CENTER FOR CLEAN AIR RESEARCH

UNIVERSITY *of* WASHINGTON

UW CCAR Scientific Advisory Committee Meeting

September 26th & 27th 2011

SCHOOL OF PUBLIC HEALTH

UNIVERSITY *of* WASHINGTON

LOVELACE RESPIRATORY RESEARCH INSTITUTE

WASHINGTON STATE UNIVERSITY

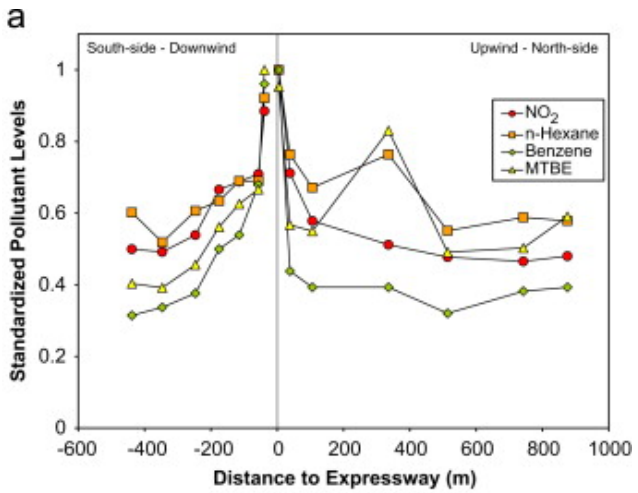
World Class. Face to Face.

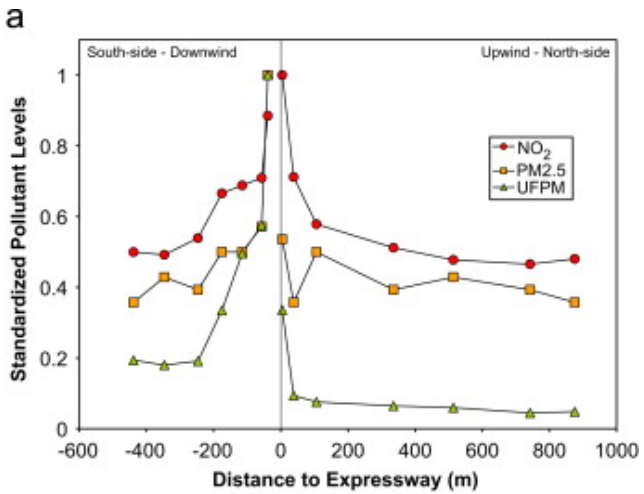
THE UNIVERSITY *of* NEW MEXICO

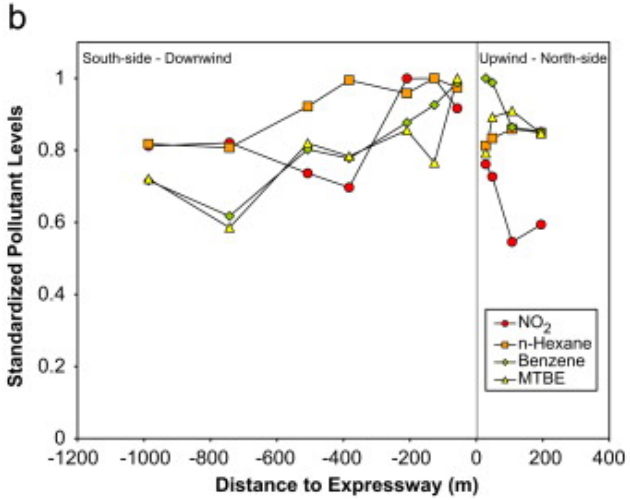
Pollutant concentrations ($PM_{2.5}$, ultrafine, NO_2, VOCs) near major roadway (Highway 401 - Toronto, Aug 5, 2004)

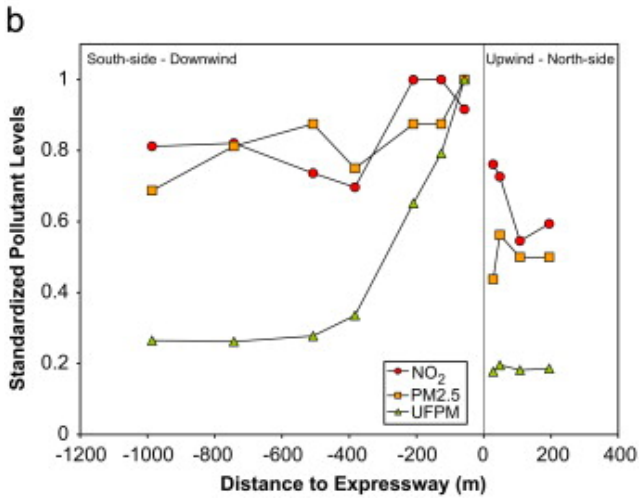
Observations:

1. distance from roadway
2. upwind vs. downwind
3. variability by site









Beckerman B, Atmos Environ 2008; 42: 275-90.

Roadway proximity and left ventricular mass (LVM) in the Multi-ethnic Study of Atherosclerosis (MESA) cohort

distance to road (m)	ΔLVMi (g/m^2 [95% CI])	p-value
>150	referent	
101–150	1.9 (0.6, 3.2)	0.003
50–100	1.6 (0.4, 2.9)	0.01
<50	2.3 (1.2, 3.4)	<0.001

Van Hee V. Am J Respir Crit Care Med 2009;179:827-34.

University of Washington
Center for Clean Air Research (CCAR)

Overall focus:

the cardiovascular health effects of near-roadway pollution

What is near-roadway pollution?

a complex mixture of particle, vapor and gas phase components that vary by vehicle emission source, road surface, extent of physical aging and the type and degree of atmospheric processing and photochemical reactions

a cause of cardiovascular disease

a prototypical case for developing research approaches to dealing with multi-pollutant exposure-effect relationships

CCAR investigators

University of Washington	Sverre Vedal (director); Tim Larson (deputy director); Joel Kaufman; Lianne Sheppard; Paul Sampson; Adam Szpiro; Mike Yost; Chris Simpson; Mike Rosenfeld
Lovelace Respiratory Research Institute	Jake McDonald (deputy director); Amie Lund
University of New Mexico	Matt Campen
Washington State University	Tom Jobson; Tim VanReken

CCAR

Center for Clean Air Research

some background

- original PM Center
- MESA and MESA Air
- NPACT (with LRRI)
- NIEHS DISCOVER Center
- mobile monitoring studies in Vancouver, BC and Tacoma, WA
- WSU DOE grant using PTR-MS characterizing diesel exhaust

CCAR projects & cores

Project 1
roadway exposure characterization

M Yost (PI), T Larson, C Simpson, T Jobson, T VanReken

Project 2
exposure atmosphere generation

J McDonald (PI), A Lund, T Larson

Project 3
toxicology

M Campen (PI), M Rosenfeld, A Lund, J McDonald

Project 4
human clinical studies

J Kaufman (PI)

Project 5
epidemiology cohort study

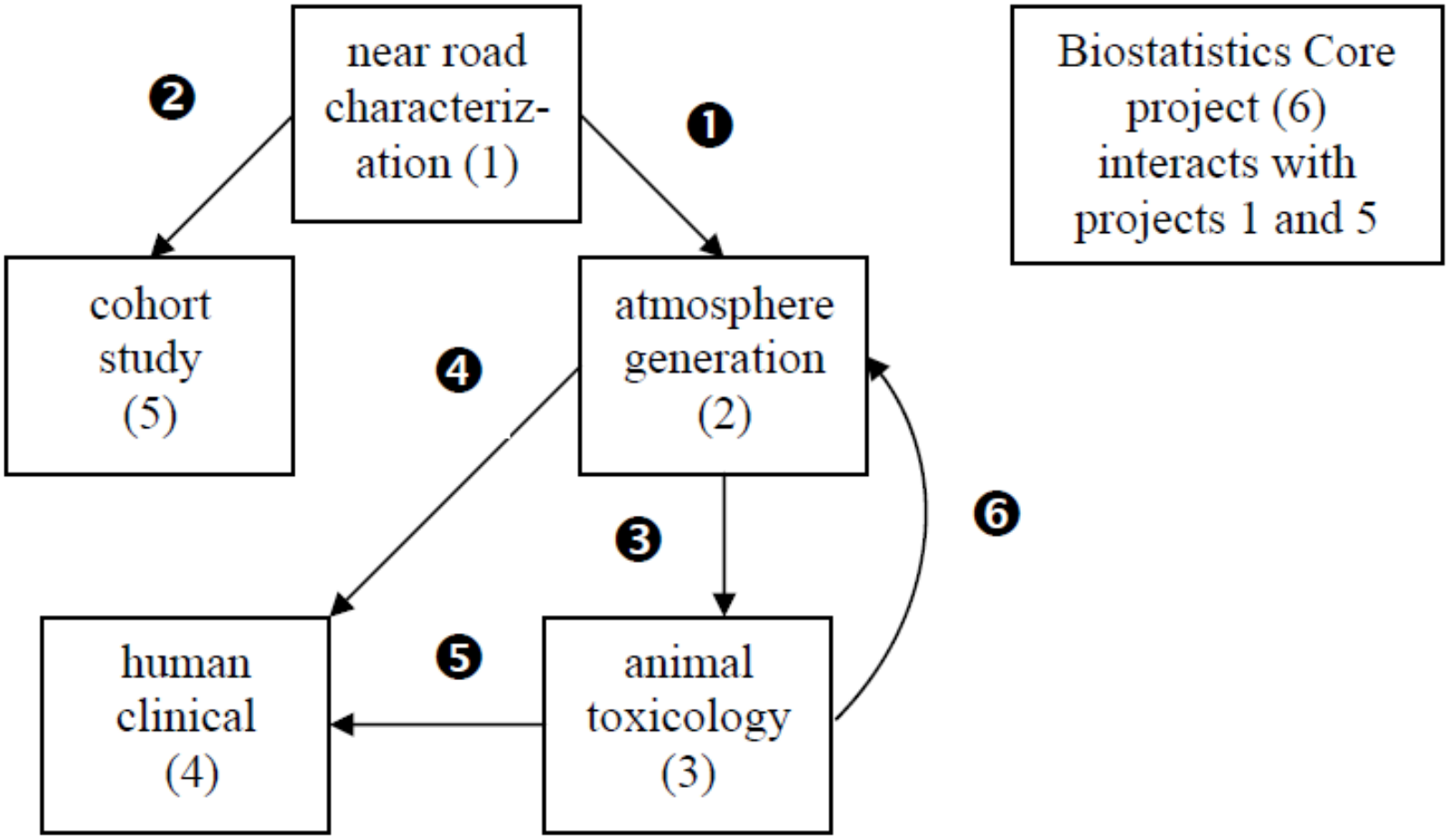
J Kaufman (PI), S Vedal

Project 6
multipollutant exposure modeling

L Sheppard (PI), A Szpiro, P Sampson

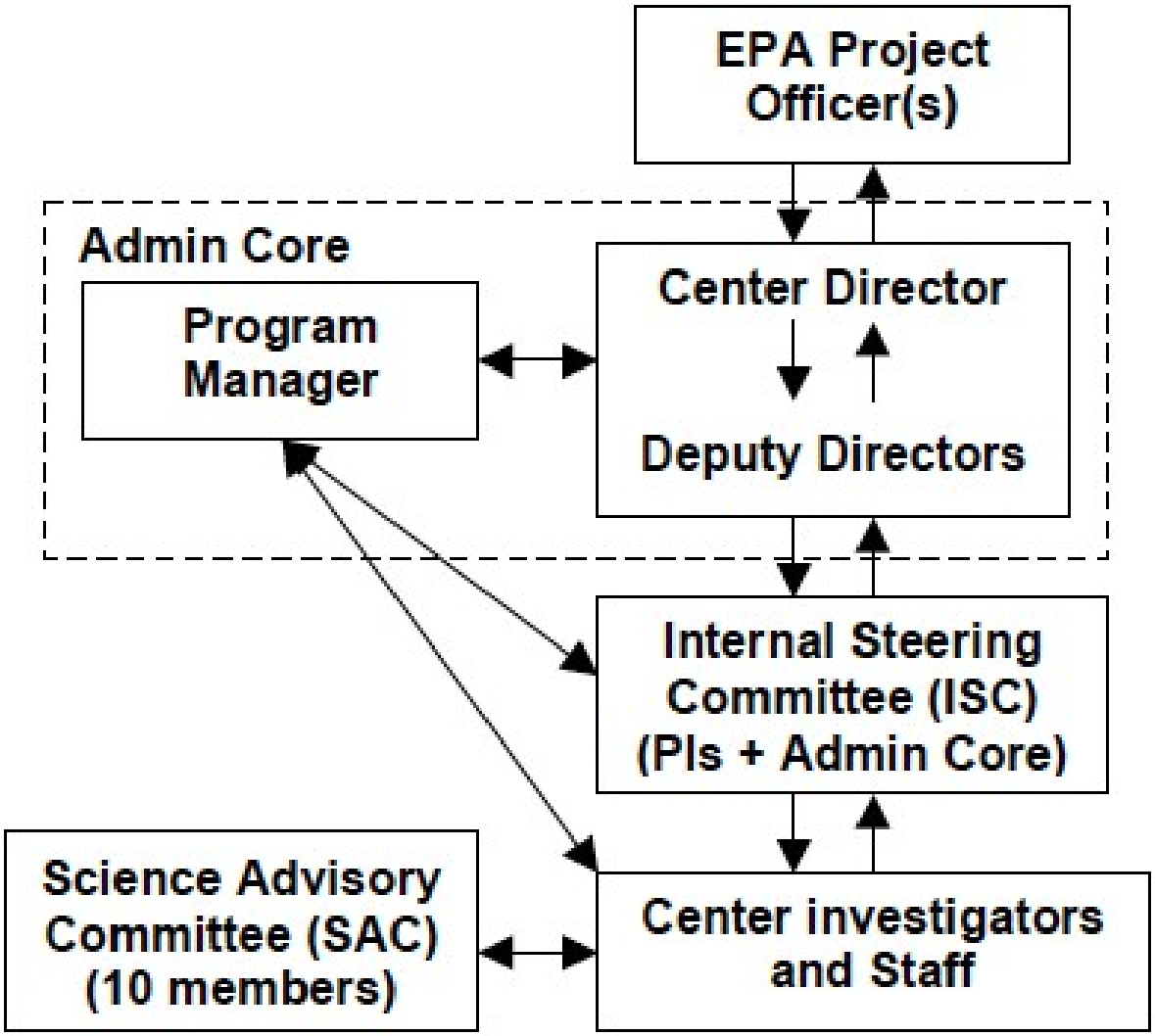
Biostats Core

Admin Core



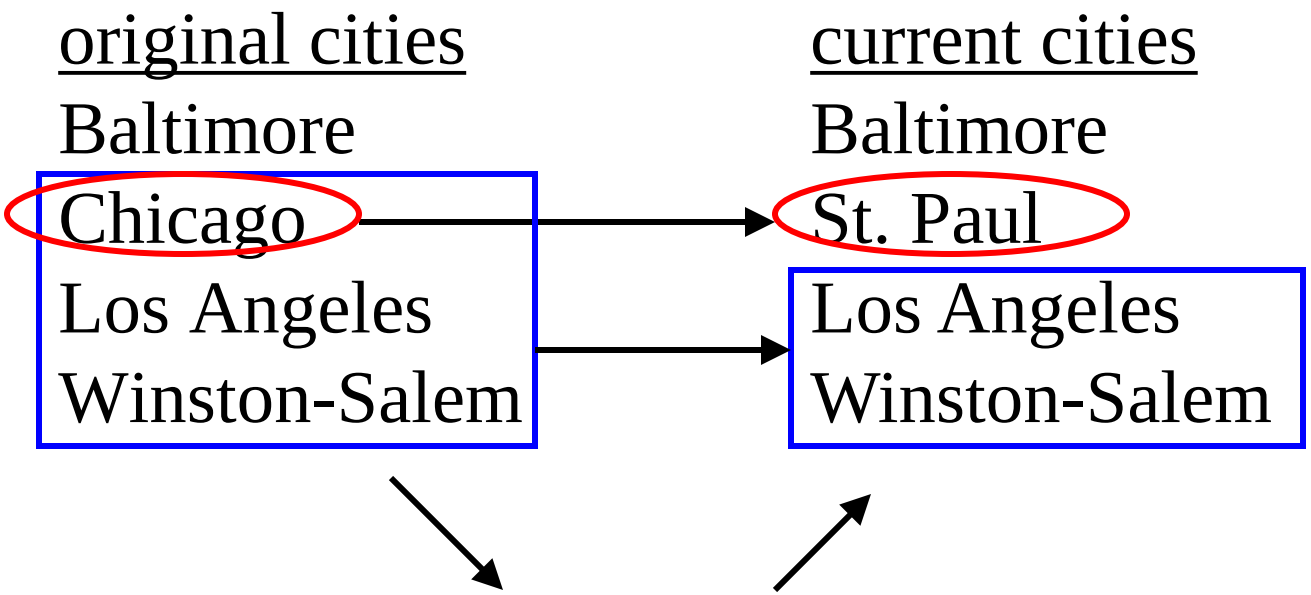
"more than the sum of its parts"

CCAR administrative structure



a heads up: switch of MESA cities

Mobile monitoring



DNA methylation data
Baltimore
New York
St. Paul
Winston-Salem

personal monitoring

CCAR Science Advisory Committee

exposure and atmospheric science	Michael Brauer (UBC) Tom Peters (U Iowa) Barbara Turpin (Rutgers)
toxicology	Ian Gilmour (EPA) Jake Lusis (UCLA) Sanjay Rajagopalan (Ohio State)
human clinical / epidemiology	John Balmes (UCSF) - chair Nick Mills (U Edinburgh) Arden Pope (BYU)
biostatistics	Brent Coull (Harvard)

CCAR SAC agenda

Monday

- introductions
- individual project/core presentations & discussions

Tuesday

- SAC “quiet time”
- SAC feedback to CCAR investigators
- optional exposure facility tour

other items - lunch, washrooms, dinner

CENTER FOR CLEAN AIR RESEARCH

UNIVERSITY *of* WASHINGTON

EPA Clean Air Research Center
Project 1:Exposure Mapping –

Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies

Lead Investigator: Michael Yost, UW
Co-Investigators: Tim Larson, Chris Simpson, UW
Tom Jobson, Tim VanReken, WSU

Objectives

- (1) Characterize multi-pollutant spatial gradients in four MESA cities
  - Mobile monitoring in four cities over two seasons
    - St. Paul, Baltimore, Los Angeles, Winston-Salem
    - heating & non-heating season – focus on TRAP*; examine possible confounding by wood smoke/biomass component
  - Concurrent fixed site monitoring (active and passive)
    - Provides fixed real-time data to complement mobile platform
    - Provides 2-week time-average spatial surfaces – complements MESA data
- (2) Characterize near-source downwind aging of traffic related air pollutants
  - (2a) Physical (and chemical?) aging using mobile platform
    - Changes in gas phase components (O_3 NO_x, HC) and particle size distribution
  - (2b) Chemical aging using laboratory mixtures
- (3) Provide detailed laboratory characterization of diluted and aged engine exhaust mixtures available for toxicology testing

Field measurements in red

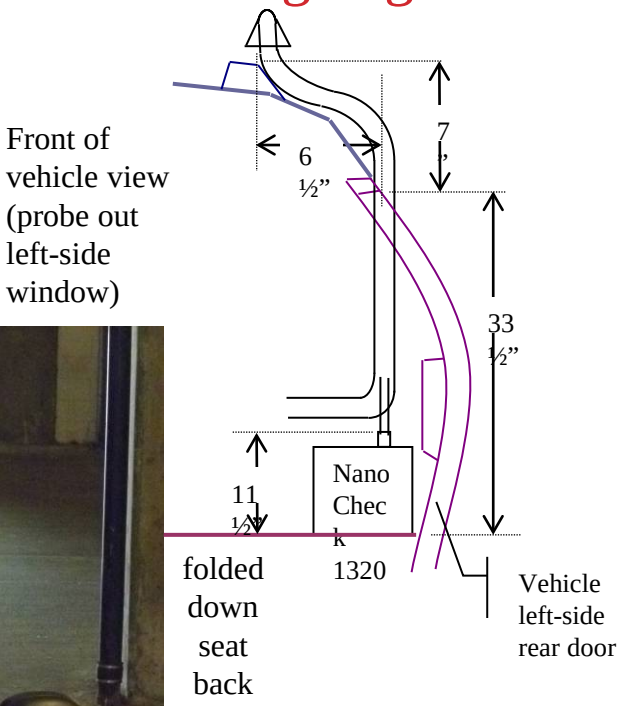
*traffic related air pollution

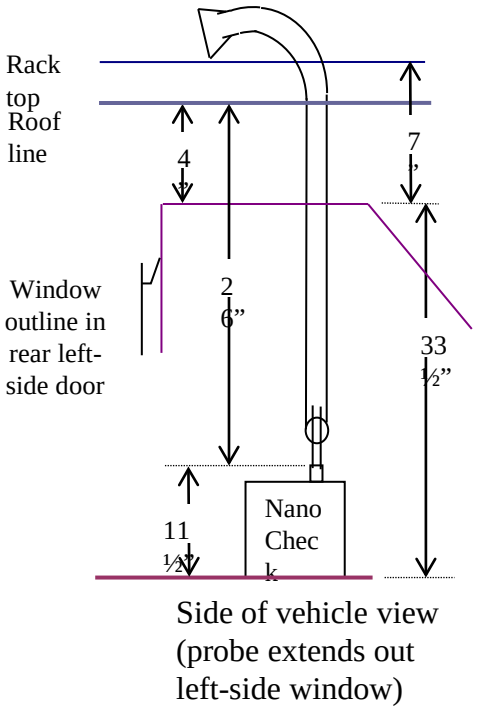
Mobile Platform - Approach

- Based on prior studies completed in Vancouver BC and Tacoma WA
- Capture multi-pollutant components in evening commute
  - Spatially-resolved ~30-sec avg of pollutant components
  - Distributional properties of components at “fuzzy points”
  - Uses concurrent real-time data at a fixed-site to capture temporal variations
- Sampling scheme
  - ~ 10 sampling days per season (two week periods)
  - Heating & non-heating to capture major seasonal changes
  - Divide each city into 3 sectors & fixed routes – based on participant locations and prior MESA sample data
  - Establish ~15 fuzz points per route (43 spatial locations)
  - Randomize route and travel direction for each sample

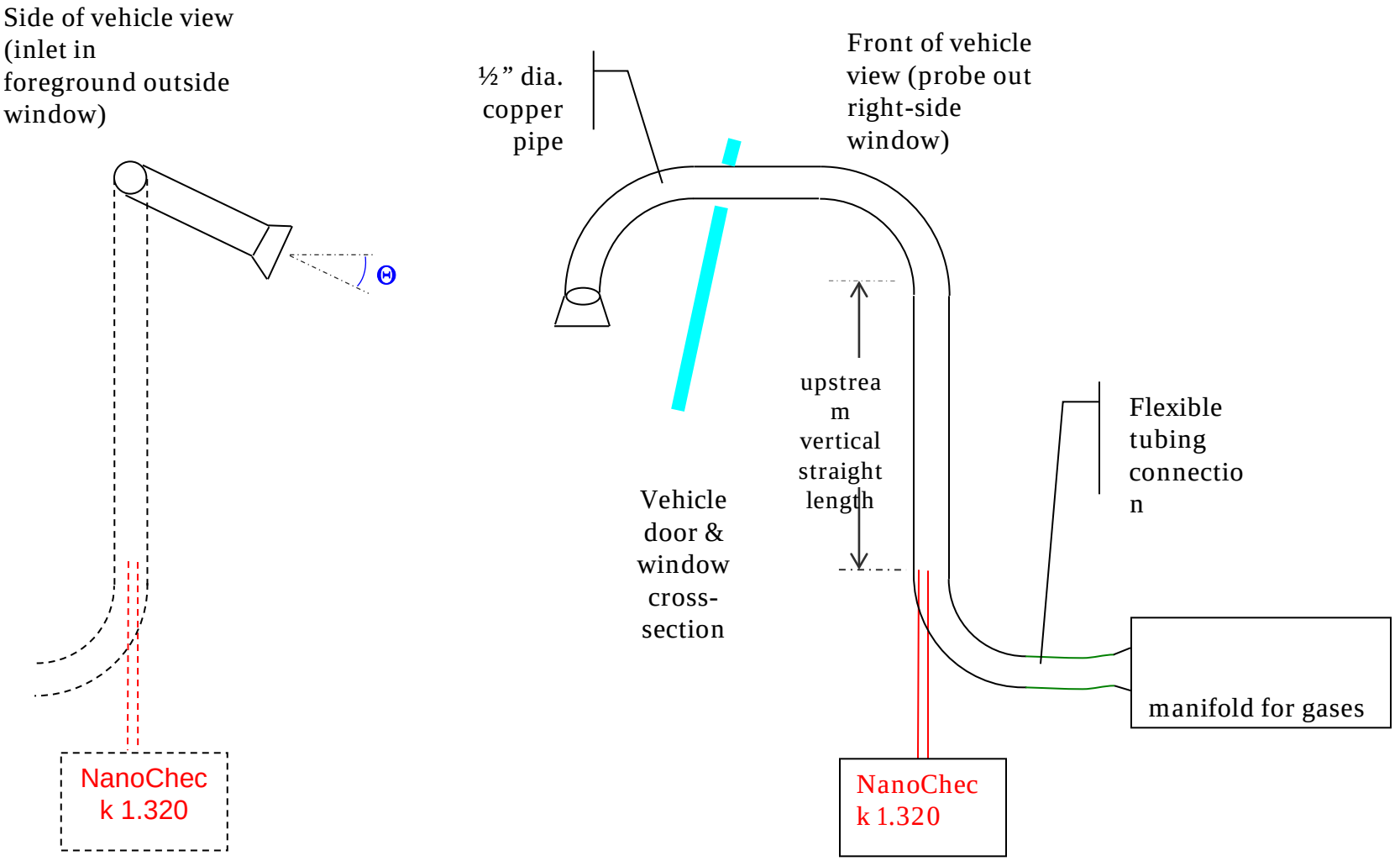
Mobile Platform

- Use Escape hybrid vehicle in all cities
  - Sample inlet attached to roof rack; matched to ~25 mph speed
  - Instrument package; samples drawn from common manifold
  - Data vector: 10-sec moving avg for all components, + position





