat to warm your body, balancing the initial decrease.

## Measuring the Exposome

### Challenges [1]

The exposome involves various types of data coming from a lot of different fields (biological, economical, behavioral, Social, Geographical...) and each of these data are dynamic and change over the course of an individual making measuring the exposome complicated.

- Analytical error measurements

  With the development of stable and cost-effective high-throughput platforms, large amounts of experimental data are generated. However, data obtained from these platforms are highly sensitive to experimental conditions, and can therefore include considerable noise in the form of measurement error. Statistical methods should be able to estimate technical nuisance variation.

- Reverse Causality

  For an exposure to be a cause, the exposure must precede the outcome. Reverse causality is when the outcome leads to a change in behavior and can lead to the miss-identification of an individual.

  Example: When a lifelong smoker are told they have lung cancer or emphysema, many may then quit smoking. This change of behavior after the disease develops can make it seem as if ex-smokers are more likely to die of emphysema or lung cancer than current smokers. This Phenomenon is of particular concern in retrospective and cross-sectional studies. In prospective cohort studies, since the exposure is determined in advance of the disease on set, the probabilities of reverse causation is greatly diminished.

- Dynamicity

  The dynamic nature of the exposome presents one of the most challenging features of its characterization. As a consequence, its myriad components need to be considered in relation to their temporal variation. In effect, at any given point in time, an individual will have a particular profile of exposures. Therefore, to fully characterize an individual's exposome would require either sequential measures that spanned a lifetime, or a smaller number of measures that captured exposure over a series of extended periods.

  - Natural Exposomic Changes [3]
  - Variability of exposure data

    For exposures with a short biological half-life and little constancy in the underlying exposure behavior, temporal variability may be particularly high. For such exposures, intra-individual compared with inter-individual variability is known to be high, and only repeat measurements over time provide improved exposure estimates. Studies to measure daily repeat biomarkers of non-persistent chemicals (phthalates, phenols, organophosphate pesticides) in urine have been proposed to characterize intra- and inter-individual variability in these urine biomarkers, and where possible, correct for the uncertainties in a larger cohort.

    Inter-individual differences are differences that are observed between people, whereas intra-individual differences are differences that are observed within the same person when they are assessed at different times or in different situations.

    https://www.mytutor.co.uk/answers/19195/A-Level/Psychology/What-is-the-difference-between-inter-and-intra-individual-differences/

  - variability over-time and between subjects

    Variability over time and between subjects is associated with a multitude of intrinsic (belonging by it's very nature) and extrinsic (not belonging) factors, some known and some unknown. Omics endpoints are dynamic and likely to show variability in different cells and tissues throughout the life of an individual.

- Tools
  - Biomarkers
    - Definition
      - Portmanteaux for biological marker : is a measurable indicator of some biological state or condition. [14]
    - Utility

- Biomarkers can be use to assess the sustainability of the environmental conditions with respect to human health. [1]

- Field of Study

  By citing few (there are many more) of the fields of studies that contribute to exposomic data, I wanted to show the inter-disciplinary requirements for evaluating the exposome and make a larger point about our real strengths as a specie which lies in mutualism and collectivism.

- Omics Biomarker

  - Epigenetics [4]

    The study of the totality of all heritable changes in genes expression that do not involve changes to the underlying DNA sequence; a change in phenotype without a change in genotype which in turn affects how cells read genes.

    You can think of DNA as being a piece of sheet music and your body the orchestra, DNA gives the instruction to your cells on how to play the piece. Some of your genes can be silenced or expressed depending on your exposome and this is partly what makes you distinct.

    Phenotype : The observable physical traits or biochemical characteristics of an organism based on a combination of the organisms genes and environmental factor.

    Genotype: The inherited genetic makeup of a cell.

    What is Epigenetics in simple terms :
    https://www.youtube.com/watch?v=g12kIu9jrIk

  - Transcriptomics [5]

    Transcriptomics is the study of all the RNA molecules within a cell, otherwise known as the transcriptome.

    The human genome is made up of DNA, a long winding molecule that contains the instructions needed to build and maintains cells. These instructions are spelled out in the form of "base pairs" of four different chemicals organised into 20, 000 to 25, 000 genes. For the instruction to be carried out DNA must be "read" and transcribed in other words copied into RNA. These gene readouts are called transcripts and a transcriptome is the collection of all transcripts in a cell. Understanding the transcriptome is essential for interpreting the functional elements of the genome and revealing the molecular constituents of cells and tissues and also for understanding development and disease."

- Proteomics [6]

  Proteomics is the large-scale study of proteoms. A proteome is a set of proteins produced in an organism, system or biological context. We may refer to, for instance, the proteome of a species (for example Homo-Sapiens) or an organ. The proteome is not constant; it differs from cell to cell and changes over time. To some degree, the proteome reflects the underlying transcriptome.

  Proteomics is used to investigate :

  1) When and where proteins are expressed.

