The exposome in Europe

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http://www.enve-lab.eu

ENVElab
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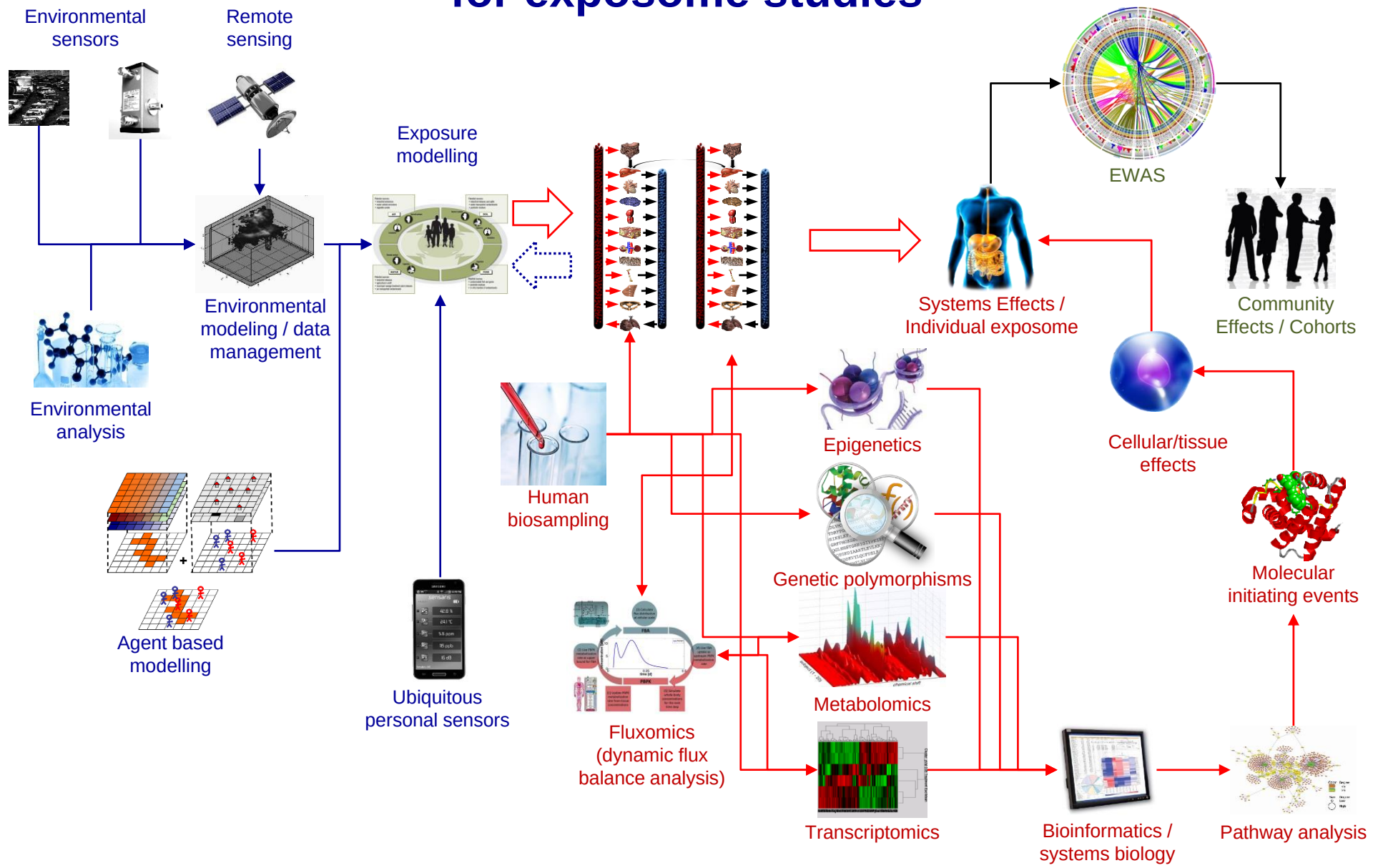
Connectivity-based workflow for exposome studies



HEALS – what's new

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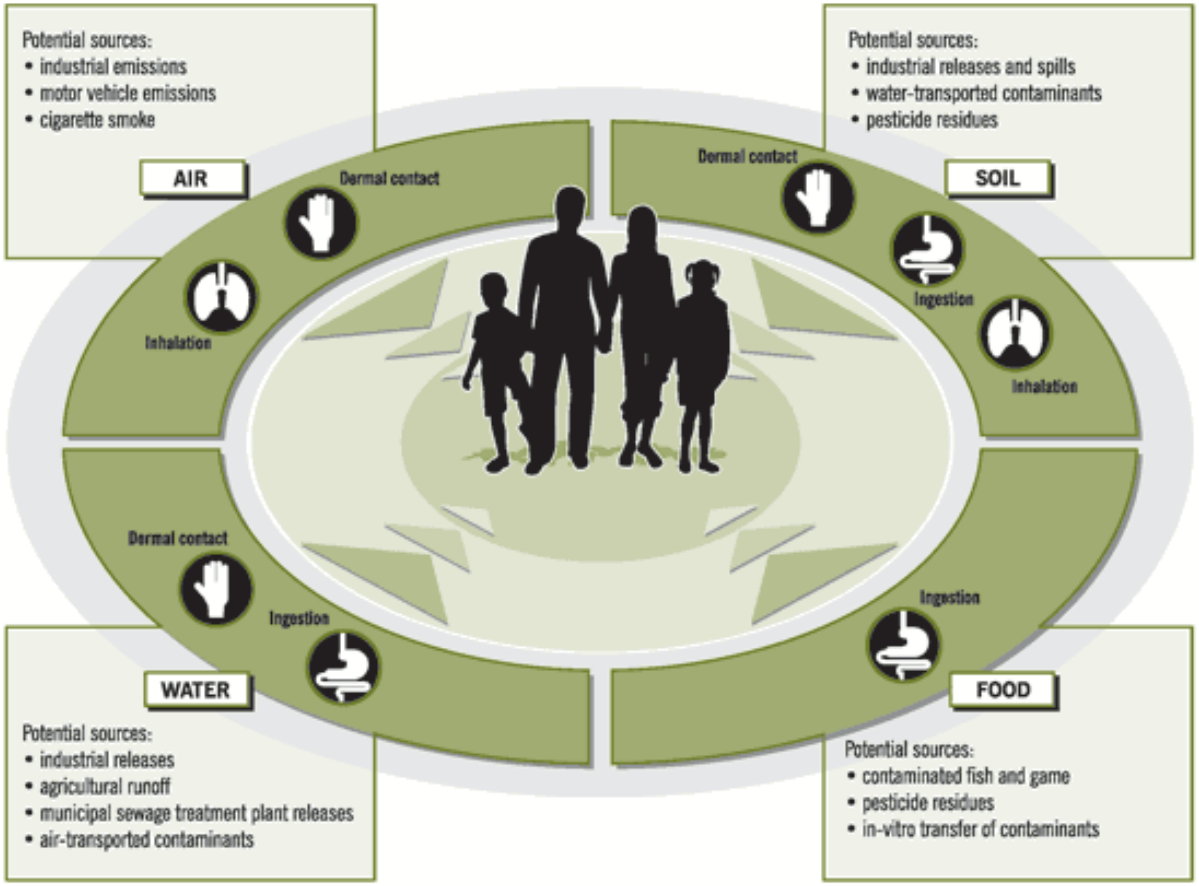
- Integrated use of existing environmental and biomonitoring data
- Improved assessment of the external exposome
  - Environmental data fusion and Agent-Based Models
  - Mobile phone apps
  - Environmental sensor-webs
  - Micro-sensors
  - Satellite remote sensing
- Linking external and internal exposome
  - Integrated use of –omics and chemical biomarker data
  - Take into account the temporal dimension
- Advanced tools for environmental and biological data analysis
  - PBBK modeling for internal dose estimation and exposure reconstruction
  - Coupling PBBK models with gene regulation models
- Novel bioinformatics strategies for biomarker prediction
  - Systems biology meta-modeling for biomarker fusion
- Environment-wide association studies
  - Linkage disequilibrium
  - Use of advanced statistical tools: DAG, Bayesian inference
- Enviromics
  - study of a wide array of environmental factors in relation to health and biology

The external exposome



External Exposome workflow

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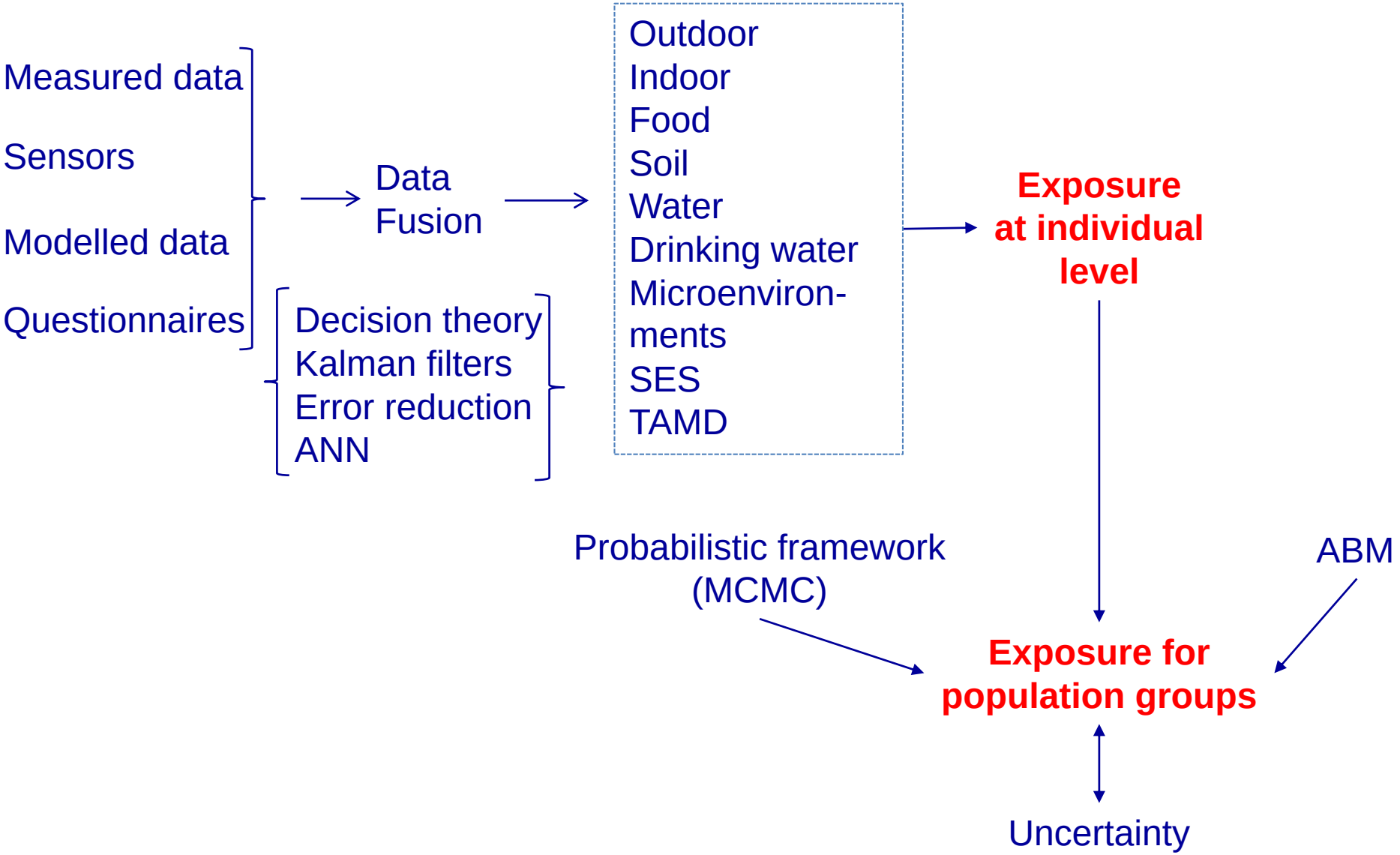

External exposure advances

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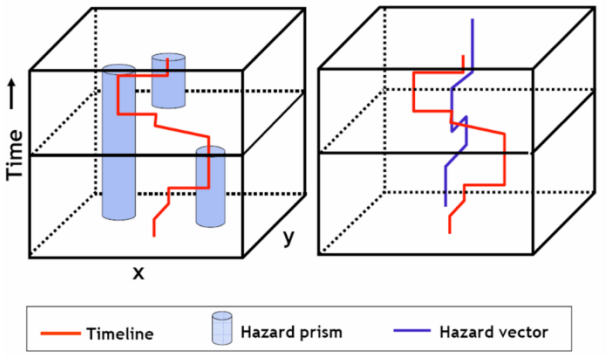
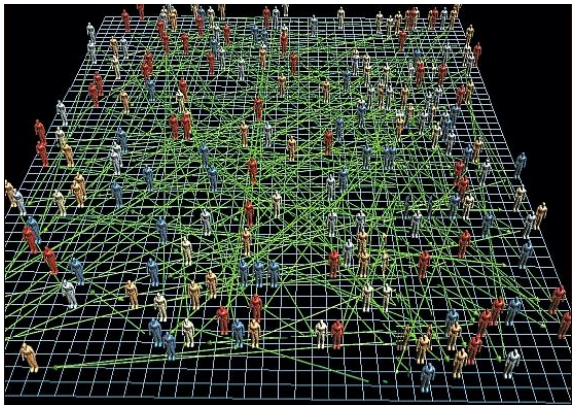
An individual's space-time activity model



Agent based modelling



Sensors for exposure assessment

WOCKETS SYSTEM VISION

Multiple, low-cost 3-axis accelerometers stream data in real-time to mobile phone

Wearable sensors (test version 1)

Sensors miniature, thin, and ergonomic; worn under clothing 24/7

Phone carried in typical fashion (e.g. in pocket)

Pattern recognition algorithms running continuously on phone detect physical activities in real-time

Innovative phone apps possible

Pilot Campaign

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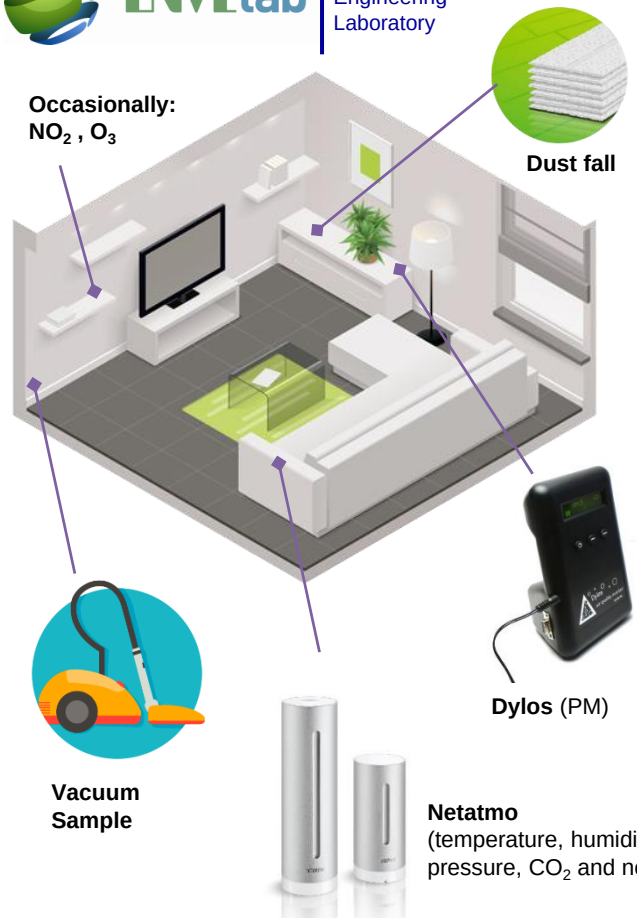
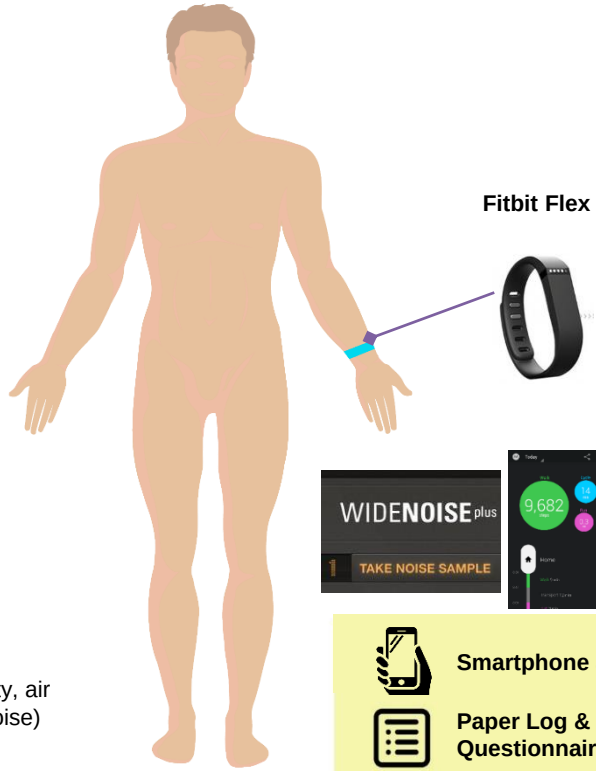
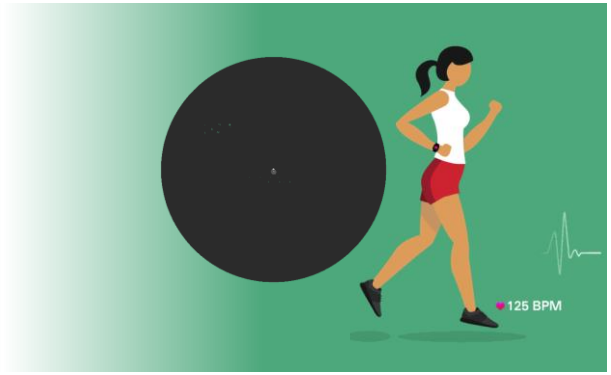