Sample manifold detail

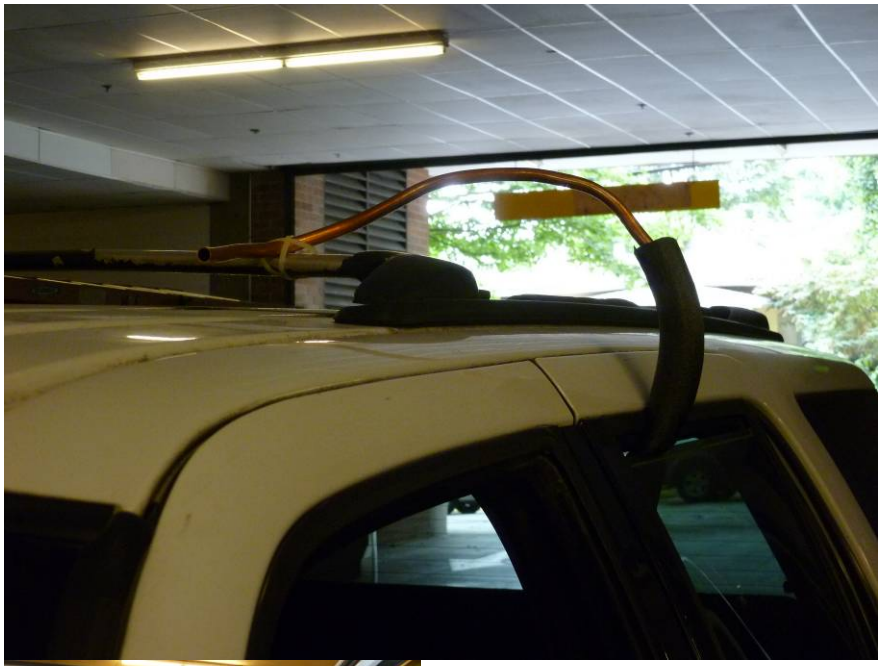


Mobile Platform Instruments

Instrument	Measurement	Mfg.
Nephelometer	PM 2.5 (scatter)	Radiance
PAS 2000CE	Particle PAHs	EcoChem
PTRAK w Diffusion Screens	Particles >30 nm	TSI
micro-Aethalometer AE52	Particle Black Carbon	Magee Scientific
Aerosol Spec. 1.109	Particles 0.25-32um (32 bins)	GRIMM
Aerosol NanoCheck 1.320	Particles 25-300 nm (count/size)	GRIMM
Ozone 3.02 P-A	O_3 (H-C insensitive)	Optec
NO 410	NO	2B Technologies
NO 410& NO2 Converter	NO_2	2B Technologies
Langan CO Monitor T15N	CO (ppb)	Langan
CO Sensor EC100 Sensor	CO	CO2Meter.com
PPB-PID	Ioniziable Hydrocarbons	Photovac
K30-1%-Fast Response CO2 Monitor	CO_2	CO2Meter.com
Integrated GPS Logger	Position & speed	GlobalSat

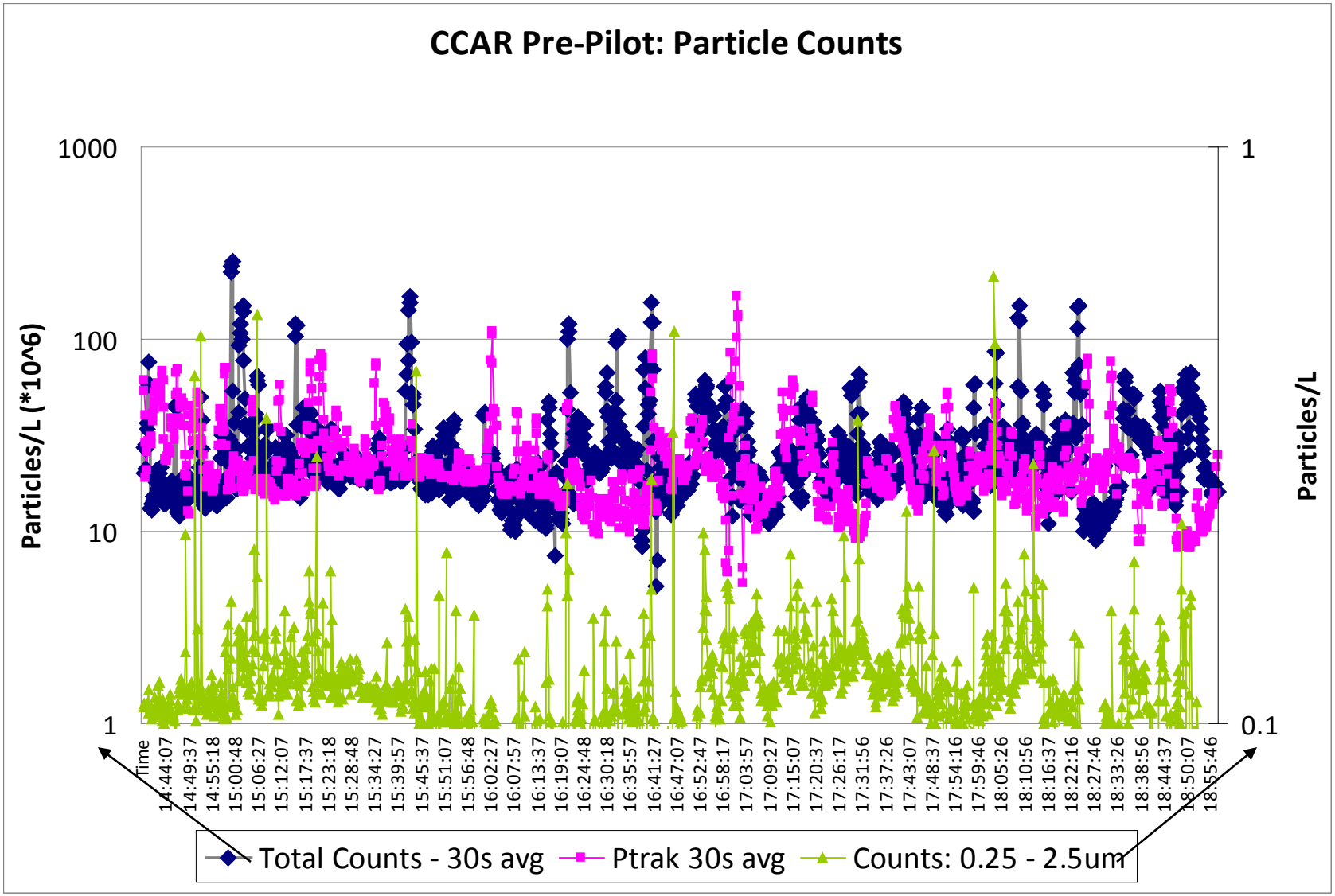
Measurement Vector: 50 parameters (6 gas, 40 particle)

Pre pilot testing, August 2011

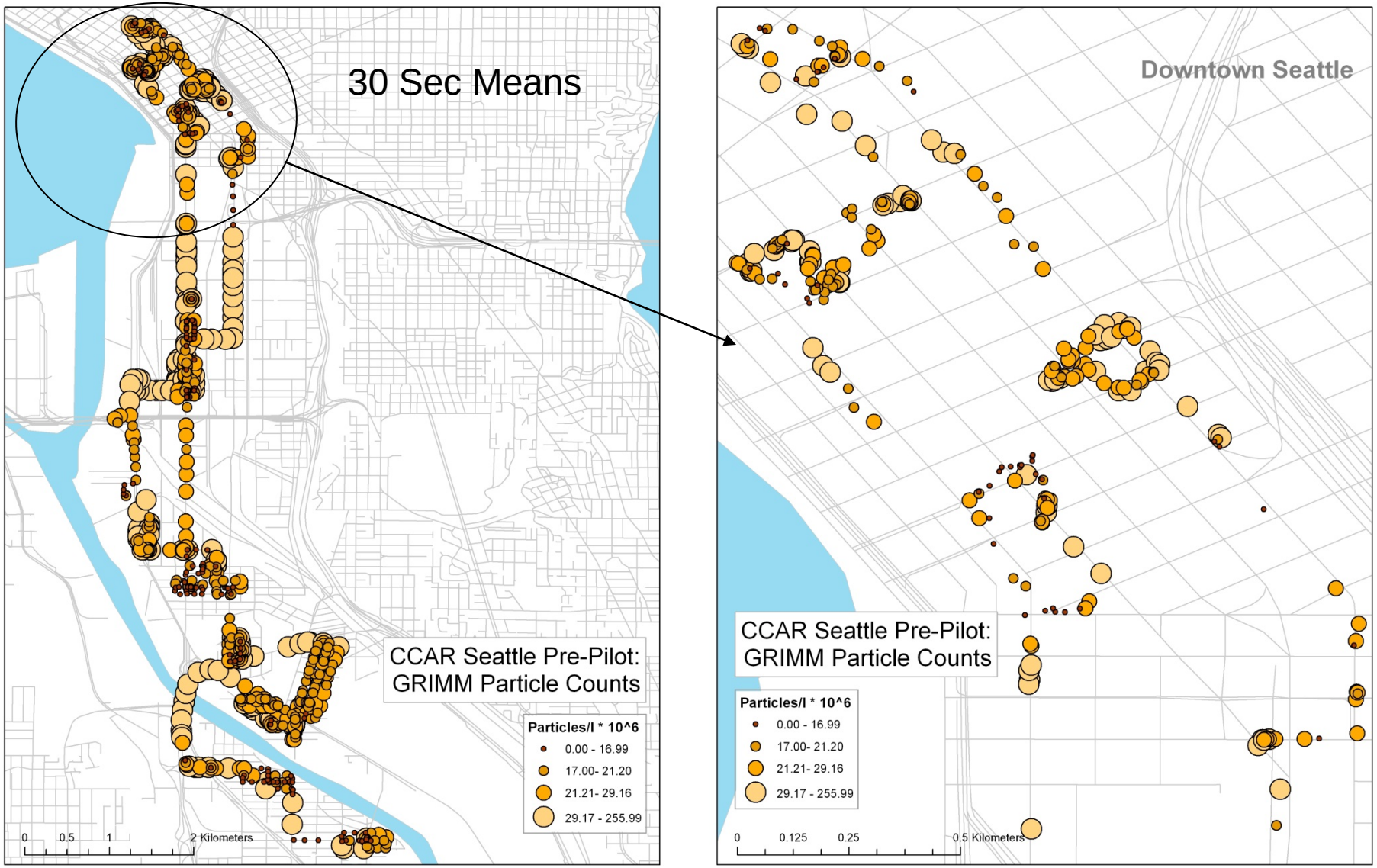


UW CCAR Project 1_Prepilot_Tape 1 of 3_081111.wmv

Pre-pilot testing: time series data



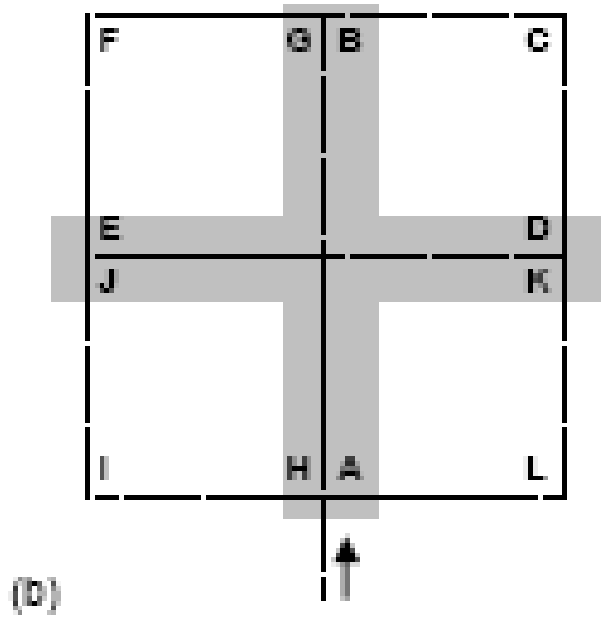
Pre-Pilot: Spatial data overlay



Mobile Platform Analysis

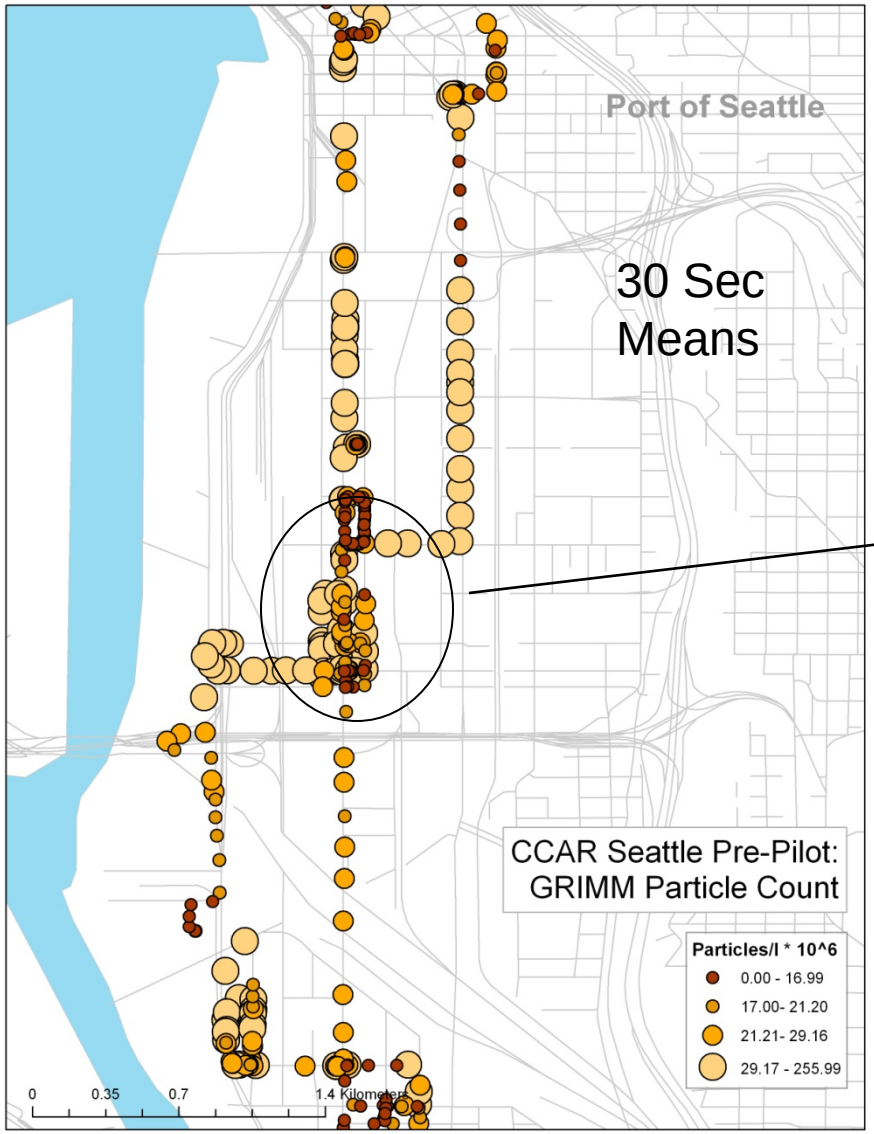
Traffic Intersections as “Fuzzy Points”

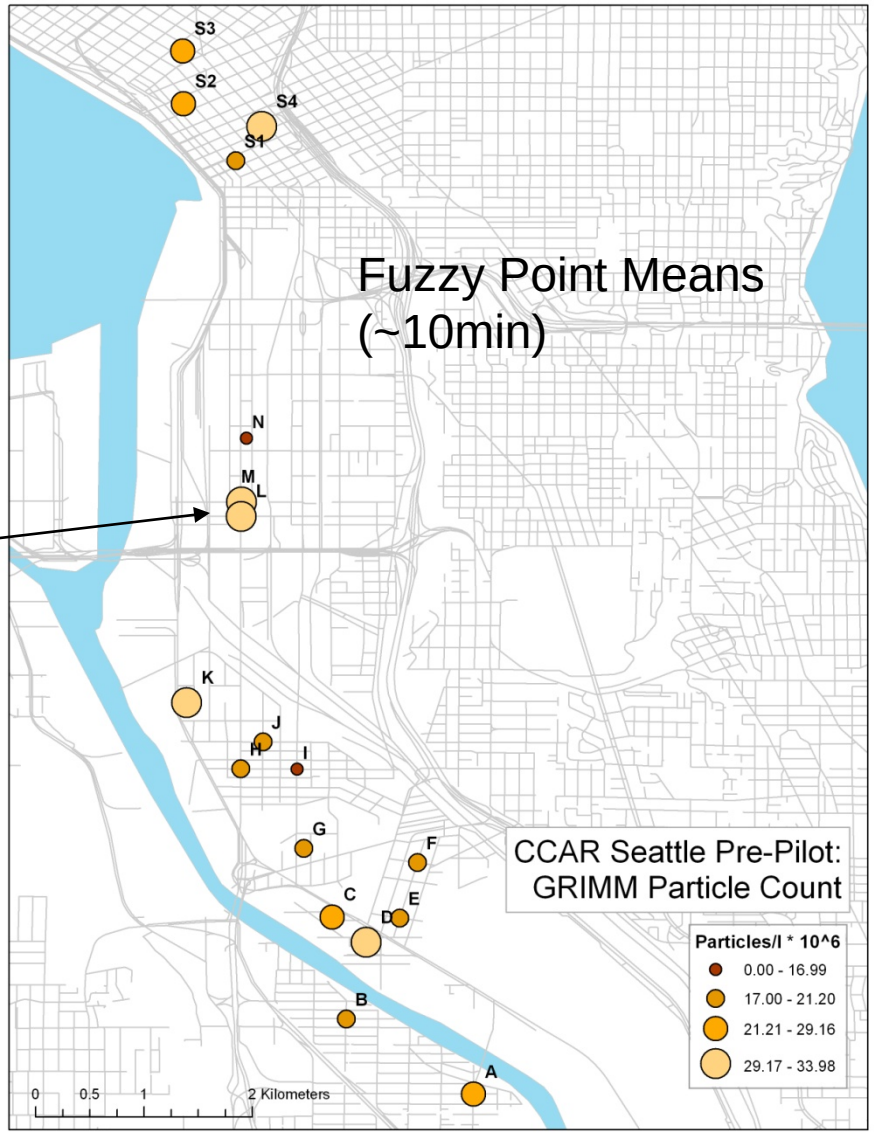
- Measure pollutant marker (e.g. σ_{ap}) at selected traffic intersections during peak afternoon traffic period
- Trace a cloverleaf / figure 8 at each intersection (~5-8 minutes)
- Determine the distribution of 30-sec values within each fuzzy point



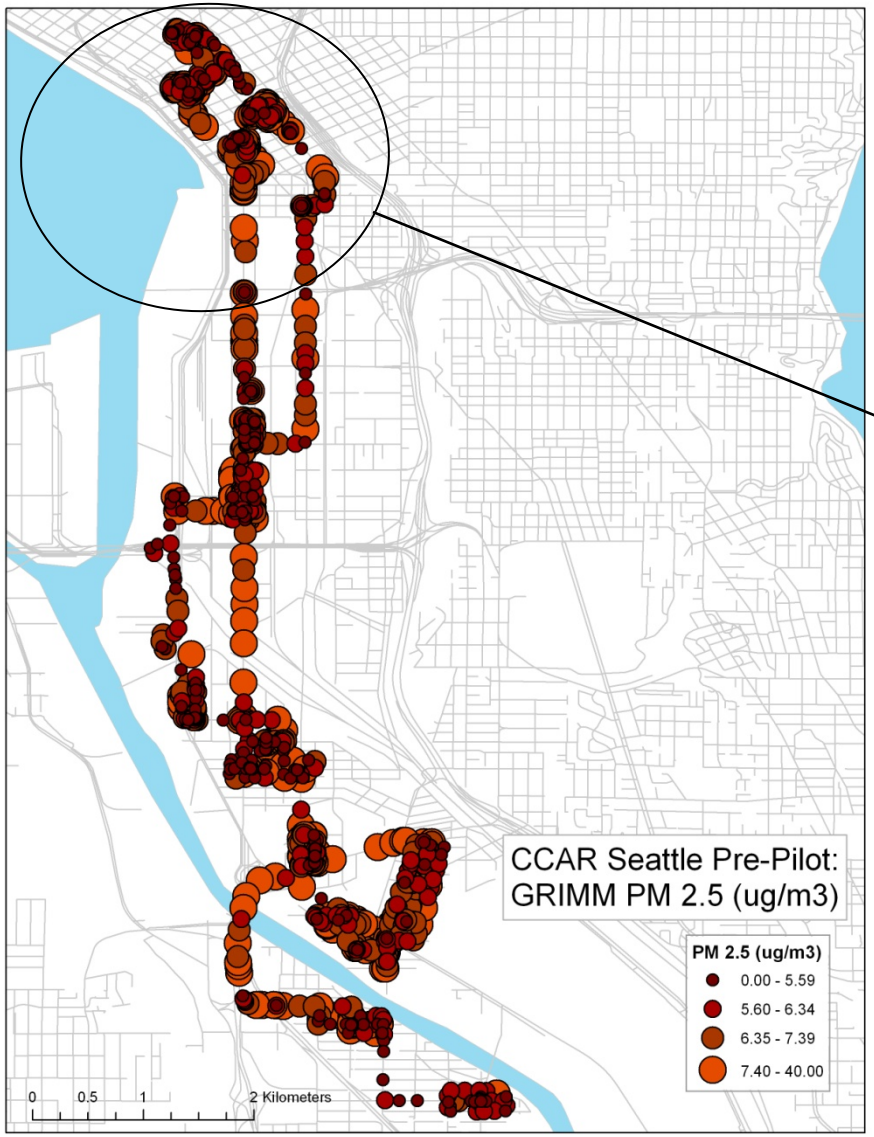
$$\text{Adjusted reading} = \frac{\text{Observed 30-sec average from mobile platform}}{\text{30-min moving average from fixed site}}$$