  2) Rates of protein production, degradation and steady-state abundance.

  3) How protein are modified.

  5) The mouvement of proteins between subcellular compartements.

  6) How Protein interact with one another

  (...)

- Metabolomics [7]

  "Metabolomics is the large-scale study of small molecules, commonly known as metabolites, within cells, biofluides, tissues or organisms. Collectively, these small molecules and their interaction within a biologial system are known as the metabolome."

  https://www.ebi.ac.uk/training/online/course/introduction-metabolomics/what-metabolomics

- Adductomics [8]

  "Adductomics is the study of DNA adducts in the context of an entire genome. DNA adducts are compounds that bind to DNA, causing damage and mutations. These mutations can result in Cancer and birth defects in multicellular organisms. The science of adductomics seeks to identify all DNA adducts and the target sequence of each adduct."

- Genomics [9]

  "Genomic, it the study of the structure, function, and inheritance of the genome, (entire set of genetic material) of an organism. A major part of genomics is determining the sequence of molecules that make up the genomic deoxyribonucleic acid (DNA) content of an organism. The genomic DNA sequence is contained within an organism's chromosomes, one or more sets of which are found in each cell of an organism. The chromosomes can be further described as containing the fundamental units of hereditary, the genes. Genes are transcriptional units, those regions of chromosomes that under appropriate circumstances are capable of producing a ribonucleic acid (RNA) transcript that can be translated into molecules of Protein."

- Molecular Epidemiology [10]

  Molecular epidemiology is a subdivision of medical science and epidemiology that emphases on the involvement of potential environmental and genetic risk factors, recognized at the molecular level, to the etiology (set of causes, or manner of causation of a disease or condition) and avoidance of sickness through populations. Molecular epidemiology can improve our knowledge about the precise pathogenesis (reproduction) of a disease through recognizing particular pathways that affect the risk of developing the disease. Furthermore, it tries to find how the collaborations between genetic characteristics and environmental exposures works in disease occurrence.

- Geographic information systems [11]

  A geographic information system is a conceptualized framework that provides the ability to capture and analyze spatial and geographical data. *GIS applications* (or *GIS apps*) are computer-based tools, that allow the user to create *interactive queries* (user-created searches), analyze spatial information output, edit datum presented within maps, and visually share the results of these operations.

- Reality mining [12]

  Reality mining studies human interactions based on the usage of wireless devices such as mobile phones and GPS systems providing a more accurate picture of what people do, where they go, and with whom they communicate with rather than from more subjective sources such as a person's own account. Reality mining is one aspect of digital foot print analysis. Reality mining data is collected by machine using specific algorithms that identify predictable patterns of behavior.

- Exposure Science [13]

  Exposure science is the study of an organism's (usually human) contact with chemical, physical, biological agents or other health risk (e.g. accidental) occurring in their environments, and advances knowledge of the mechanisms and dynamics of events either causing or preventing adverse health outcomes.

- Human Biomarkers [2]

  Pre-Reading Note : While reading do not get intimated by the scientific jargon as their specificities matters less than the point the author is trying to make.

  Humans tend to focus on how changes in the environment affect them directly. This is captured by the disciplines of environmental
  exposure science, environmental toxicology, and environmental epidemiology that describe
  the physical, chemical, and mathematical links among exposure, dose, and effect in response to environmental stressors.

  Post Reading Note : Human Biomarkers may be categorized in different ways in the literature, but their interpretation, and their ultimate use in deriving conclusions are not unique to any given grouping scheme.

  - Medium

    Major available and culturally accepted human Biological media.

    - Blood

      "Blood is considered the gold standard as a biological fluid because it represents the central compartment of the body; every living cell interacts with the circulating blood and exchanges nourishment for waste. Essentially all medical and environmental biomarker compounds previously discussed
      are found at some level in the blood.

      The caveats (cons) are that blood sampling is invasive, the sampling volume and frequency are limited, the levels of many compounds of interest are low, and the blood matrix itself is complex."

    - Breath

      "Exhaled breath is an extremely versatile biomarker medium in that its collection is noninvasive, the supply is essentially unlimited, and it serves both as a window into the blood as well as a quantitative elimination pathway. Furthermore, the breath matrix is dilute and lends itself well to analytical methods developed for air. The main disadvantage of breath sampling is that biomarkers are generally limited to gas-phase (volatile) compounds."

    - Urine

      "Urine is the most commonly used biological medium for human biomarker studies. It is relatively easy to obtain, has general acceptance with the public (in comparison to blood), and serves as a major quantitative elimination
      pathway for model inputs. In some
      cases, the native compounds (e.g., benzene,naphthalene, phenanthrene) in urine can also be used as an indicator of previous exposure. One of the main drawbacks is that urinary
      concentrations are confounded by a variety of parameters, including hydration, void volume, current metabolism state, and time since last
      void. In addition, urine sample availability is not predictable; that is, human subjects cannot generally provide samples on command."