Fitbit Flex

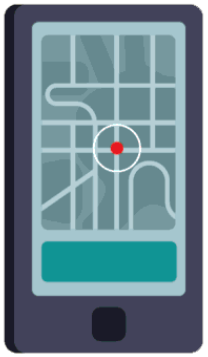


Smartphone apps

Paper Log & Questionnaires

ACTIVITIES

Sleep



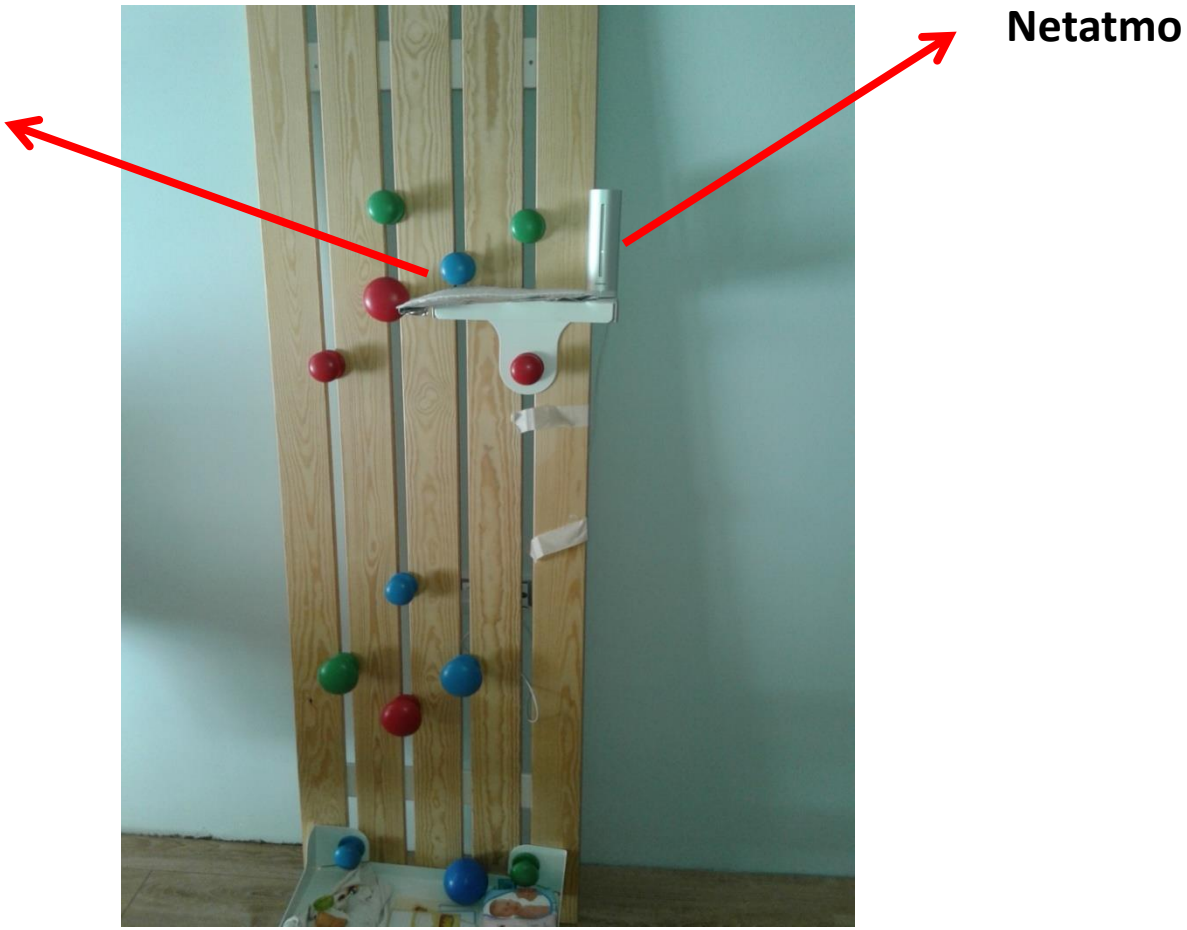
2 Homes per Week

AQ Monitor	CO_2, TVOC, CO, NO_2, NO, H_2S, HCHO, T, RH, P
Grimm 1.108	PM 0.23-20µm
Aerocet	PM 0.5, 1.0, 5.0, 10µm
Aeroqual 1	NO_2
Aeroqual 2	O_3
Radiello Passive Samplers	BTX, Aldehydes
Dylos	PM >0.5 and >2.5 µm
Netatmo	T, RH ,CO_2, Noise
Swiffer	Dust

Living Room


Aerocet
Radiello
Dylos
Netatmo
Aeroqual 1,2
AQ Monitor
Grimm

Child Bedroom



Activity tracker and Applications

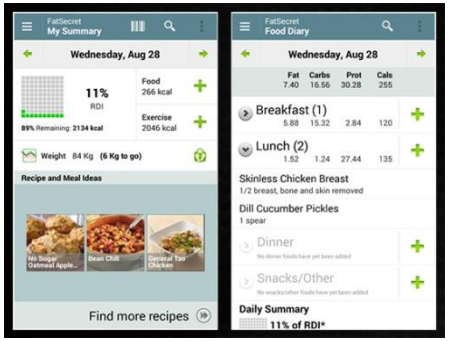
Fitbit	Steps, Km, very active minutes, calories burned, sleep
Moves App	Location, steps, Km, minutes of walking/running/cycling,
WideNoise Plus App	Noise and Location of the sample
Redlaser App	Barcodes of consumer products
Fatsecret App	Meals

Activity tracker and Applications

Fitbit Flex

Moves App

Fatsecret App



WideNoise plus

Consumer Products

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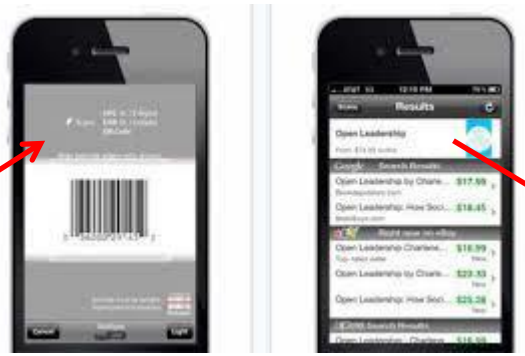
Cleaning products

Child care

Mother care

Redlaser App – scanning products



Dates of use

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Daily PM profile in a house

1/7/2015

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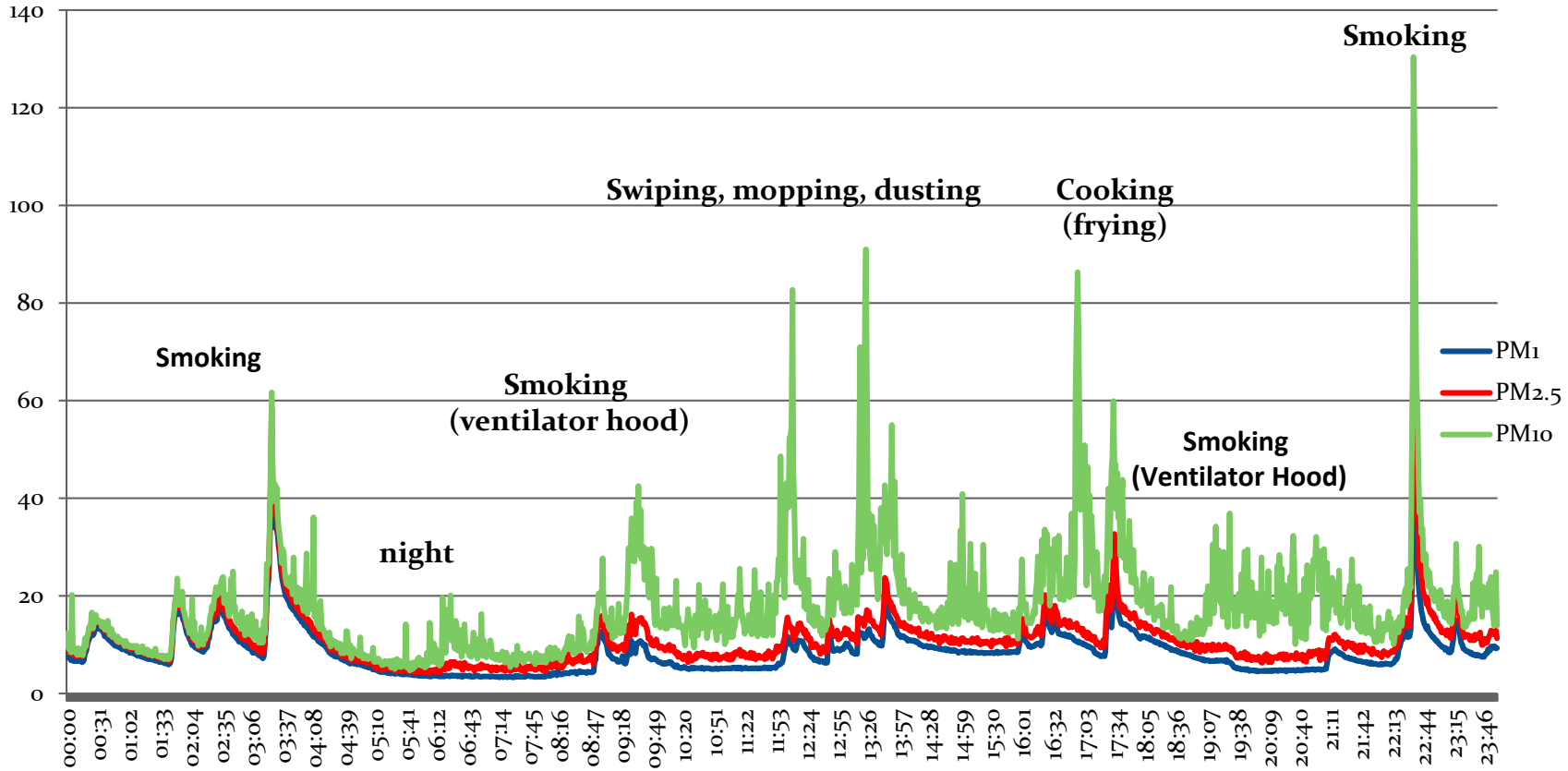

- At night the number of particles is significantly reduced (since no activities are carried out).
- In the morning, when activities such as walking-particles resuspension and preparation of breakfast are carried out, the number of particles increases.
- Smoking is a major source of PM, even when it is carried out under the ventilator hood.
- Cleaning activities (sweeping, vacuuming, mopping) and cooking activities (especially frying) are important contributors of PM in a house.

Tracking mobility behaviour

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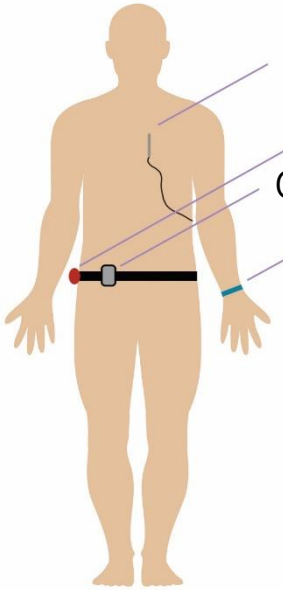
Sensors Campaign



temperature logger
accelerometer
GPS tracker
fitness monitor

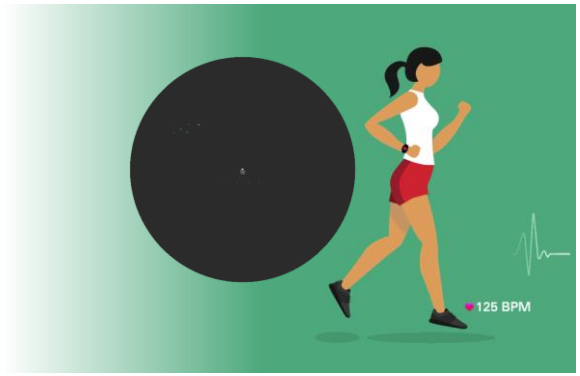
Moves app
Paper log

Data Analysis

time
activity

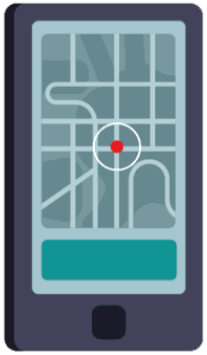
ANN model

location



ACTIVITIES

Sleep



"Intelligent" location tracking

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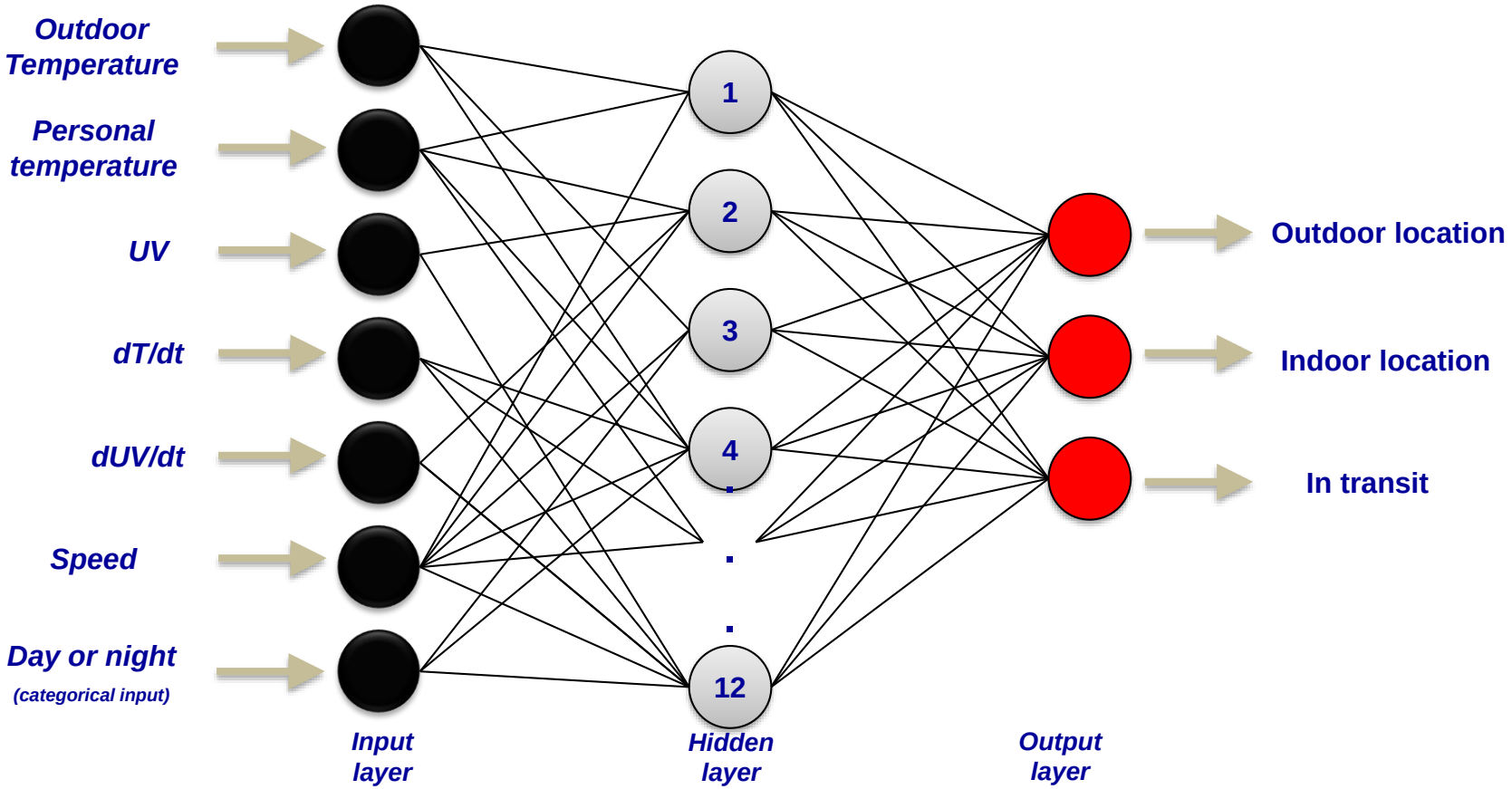
Statistical Method: Predicting location based on temp and UV logs through an Artificial Neural Network

7 input nodes (6 numerical and 1 categorical)
12 hidden nodes (found to yield the best results among several combinations)
3 output nodes (corresponding to the 3 different classes)
Data from 5 days were used for training the ANN model
Data from 2 days were used as an independent dataset to validate the ANN model



Predicting location through ANN

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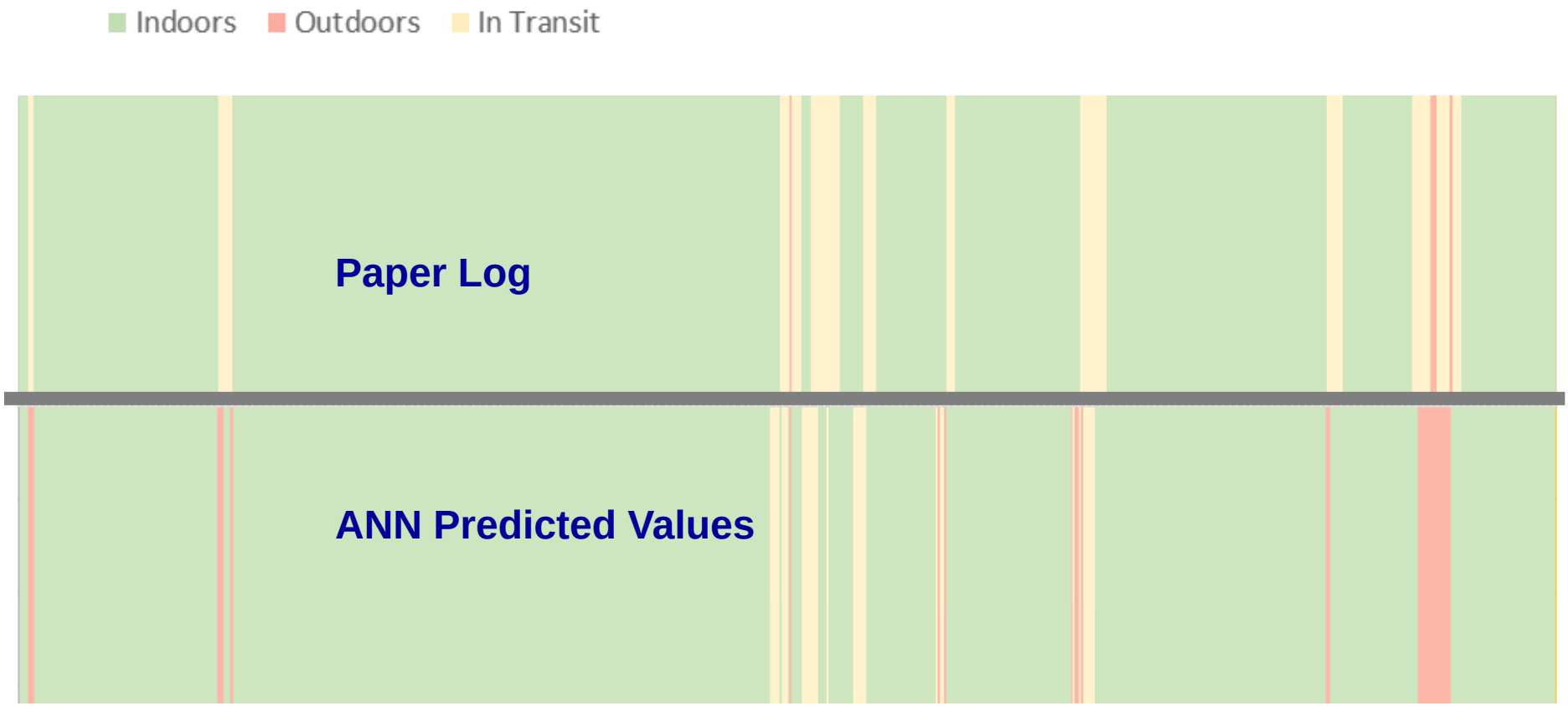
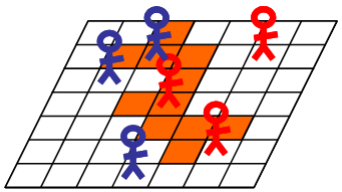
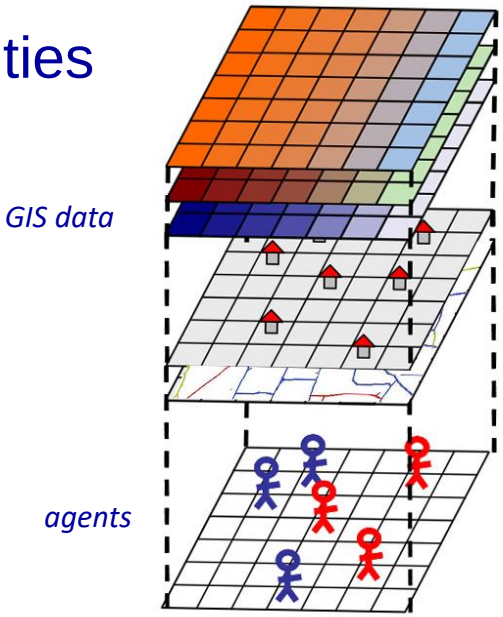


Indoor-to-outdoor transition captured satisfactorily

Agent Based Modelling (ABM)

- A system is modeled as a collection of agents and the relationships between them.
- The agents, programmed as autonomous decision-makers, react and act in their environment.
- Take into account the heterogeneity of the entities composing the system.
- Behaviours emerge through the agents interactions.