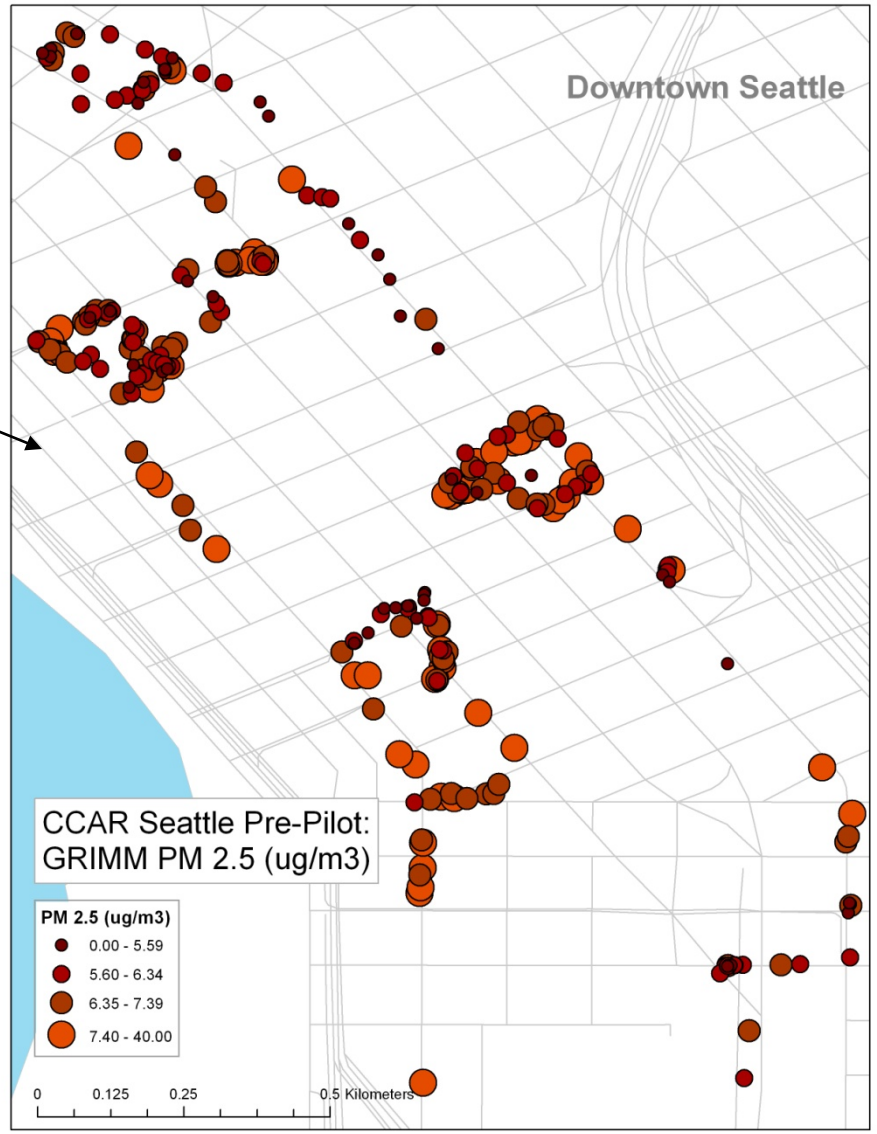
Fuzzy Points - Detail Maps





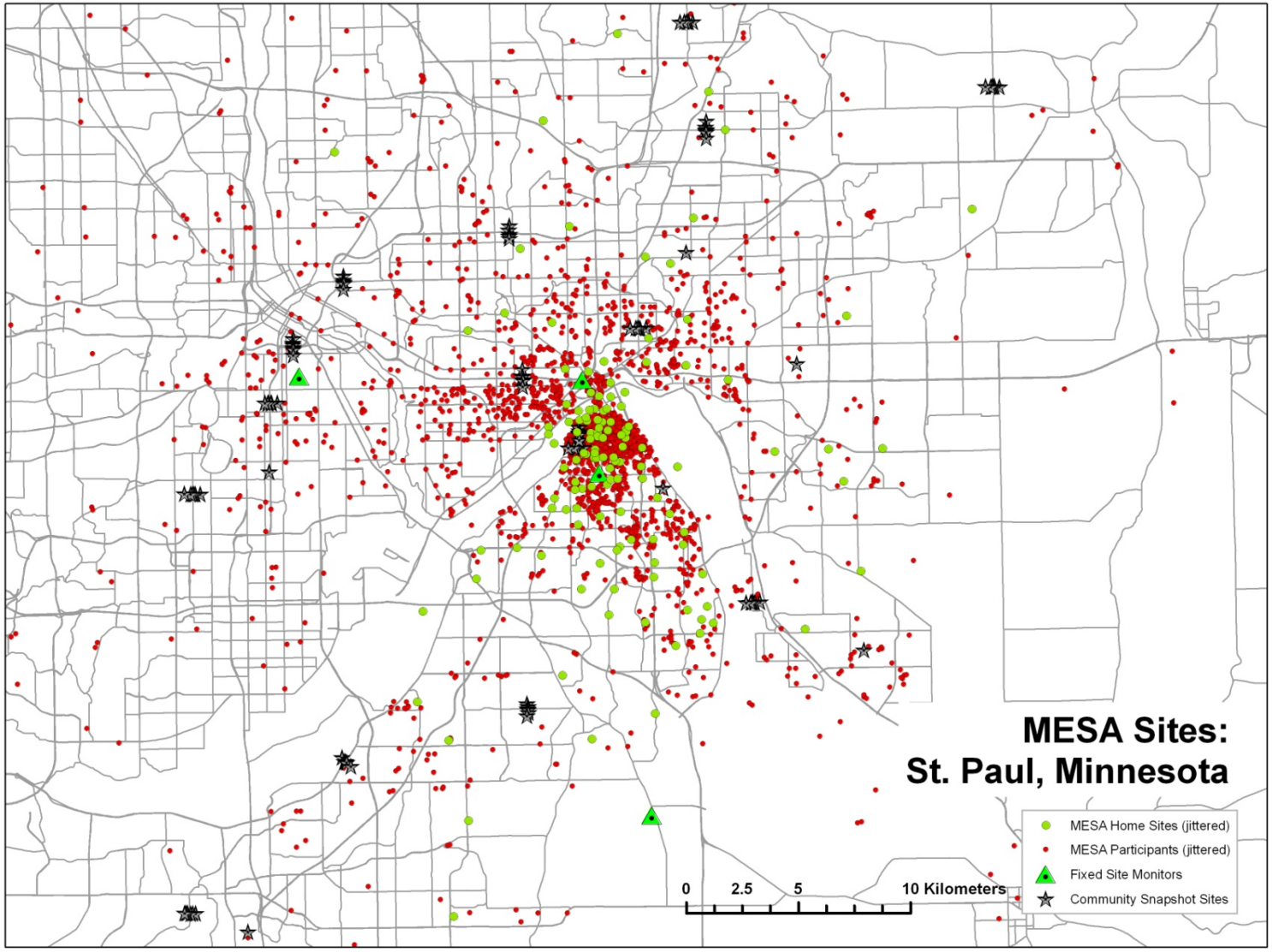
PM2.5 mass (estimate)



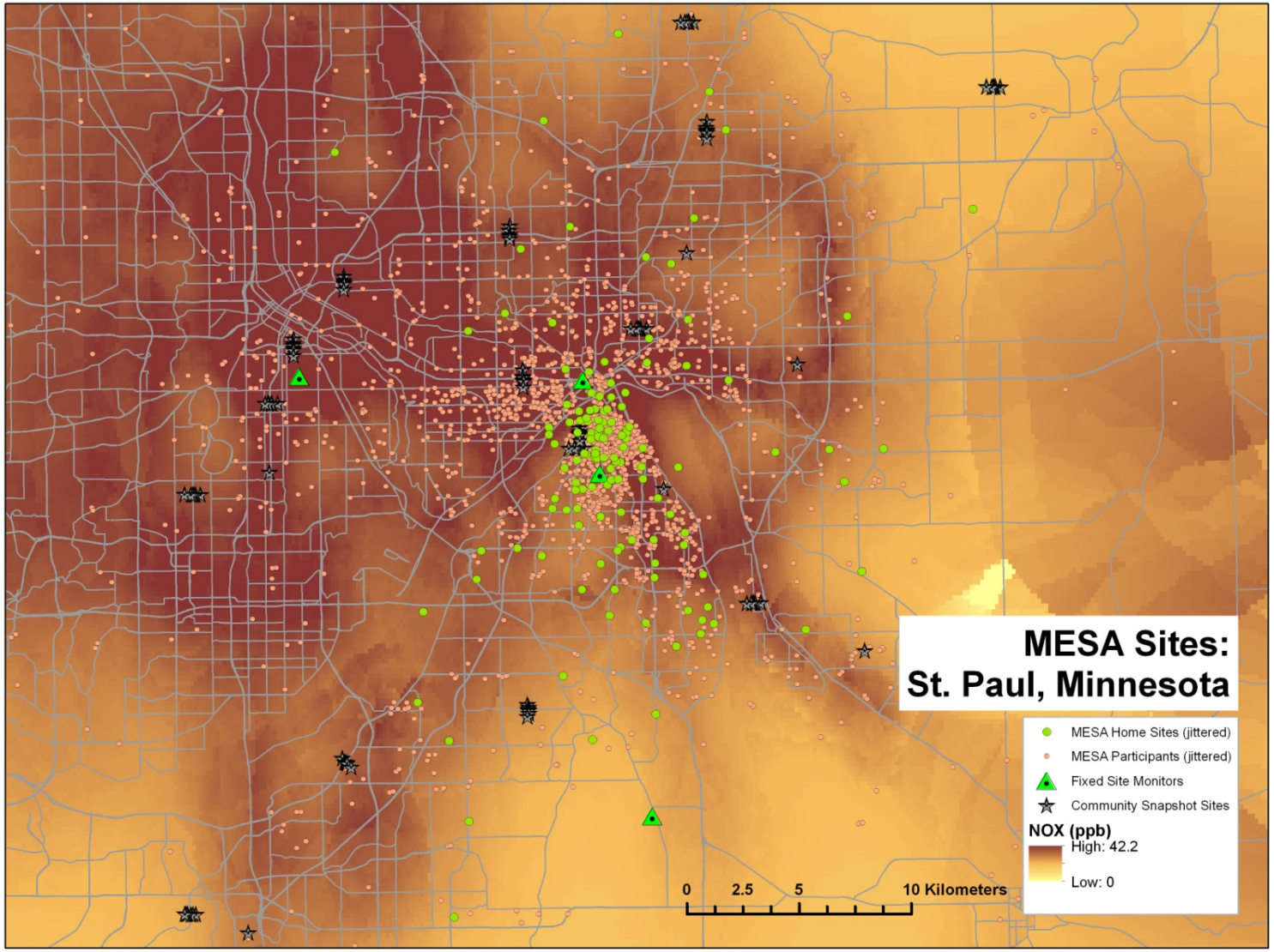


Pre-Pilot testing

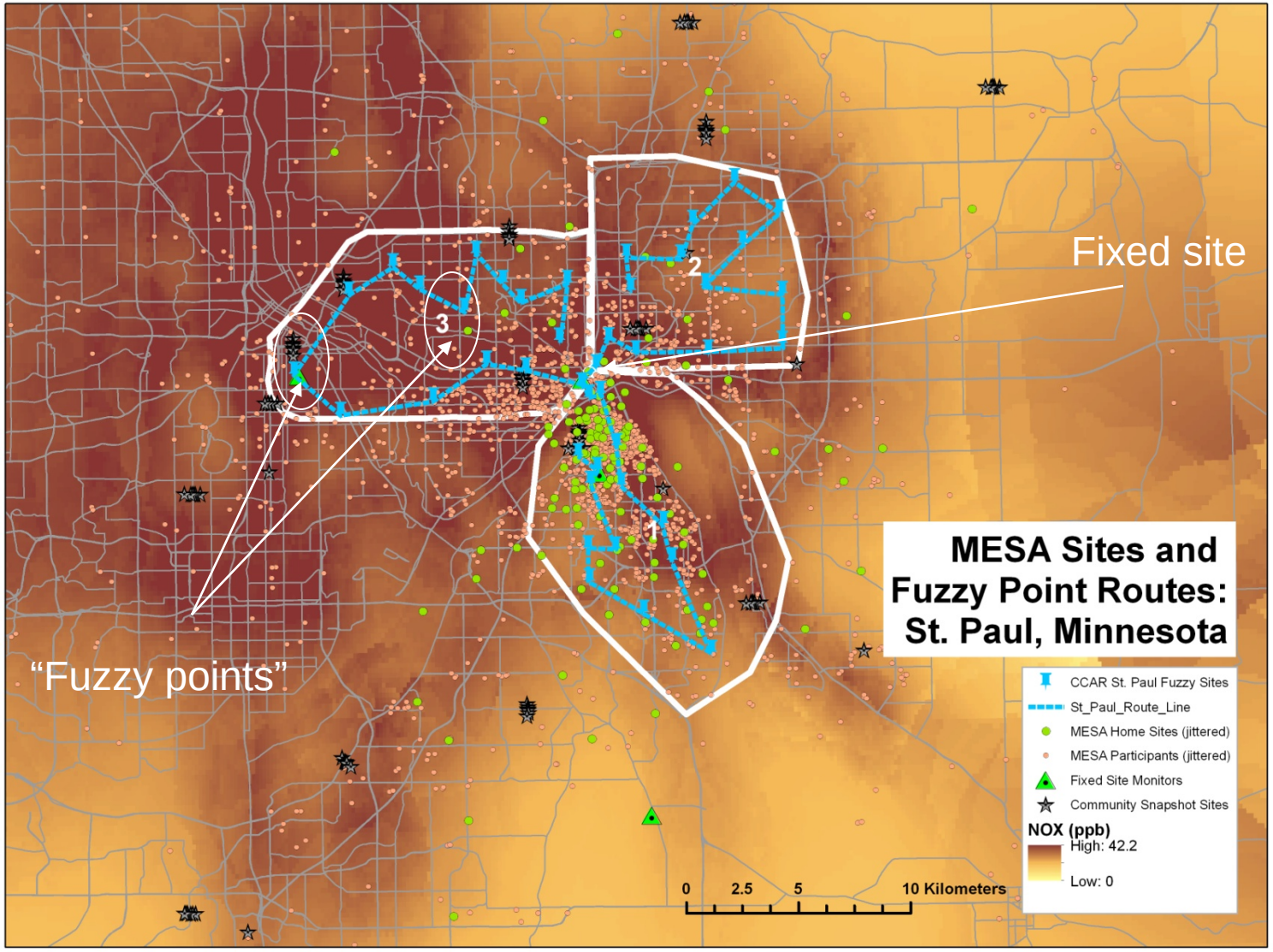
St. Paul MESA sites



St Paul NO_x Surface



St Paul Route Selection



Passive Sampling at Fixed Sites

- Same four MESA cities
- ~43 sites per city
- 2-wk averages
- 2 seasons (heating, non-heating)
- Located at “fuzzy sites”
- Near MESA subject residences
- Compare with exposure laboratory characterization

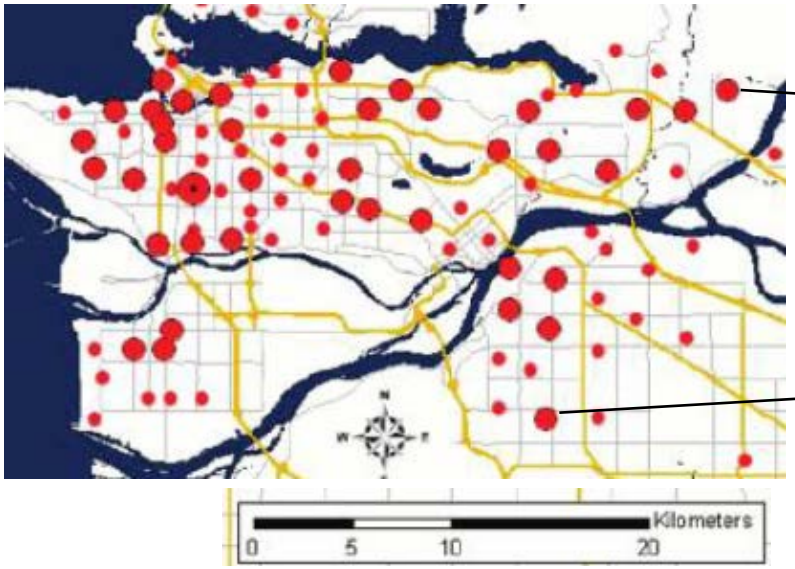
Compound
Benzene Isoprene Toluene
N-Decane
Nonane
2-methylpentane
M-Xylene
Undecane
i-Pentane
N-Pentane
O-Xylene

Proposed Sampling Schedule

Activity	Study Period	Location
Pre-Pilot Testing	Aug, 2011	Seattle
Pilot Testing	October, 2011	Seattle
Field Sampling	Nov 28, 2011	St. Paul
Field Sampling	Jan, 2012	Baltimore
Lab Characterization I	April, 2012	Albuquerque
Field Sampling	June, 2012	Baltimore
Field Sampling	Aug, 2012	St Paul
Lab Characterization II	Oct, 2012	Seattle
Field Sampling	Jan, 2013	Winston-Salem
Field Sampling	Feb, 2013	Los Angeles
Field Sampling	June, 2013	Winston-Salem
Field Sampling	Aug, 2013	Los Angeles

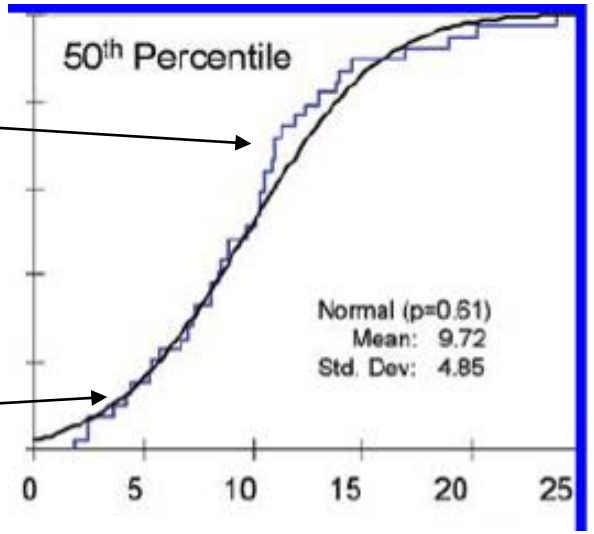
Observed properties of the “fuzzy” points (one observation per site)

Vancouver, BC



All sites

Observed 50th percentiles



σ_{ap} (10^{-6} m^{-1})

LUR Model Predictions of 50th Percentile Values

Vancouver, BC

c.v. $R^2 \sim 0.7$

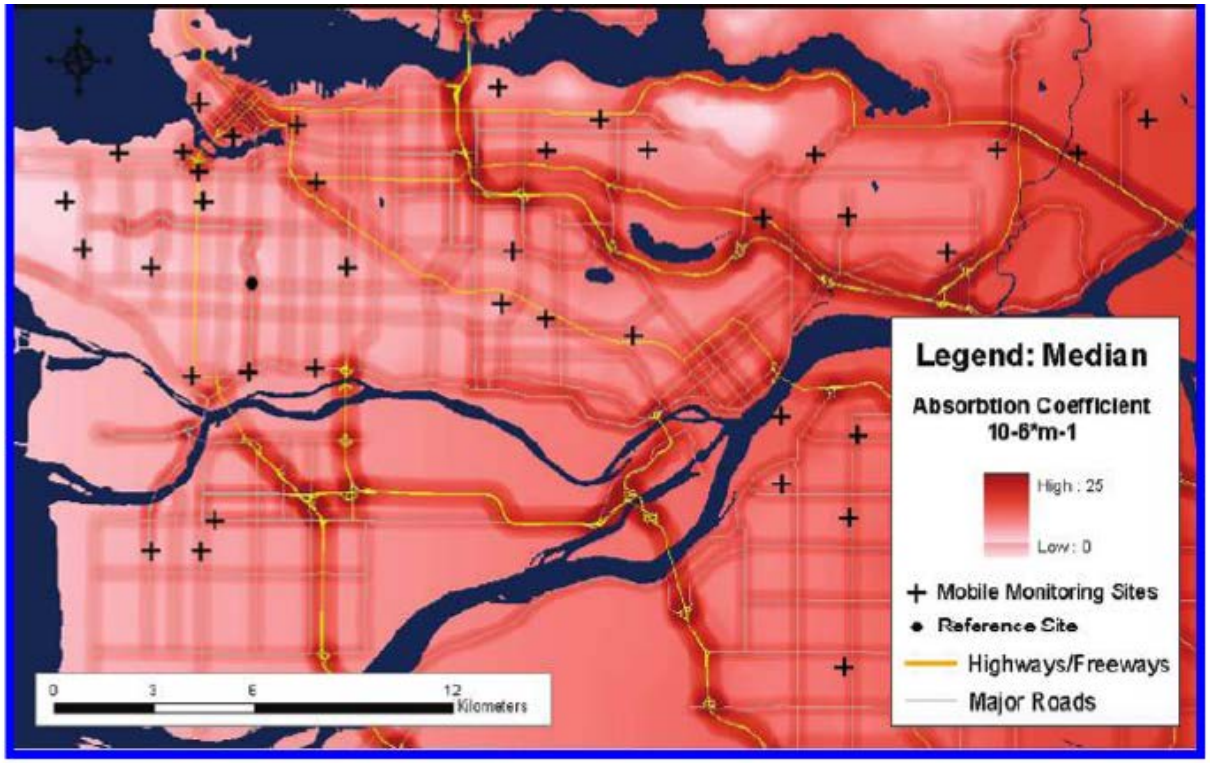
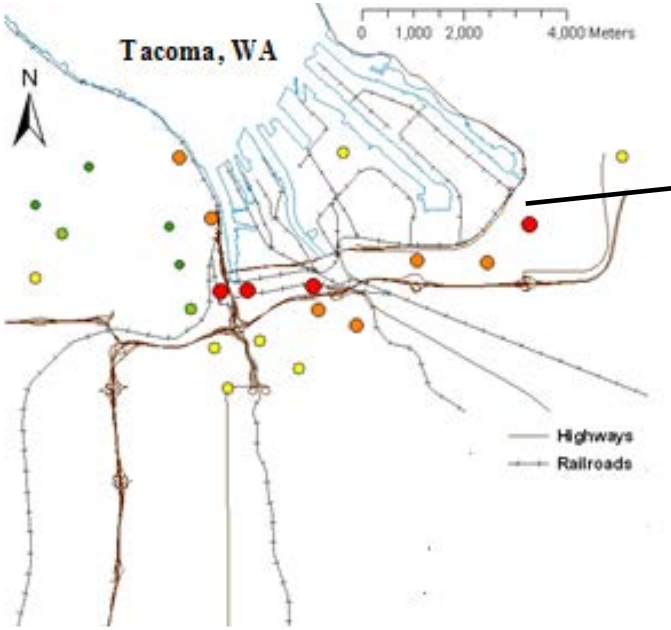


FIGURE 4. Map depicting land use regression model for median σ_{ap}, as reported in Table 1.

Larson T.V., Henderson, S.B., Brauer, M. (2009) Mobile Monitoring of Particle Light Absorption Coefficient in an Urban Area as a Basis for Land Use Regression *Environmental Science and Technology* 43(13), 4672-4678.

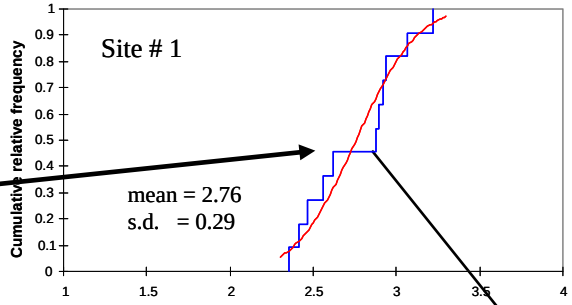
Repeated Sampling improves long-term estimate

Observed median values at each intersection over repeated days in summer and winter in Tacoma, WA



σ_{ap} Site # 1

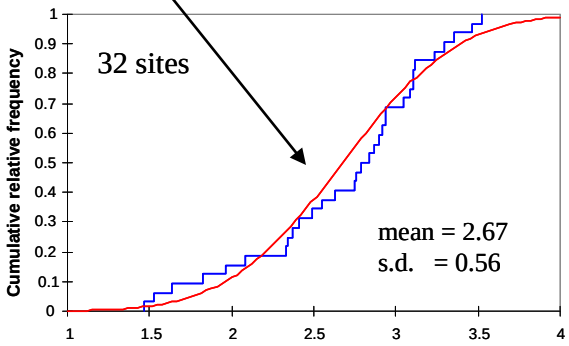
Distribution of 50th percentiles



$$\ln\left(\sigma_{ap}^{50th}\right)$$

σ_{ap} All sites

Site mean 50th percentiles

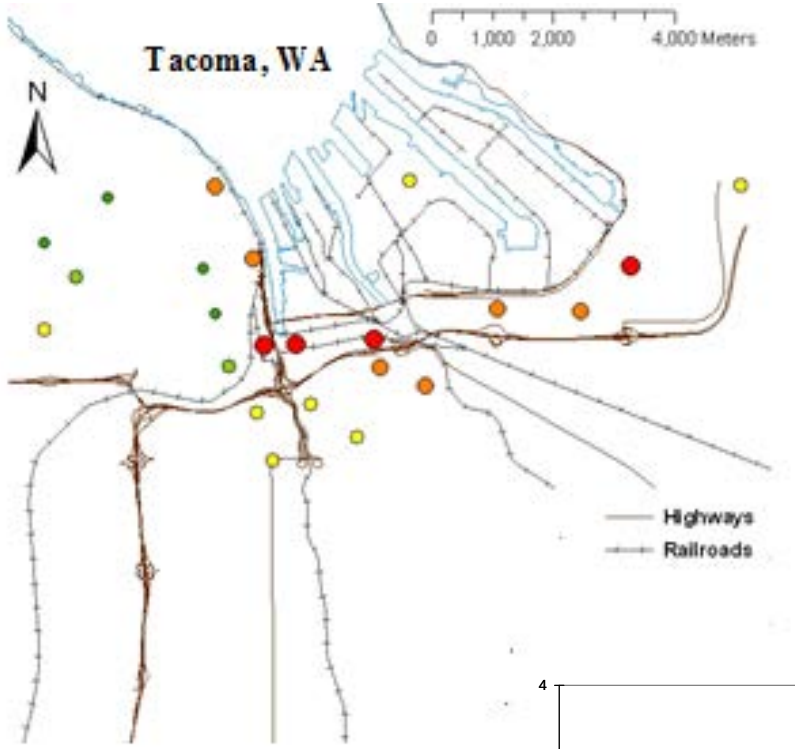


$$\text{mean}\left[\ln\left(\sigma_{ap}^{50th}\right)\right]$$

Park et al (in preparation, 2011)

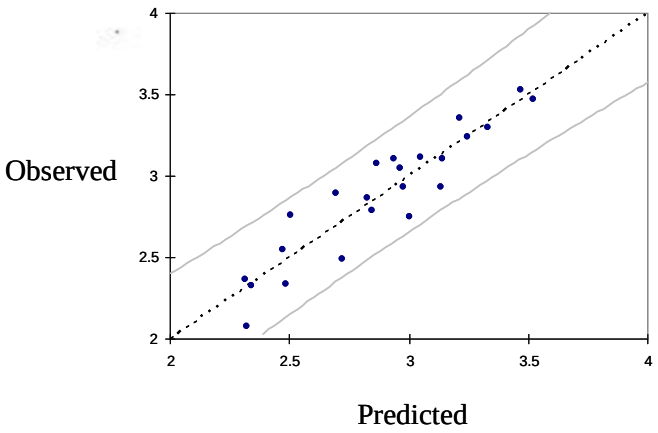
Improved LUR model

σ_{ap} Predictive Model



Variable	
Railroad within 300 m	+
Freeway within 300 m	+
Population density within 1000 m	-
Freight Routes within 300 m	+
c.v. $R^2 = 0.83$	

$$\text{mean}\left[\ln\left(\sigma_{ap}^{50th}\right)\right]$$



Park et al (in preparation, 2011)

Multivariate data reveals sources

Principal Component Analysis with subsequent **Varimax** rotation produced three independent, identifiable factors in Tacoma that are a combination of the original variables.