- Kinetic

  "Kinetic Biomarkers are used to track chemicals entering and moving through the body. The subcategories are mostly
  self-explanatory and the measured compounds are generally exogenous (typically environmental) chemical biomarkers."

  - Absorption

    Absorption is the total systemic uptake and can be further interpreted to reflect exposure pathway (inhalation, ingestion, dermal contact) and environmental medium such as air, water, food, soil or dust. Typically, the biomarker measurements for absorption are the actual native compounds as found in blood or breath. Other meta-data including environmental concentrations, breathing and ingestion rates, and activity patterns are used to achieve context and quantitation of absorption. For example, the difference between inhaled and exhaled chloroform
    concentrations serves as an estimate of chloroform absorption through both dermal and inhalation pathways.

  - Distribution

    Distribution is a more generic form of biomarker application
    and refers to the empirical partitioning within the body; for example, blood-borne benzene and exhaled benzene measurements are a direct measure of the blood/breath partition coefficient.

  - Metabolism

    Metabolism is estimated via the relative amount of disappearance of a native compound and the
    appearance (if detectable) of a chemical metabolite. For example, absorbed methyl-tertiary-butyl ether (MTBE) gives rise to the
    production of the phase-1 metabolite tertiary-butyl alcohol (TBA); both can be measured in the blood and breath of a human subject and subsequently provide empirical evidence of metabolism.

  - Elimination

    Elimination is often estimated by measurement of compounds in excretion pathways such as breath, urine, and feces. For example, absorption of the pesticide chlorpyrifos
    can be monitored by the urinary elimination of the metabolite 3,5,6-trichloro-2-pyridinol.

- Function

  "The Biomarkers function reflects how biomarker measurements are interpreted or used."

  - Effect

    The subcategory of effect biomarkers overlaps the susceptibility biomarkers to the extent that deviations from expected normal levels may indicate a change such as DNA strands breaks. In addition, effects biomarkers include
    certain chemical biomarkers that could be mapped forward to effects; for example, measurements of polycyclic aromatic hydrocarbons
    (PAH) adducts of DNA, either in adult circulating blood or in umbilical cord blood, are indicators of potential adverse health or birth outcome.

- Suceptibility

  The subcategory of susceptibility is generally composed of the “omics” biomarkers; that is, particular sequences in the protein coding DNA can make a subject more or less able to detoxify certain chemicals, relative abundances of certain circulating proteins themselves may indicate quality of repair function.

- Exposure

  The subcategory of exposure could include any of the exogenous chemical compounds of column 1, as well as certain members of the endogenous, response groups and their possible health outcomes. For example, benzene or chemical biomarkers of benzene certainly reflect benzene exposure; however, cytokine production or protein expression may mark pulmonary inflammation from inhaled chemicals such as NO2, or a change in heart-rate variability may reflect PM2.5 exposure.

▾ Origin

"The Biomarkers origin reflects decisions made when biomarker analytical methods are developed and are represented as their chemistry or type.

For example, a method for nonpolar low molecular-weight hydrophobic compounds from fuels exposure will require a completely different sampling and analytical strategies than would polar hydrophilic compounds resulting from internal human oxygen metabolism and enzymatic processes."

This because the chemicals found in fuel are Exogenous and the compounds resulting from internal human oxygen metabolism are Endogenous and therefore require different analytical tools/Strategies.

- Exogenous

  The exogenous subcategory is comprised of compounds that are, or contain, the original chemical of exposure. Blood-borne benzene from fuel exposure, benzene oxide and phenol from phase-1 metabolism, benzene hemoglobin adducts, and urinary benzene diols and s-phenylmercapturic acid are all examples of this subcategory. In general exogeny is the fact of an action or object originating externally and in biology an exogenous factor is any material that is present and active in an individual's organism or living cell but that originated outside that organism.

- Endogenous

  The endogenous compounds, are typically composed of volatile oxygenated species such as alcohols, ketones, aldehydes, and organic acids, and of larger molecules such as heat-shock proteins and cytokines. Here there are no unique chemical units to focus on, and, in addition, these compounds are always present at significant levels.
  The analytical strategy is to look at patterns of the endogenous compound classes and determine their relative abundances as the probative signal.

- Response

  This subcategory is not technically part of the chemical exposome but refers to some form of overt change or condition that might be linked to chemicals or a perturbation in the exposome. Some examples are: cherry red fingernails as a biomarker of CO exposure; blue lips from oxygen deficit or hypothermia; body temperature, heart rate, and blood pressure representing current metabolism; breath and urine odor indicating diet or health state.

- Sources

  Sources For Exposome Map - Googl…

  Click on the the link below to access the Sources.

  If number on one of the main branches and it's  subdivision do not have numbers  then all of the subdivision belong to the same reference on the source page.

Sources (Full Link)
https://docs.google.com/document/d/1l8xHsQQvBA-W7XlXfiVIc2O1wDbRZvoDbAkEIaw7fik/edit?usp=sharing