Human Agents rules

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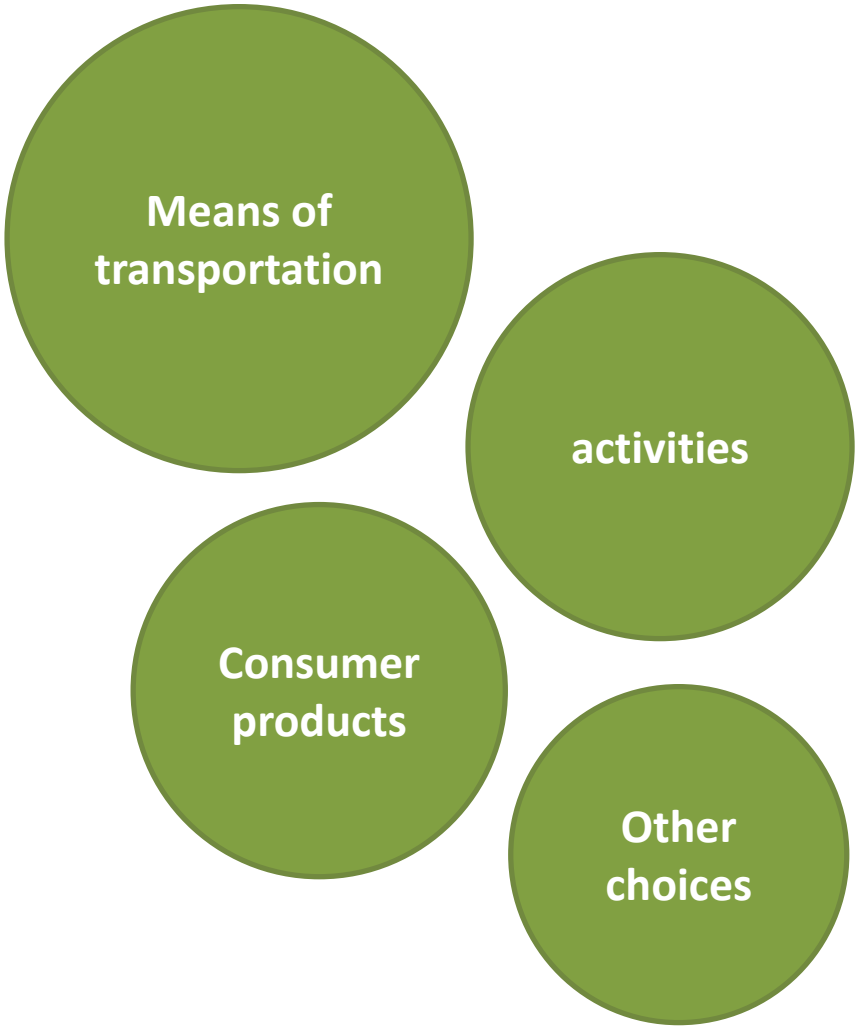
- **age**
- **gender**
- **socio-economic status (SES)**
  - income
  - occupational status
  - level of education
  - marital status
  - ethnicity



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Personal Exposure Assessment

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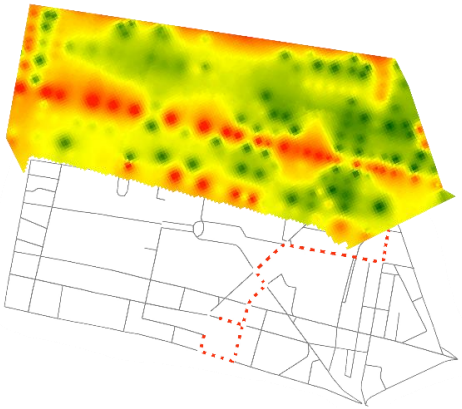
INPUT — SIMULATION — OUTPUT

Air Quality Data



Personal Exposure

Human Agent Trajectories

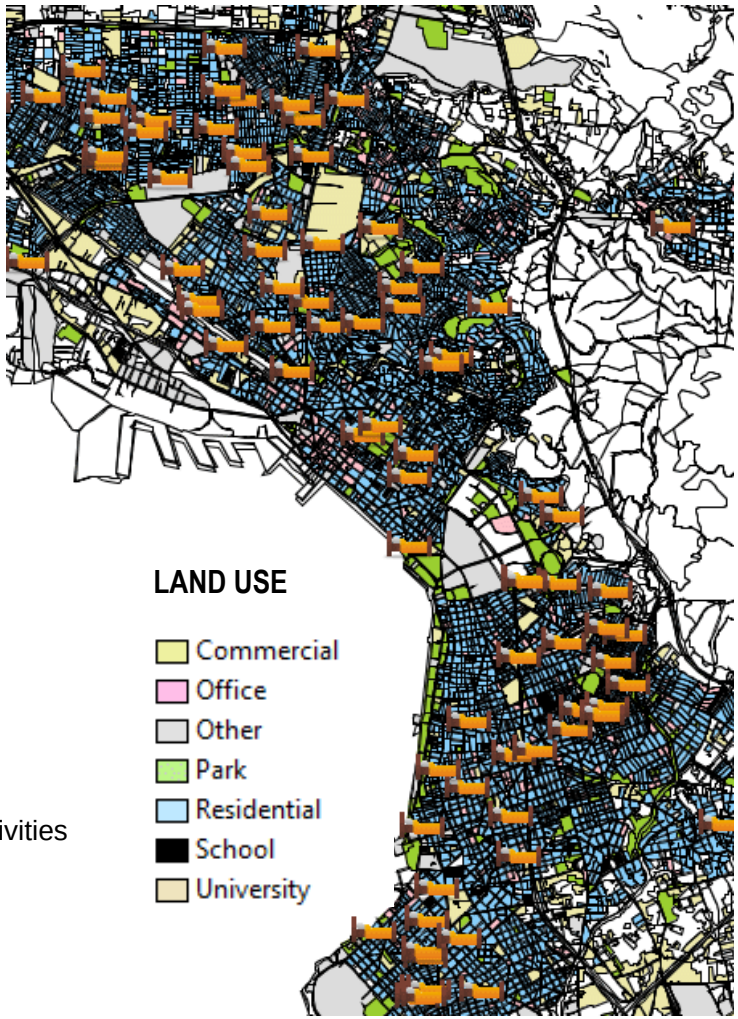
Population Data

Agent Based Modelling

Buildings, Land Use

Road Network

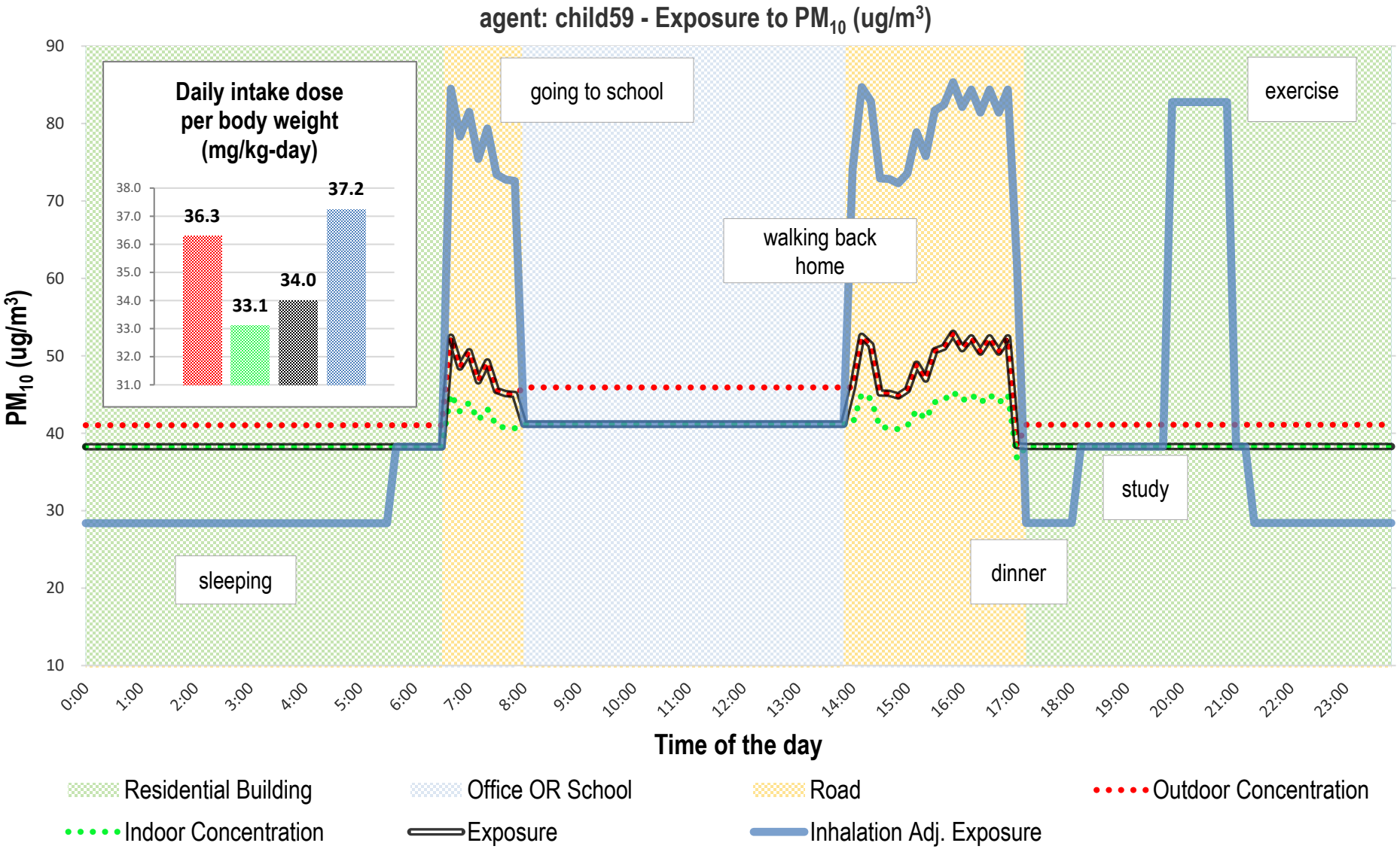
ABM simulation preview



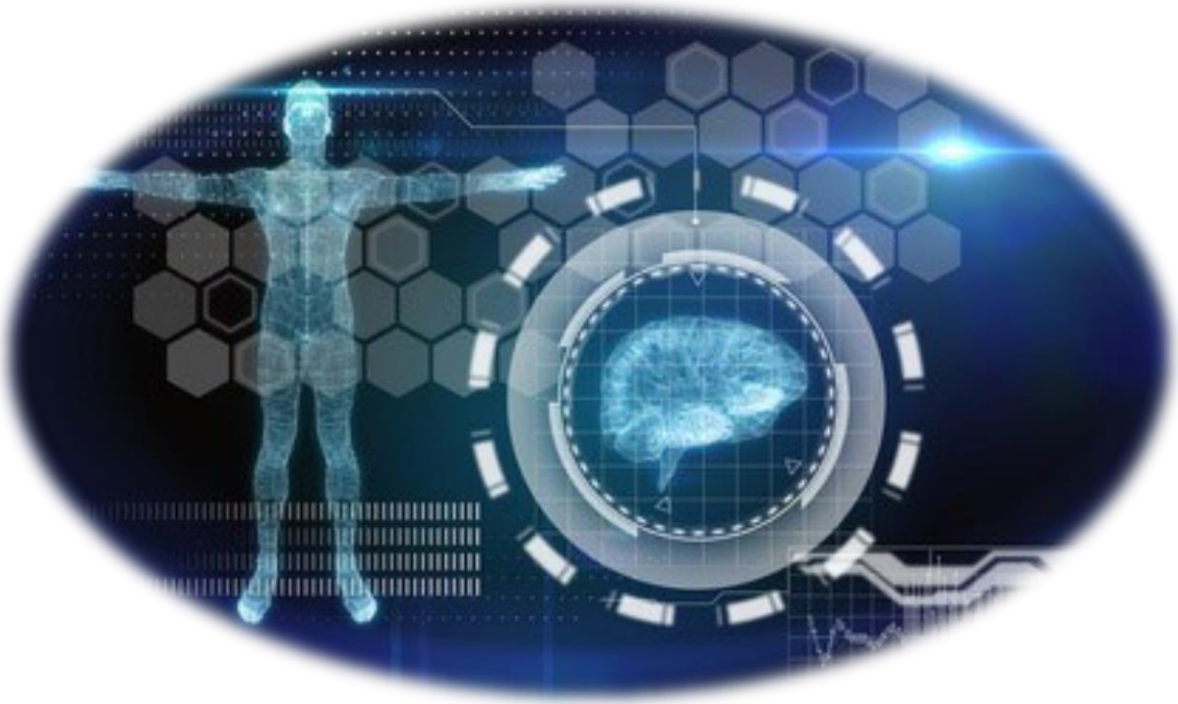
Thessaloniki, Greece

Results

Personal Intake Dose of agent

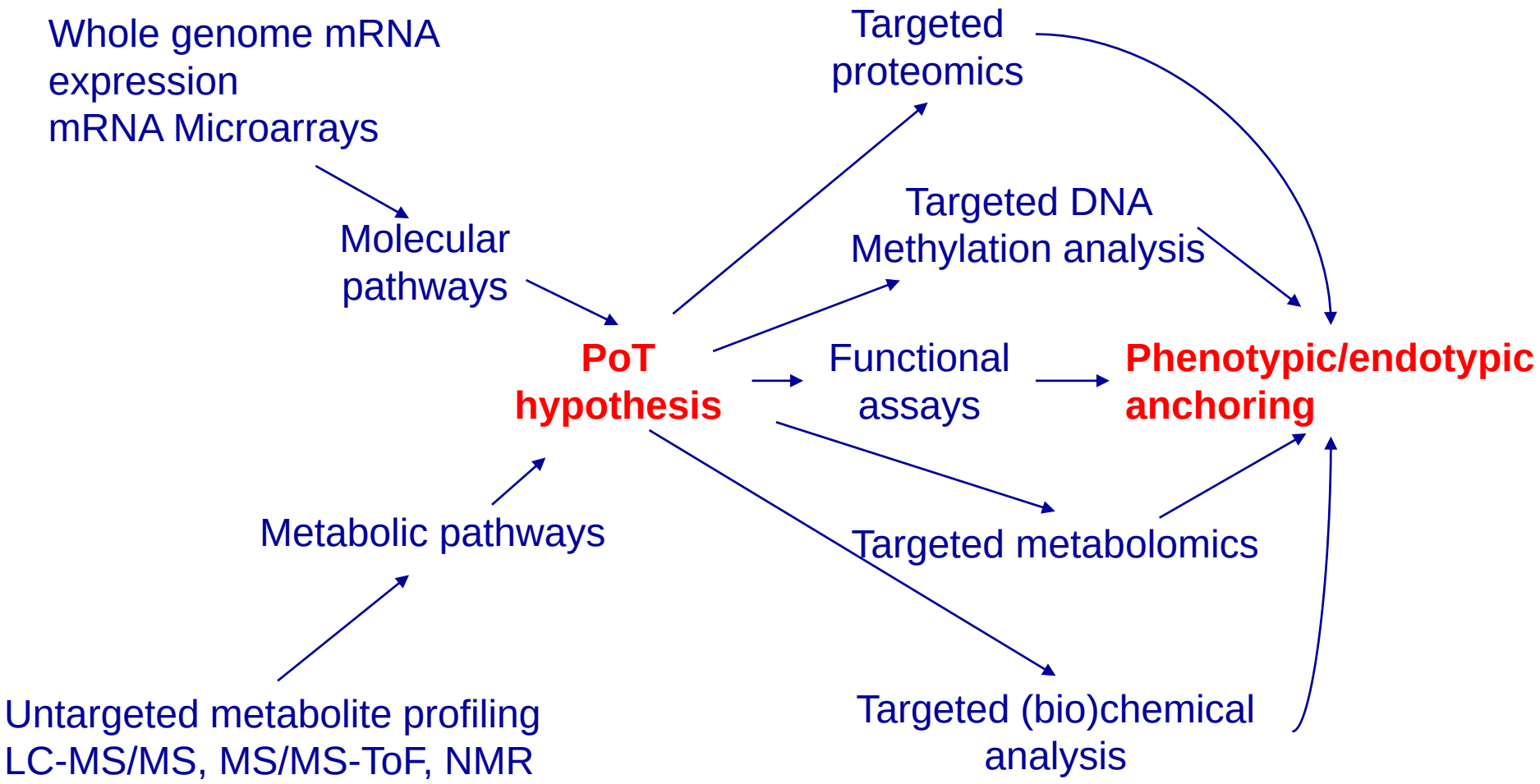


The internal exposome



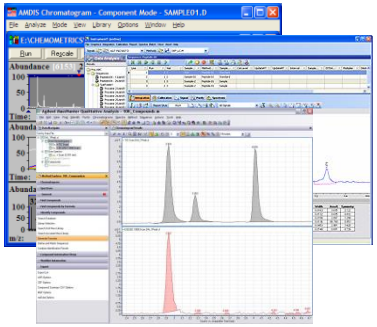
Exposure biology workflow

Rendering high dimension biology operational



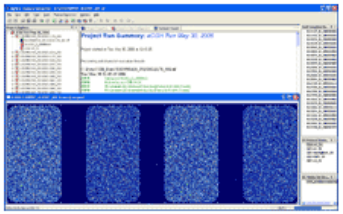
Exposure biology workflow

LC-MS/MS
GC-MS/MS



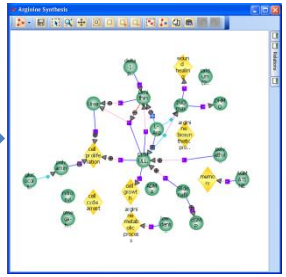
MassHunter Qual/Quant
ChemStation AMDIS

Microarrays



Feature Extraction

GeneSpring Platform



Biological Pathways

NGS

Alignment to Reference Genome

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Disease programming through life

Before conception | **Fetal life** | **Childhood & adult life**

Preconceptional exposures

In-utero exposures

Early life exposures

Later life exposures

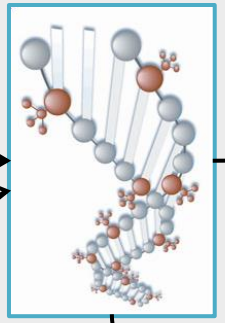
Exposure of gametes

Epigenome (Parental)

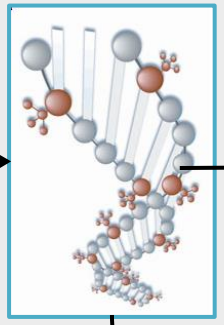
Genome (parental)

Genome (offspring)

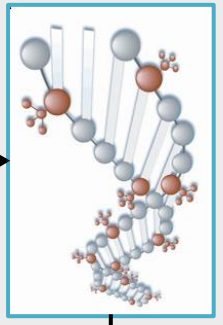
Epigenome at birth



Epigenome in childhood



Adult/aging epigenome



Programming of **disease** risks

Figure adapted from Fleisch, Wright & Baccarelli, J Mol Endocrinol, 2012

Internal exposure

Development of generic lifecourse PBBK model

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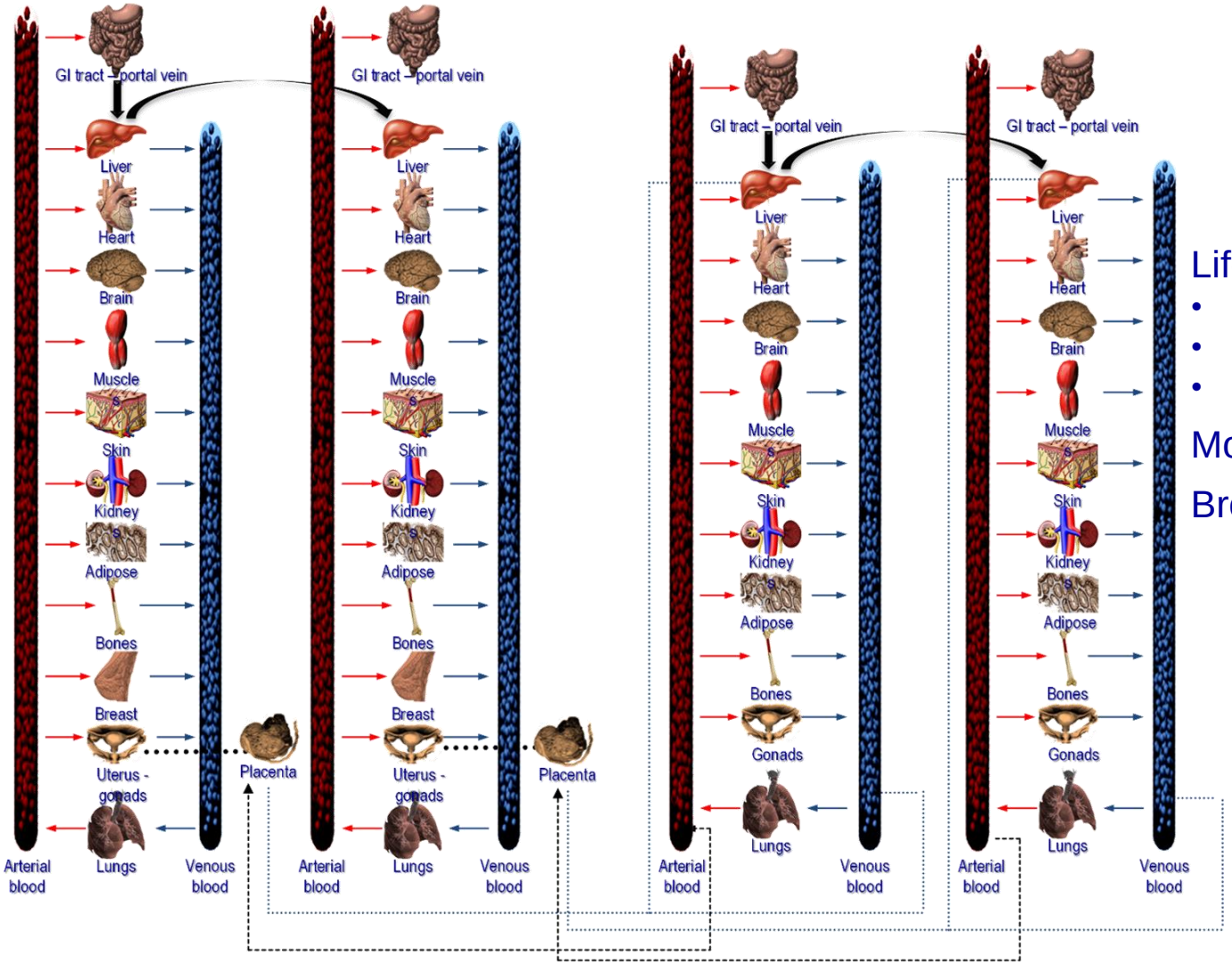