	Factor 1	Factor 2	Factor 3
b_{sp}	0.92	0.18	0.36
PAH	0.17	0.96	0.23
b_{ap}	0.42	0.29	0.86

Woodsmoke

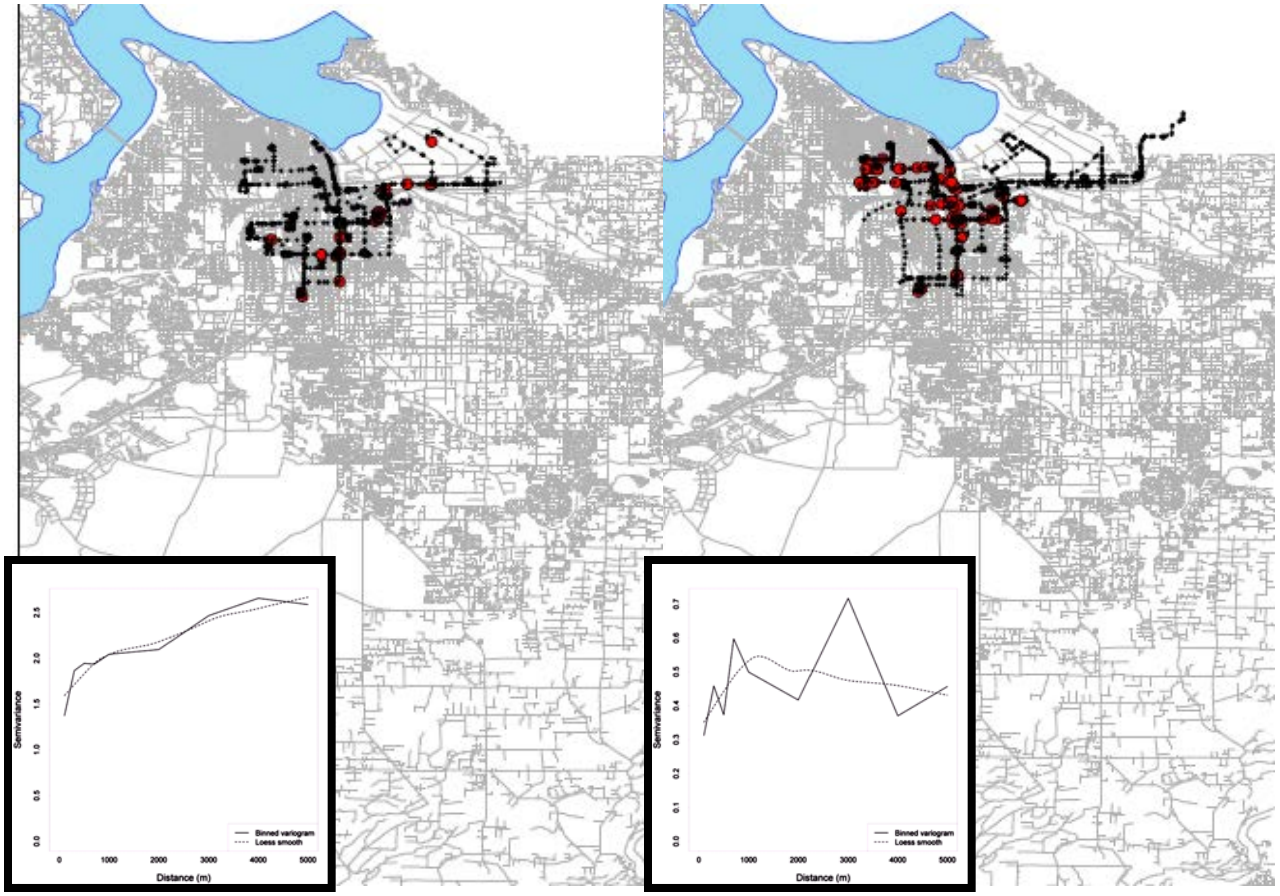
mobile sources

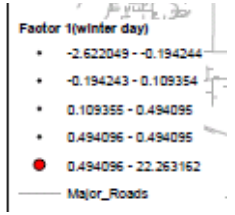
PAH peaks

Factor 1 scores are relatively low in the afternoon in high traffic areas…

Summer

Winter

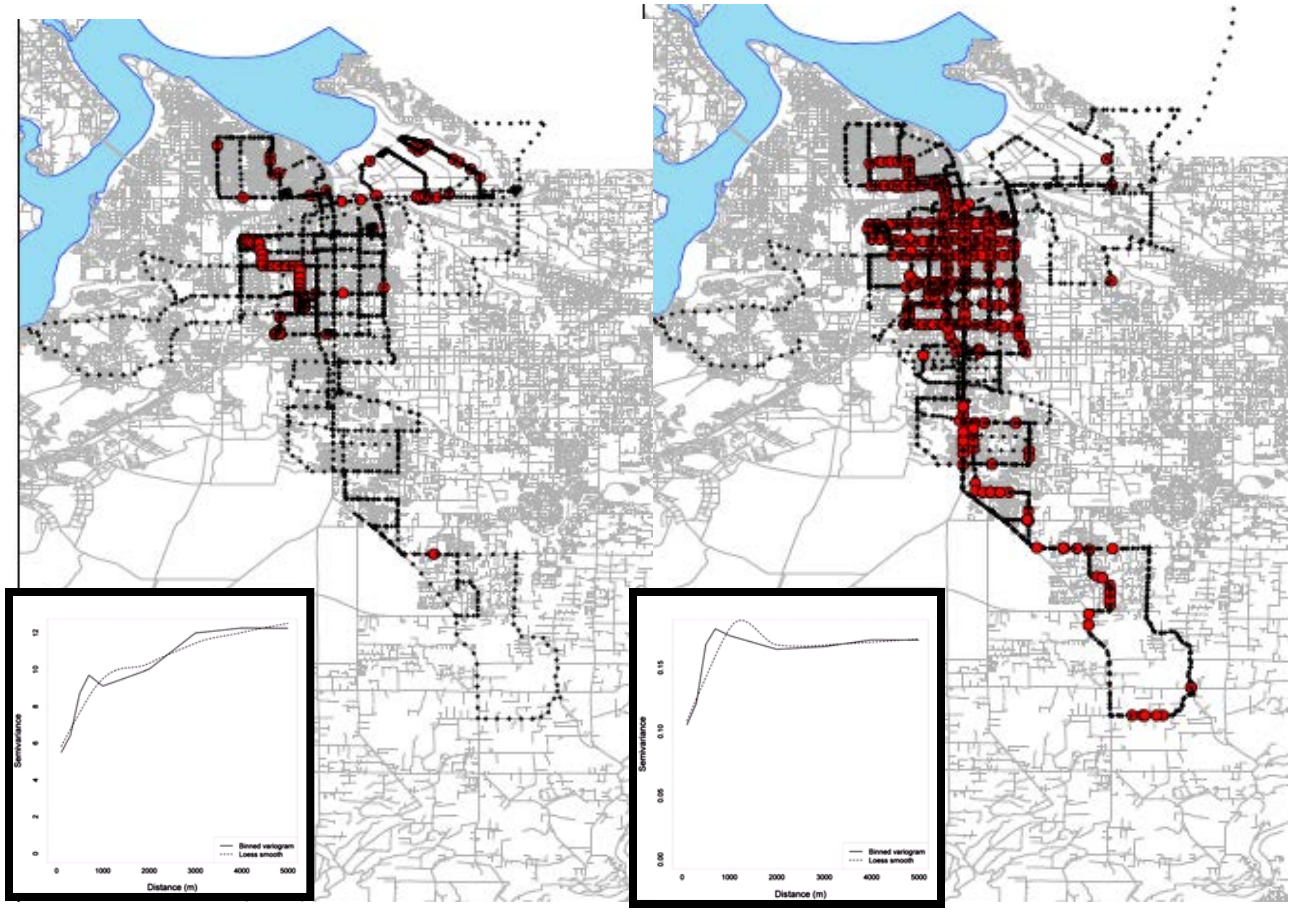




…and relatively high at night in residential areas in winter.

Summer

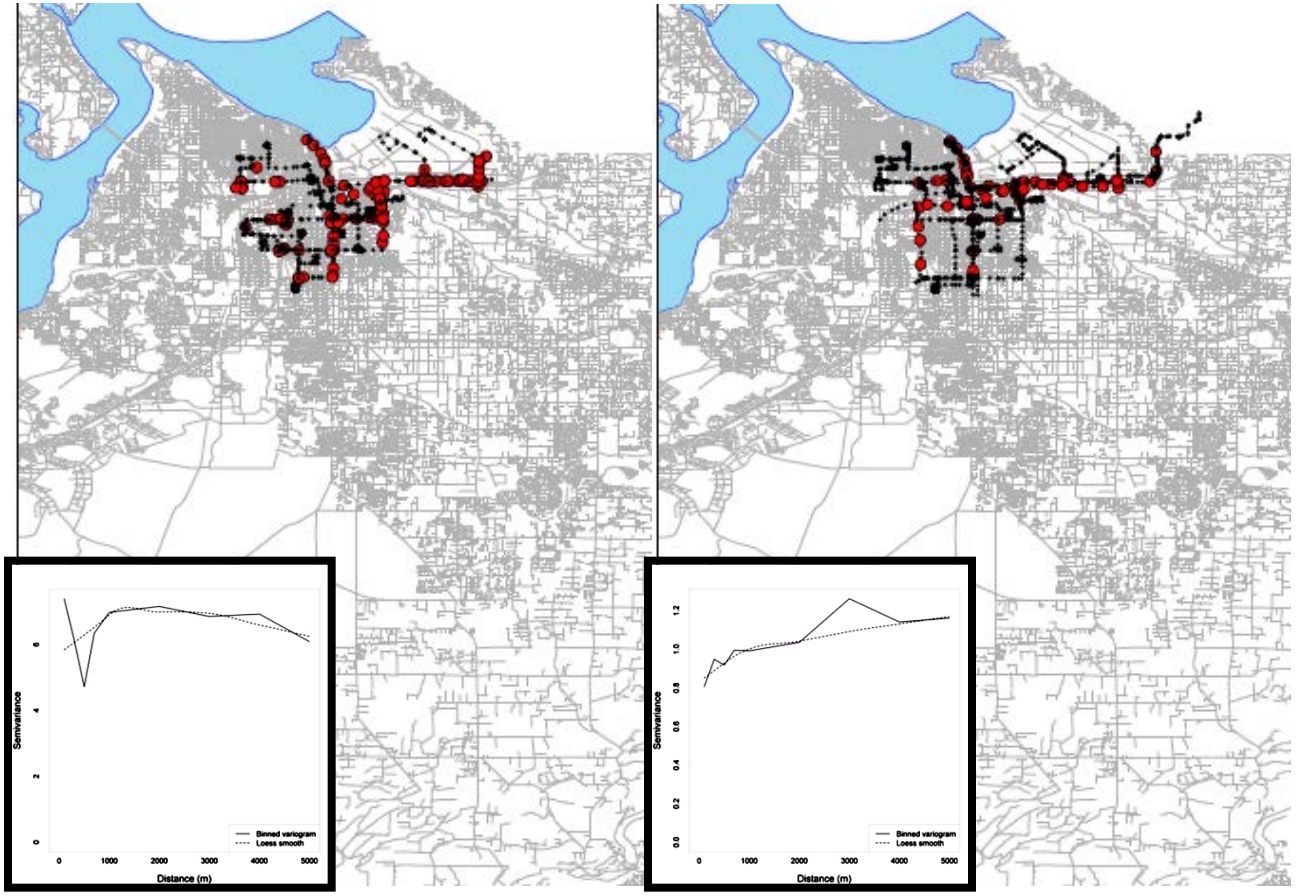
Winter



Factor 3 is relatively high near the busy freeway in the afternoon..

Summer

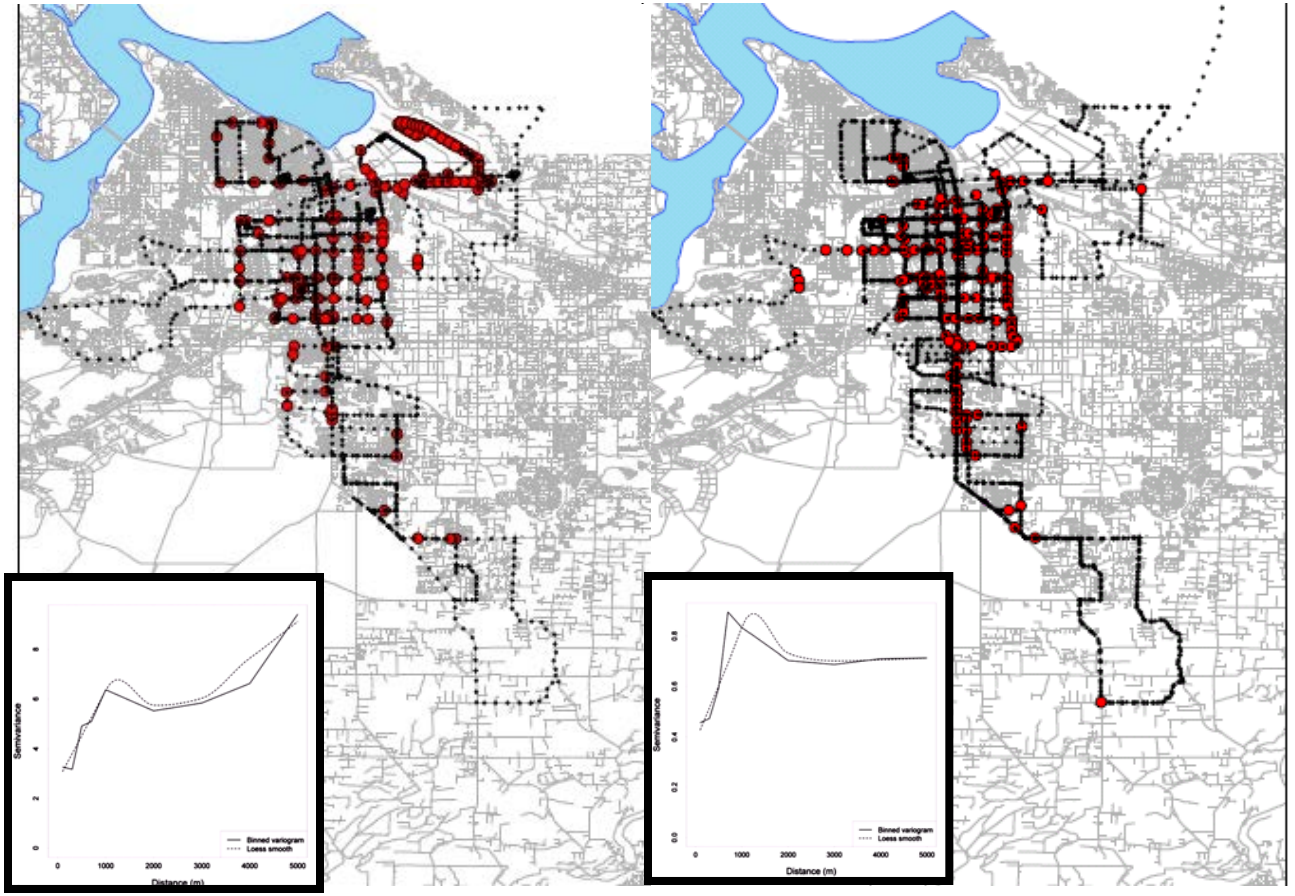
Winter



…and also has high values near high traffic areas at night.

Summer

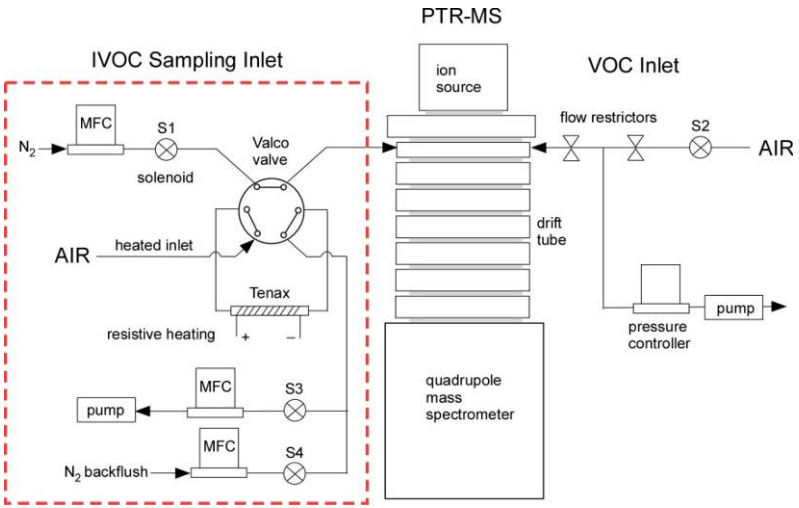
Winter



Characterization of Controlled Laboratory Exposure Atmospheres

- Washington State University
  - Proton Transfer Reaction Mass Spectrometer
  - High Resolution Aerosol Mass Spectrometer
- University of Washington
  - Mobile platform instruments
  - Passive samplers
- LRRI
  - Gas and aerosol measurements (discussed in project 2 presentation)

WSU Proton Transfer Reaction Mass Spectrometer



Measurement principle

$H_3O^+ + R \rightarrow RH^+ + H_2O$

Full mass scans or multiple ion monitoring.

High time resolution possible. Typical ambient operation scan for 30 ions in 1 minute.

Quantitative VOC det. limits ~ 50 pptv.

Two sample modes, alternate between

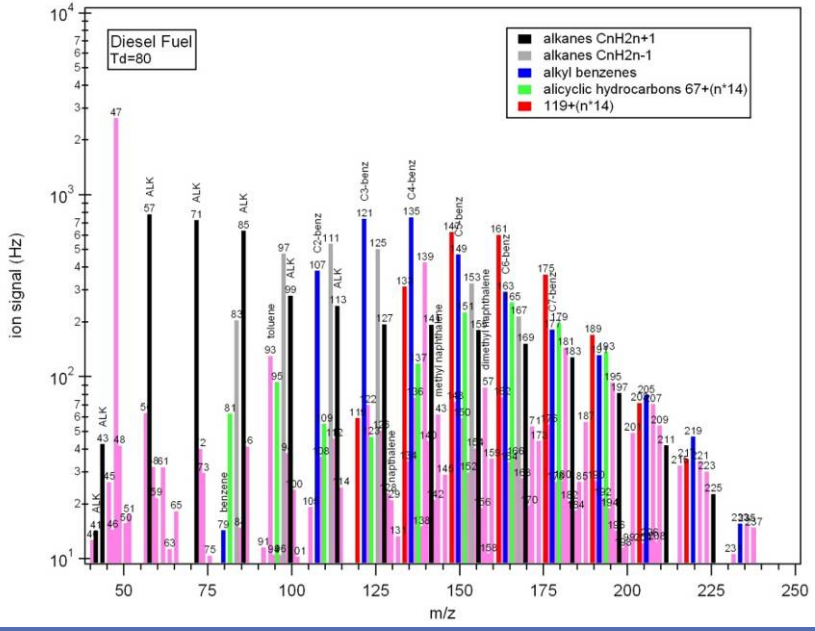
1.VOC Mode:

Formaldehyde
Acetaldehyde
BTEX compounds
Others …

2.IVOC mode:

thermal desorption based sampling for heavier organics emitted in diesel engine exhaust.

long chain alkanes
monocyclic aromatics
polycyclic aromatics



Objective 3

Vehicle Exhaust Emissions - field measurements results from WSU PTR-MS

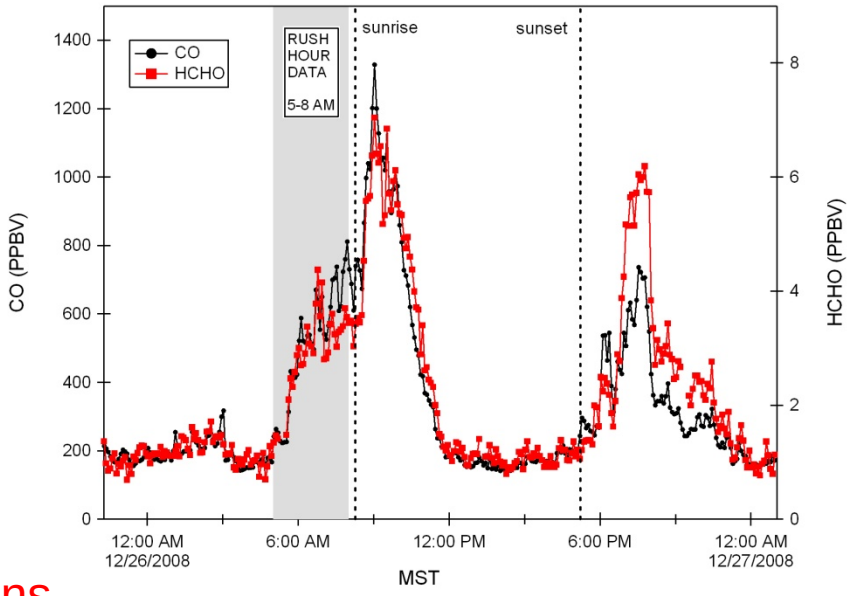
1. Formaldehdye

air toxic

Boise, Idaho: winter HCHO emission rate from vehicles = 0.3% CO emission rate.

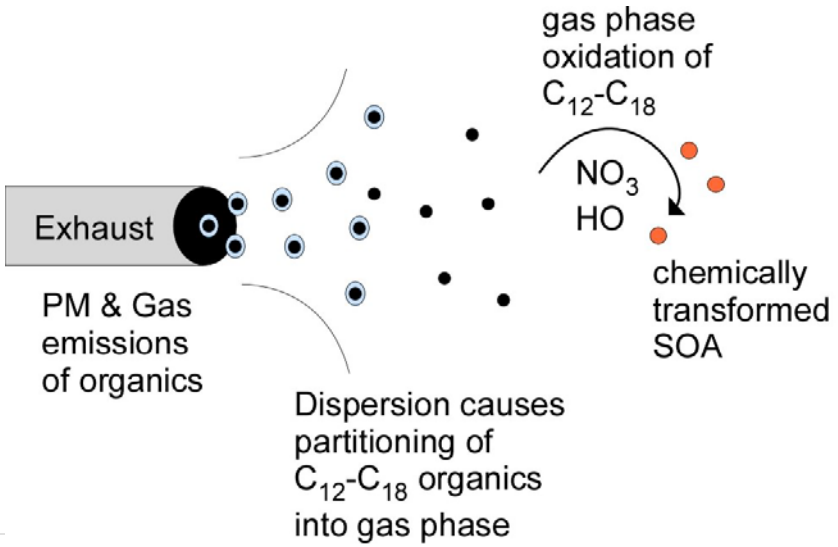
Are off-network emissions from vehicles important sources of urban air toxics?