Lifetime evolving parameters

- *Organ volumes*
- *Blood flows*
- *Age-dependent clearance*

Mother – Fetus interaction

Breast feeding

Expanding the chemical space – use of QSARs

According to Abraham's solvation equation, a biological property *SP is described by the following equation*

$$\log SP = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \Sigma\alpha_2^H + b \cdot \Sigma\beta_2^H + v \cdot \log V_x$$

Where:

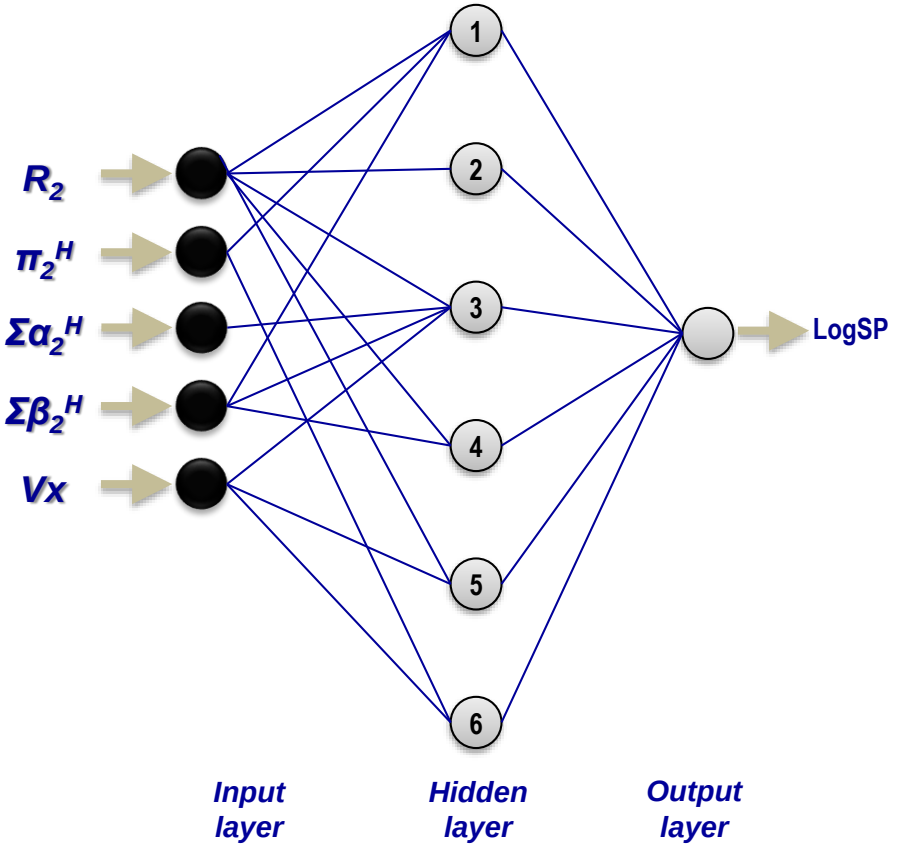
R_2 is an excess molar refraction that can be determined simply from a knowledge of the compound refractive index

π_2^H is the compound dipolarity/polarizability

$\Sigma\alpha_2^H$ is the solute effective or summation hydrogen-bond acidity

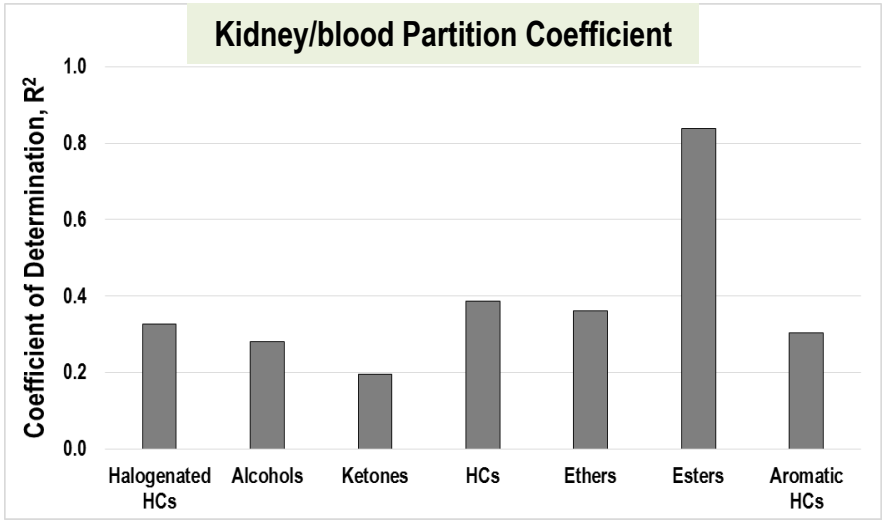
$\Sigma\beta_2^H$ is the solute effective or summation hydrogen-bond basicity

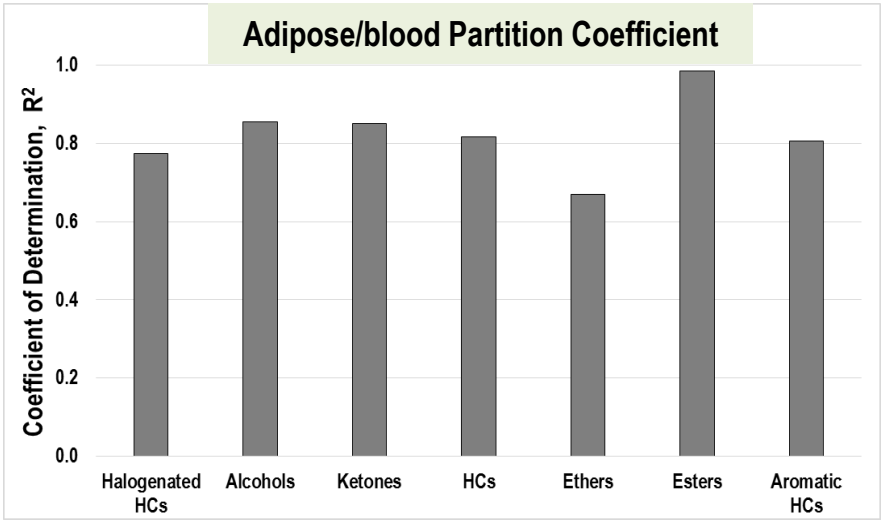
V_x is the McGowan characteristic volume

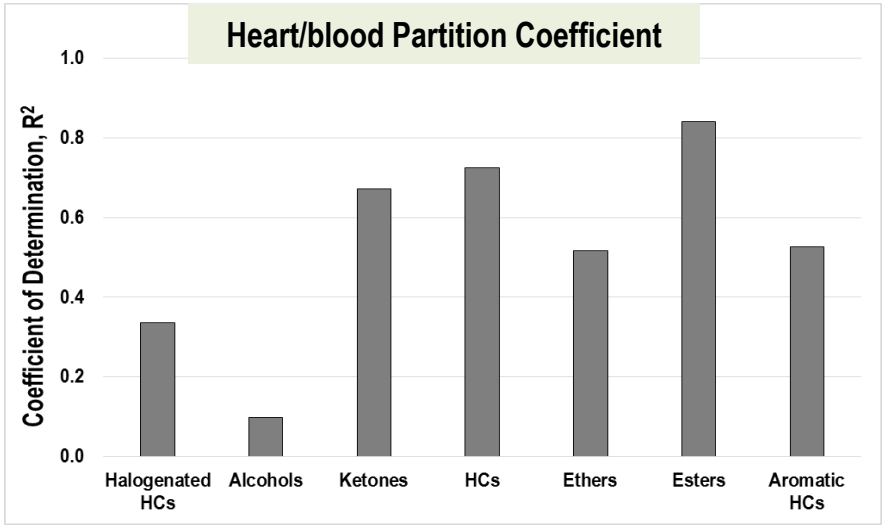


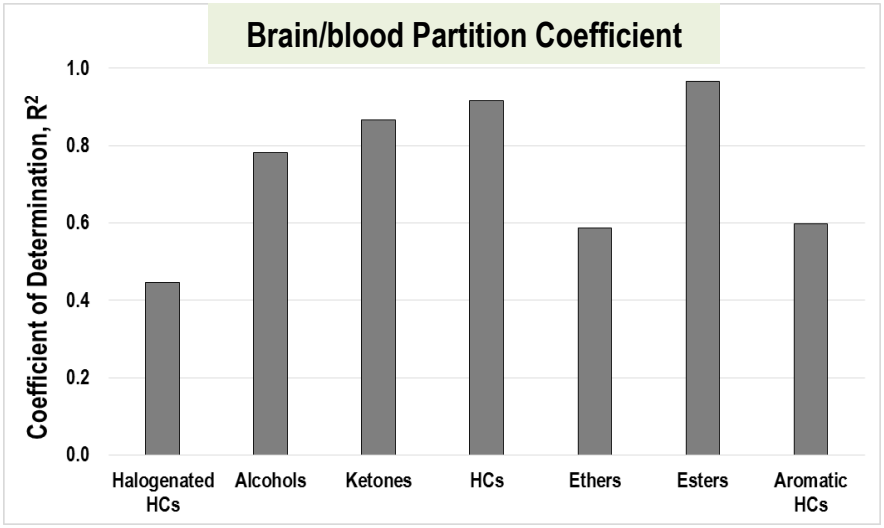
Results

Domain of Applicability

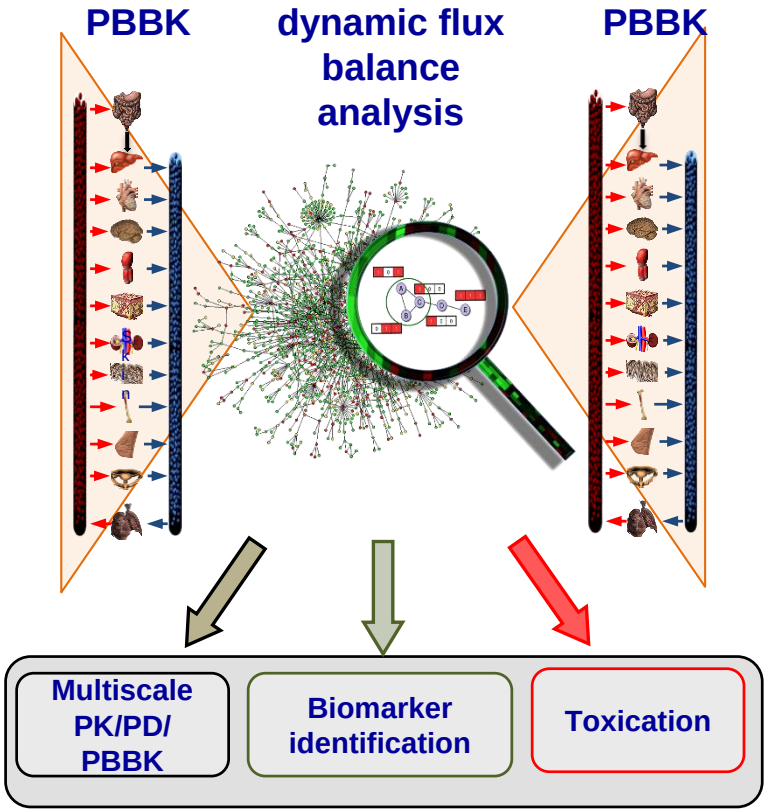


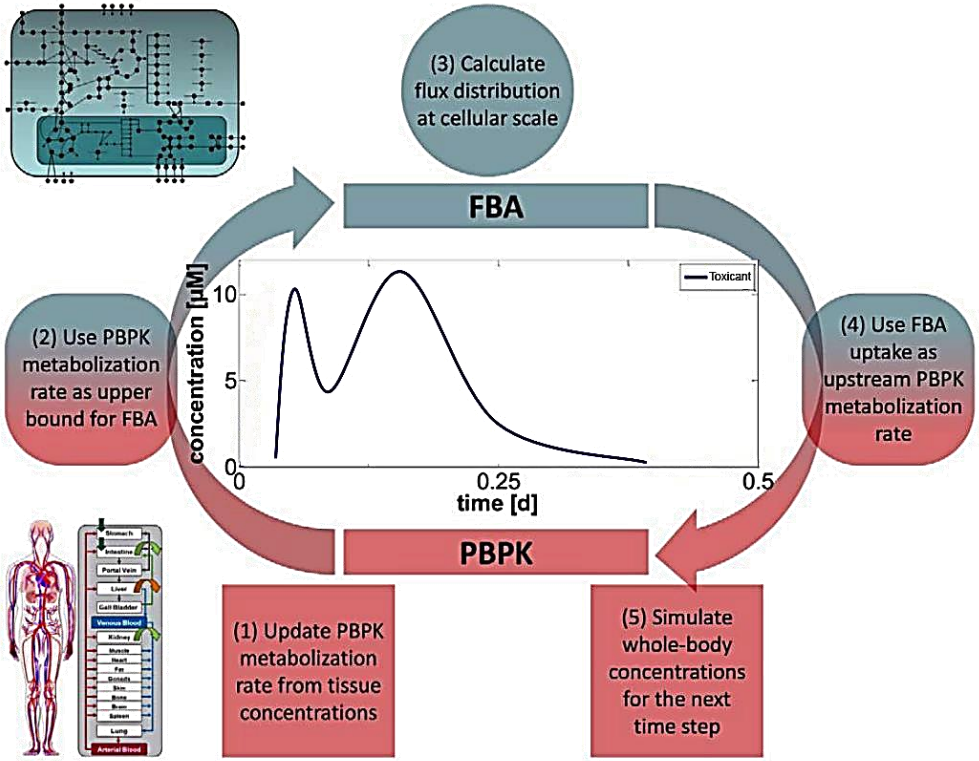






Extracellular perturbations on metabolic states





Biomonitoring data assimilation

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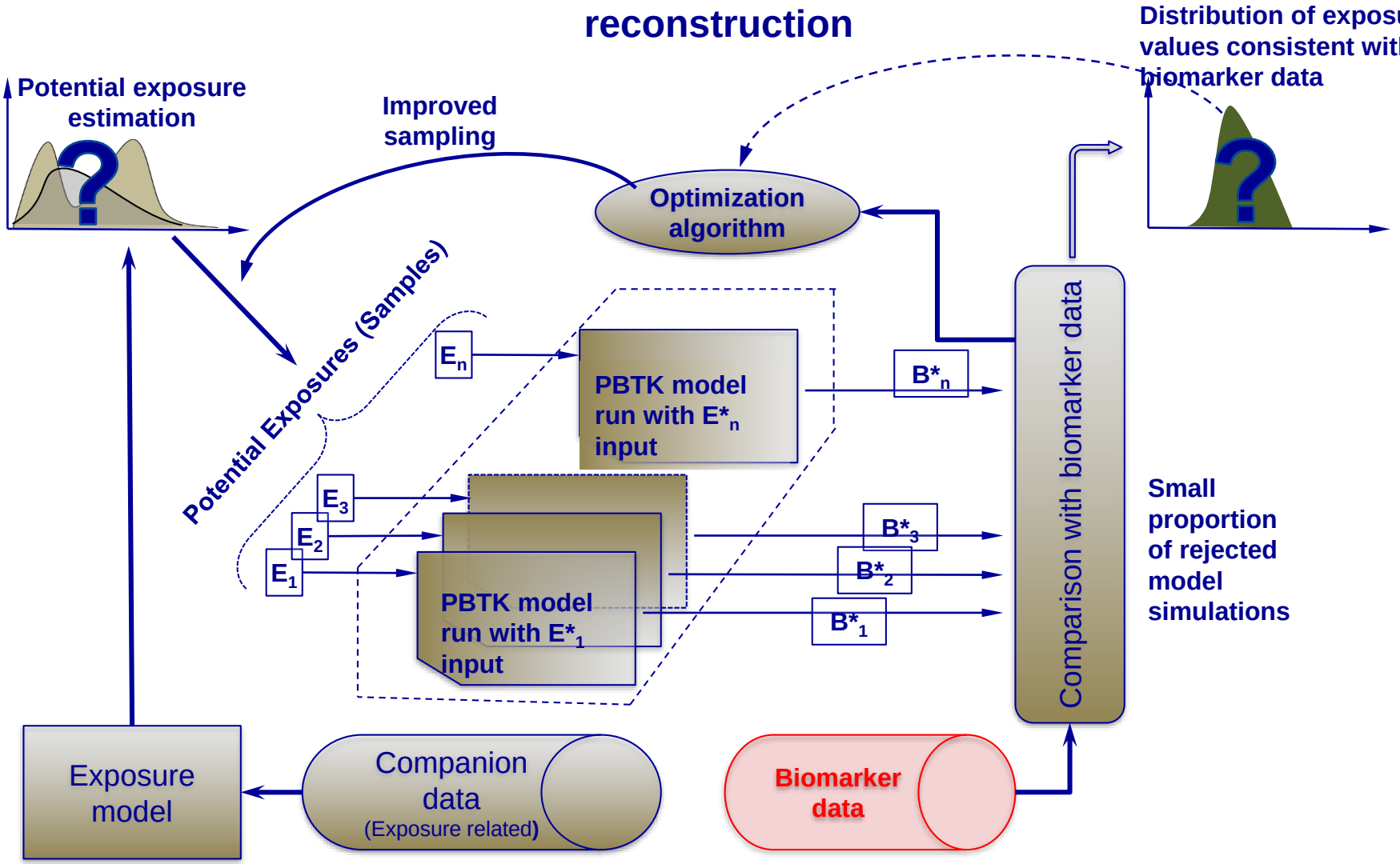
Optimal methodological scheme for exposure reconstruction



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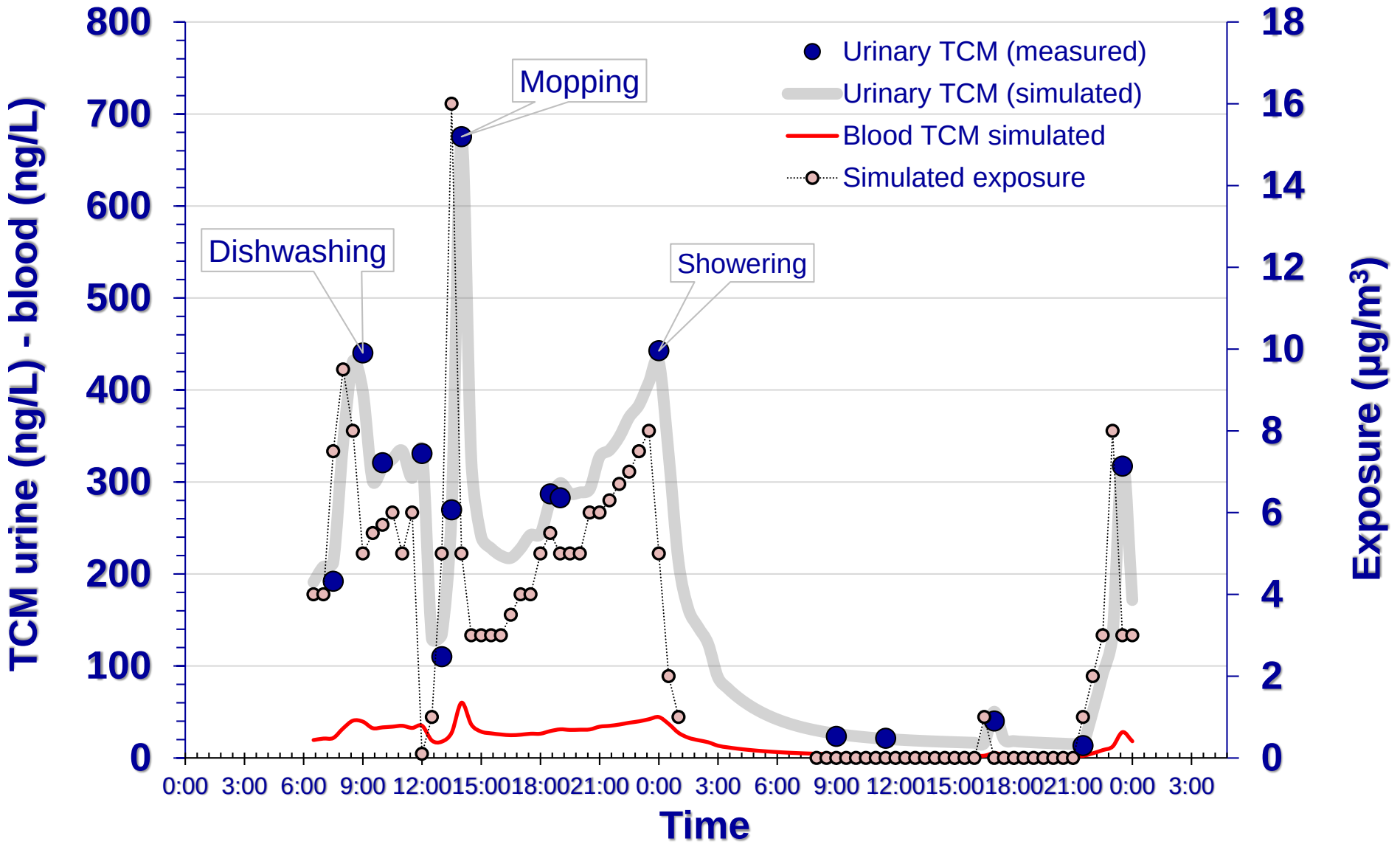
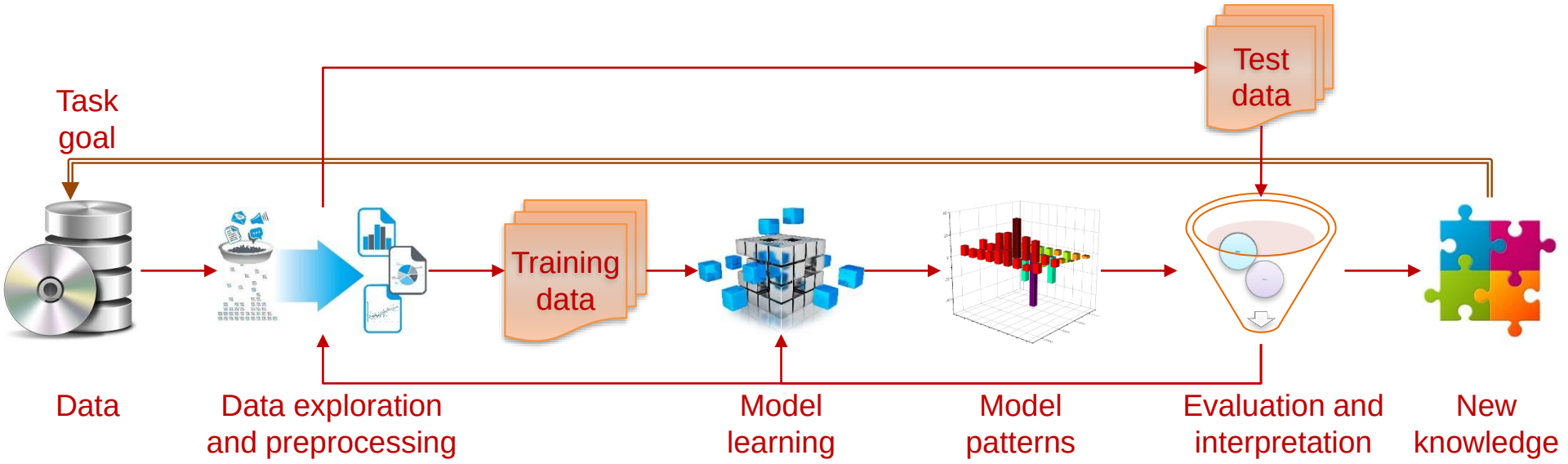
Reconstructing exposure from time-dynamic data



Novel bioinformatics for predictive biomarker discovery



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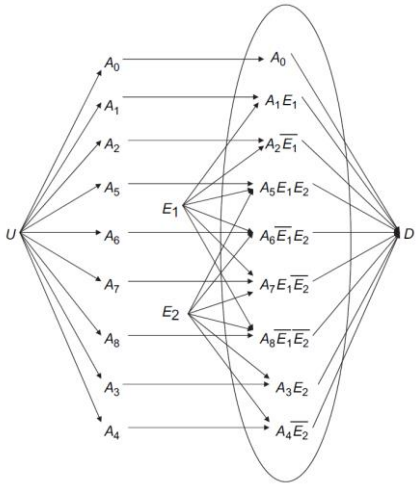
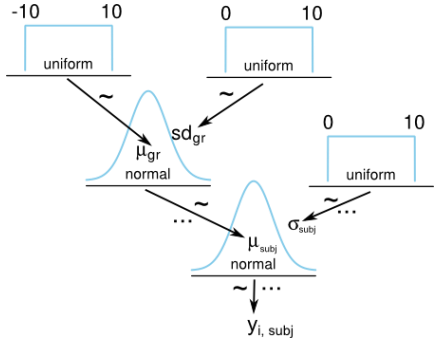
Exposome-Wide Association Studies (EWAS)

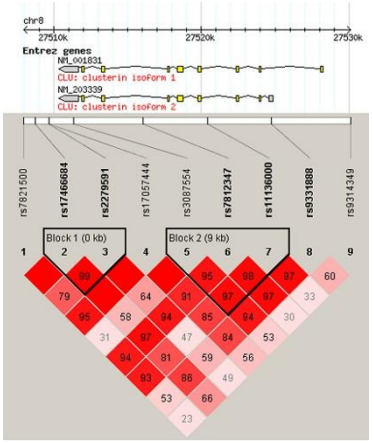
Directed Acyclic graphs (DAGs)

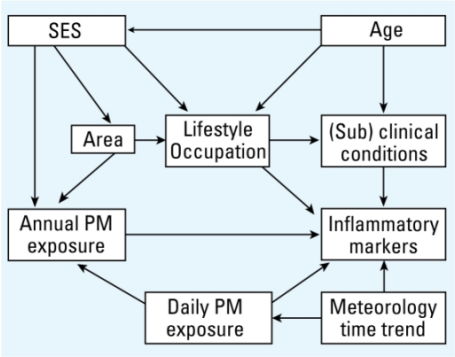


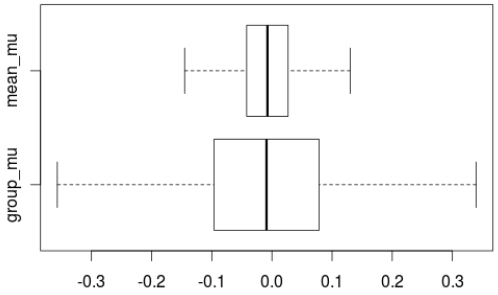
Bayesian Inference

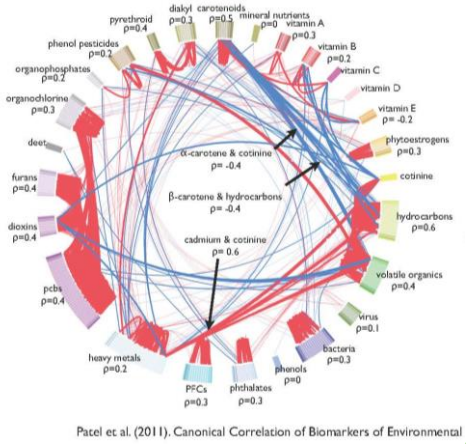


Linkage disequilibrium









Patel et al. (2011). Canonical Correlation of Biomarkers of Environmental

Population studies: Health outcomes

- Already existing cohort data
  - Allergy and asthma - link with particulate matter (PM) and biologicals
  - Neurodevelopmental and neurodegenerative disorders - link with metals/metalloids and pesticides (incl. endocrine disruptors)
  - Obesity and childhood diabetes - link with endocrine disruptors

- Pilot European Exposure and Health Examination Survey (EXHES)
  - Mother-Father-Children longitudinal and nested case-control study
  - Two phases foreseen:
    - Phase 1:
      - 200 twins, 200 matched singletons, 500 unselected singletons, parents
      - Recruitment within 18 months – follow up for 3 years
      - 10 countries
    - Phase 2:
      - Nested case-control
      - 140 twins, 70 singletons, 140 mothers and fathers
  - ✸ Ethnic minorities included and targeted to the extent possible

Environmental Engineering Laboratory

EXHES Campaign

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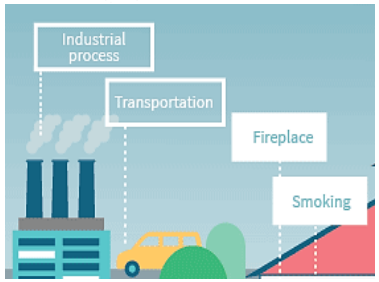
ENVIRONMENTAL ASSESSMENT

- *living room*
- *child's bedroom*

Chemical Compounds

Particulate Matter (PM)



allergens

Temperature | Humidity

Ventilation | Noise

HEALTH & BIOLOGICAL DATA

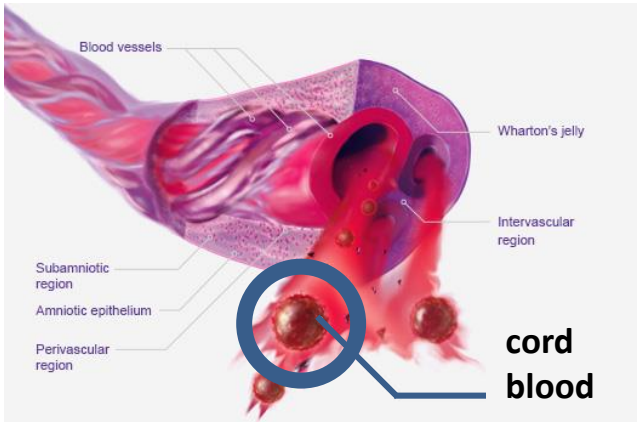
- *mother*
- *father*
- *children*

urine

blood

hair

saliva



cord blood

maternal milk

QUESTIONNAIRES

pregnancy → at delivery → post-partum → 1 year → 3 years → XX years

Application of exposome based studies

From agnostic to targeted approaches / environmental exposure to phthalates

Research question

- Several environmental compounds have been found to interact with child neurodevelopment
- It is important to identify the compounds that have the highest influence on given population groups
- **Which is the category of environmental compounds in the Polish population that relates to these outcomes?**

Combined untargeted and targeted metabolomics is a valuable tool towards this direction…….

Outlook of a metabolomics study

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- Sample preparation
- Analysis
- Pre-processing of the analyzed data
- Multivariate data analysis
- Identification of the compounds
- Evaluation of the results

Nuclear Magnetic Resonance

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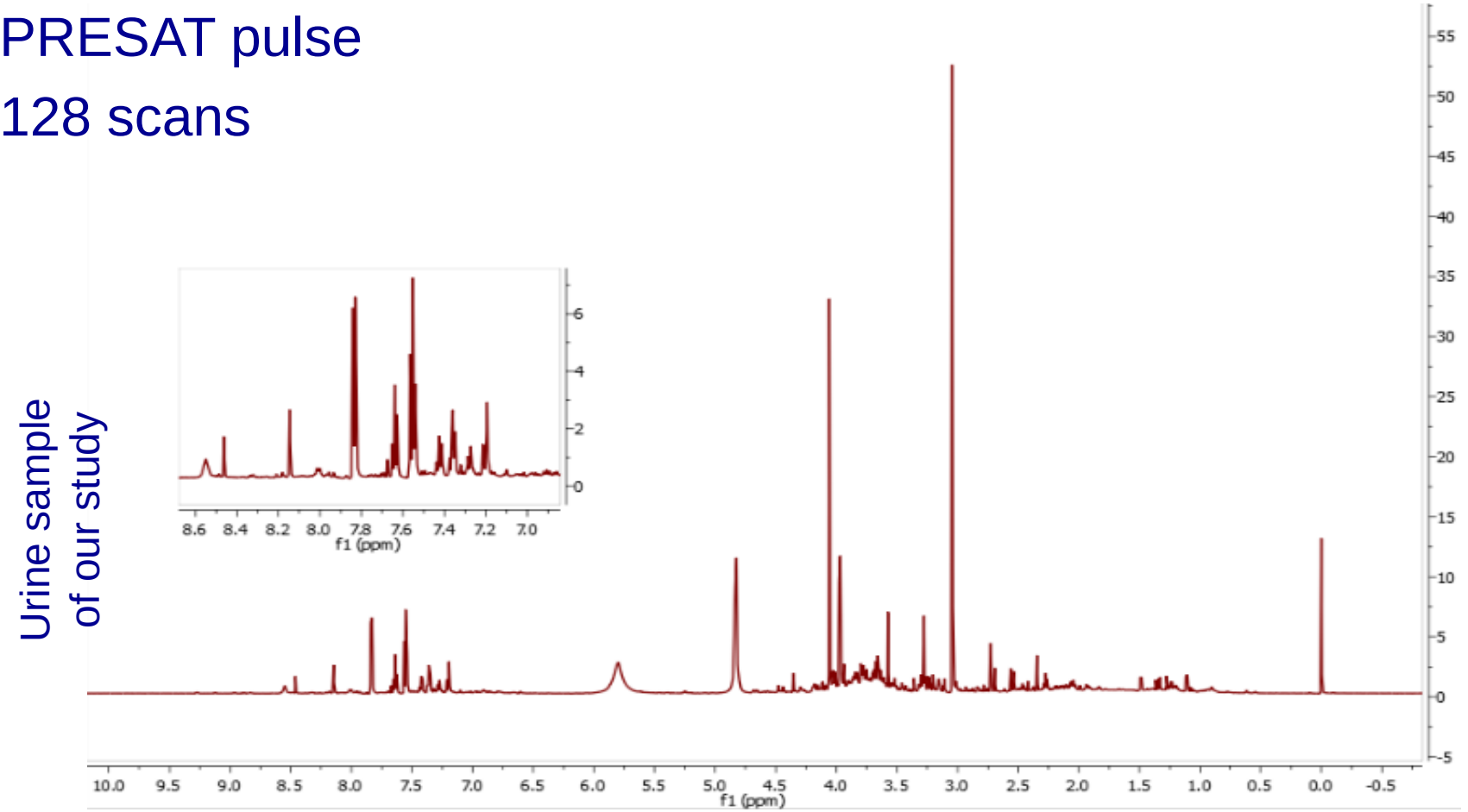
- (+) Simple sample prep
  Quick analysis
  Reproducible technique
  Nondestructive
  Quantitative

- (-) Cost intensive

Agilent 600 MHz PremiumCOMPACT

Analysis

- 1490 **urine** samples of pregnant women exposed to environmental contaminants
- PRESAT pulse
- 128 scans



Multivariate data analysis

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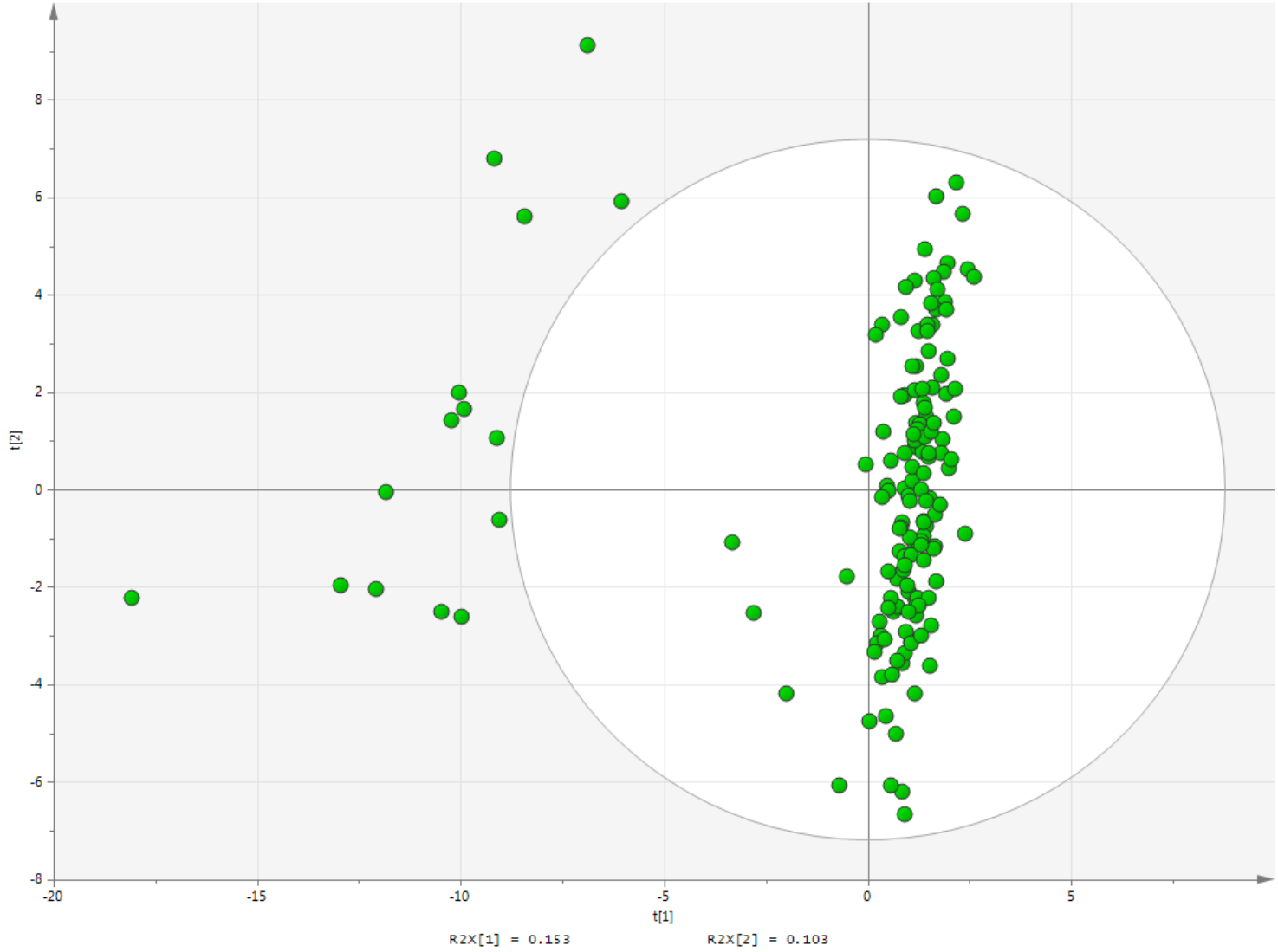