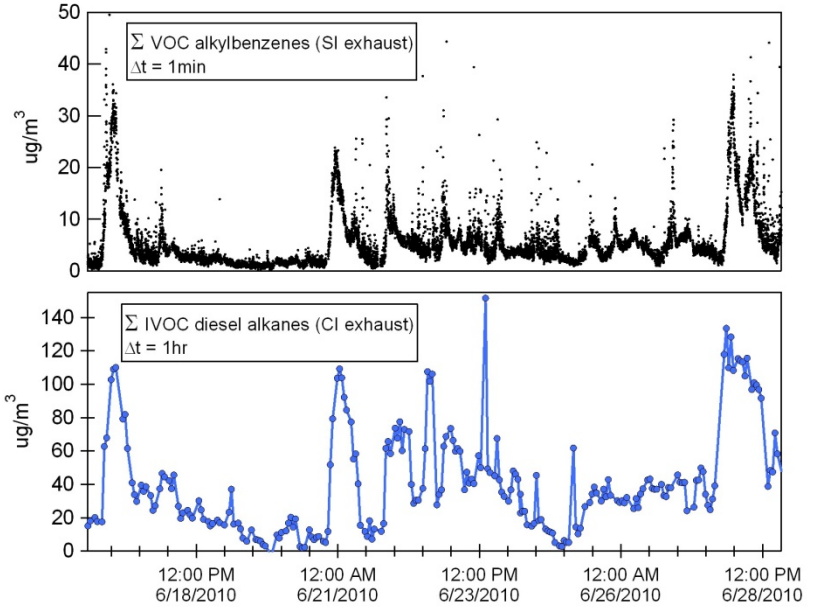
Compare to EPA MOVES emission model



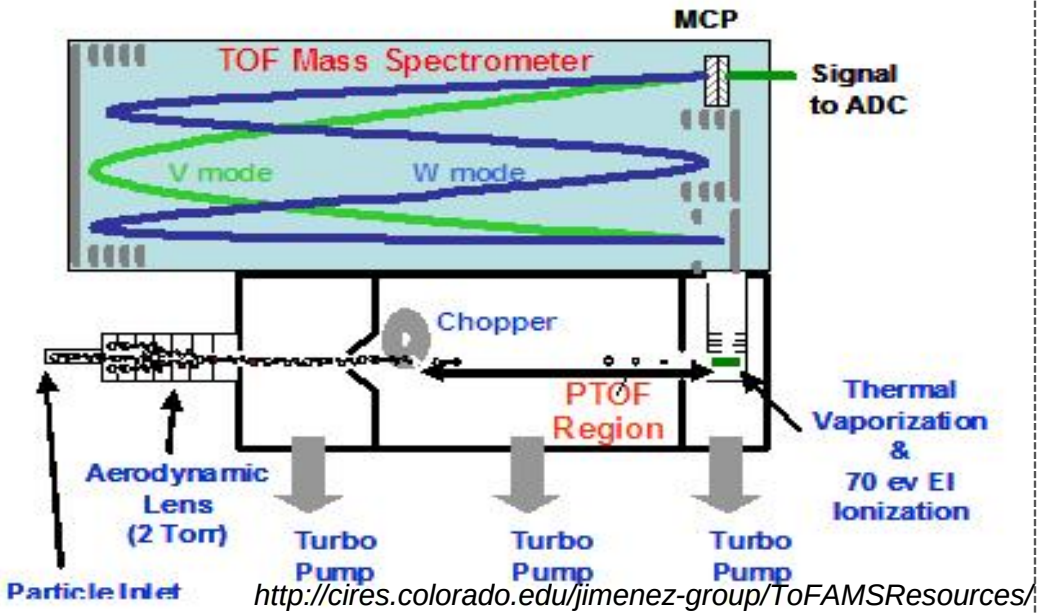
2. Diesel exhaust gas phase organics

Sacramento, CA : Are diesel exhaust emissions *precursors for secondary organic aerosols?*





WSU High Resolution Aerosol Mass Spectrometer

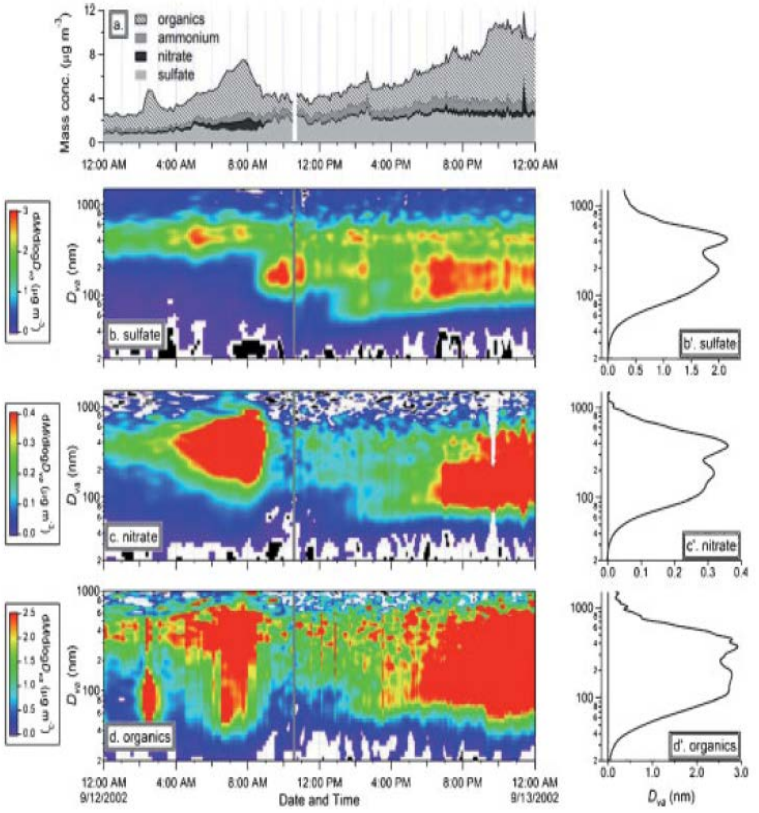


http://cires.colorado.edu/jimenez-group/ToFAMSResources/

Measurement principle:

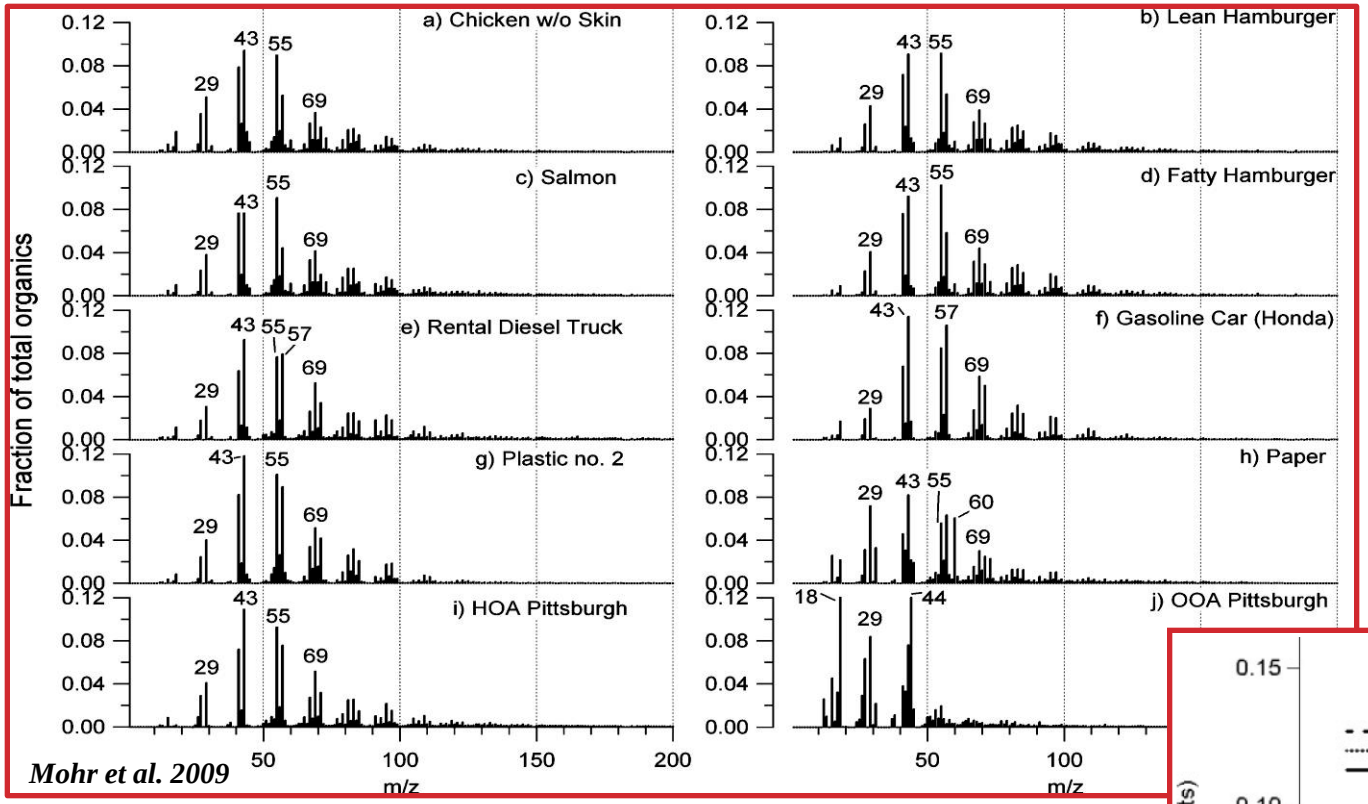
•Particles 50 < *Dp* < 1000 nm are efficiently concentrated by an aerodynamic lens.
•Particles are sized according to travel time between chopper and vaporization region.
•'Non-refractive': Only material that volatizes below ~600 C is measured.
•Time-of-Flight Mass Spectrometer allows high resolution mass spectral data.
•Complex fragmentation patterns- chemical patterns can be identified but organic speciation is not possible.

- Analysis of ambient data typically involves lumping fragments into major compositional categories:
  - Organics, sulfate, nitrate, etc.
- Mass classification can be binned by size or integrated.
- With PMF analysis, the organics category can be further divided.

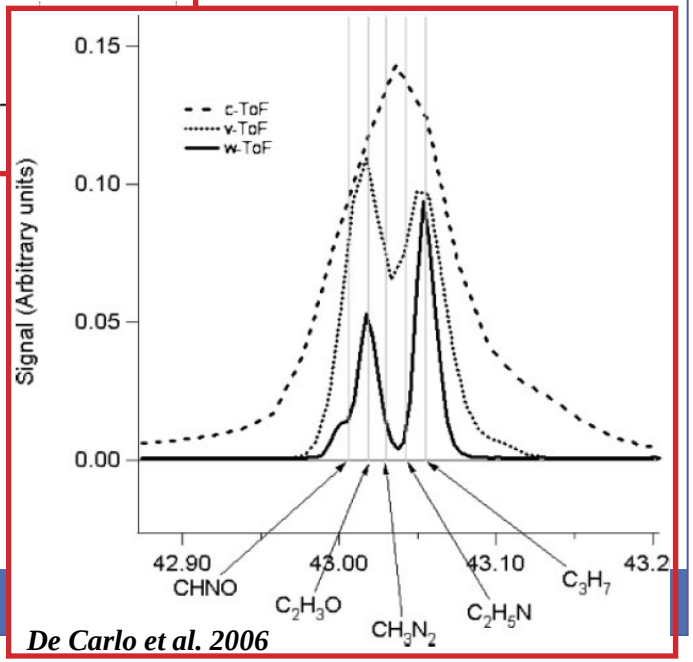


Objective 3

Source Characterization with the AMS



- Known sources can be characterized with a spectral 'fingerprint'.
- This fingerprint can later be compared with ambient factors derived via PMF.
- The High Resolution AMS offers a much higher mass spectral resolution, allowing for more refined source characterization.



Objective 3

Comparing Laboratory and Field Measurements

- Laboratory Profiles
  - Mobile platform instruments
  - AMS results
  - Passive hydrocarbon measurements
- Mobile and Fixed Site Features
  - Mobile platform suite
  - Similar fixed site platform suite
  - Fixed site passive hydrocarbon measurements at fuzzy sites
- Comparison metrics (lab vs. lab, lab vs. field)
  - Simple ratios
  - Multivariate features

Project 1: Summary/Objectives

- (1) Characterize multi-pollutant spatial gradients in four MESA cities
  - Mobile monitoring in four cities over two seasons
- (2) Characterize near-source downwind aging of TRAP*
  - Physical and chemical aging using mobile & fixed platforms
- (3) Provide detailed laboratory characterization of diluted and aged engine exhaust mixtures available for toxicology testing
  - Detailed characterization of test atmospheres; linkage with field data

*Traffic Related Air Pollution

Project 2: Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies

Jake McDonald, LRRI
Amie Lund, LRRI
Tim Larson, UW

Objectives

- **Simulate ambient exposures in the laboratory**
  - Bridge these exposures to ambient measurements/modeling (Project 1)
- **Compare toxicity of exposures**
  - Use these results to determine mechanisms (Project 3) and to define priorities and atmospheres for human exposures (Project 4)

Conceptual Paradigm: Exposures

Background + **Traffic Emissions** → **Exposures**

100 m 500 m 1 km ??

Distance From Roadway

Background

O_3, $(NH_4)_2SO_4$, NH_4NO_3, VOC, Ni, V

Traffic Emissions

Tailpipe, Evaporative, Tire & brake, Resuspended Dust

Chemical Transformation

OH^-, Sunlight

Aging

Nucleation, Agglomeration

Comparative Exposure/Toxicology

Hypothesis:

1. Motor vehicle emissions toxicity decreases when transformed in the atmosphere.

2. Background air and non-exhaust roadway emissions (road surface dust, tire and brake wear material, inorganic ions, metals, and ozone) do not contribute significantly to roadway-associated cardiovascular morbidity

Key Research Questions

- Does agglomeration and physical transformation of particulate motor vehicle emissions alter their toxicity (does size matter)?
- Does chemical transformation, and formation of secondary organic aerosol from motor vehicle emission precursors, enhance or diminish the toxicity of roadway atmospheres?
- Do ozone and other background co-pollutants alter or exacerbate the toxicity of motor vehicle emissions?
- Does road dust, a significant non-tailpipe roadway emission, confer any cardiovascular toxicity that may confound associations with tailpipe emissions?

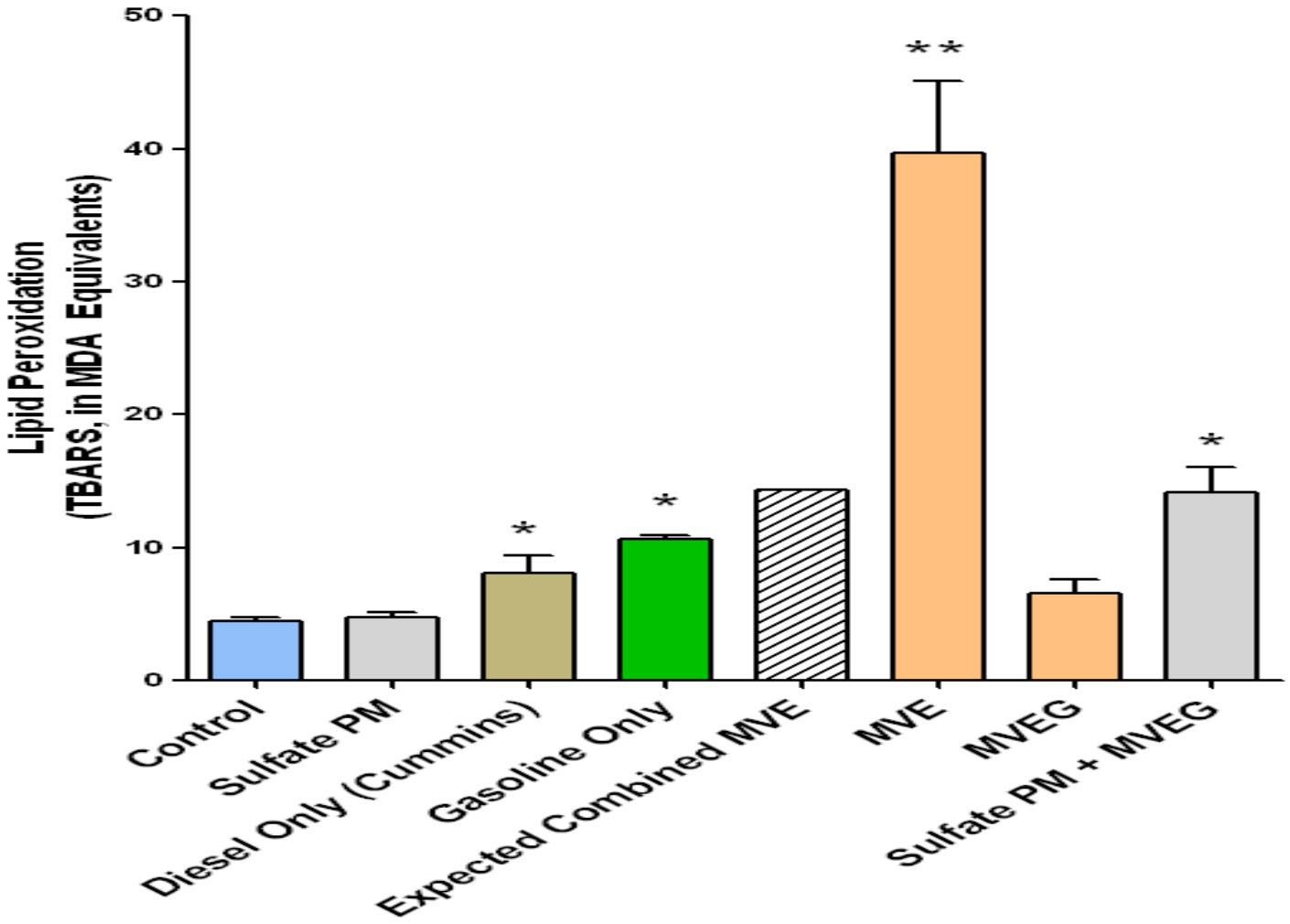
Specific Aims

- Aim 1: Develop and characterize laboratory-generated exposure atmospheres simulating the key components of near-roadway exposures, including transformed emissions and co-exposures.
- Aim 2: Conduct inhalation exposures of laboratory animals.
- Aim 3: Conduct inhalation exposures of human subjects.

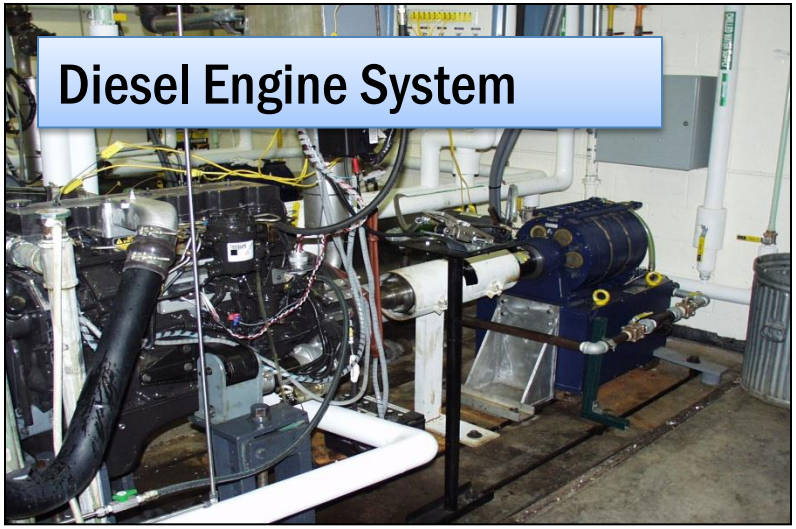
Methodology

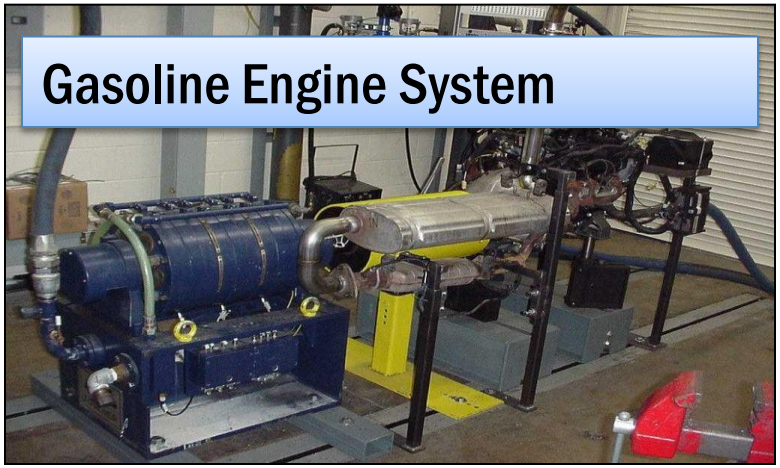
- Laboratory generated simulated atmospheres
  - Gasoline + Diesel
    - Physical and/or Chemical Transformation
  - Urban air simulated mixture (O_3, Inorganic Ions, Road dust)
  - Paved Road Dust (non-motor vehicle roadway emission)
- Detailed Characterization (complements Project 1 Ambient Measurements)
  - Particle size, number, mass, composition
  - Gas composition

We study both gasoline and diesel engine emissions combined.....



Aim 1: Develop Atmospheres



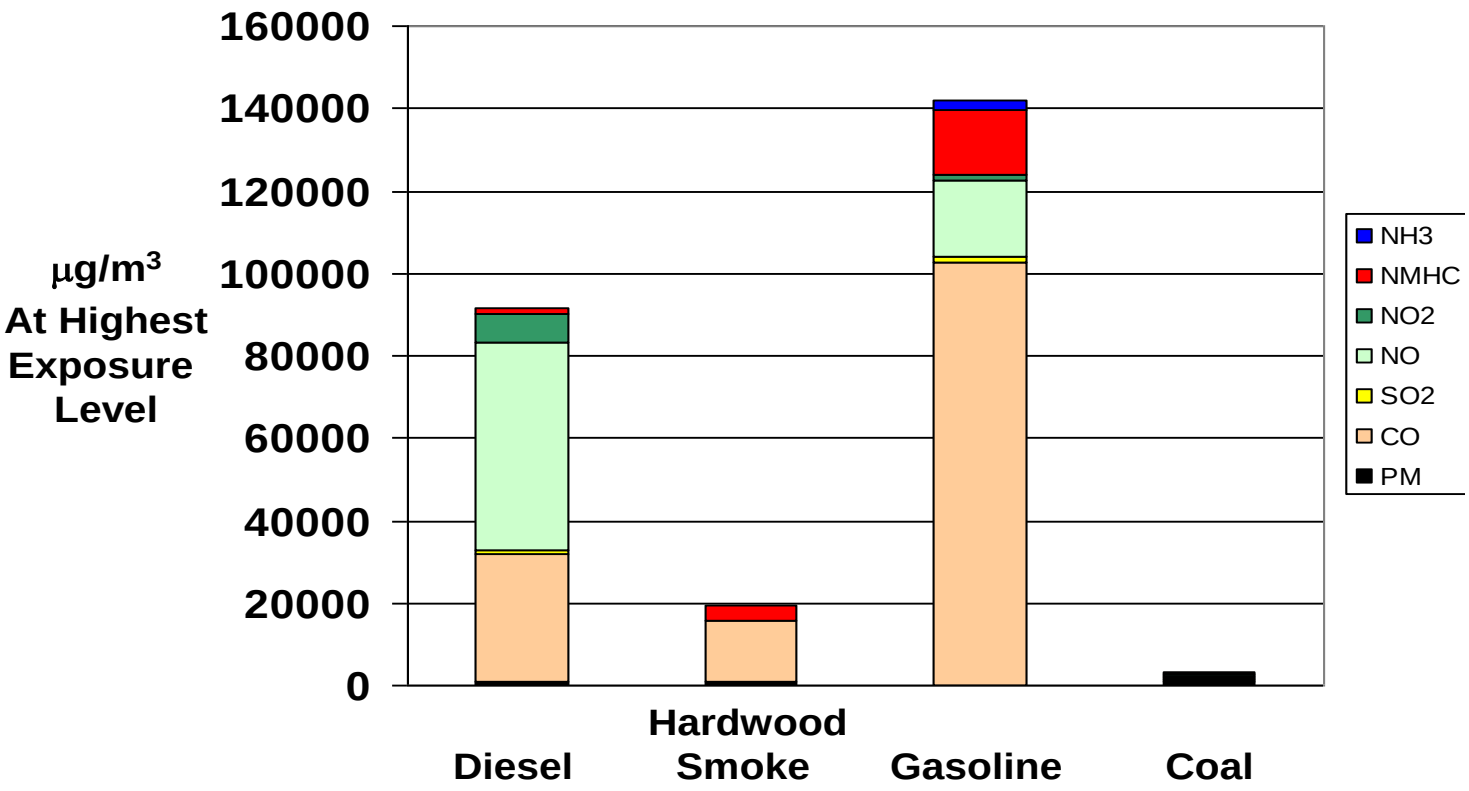


Diesel and Gasoline Contributions

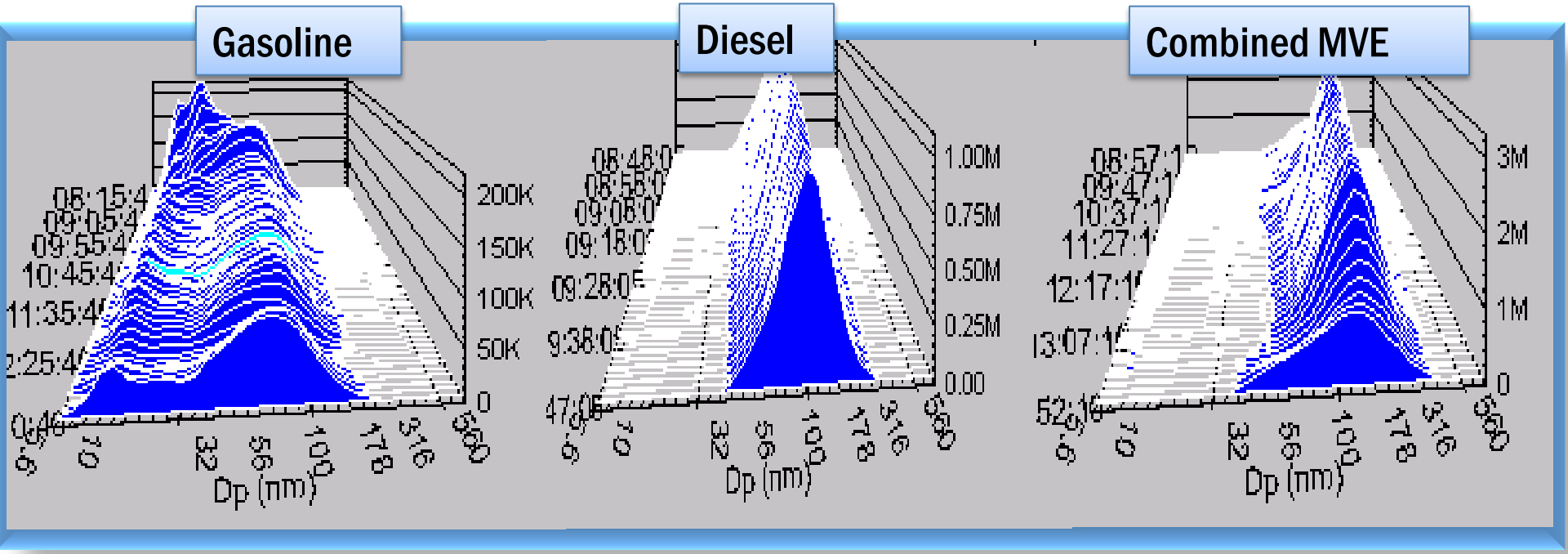
	Diesel	Gasoline
Dilution factor	10	10
Total mass (mg/m^3)	84	116
Particles		
Mass ($\mu g/m^3$)	1005	60
Number ($10^6/cc$)	1.0	0.5
Size (MMAD, µm)	0.15	0.15
%OC	22	19
%EC	64	47
%sulfate	6	21
%nitrate	4	0.8
%ammonium	4	12
%elements (ash)	0.1	0.9
Gases & Vapors		
CO (ppm)	30	80
NO (ppm)	45	18
NO_2 (ppm)	4	1
SO_2 (ppm)	0.4	0.6
THC (ppm)	2	12