all 149 samples

Multivariate data meta-analysis - Correlations

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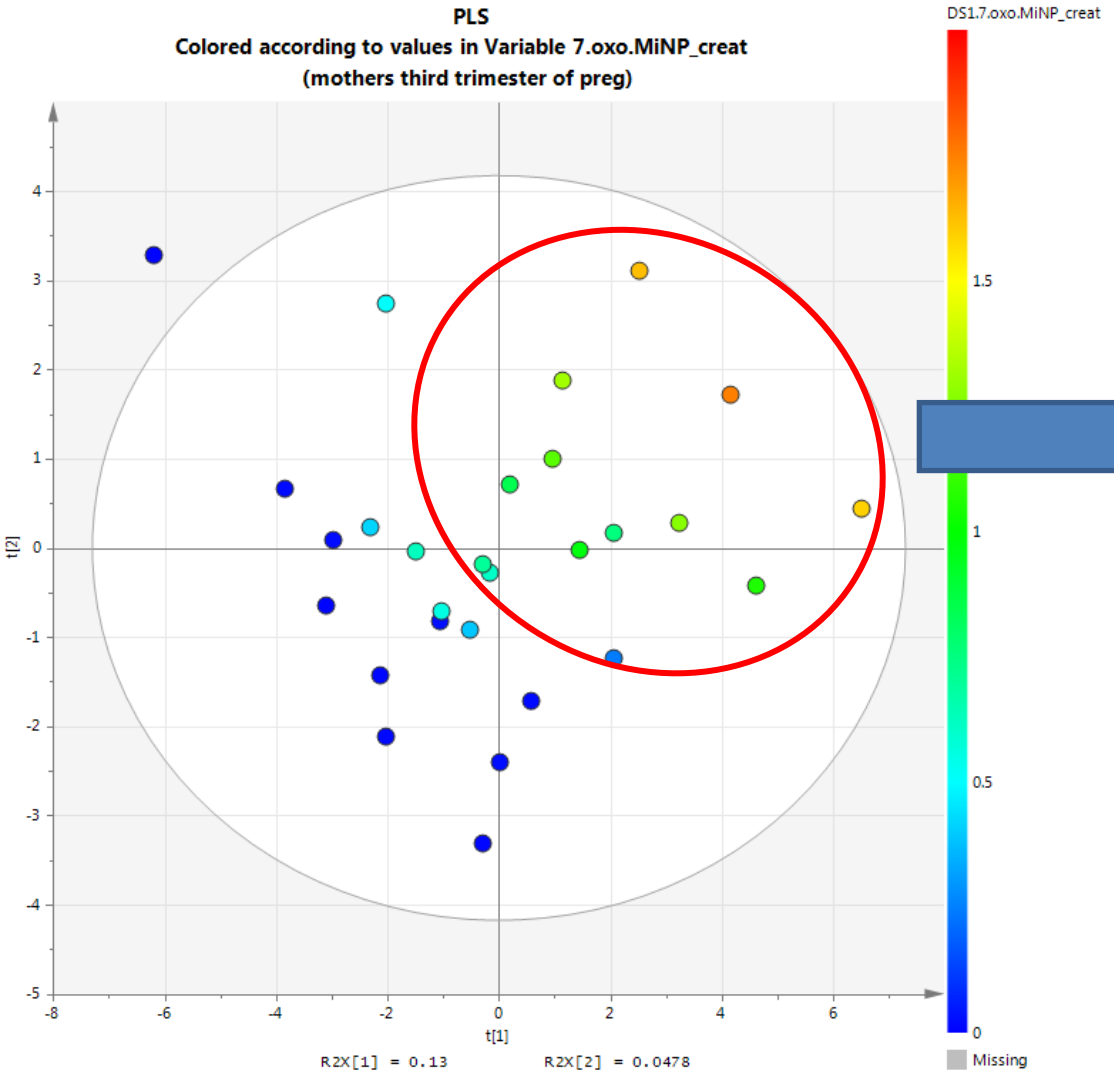


Need for targeted metabolomics analysis

LC/MS-MS

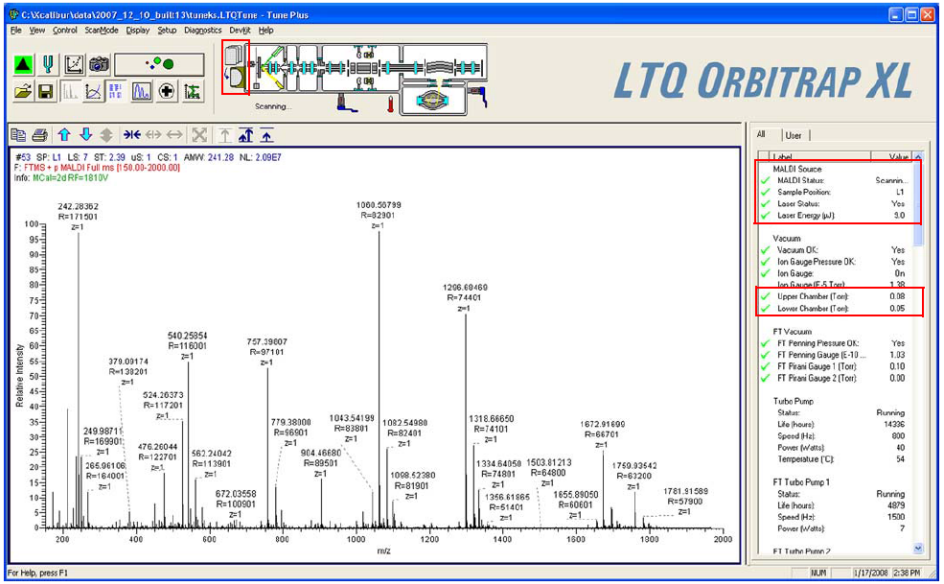
- (+) Reproducible technique
  Quantitative
  Low LD/LQ
  High mass accuracy

- (-) Cost intensive
  Time intensive

THERMO Orbitrap LTQ LC/MS-MS

Analysis

- **1490 urine** and **1070 cord blood** samples of pregnant women exposed to environmental contaminants
- Mass spectrometry conditions: positive and negative ion electrospray (ESI) mode in two separate runs. Acquisition off full scan data from 100 to 800 m/z over a period of 18 min with a scan time of 0.3 s and interscan delay of 0.1 s



Results

Creatinine-corrected phthalate metabolites[a]	Model 1 β (95% CI)			Model 2 β (95% CI)		
	Cognitive	Language	Motor	Cognitive	Language	Motor
MEP	−0.3 (−1.8 to 1.2)	−0.2 (−1.6 to 1.3)	−0.5 (−2.2 to 1.3)	0.3 (−1.3 to 1.8)	0.2 (−1.2 to 1.7)	0.1 (−1.5 to 1.8)
MiBP	−0.6 (−1.3 to −0.01)*	−0.5 (−1.1 to 0.1)	−1.2 (−1.9 to −0.5)**	−0.3 (−1.0 to 0.4)	−0.3 (−1.0 to 0.3)	−0.6 (−1.3 to 0.2)
MnBP	−1.1 (−2.3 to 0.1)	−1.0 (−2.1 to 0.2)	−2.2 (−3.5 to −1.0)**	−0.5 (−1.8 to 0.7)	−0.6 (−1.8 to 0.6)	−1.2 (−2.5 to 0.1)
3OH-MnBP	−1.9 (−3.3 to −0.5)*	−1.6 (−2.9 to −0.2)*	−3.8 (−5.3 to −2.3)**	−0.5 (−2.2 to 1.2)	0.4 (−1.1 to 2.0)	−2.3 (−4.0 to −0.6)*
DnBP	−1.7 (−3.1 to −0.4)*	−1.4 (−2.7 to −0.1)*	−3.2 (−4.7 to −1.8)**	−0.8 (−2.3 to 0.7)	−0.4 (−1.9 to 1.0)	−1.9 (−3.4 to −0.4)*
MBzP	−1.5 (−3.0 to −0.01)*	−0.8 (−2.2 to 0.6)	−1.3 (−3.0 to 0.3)	−1.0 (−2.6 to 0.6)	−0.6 (−2.1 to 0.9)	−0.4 (−2.1 to 1.3)
MEHP	−0.1 (−1.4 to 1.3)	−0.7 (−2.0 to 0.6)	0.4 (−1.1 to 2.0)	0.1 (−1.3 to 1.6)	−0.7 (−2.1 to 0.6)	0.2 (−1.3 to 1.7)
5OH-MEHP	−1.0 (−1.8 to −0.2)*	−0.5 (−1.3 to 0.2)	−1.9 (−2.8 to −1.1)**	−0.5 (−1.4 to 0.4)	−0.3 (−1.1 to 0.6)	−1.2 (−2.2 to −0.3)*
5oxo-MEHP	−1.8 (−3.0 to −0.6)*	−0.9 (−2.0 to 0.2)	−2.8 (−4.1 to −1.5)**	−1.1 (−2.6 to 0.3)	−0.1 (−1.5 to 1.2)	−1.8 (−3.3 to −0.2)*
DEHP	−1.8 (−3.0 to −0.6)*	−1.0 (−2.2 to 0.1)	−3.2 (−4.4 to −2.0)**	−0.8 (−2.2 to 0.6)	−0.4 (−1.7 to 0.9)	−2.2 (−3.6 to −0.8)*
OH-MiNP	−0.5 (−2.0 to 0.9)	−0.4 (−1.8 to 0.9)	−0.1 (−1.7 to 1.6)	−0.6 (−2.0 to 0.8)	−0.6 (−1.9 to 0.8)	−1.0 (−2.5 to 0.5)
oxo-MiNP	1.0 (−0.2 to 2.2)	0.4 (−0.8 to 1.6)	2.1 (0.7 to 3.5)*	0.4 (−0.9 to 1.7)	−0.1 (−1.3 to 1.1)	0.6 (−0.8 to 1.9)
DiNP	−0.5 (−2.0 to 0.9)	−0.4 (−1.8 to 0.9)	−0.1 (−1.7 to 1.6)	−0.6 (−2.0 to 0.8)	−0.6 (−1.9 to 0.8)	−1.0 (−2.5 to 0.5)
MnOP	−0.8 (−2.2 to 0.5)	−0.6 (−1.9 to 0.7)	−2.2 (−3.6 to -0.7)*	−0.7 (−2.1 to 0.8)	−0.6 (−2.0 to 0.8)	−1.1 (−2.6 to 0.4)
∑Low-MWP	−1.1 (−2.5 to 0.4)	−1.0 (−2.4 to 0.4)	−2.1 (−3.7 to −0.5)*	0.1 (−1.5 to 1.7)	0.1 (−1.5 to 1.6)	−0.5 (−2.2 to 1.3)
∑High-MWP	−2.1 (−3.5 to −0.7)*	−0.9 (−2.2 to 0.4)	−3.3 (−4.8 to −1.9)**	−1.3 (−2.8 to 0.3)	−0.6 (−2.0 to 0.9)	−2.5 (−4.1 to −0.9)*

DnBP (∑MnBP and 3OH-MnBP), DEHP (∑MEHP, 5OH-MEHP and 5oxo-MEHP), DiNP (∑OH-MiNP and oxo-MiNP), ∑Low-MWP (MEP, MiBP, MnBP, 3OH-MnBP and MBzP), ∑High-MWP (MEHP, 5OH-MEHP, 5oxo-MEHP, OH-MiNP, oxo-MiNP and MnOP).

Model 1 — adjusted for examiner.

Model 2 — adjusted for examiner, parental age, parental education, child gender, pre and postnatal ETS exposure and for cognitive development additionally marital status and child nursery attendance.

[a] Prenatal maternal urinary concentrations were natural log-transformed, urine samples with creatinine values N 0.2 g/l were used, scores of Bayley-III per natural log changes in μg/g creatinine.

* p b 0.05.

** p b 0.001.

Results

Prenatal exposure to phthalates in Poland is inversely associated with child motor development within the first two years after birth.

Metabolic pathway analysis revealed that alterations in urine metabolites are related to the **TCA cycle**, suggesting impaired mitochondrial respiration; the latter is central to energy metabolism and cellular signaling and plays fundamental roles in synthesis of nucleotides and active transport processes.

The most significantly perturbed metabolic pathways include carbohydrate, amino acid, lipid, and purine metabolism.

Inhibition of mitochondrial oxidative phosphorylation could also cause a defective mitochondrial energy production during the process of fetus formation and development that are reflected in early life motor development.

↓

Prenatal phthalate exposure in Poland may be detrimental to child neurodevelopment and underscore the importance of policies and public health interventions aiming at reduction of such exposures

Association to socioeconomic components

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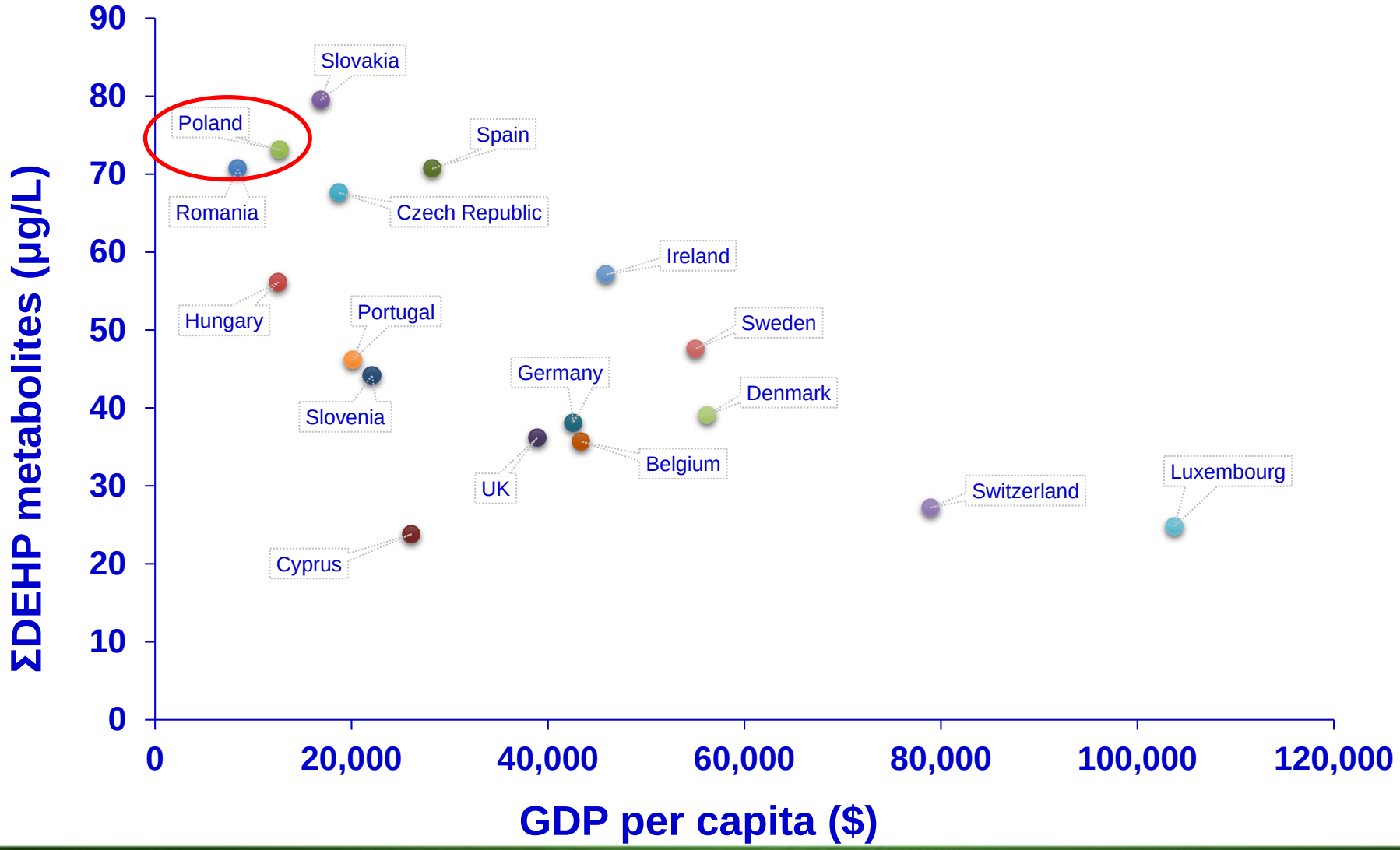


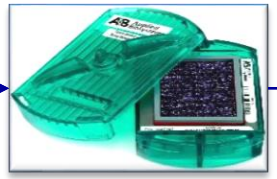
Application of exposome based studies

Discovering disease mechanisms through multi-omics pathway analysis coupling *in vitro*, *in vivo* and human data

Thesis and study design

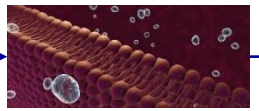
The complexity of biological responses following exposure to engineered nanotubes underlines the need for the development of dedicated and comprehensive methodologies to approach the potential health effects of nanomaterials.

In vitro



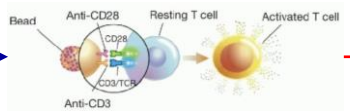
Transcriptomics

***In vivo* (animal model)**

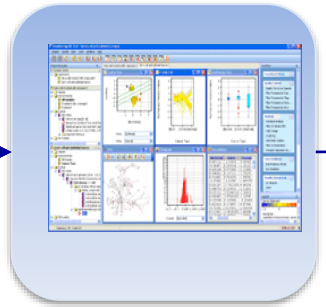


Lipidomics

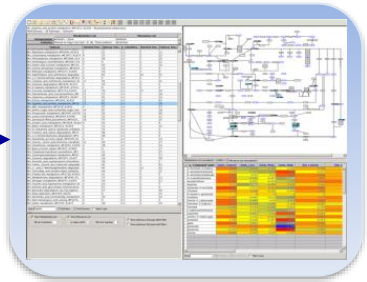
***In vivo* (human volunteers)**



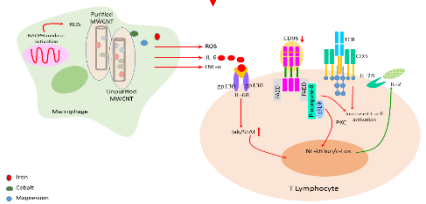
Immunologic response



GeneSpring Platform



Pathway Architect



Mechanism identification

Carbon nanotubes

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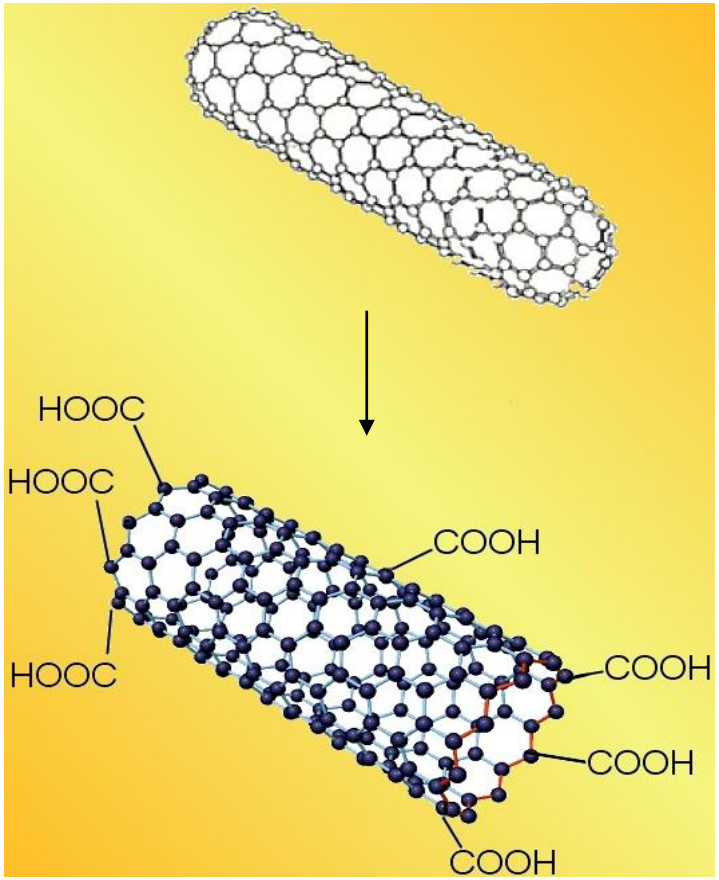
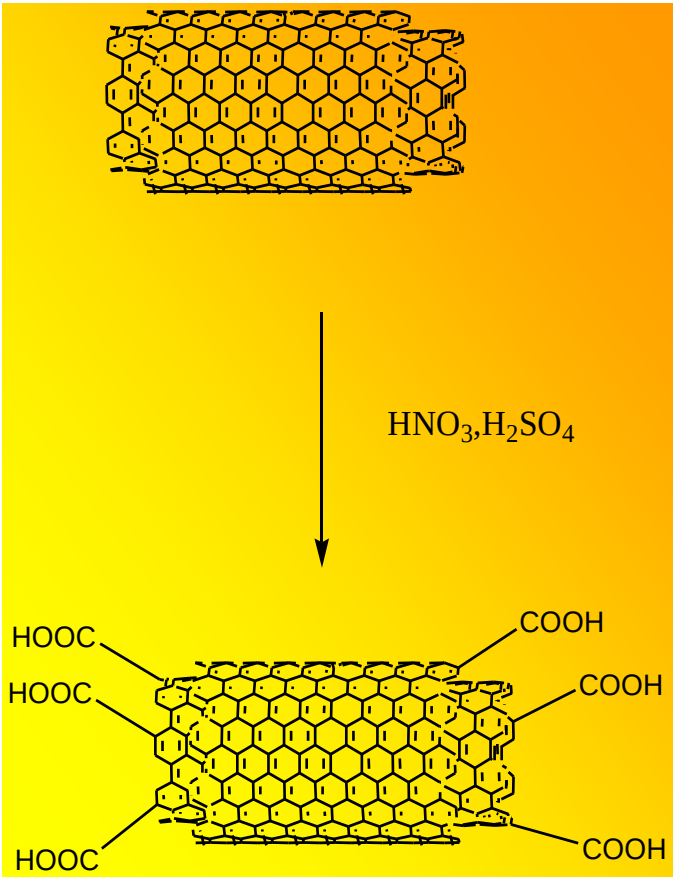