NERC EXPOSURE ATMOSPHERES BY MASS

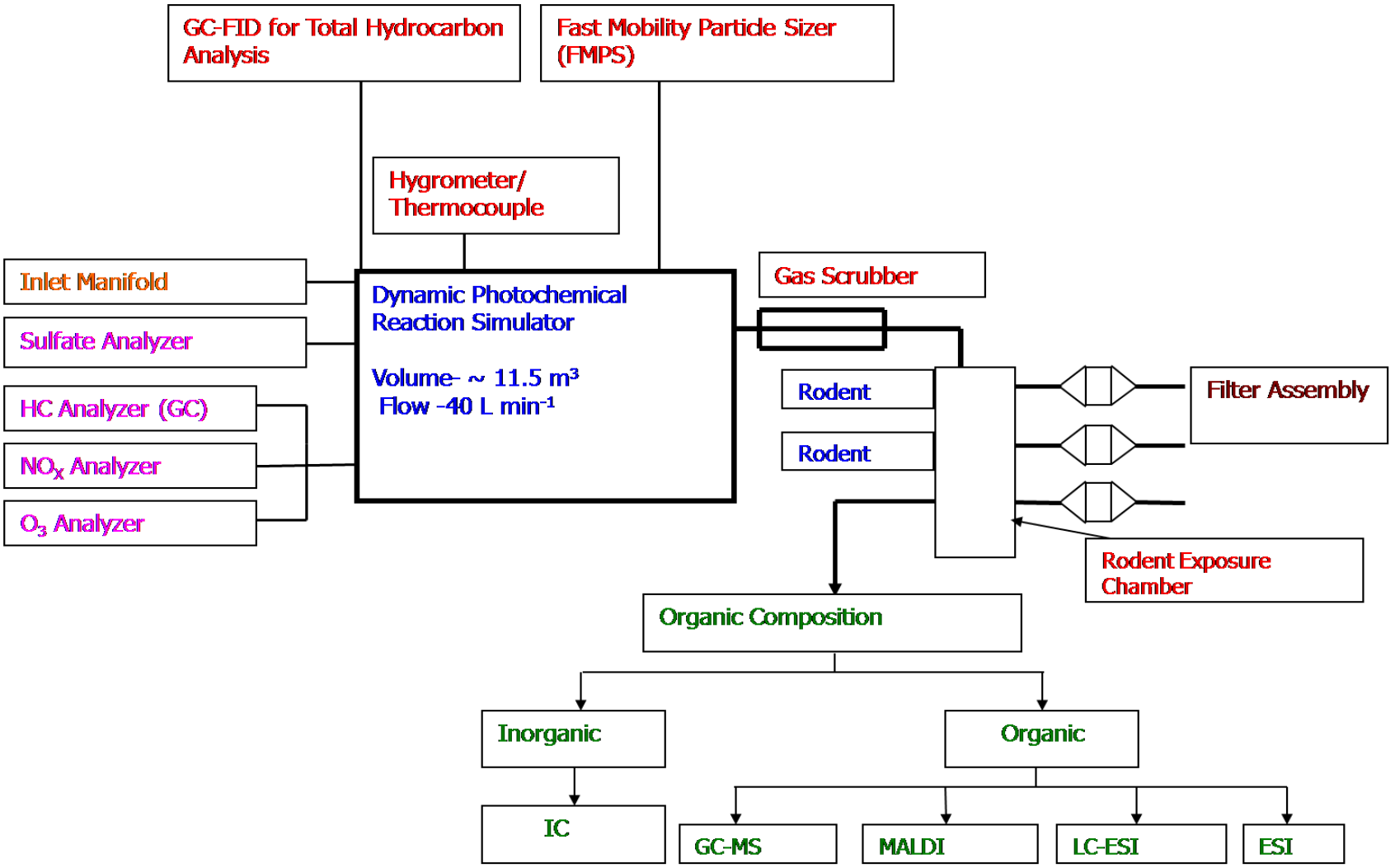
(Less CO_2, H_2O, and CH_4)



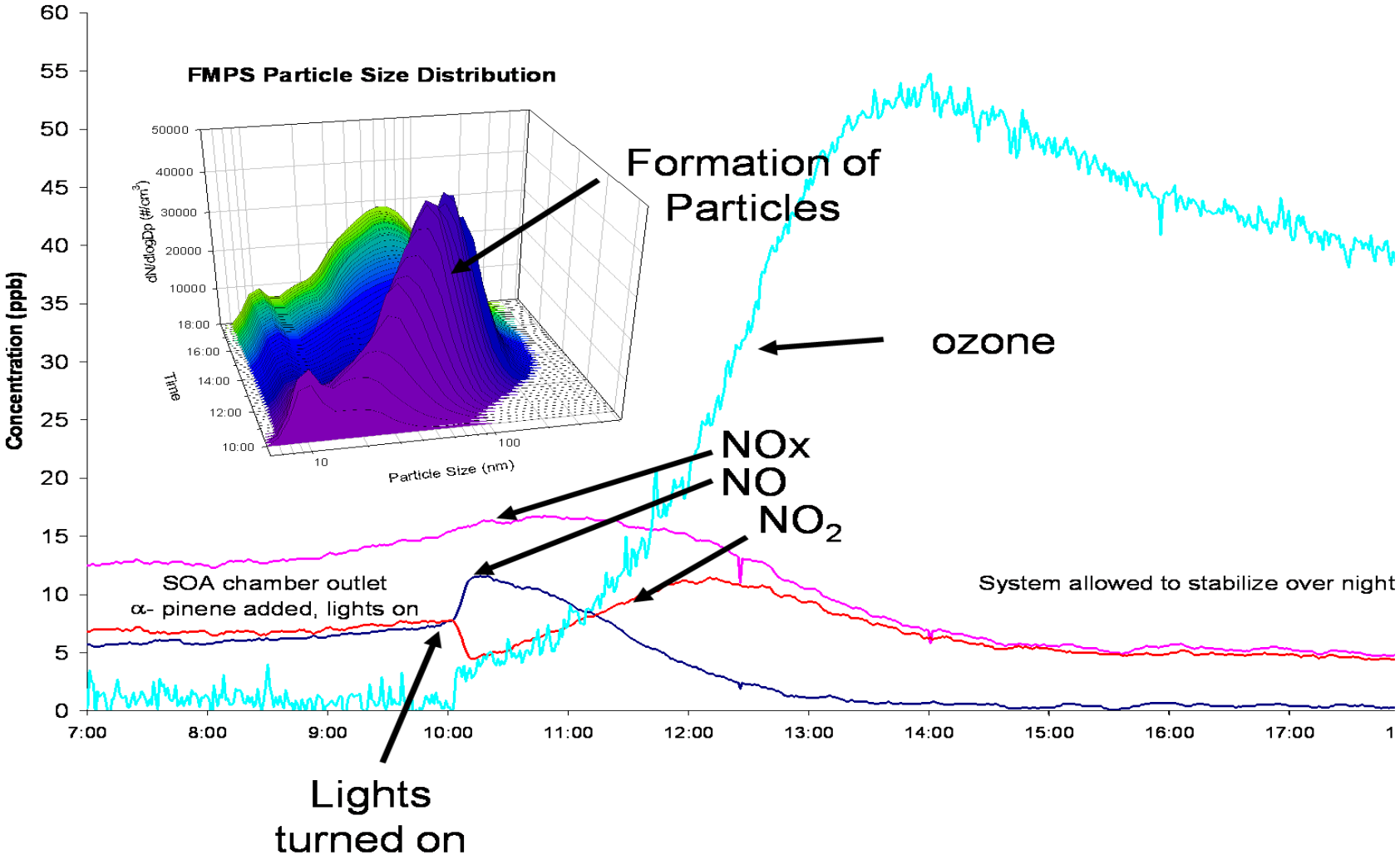
Combining Motor Vehicle Atmospheres



Irradiation Chamber



Secondary Organic Aerosol



McDonald et al., 2010; Campen et al., 2010

Methodology

- Physical Aging of Mve
  - We will alternate dilution/operating conditions to attempt to modify particle size
- Paved Road Dust:
  - Composite of dust collected in multiple US Regions
- Urban Air Simulation:
  - Based on measurements in field campaigns (Project 1)

Test Matrix

	Primary (Fresh)	Aged	Chemically Transformed
MVE	+	-	-
MVE	-	+	-
MVE	-	-	+
Urban Background	-	-	-
Urban Background	+	-	-
Paved Road Dust	-	-	-
Paved Road Dust	+	-	-

Current Activities

- Range finding studies with Mve to determine optimal dose, strain, operating conditions.
  - Dose-response at 30, 100, 300 µg/m^3
  - Evaluation of diesel/gasoline ratios (3:1, 10:1)
  - Characterization of mouse strain response
- Test and evaluation for atmosphere development (e.g., physical aging conditions)
- System integration with Irradiation Chamber
- Coordination with Project 1 for characterization/atmosphere design

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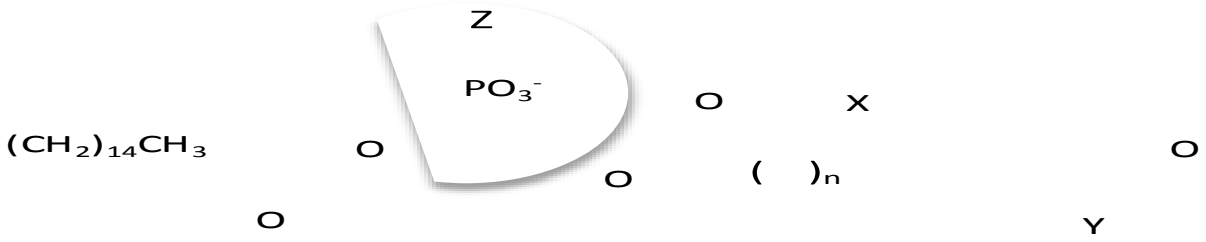
Project 3:Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions

Michael Rosenfeld - UW
Matthew Campen - UNM
Amie Lund – LRRI
Jake McDonald- LRRI

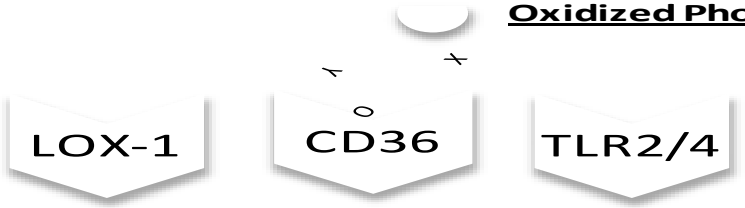
Exogenous Toxicants

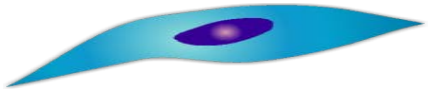
Phospholipid



X = -H, -OH
Y = - O, -OH
Z = choline, inosital, -H, etc

Oxidized Phospholipid

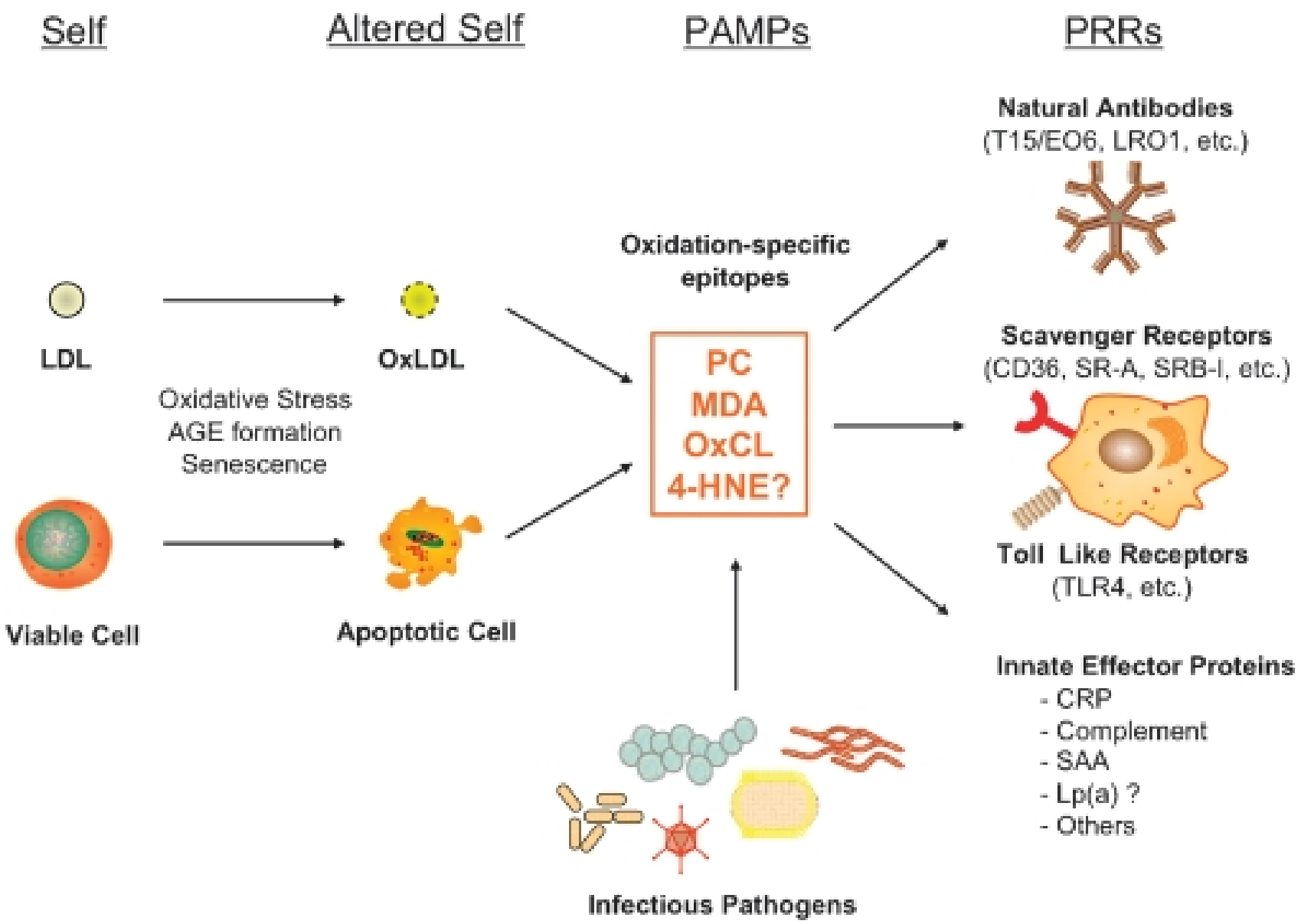




B-Cells

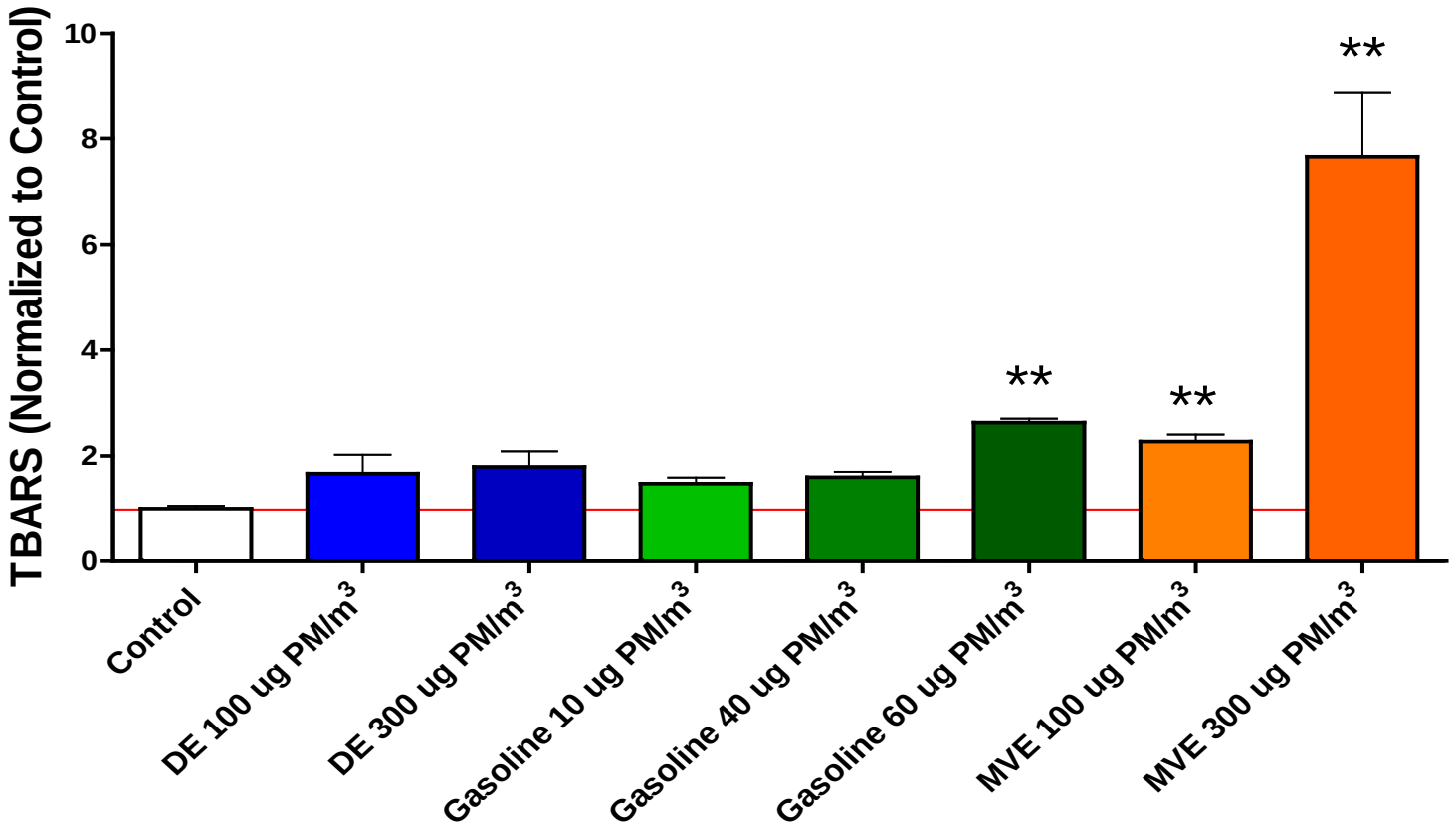
Immune Cells

Endothelium


Self
Altered Self
PAMPs
PRRs
Natural Antibodies
(T15/EO6, LRO1, etc.)
Oxidation-specific
epitopes
LDL
OxLDL
Oxidative Stress
AGE formation
Senescence
PC
MDA
OxCL
4-HNE?
Scavenger Receptors
(CD36, SR-A, SRB-I, etc.)
Toll Like Receptors
(TLR4, etc.)
Viable Cell
Apoptotic Cell
Innate Effector Proteins
- CRP
- Complement
- SAA
- Lp(a) ?
- Others
Infectious Pathogens

We hypothesize that emissions-induced oxidation of endogenous phospholipids, presumably in the pulmonary surfactant, can stimulate the activity of immune and vascular cells through pattern recognition receptors and in turn promote the leukocytic invasion of existing vascular lesions.

We will test this hypothesis concomitantly with investigations as to the relative potency of roadway-related pollutants, including mixed vehicular emissions and road dust.



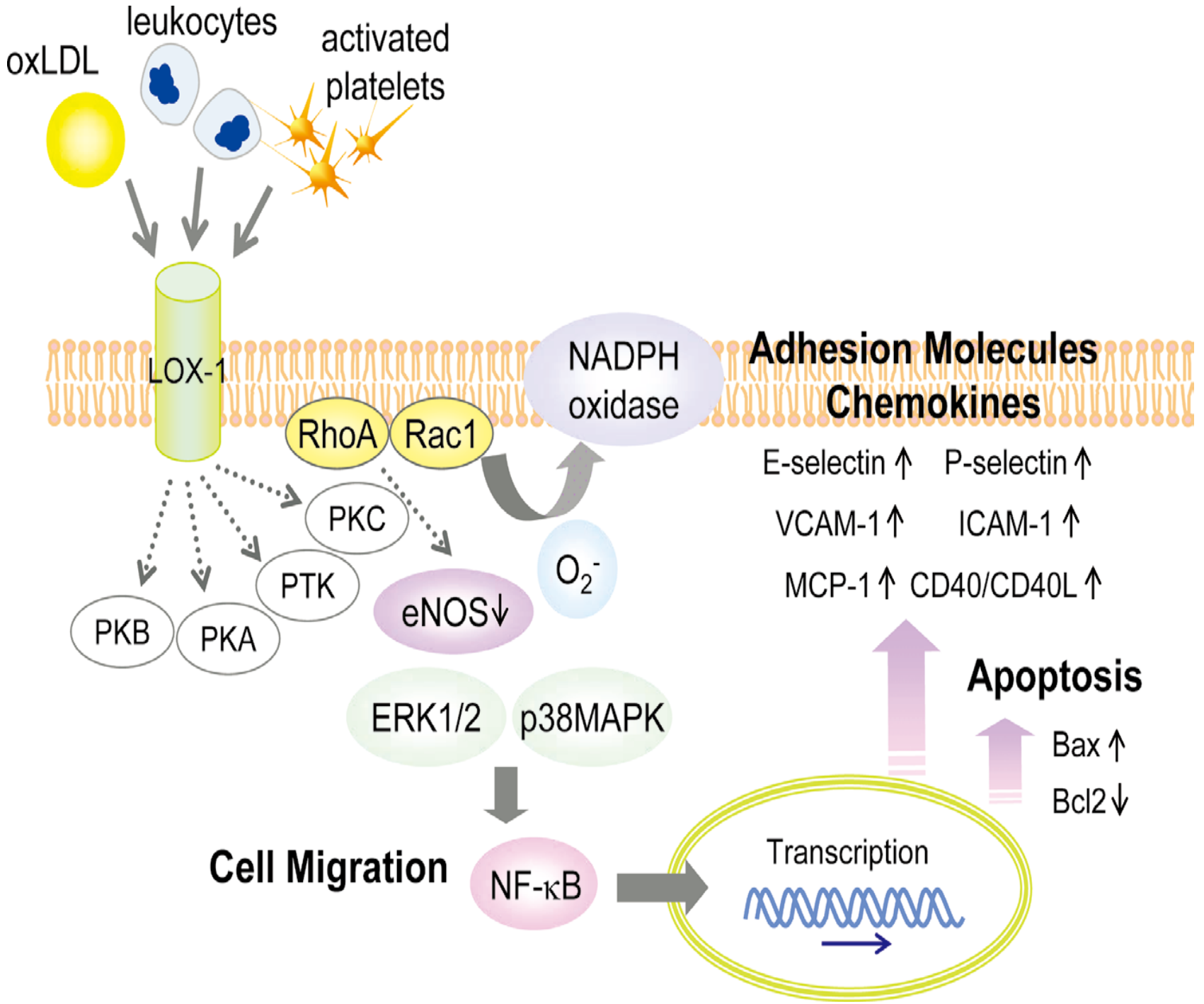
Comparison of lipid peroxidation effects from diesel, gasoline, and combined (MVE) emissions at various concentrations. Aortas were obtained from apoE-/- mice following 50 days of exposure. Asterisks indicate significant difference from control ($P<0.01$ by ANOVA with Bonferroni Posthoc Comparison).

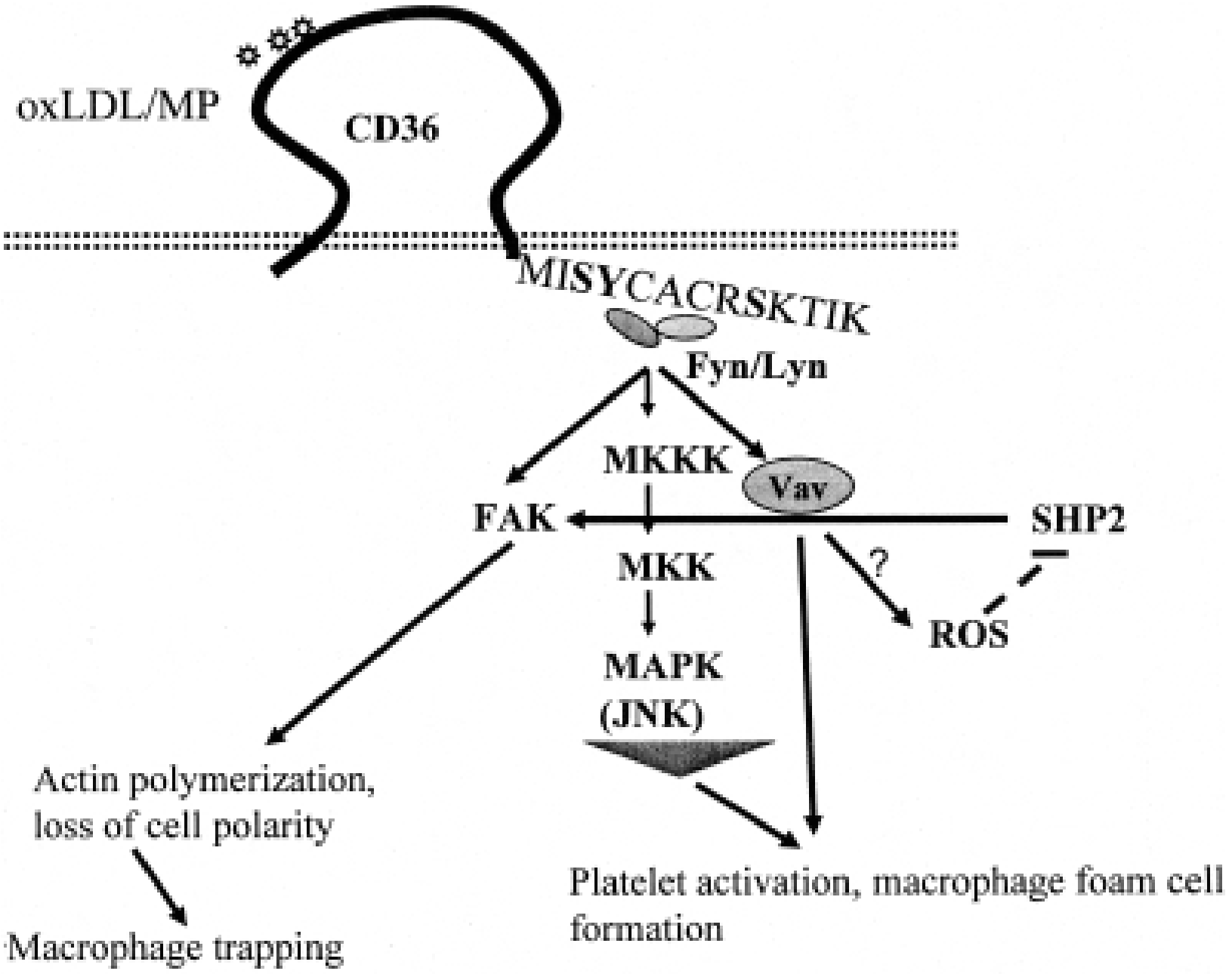
Aim 1: To ascertain the potentiating effects of physical and photochemical aging on fresh mixed vehicular emissions, in terms of driving pulmonary and vascular oxidative stress.