SWCNTs



MWCNTs

Both the SWNTs and the MWNTs are oxidised by treating them with $HNO_3 + H_2SO_4$

Carbon nanotubes

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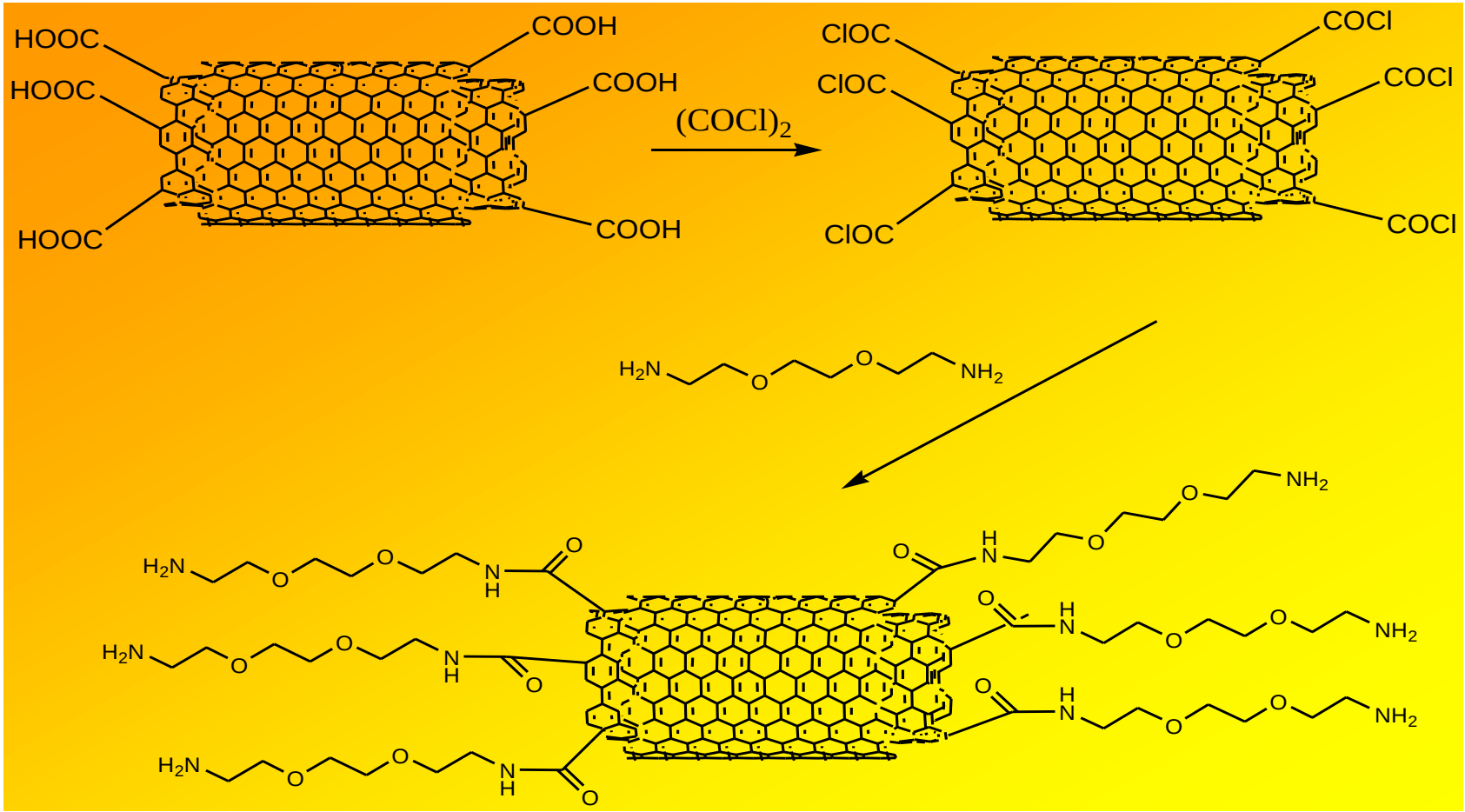
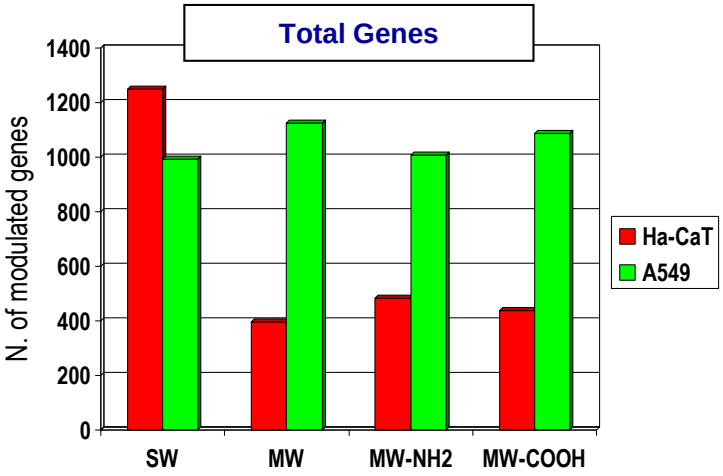
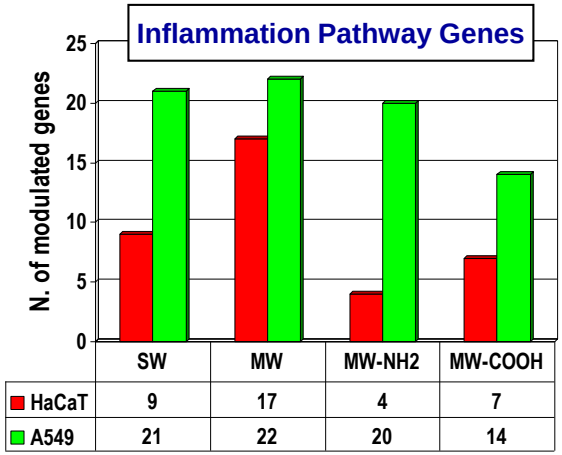


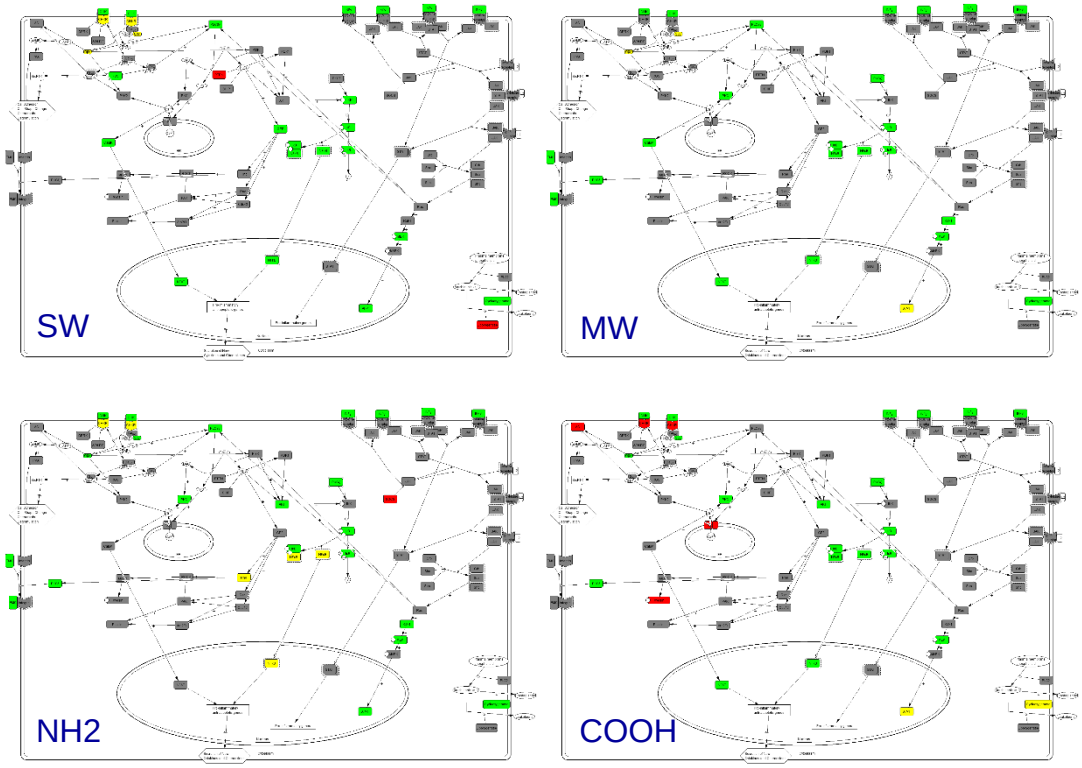
The carboxylic groups obtained by oxidation are converted to acylic chlorides by reacting with oxyalyl chloride, and then to ammides by reacting with the the proper amine.

Comparison between cell lines: Ha-CaT and A549 (48h)





Inflammation mediated by chemokine and cytokine signaling pathway



In Vivo CD-1 Mice + Human volunteers

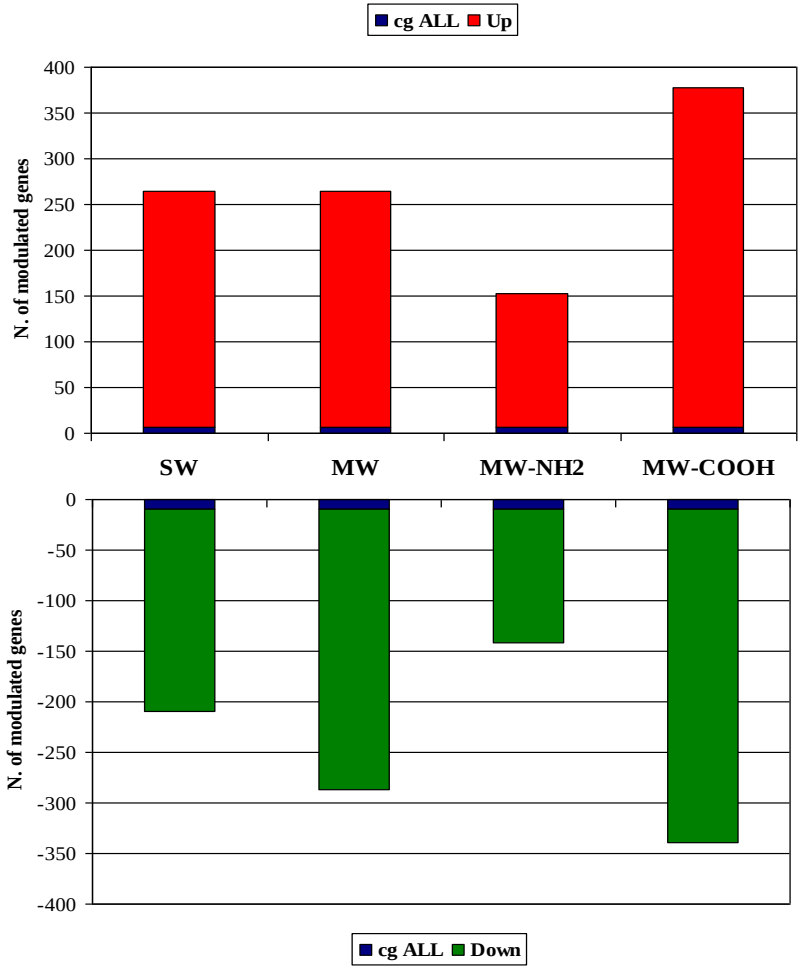
- **Animal Model**:
  - **CD-1 male mice** exposed by intra-tracheal instillation
    Lung samples at day 1 after exposure

- **Test compounds**:
  - Single walled carbon nanotubes (SW): 0.1-100 μg/ml
  - Multi walled carbon nanotubes (MW): 1-100 μg/ml
  - Multi walled-COOH carbon nanotubes (MW-COOH): 1-100 μg/ml
  - Multi walled-NH_2 carbon nanotubes (MW-NH_2): 1-100 μg/ml

- **Toxicogenomic Assays:**
  - Total gene expression by DNA-microarrays
  - Quantitative Real Time PCR

- **Human blood samples**
  - **Lipid peroxidation products**
  - **Immunological parameters**

Gene expression modulation in lung of mice 1d after i. tr. exposure to nanotubes (1mg/Kg b.w.)



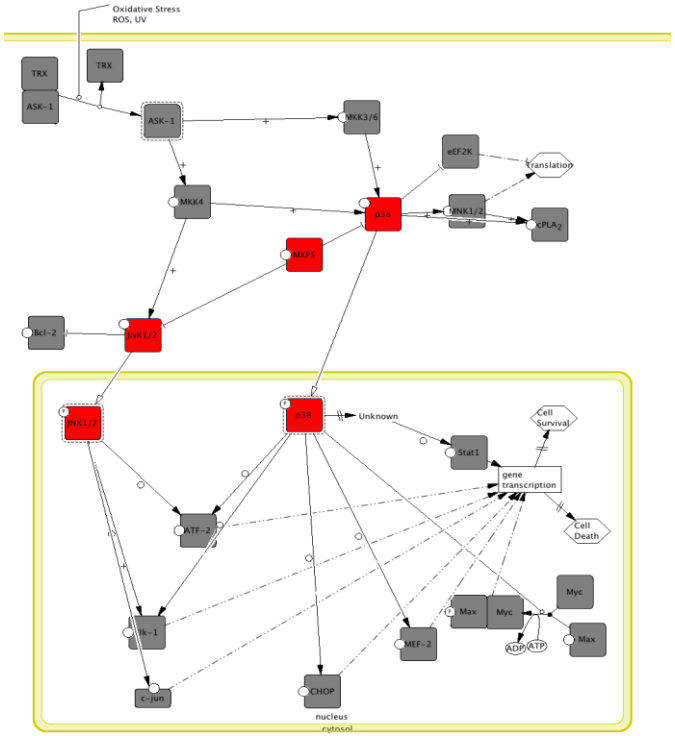
	SW	MW	MW-NH2	MW-COOH
Up	258	258	147	372
cg ALL	6	6	6	6

	SW	MW	MW-NH2	MW-COOH
Down	200	278	133	330
cg ALL	9	9	9	9

Lung, mice 24h, Oxidative stress response pathway

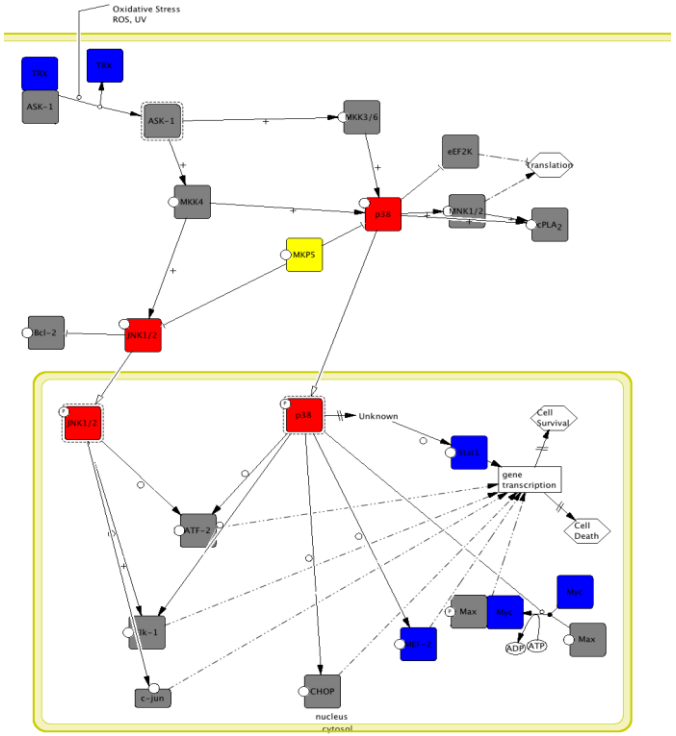
MWCNT -NH2

= MW
= NH2
= common



MWCNT -COOH

= MW
= COOH
= common

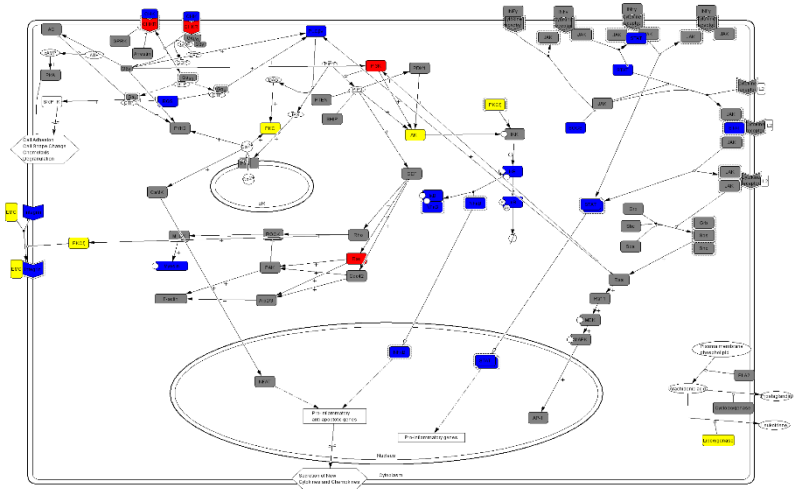


In vivo (mice)

Lung, 24h, Inflammation mediated by chemokine and cytokine signaling pathway

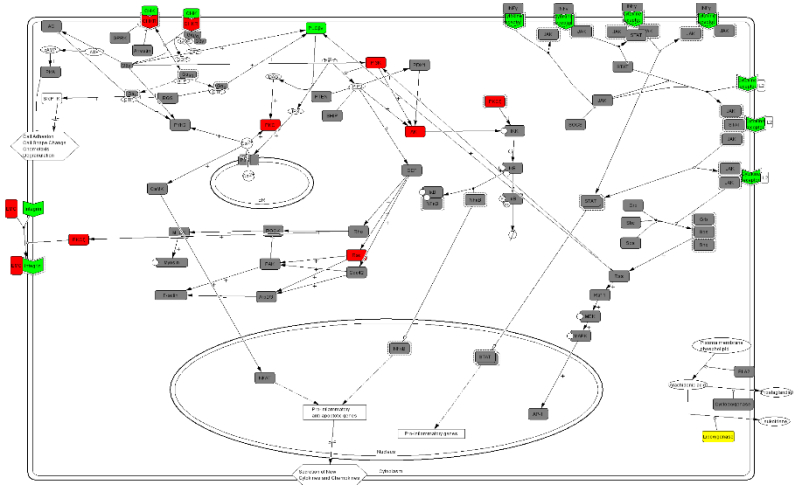
MWCNT -COOH

= MW
= COOH
= common



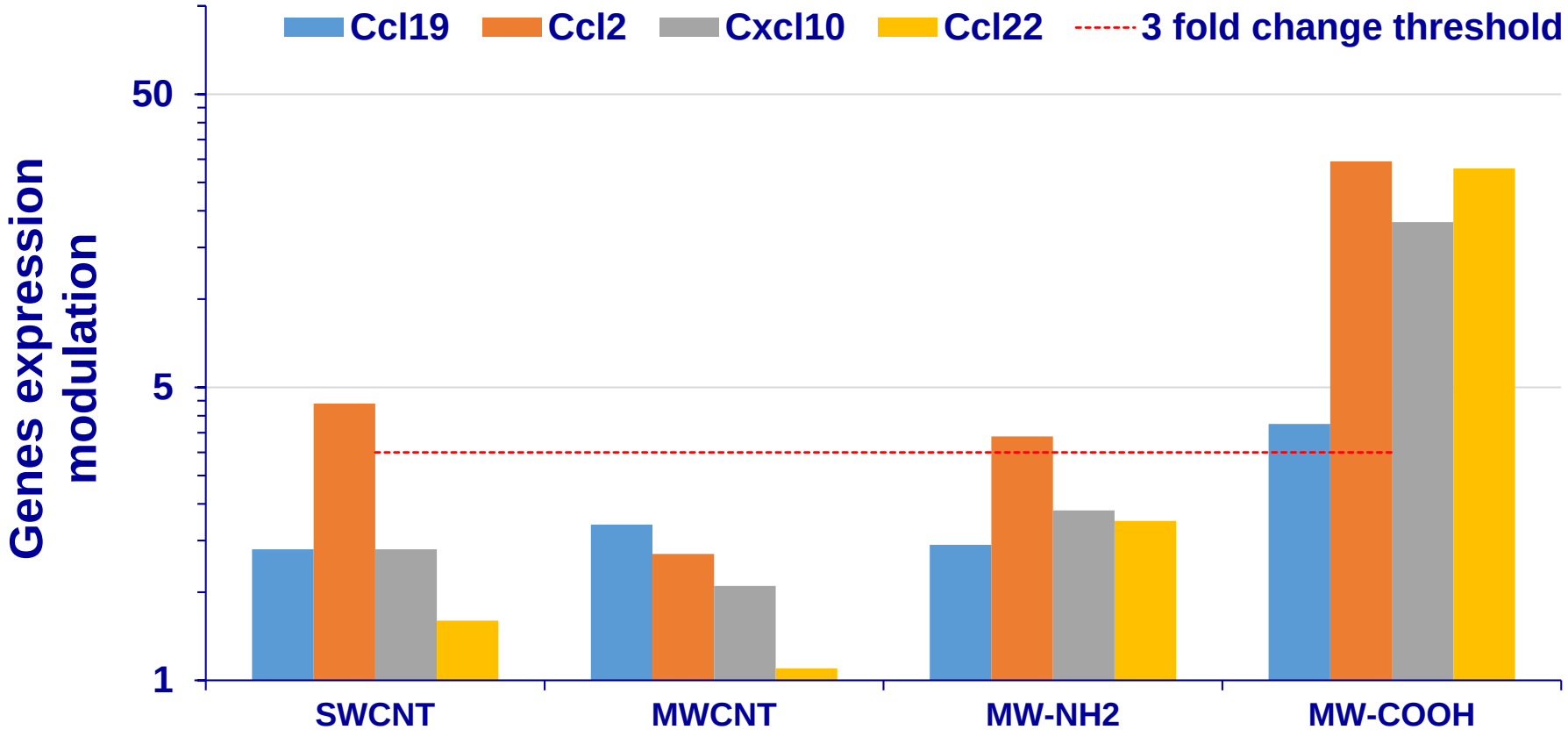
MWCNT -NH2

= MW
= NH2
= common



In vivo (mice)

Modulation of chemokines gene expression in lung of mice 1d after i. tr. exposure to nanotubes (1mg/kg_bw)

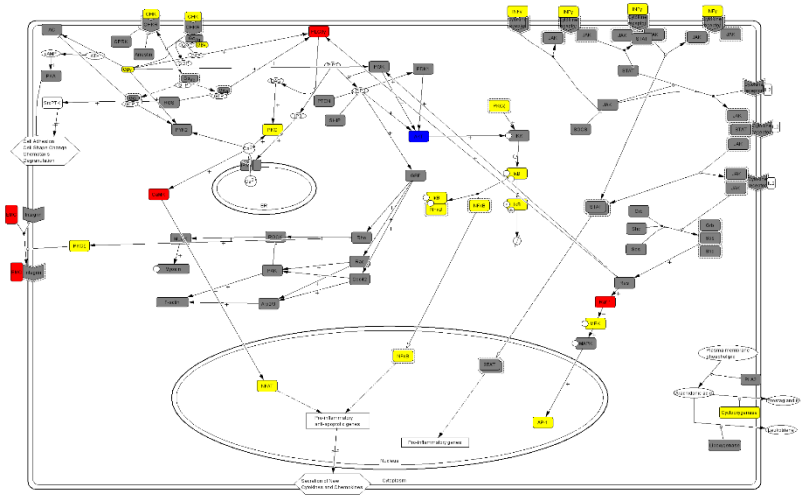


Value of gene expression by Quantitative RT-PCR and microarrays.
RT-PCR: significantly modulated over 96 tested.
Fold Change (FC) > 3

In vitro (A549) and *in vivo* (mice lungs)

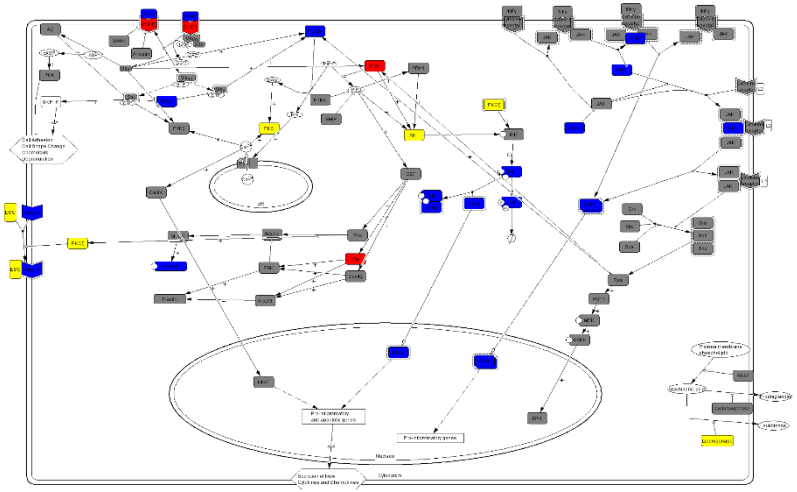
Inflammation mediated by chemokine and cytokine signaling pathway

A549



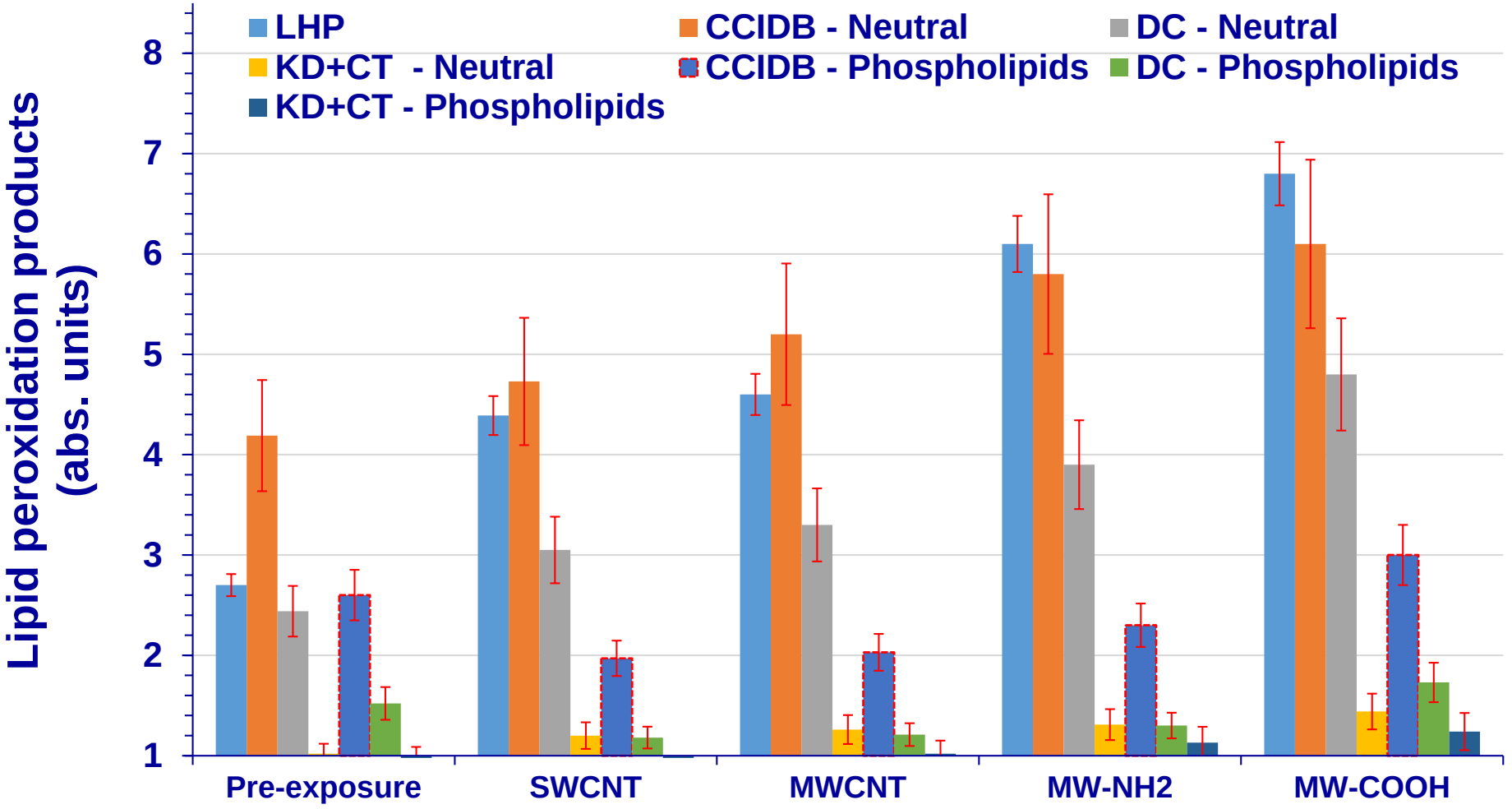
= MW
= COOH
= common

Mice Lungs



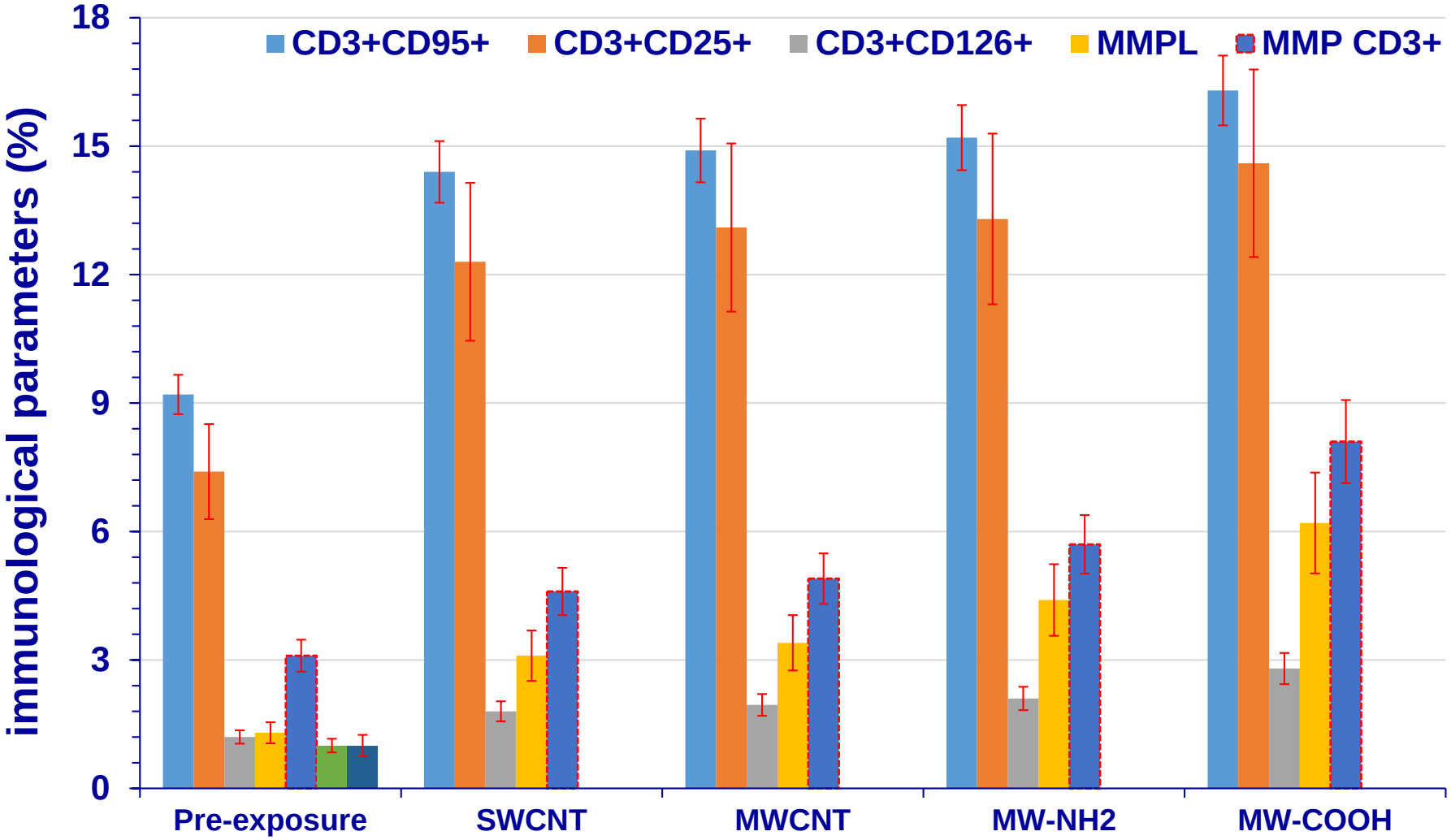
Human volunteers

Lipidomics in the blood of healthy volunteers after exposure to SWCNTs and MWCNTs of different functionalization

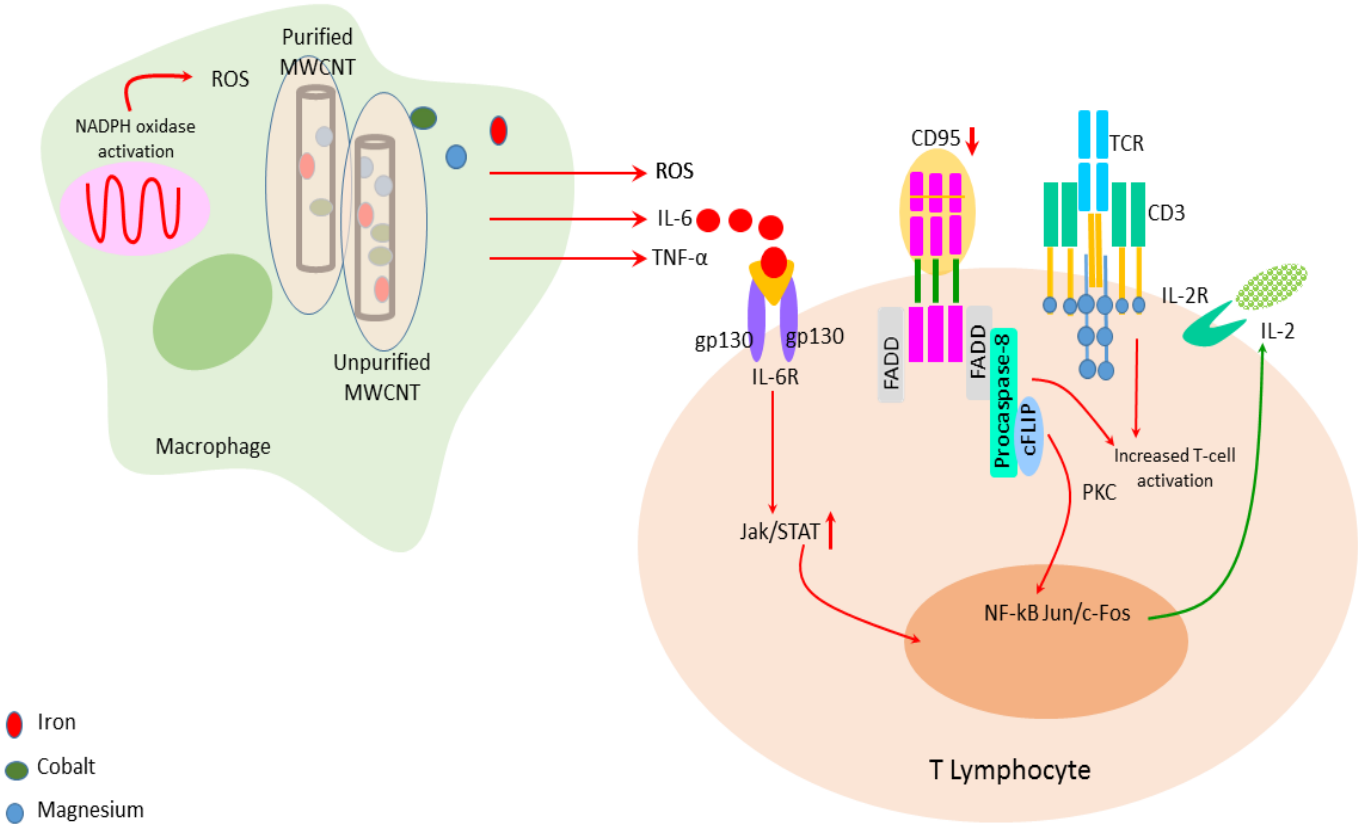


Human volunteers

Immunological parameters in the blood of healthy volunteers after exposure to SWCNTs and MWCNTs of different functionalization



Up-regulation of anti-apoptotic pathway in the presence of multi-walled carbon nanotubes



Conclusions

- Exposome science can overhaul the current environmental health risk assessment paradigm. This requires combination of high dimensional biology and system science aiming at integration using big data analytics and bioinformatics
- Integrated multi-scale methodology focusing on high dimensional biological connectivity permits the identification of the biological processes underlying the onset or exacerbation of disease phenotypes associated to exposure to environmental stressors over one's lifecourse (the exposome)

Conclusions

- PBBK and systems biology modeling is the connecting layer for integrating high dimension biology and environmental interactions dynamics
- The connectivity approach to the exposome elucidates toxicity pathways and assigns causal associations between environmental stressors and health
- Precise prevention towards environmental risks by identifying the susceptible or vulnerable individuals or age-groups

Conclusions

Exposome science will:

- make public health and environmental policies more cost effective by overhauling the “nature vs. nurture” paradigm
- stimulate innovation in environmental health science and technology, in ubiquitous sensing, in high throughput biological analysis technologies and in big data analytics
- promote transdisciplinary education and training to create a new breed of environmental health scientists who would be science “integrators” and “translators” into improved prevention of disease.

Bertold Brecht's *Life of Galileo*:
"*The main objective of science is not to open the door to infinite wisdom but to roll back the boundaries of infinite error*.

Thank you for your attention

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A connectivity perspective to environmental health