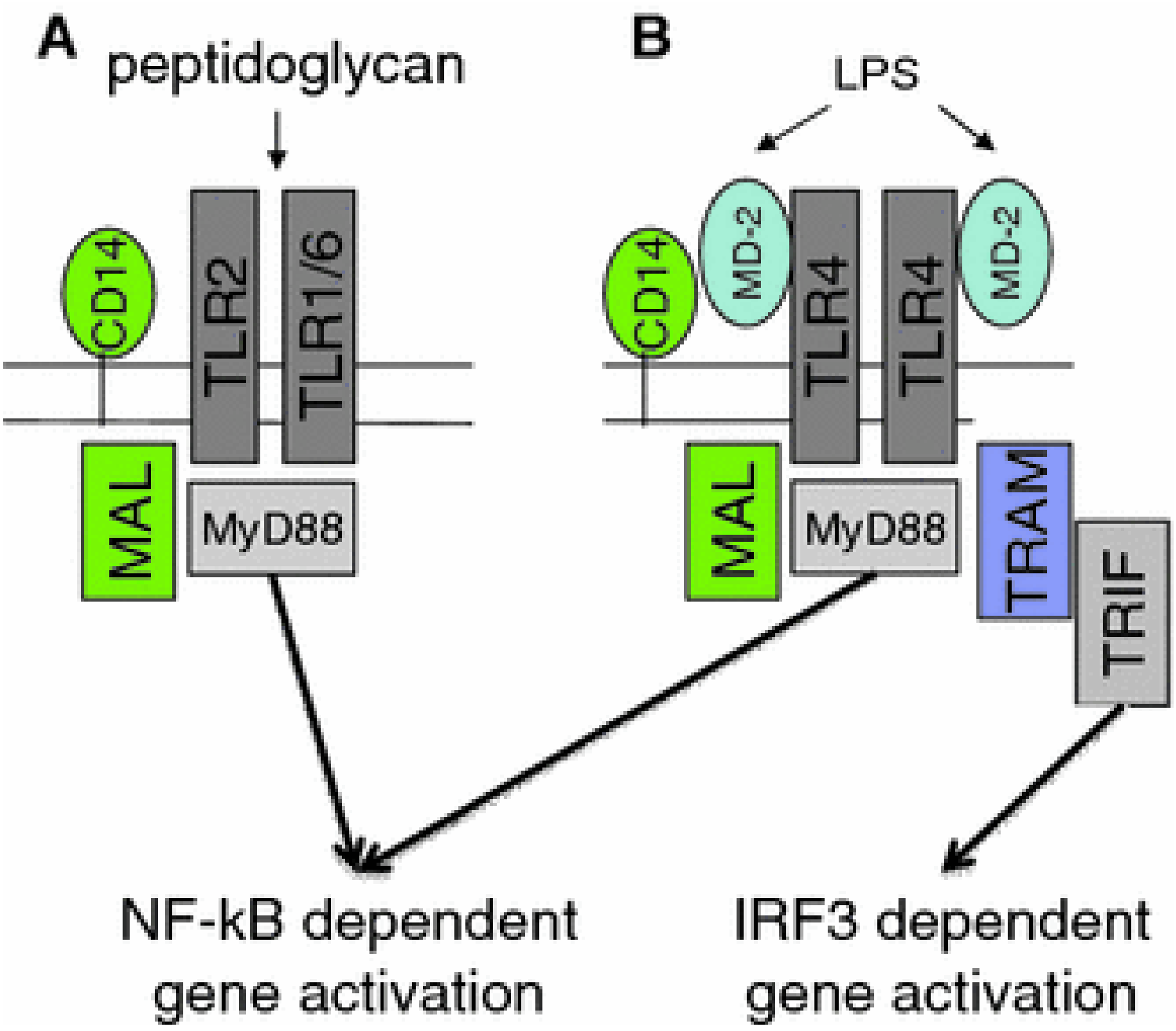
Hyperlipidemic mice will be exposed to various ratios and doses of combined diesel and gasoline emissions that will be modified by physical and photochemical aging, and also produced in combination with re-suspended road dust and a modeled urban background (with Project 2).

Aim 2: To examine effects of the emissions-induced oxidative modifications to endogenous phospholipids on the activation of immune-modulating receptors LOX-1, CD-36, TLR-2, and TLR-4.

This Aim will utilize receptor-deficient mouse models to examine the roles of these receptors, as well as characterize the lipidomic alterations in various tissues.


oxLDL
leukocytes
activated platelets
LOX-1
NADPH oxidase
RhoA
Rac1
PKC
PTK
PKB
PKA
eNOS↓
O_2^-
ERK1/2
p38MAPK
Cell Migration
NF-κB
Transcription
Adhesion Molecules
Chemokines
E-selectin ↑
P-selectin ↑
VCAM-1 ↑
ICAM-1 ↑
MCP-1 ↑
CD40/CD40L ↑
Apoptosis
Bax ↑
Bcl2 ↓


oxLDL/MP
CD36
MISYCACRSKTIK
Fyn/Lyn
MKKK
Vav
FAK
SHP2
MKK
?
ROS
MAPK
(JNK)
Actin polymerization,
loss of cell polarity
Macrophage trapping
Platelet activation, macrophage foam cell
formation


A
peptidoglycan
CD14
TLR2
TLR1/6
MAL
MyD88
B
LPS
CD14
MD-2
TLR4
TLR4
MD-2
MAL
MyD88
TRAM
TRIF
NF-kB dependent
gene activation
IRF3 dependent
gene activation

Specific outcome measures will include:

Products of lipid peroxidation (TBARS, HETES) and the oxidative alterations to endogenous PLs in the lung and isolated surfactant, serum, and aorta, using a lipidomic approach (LC-MS).

Serum IgG and IgM that bind ox-PLs generated under controlled conditions *in vitro*.

Histopathology of lungs and blood vessels

Receptor mediated signal transduction in isolated alveolar macrophages

Aim 3: To further explore the role of immune cell populations as participants in the innate and adaptive responses to emissions-induced phospholipid modifications.

In this Aim, we will utilize a mouse model of immunodeficiency, the severe combined immune deficiency (SCID) mouse lacking T and B cells. Additionally, we will pursue bone-marrow transplants from control mice and mice lacking the pattern recognition receptors described in Aim 2 into SCID mice to establish the involvement of the receptors specifically in leukocytes. Outcome measures as in aim 2.

Pilot Study Comparing Apo E-/- and LDLR-/- Mice.

Duration of Exposure = 7 days, 7AM-1PM

Concentrations of mixed exhaust = 100 ug PM/m^3 (30 ug PM/m3 from gasoline exhaust; 70 ug PM/m^3 from diesel engine exhaust).

Groups included both chow fed and high fat fed male mice. High fat diet was fed for about 3 weeks before exposures began.

Apo E-/- mice were ~10-11 weeks of age and LDLR-/- mice were ~16 weeks of age at beginning of exposure.

Outcome measures include: Aortic TBARS, MMP activity (zymography), and MOMA-2 (macrophage) staining.

Chamber 4 Exposure

Day	Average PM (µg/m3)	Average NO_x (ppm)	Average CO (ppm)
1	99	19.646	101.6
2	102	20.350	95.7
3	158	24.898	100.9
4	114	26.700	102.8
5	86	25.162	100.6
6	93	21.268	101.9
7	92	20.172	100.8
Average	**106**	**22.599**	**100.6**

Chamber 7
Control

Day	Average PM (µg/m3)	Average NO_x (ppm)	Average CO (ppm)
1	37	0.073	0.3
2	9	0.064	0.2
3	5	0.070	0.6
4	7	0.022	0.1
5	10	0.271	0.5
6	4	0.146	0.2
7	3	0.120	0.0
Average	**11**	**0.109**	**0.3**

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Project 4: Vascular Response to Traffic-derived Pollutants in Humans

Joel Kaufman

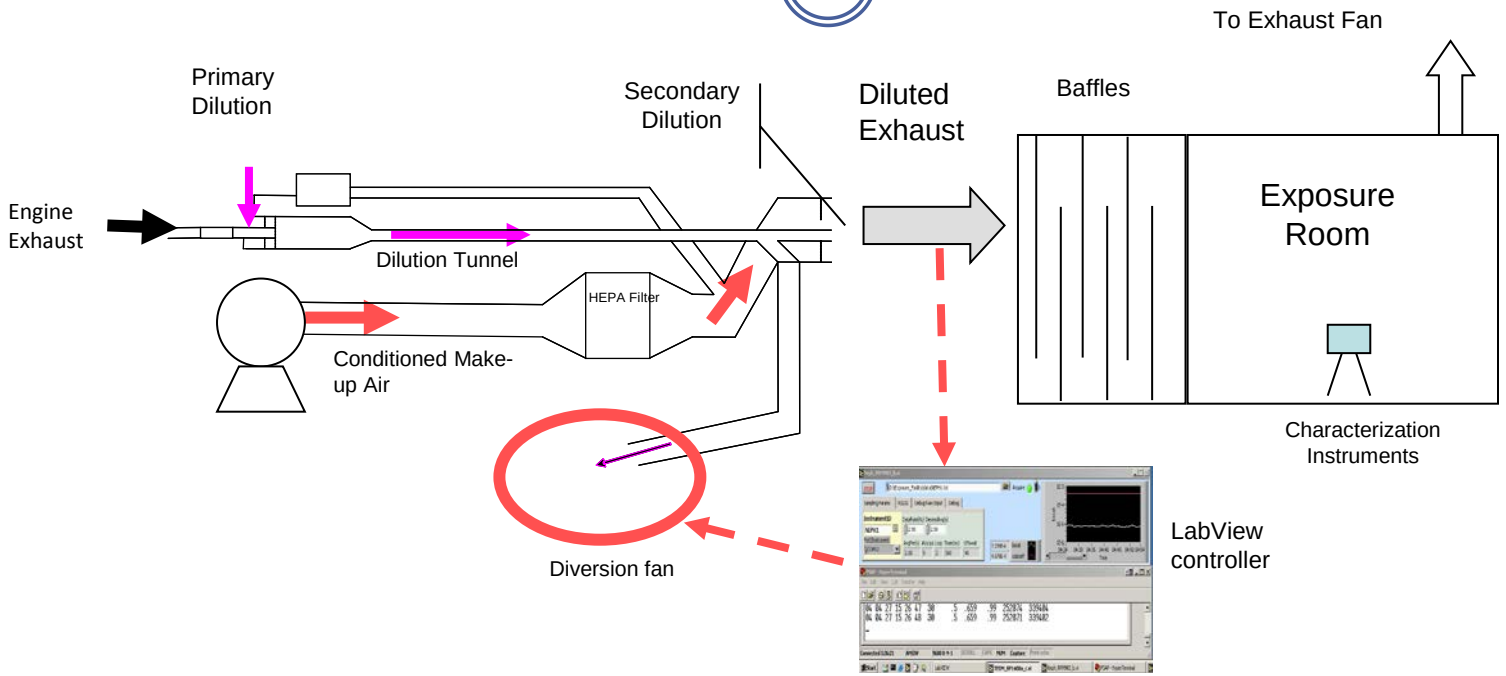
September 26, 2011

Human Controlled Exposure Study

- 2 hr of test environment or FA
- Monitor blood pressure
- Serial blood collection measurements
  - Plasma and serum markers
  - Gene expression in circulating cells
  - DNA methylation in circulating cells
- Brachial artery dimensions and FMD

- Evaluate effects of genotypic difference
- Evaluate effects of pharmacologic intervention

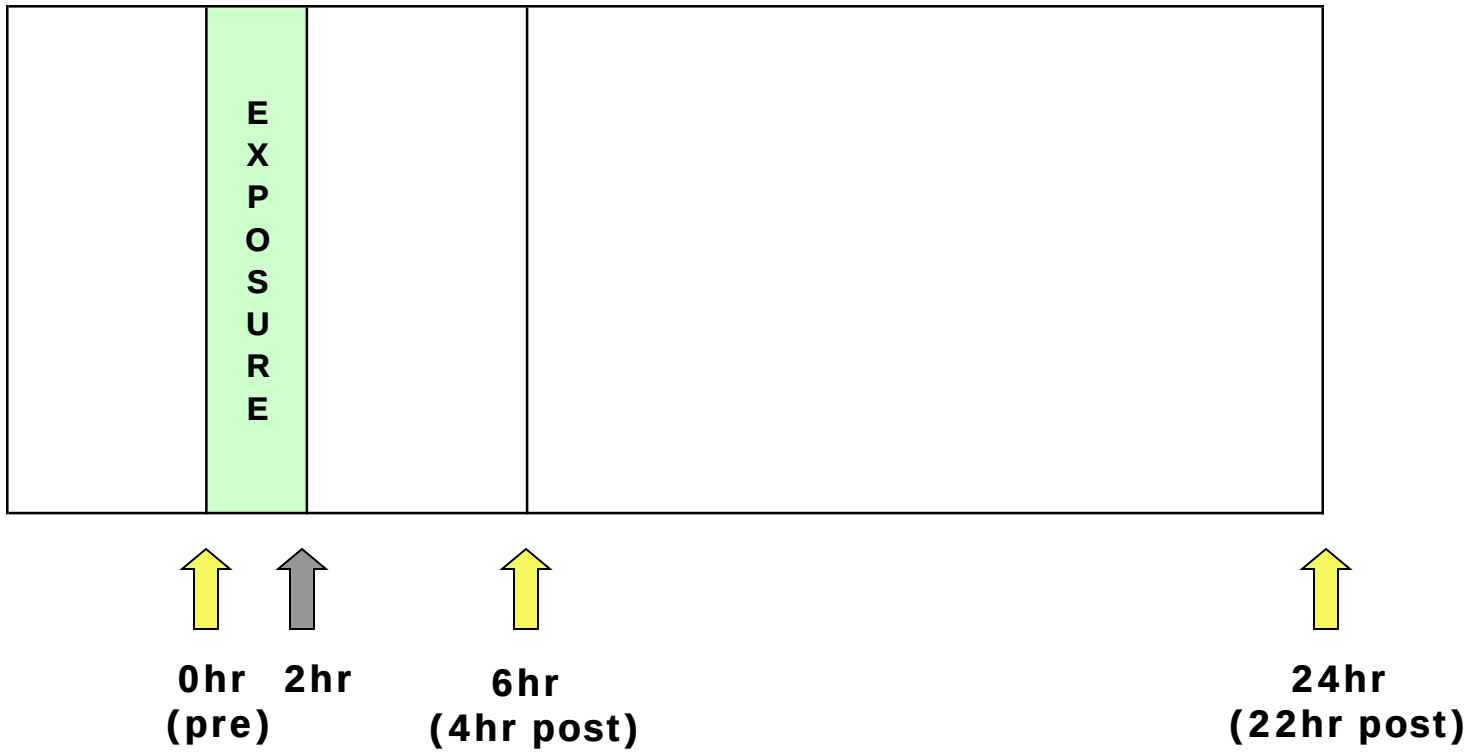
Northlake Exposure Facility

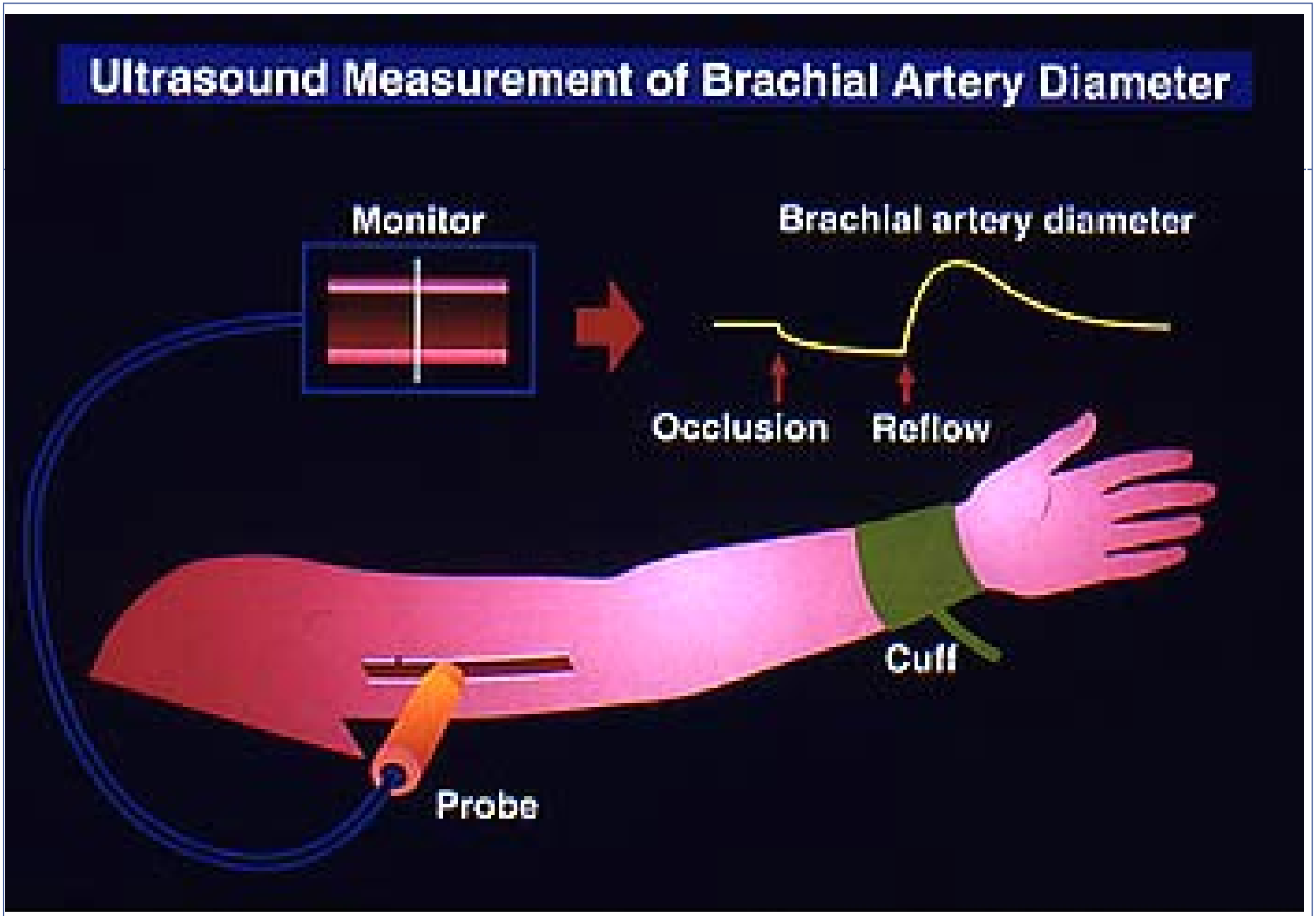


Human Controlled Exposure Study

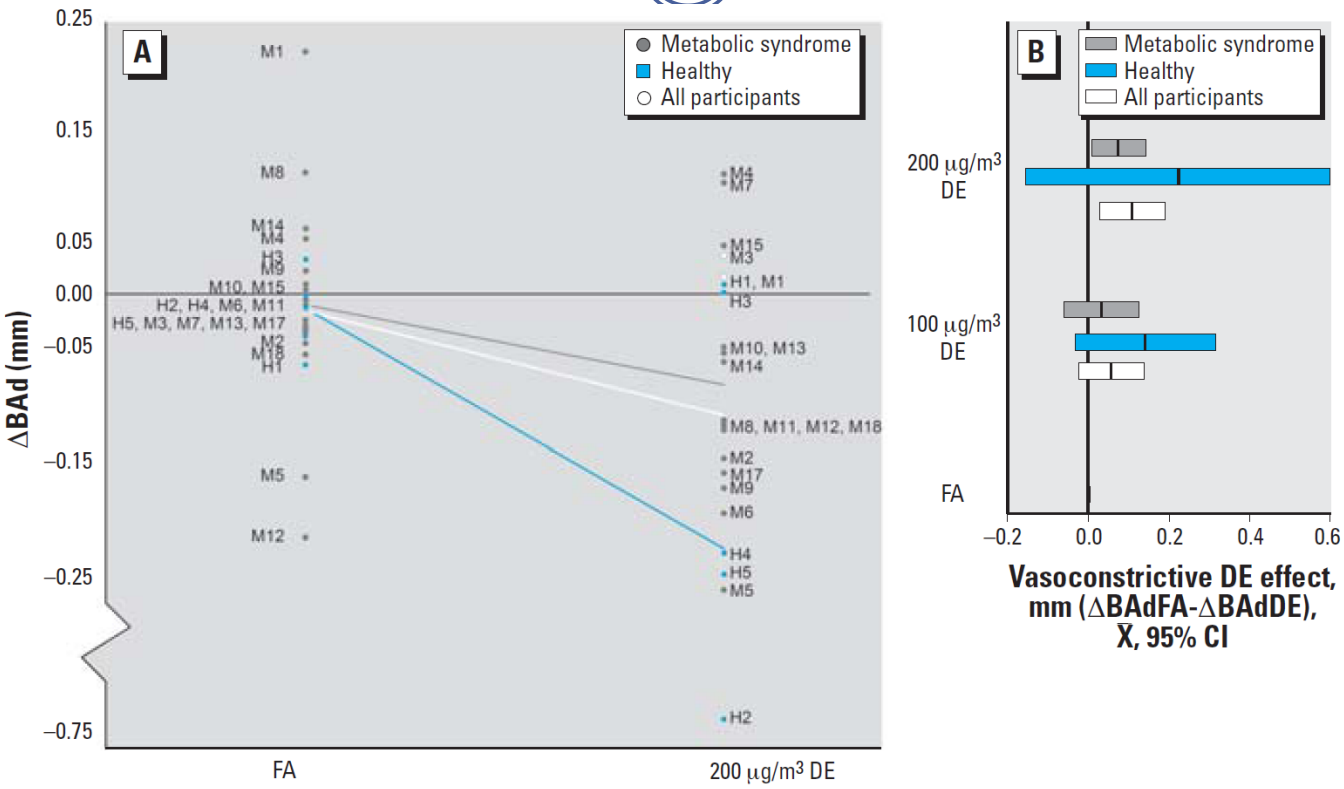
- 2 hrs at specified concentrations of pollutants or FA
- Monitor BP
- Serial blood draws
- Serial brachial artery dimensions and FMD

Timeline of exposure day




Ultrasound Measurement of Brachial Artery Diameter
Monitor
Brachial artery diameter
Occlusion
Reflow
Cuff
Probe

Change in Brachial Artery Diameter



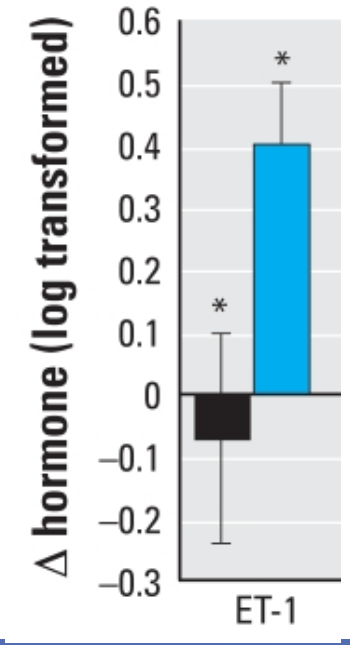
Vasoconstriction with Diesel Exhaust Inhalation

A. Changes in brachial artery diameter (BAd) following exposures to 200μg/m^3 DE or FA; lines represent mean Δ BAd (pre-to-post) at each exposure level.

B. Dose-response relationship of diesel exhaust effect on brachial artery diameter. Bars show mean and 95% confidence interval for vasoconstrictive effect for two study sub-populations and overall group. Wide confidence intervals for healthy group reflect small sample size and not higher variance.

DE and Plasma Endothelin-1

Biomarker	FA		200 µg/m^3 DE	
	Preexposure	Postexposure	Preexposure	Postexposure
ET-1				
Healthy (n = 6)	1.47 ± 0.21	1.35 ± 0.27	0.86 ± 0.06	1.62 ± 0.18
Metabolic syndrome (n = 16)	1.35 ± 0.17	1.41 ± 0.15	1.31 ± 0.18	1.62 ± 0.18
All participants (n = 22)	1.38 ± 0.13	1.39 ± 0.13	1.19 ± 0.14	1.62 ± 0.13

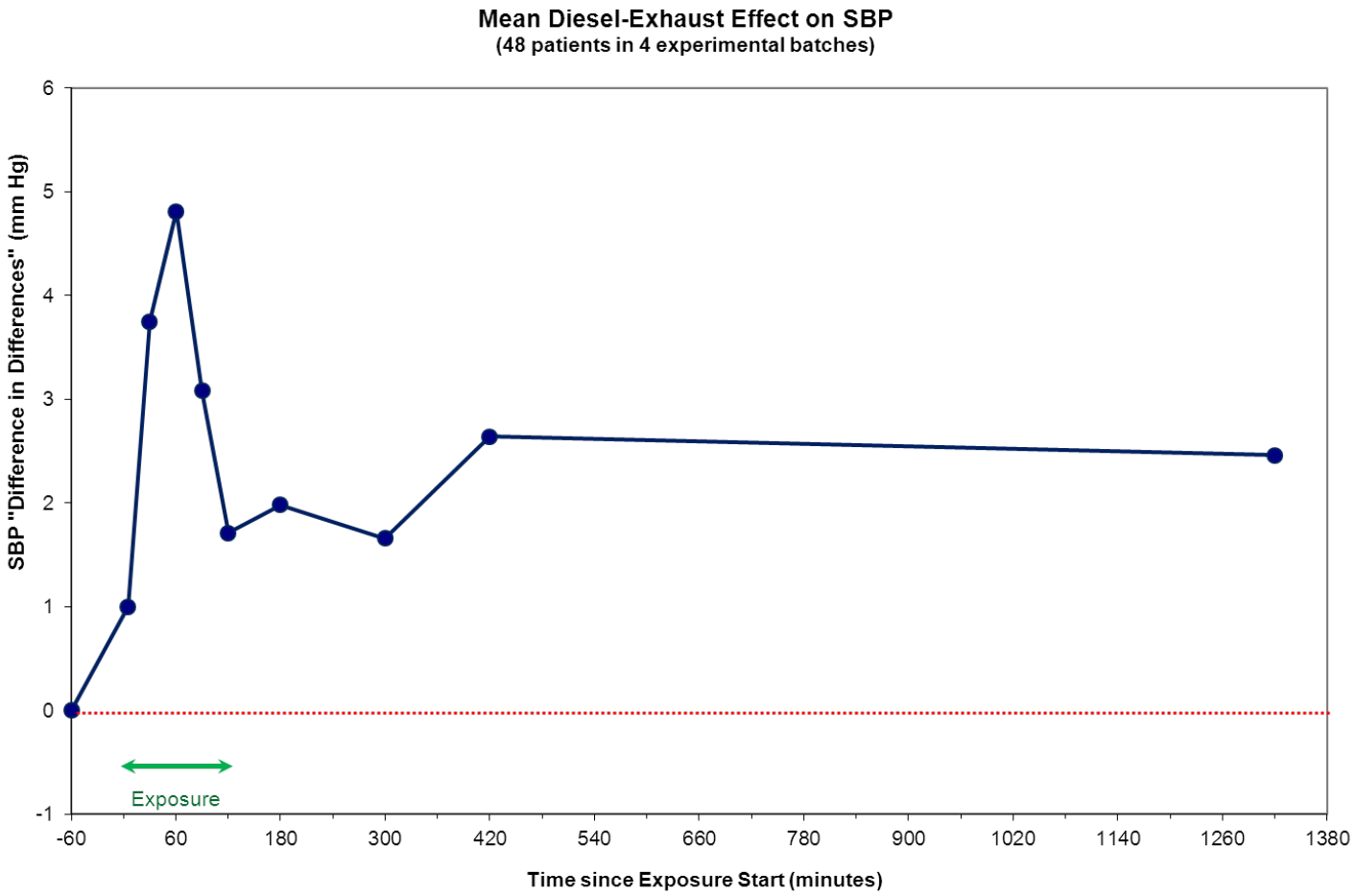


Graphic: Fold-change in log-transformed plasma endothelin-1 levels from preexposure to 3 hr from initiating exposure to 200 µg/m3 DE or FA. *p = 0.01

Table: Mean values in pg/ml

Peretz et al, *EHP* 2008

DE Impact on Blood Pressure



DE Impact on Blood Pressure

Minutes from Exposure Start	5	30	60	90	120	180	300	420	1320	Model: mid-exposure, pooled (30-90 min.)	Model: Post-Exposure, pooled (180-1320 min.)
DE Effect Estimate, mmHg	1.0	3.8	4.8	3.1	1.7	2.0	1.7	2.6	2.5	3.9	2.1
P-value, raw	0.58	0.04	0.01	0.10	0.38	0.35	0.48	0.20	0.29	-	-
P-value, adjusted										0.01	0.15

N=48

Adjusted model includes adjustment for gender, AGTR1 genotype, perception of exposure (DE vs. FA), metabolic syndrome, first visit to facility

Ongoing Work

- Analysis by genotypic strata
- Analysis of impact of anti-oxidant cocktail
- Gene expression in peripheral leukocytes
- Epigenetic characterization

- Next genotype stratified trial about to launch
  - From DISCOVER Center portfolio

Project 4 Plans

- Launch in CCAR Year 3 (follows experiment now beginning)
- Aims
  1. TRAP related to vasoconstriction, ET-1, SBP
     a) Higher potency (from Project 2 and 3) with greater effects than lower potency TRAP, compared to FA
     b) Genotype stratified trial (increased response with polymorphism in ALOX15, a SNP identified in ongoing work in MESA Air)
  2. TRAP will result in evidence of lipid peroxidation, pro-atherogenic gene transcription, and pro-atherogenic epigenetic changes
     a) Plasma oxLDL, malondialdehdye, anti-phospholipid Ab
     b) Monocytes with increased mRNA of HMOX1, GCLC, PPARα
     c) Attenuation with α-lipoic acid, compared to placebo
     d) Increased methylation of promotor site of FOXP3

Human Controlled Exposure Study

- Crossover Design (target n = 24)
- Years 3-5 of Center
- Exposures Chosen Based on Project 3 results
- Project 2 Provides Exposure Generation and Characterization Leadership
- Randomized with regard to order, blocked
  - FA / Placebo
  - FA / Pharmacologic Agent
  - Traffic Pollution Low Toxicity/ Placebo
  - Traffic Pollution High Toxicity / Placebo
  - Traffic Pollution High Toxicity / Pharmacologic Agent
- Genotype-Stratified Trial

Hypotheses to be tested

	Lipoic Acid	*Placebo*
High Potency Atmosphere	A	B
Low Potency Atmosphere		C
Filtered Air	D	E

- Allowing for changes based on scientific advances
- Aim 1
  - 1A: SBP (at one hour of exposure vs. before exposure) in session B to that found in both exposures C and E.
  - 1B: SBP in session B to exposure E, and test for effect of interaction term with number of G alleles at rs2664593.

Hypotheses to be tested

	Lipoic Acid	*Placebo*
High Potency Atmosphere	A	B
Low Potency Atmosphere		C
Filtered Air	D	E

- Aim 2
- 2A, 2B, 2D: compare in B to E
  - MDA (3 hours post exposure initiation vs. before),
  - anti-phospholipid antibodies (next day vs. before exposure)
  - plasma oxidized LDL (next day vs. before exposure) in session B to E.
  - monocyte mRNA concentrations (3 hrs vs before) [2B]
  - % monocyte DNA FOXP3 regions hypermethylated
  - If different, then is C different from either B or E?
- 2c
  - change in fold-differences in monocyte mRNA PPARα concentrations (3 hrs vs before) between A and D compared to the change between B and E.

Human Controlled Exposure Study

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CENTER FOR CLEAN AIR RESEARCH

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Project 5:

Effects of long-term exposure to TRAP on subclinical measures of CVD in the Multi-Ethnic Study of Atherosclerosis

Joel Kaufman, Sverre Vedal

September 26, 2011

Background: The Multi-Ethnic Study of Air Pollution (MESA Air)

1. To prospectively examine the relation between an individual assessment of long-term air pollution exposures and the progression of subclinical CVD
2. To assess individual-level exposure to specific particulate and gaseous ambient-derived air pollutants
3. To assess the relation between individual assessments of long-term air pollution exposures and incidence of CVD events, including MI and CVD mortality

MESA Air Pollution

Our Approach in MESA Air

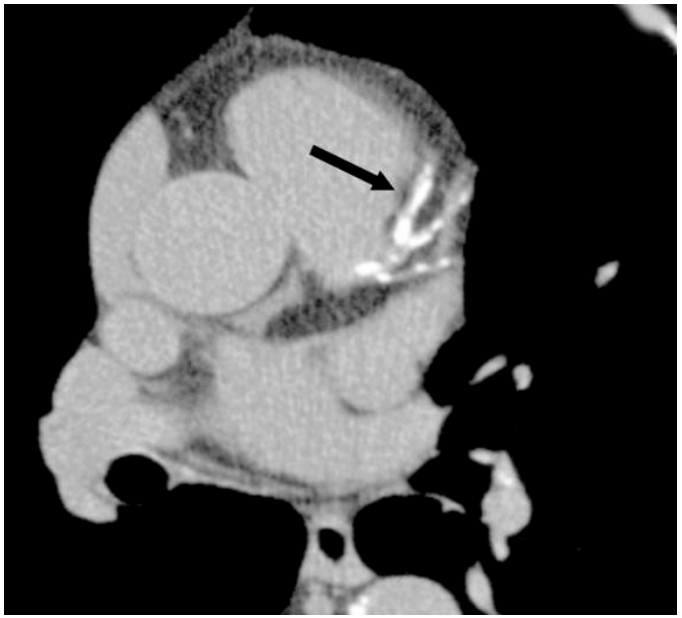
- Pair state-of-the-art cardiovascular epidemiology with state-of-the-art exposure estimation
  - Unusual dedication of resources
- Encourage extensive collaborations and promote opportunities for ancillary studies
  - MESA Air as research platform

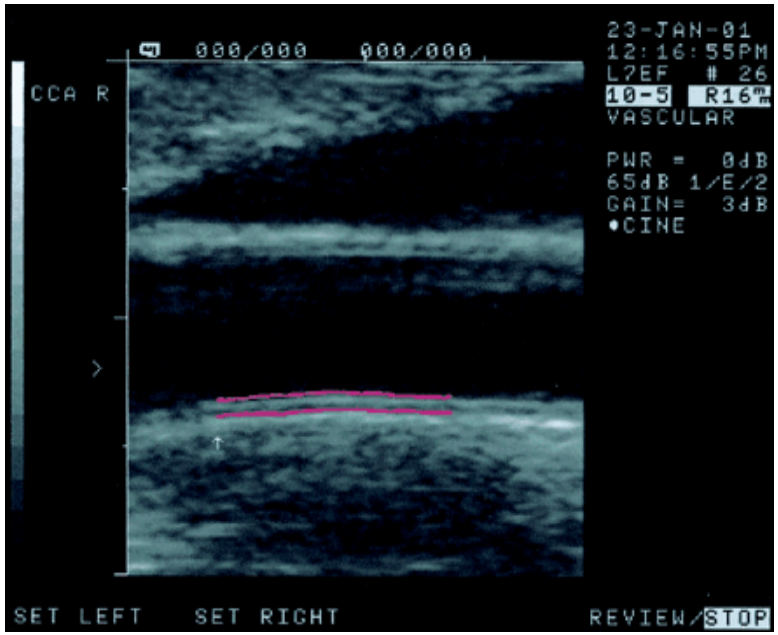
State-of-the Art Epidemiology

- Multi-city (providing exposure heterogeneity)
- ~7,000 ppts, 45-84 yrs old, CVD-free at baseline
- Multi-ethnic sampling strategy (Caucasian, African-American, Hispanic, Chinese-American)

Primary Subclinical Outcomes

- Coronary Artery Calcium (CAC)
- Carotid Artery Intima Medial Thickness (IMT)





Adjudicated clinical events

- Myocardial Infarction
- Stroke/TIA
- Congestive Heart Failure
- Coronary Revascularization
  - PTCA
  - CABG
- Angina
- Peripheral Vascular Disease
- Cardiovascular Death

Extensive interviews

- Medical History
- Medications
- Personal History
- Family History
- Health and Life
- Physical Activity
- Diet
- Neighborhood Characteristics
- Residential History
- Sleep History
- Cognitive Assessment

Other Measures and Specimens

- Anthropometry
- Resting Blood Pressure
- Ankle/Brachial Blood Pressure Index
- ECG
- Spirometry (MESA Lung)

- Cardiac MRI
- Retinal Photography (MESA Eye)
- Quantitative Lung CTs (MESA Lung)

- Urine Collection
- Blood Collection

- Genomics/Epigenomics
  - MESA Family
  - Candidate Genes
  - CARe
  - SHARe
  - DNA methylation
  - Gene Expression

Between-City Exposure Heterogeneity

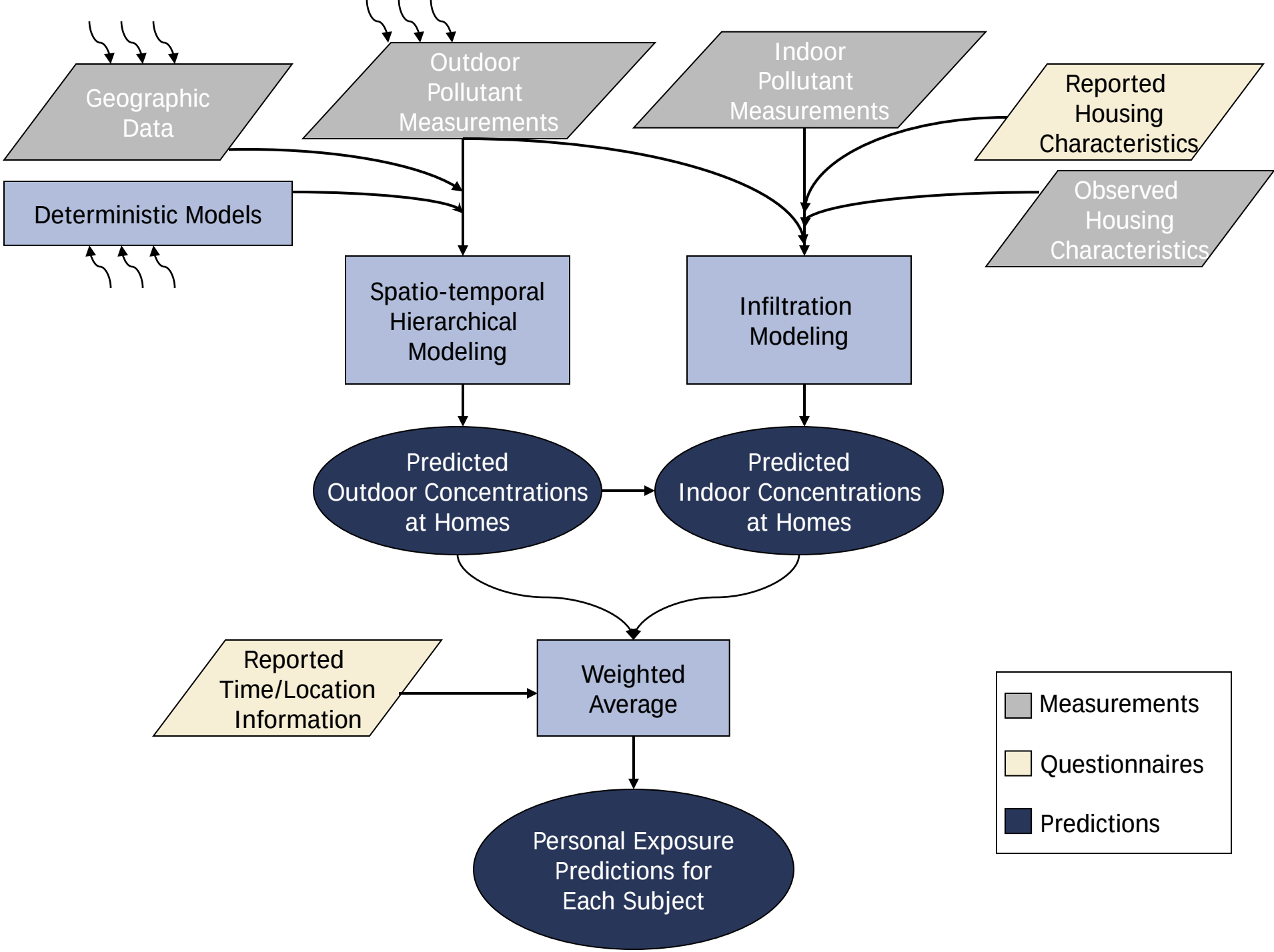
Exposure Characteristics of Communities

	Alhambra	Coastal LA County*	Rubidoux/ Riverside*	St. Paul	Chicago	Manhattan/ Bronx	Rockland County*	Baltimore	Winston-Salem
PM2.5	H	M	VH	L	M	M	L	M	M
PM10	H	M	VH	M	H	H	M	M	L
CO	H	M	H	M	M	H	L	L	M
NO2	H	H	VH	L	M	H	L	L	L
Ozone	H	M	VH	L	M	M	M	H	VH
SO2	L	L	L	M	M	H	H	M	M
Urban contribution	+	+	+	-	+	+	-	+	-
Long-Range Transport	-	-	-	+	+	+	+	+	+

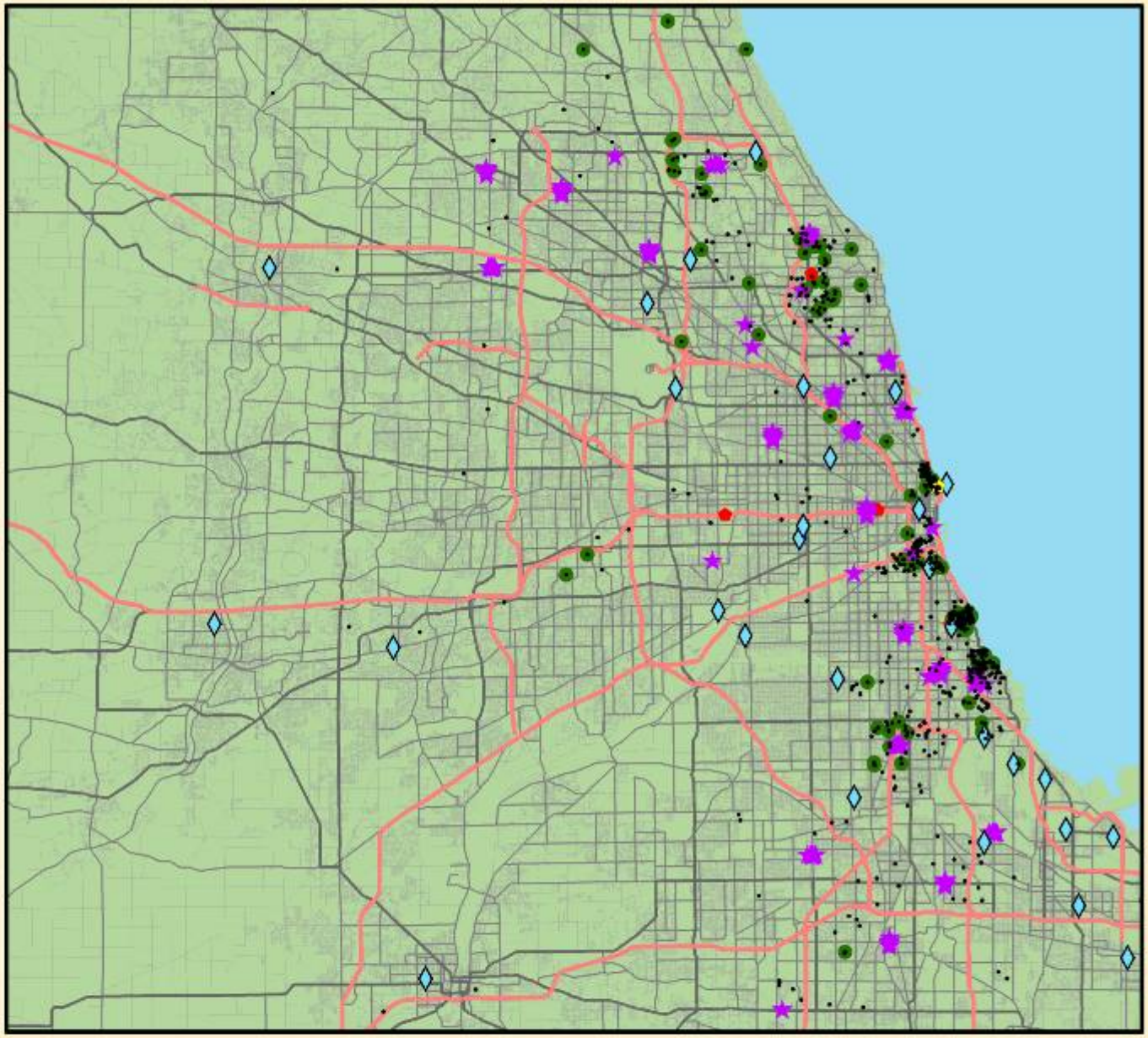
L=Low, M=Medium, H=High, VH=Very High

e.g., for $PM_{2.5}$: L= (~12 $\mu g/m^3$), M= (~16 $\mu g/m^3$), H = (~20$\mu g/m^3$), VH= (~24 $\mu g/m^3$) annual averages

Blue = Areas of New Recruitment for MESA Air


Geographic Data
Outdoor Pollutant Measurements
Indoor Pollutant Measurements
Reported Housing Characteristics
Deterministic Models
Observed Housing Characteristics
Spatio-temporal Hierarchical Modeling
Infiltration Modeling
Predicted Outdoor Concentrations at Homes
Predicted Indoor Concentrations at Homes
Reported Time/Location Information
Weighted Average
Personal Exposure Predictions for Each Subject
Measurements
Questionnaires
Predictions

Focus Area



Legend

- MESA Air Participants
- Home Monitoring Sites
- Community Co-pollutant Monitors
- Fixed Monitoring Sites
- Field Center
- EPA Monitoring Sites
- Primary Interstate highways
- Primary US and State highways
- Secondary State and County highways
- Local, neighborhood, rural streets

All monitoring data are as of December 17, 2007.
Road network data are as of April 1, 2006.
Participant information provided by the
Collaborative Health
Studies Coordinating Center.

Universal Transverse Mercator Zone 18 (NAD '83)

0 2.5 5 10 15 20

Kilometers

Northwestern University Study Area

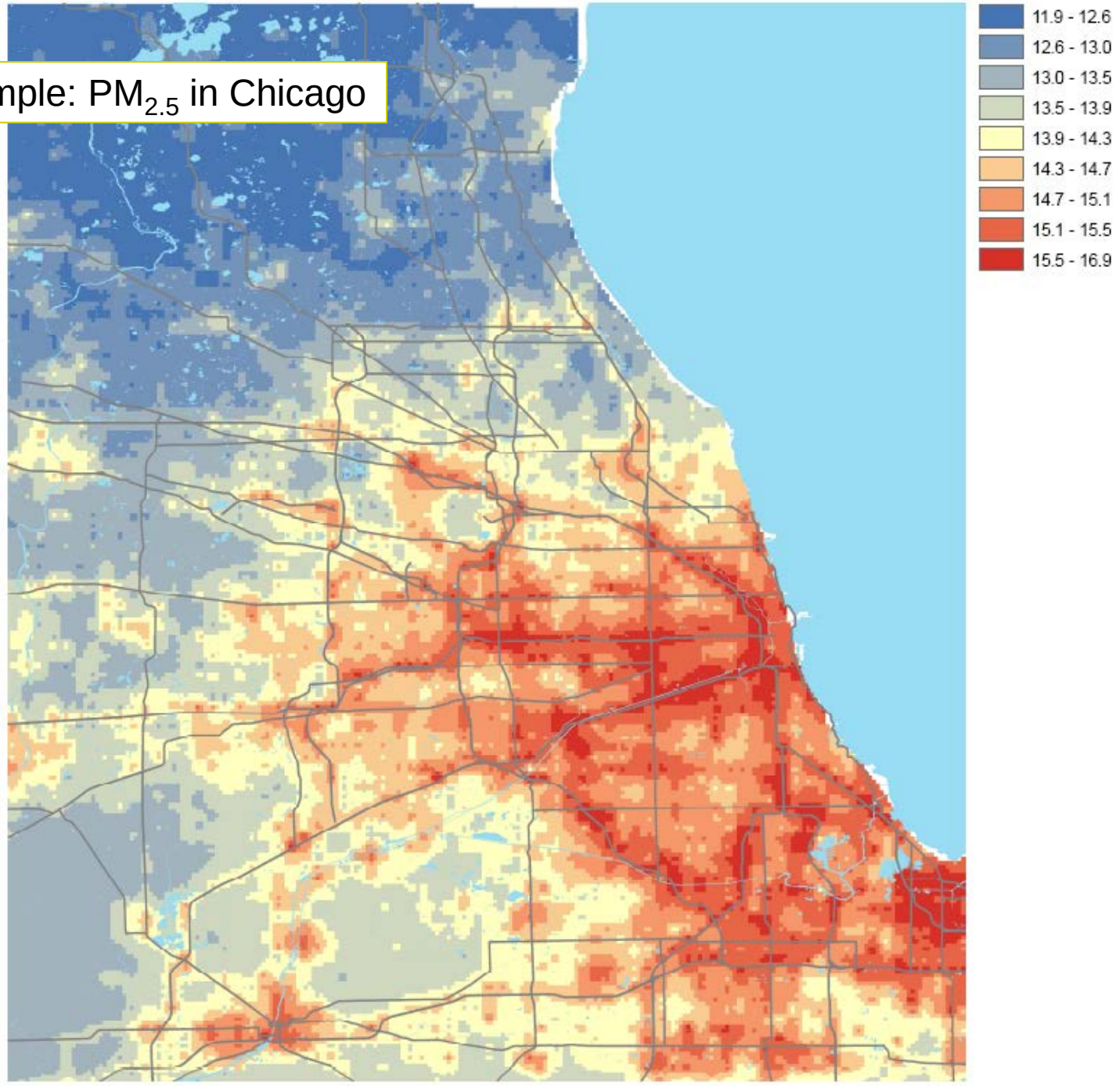
Chicago, Illinois

MESA Air Pollution Study
December 17, 2007

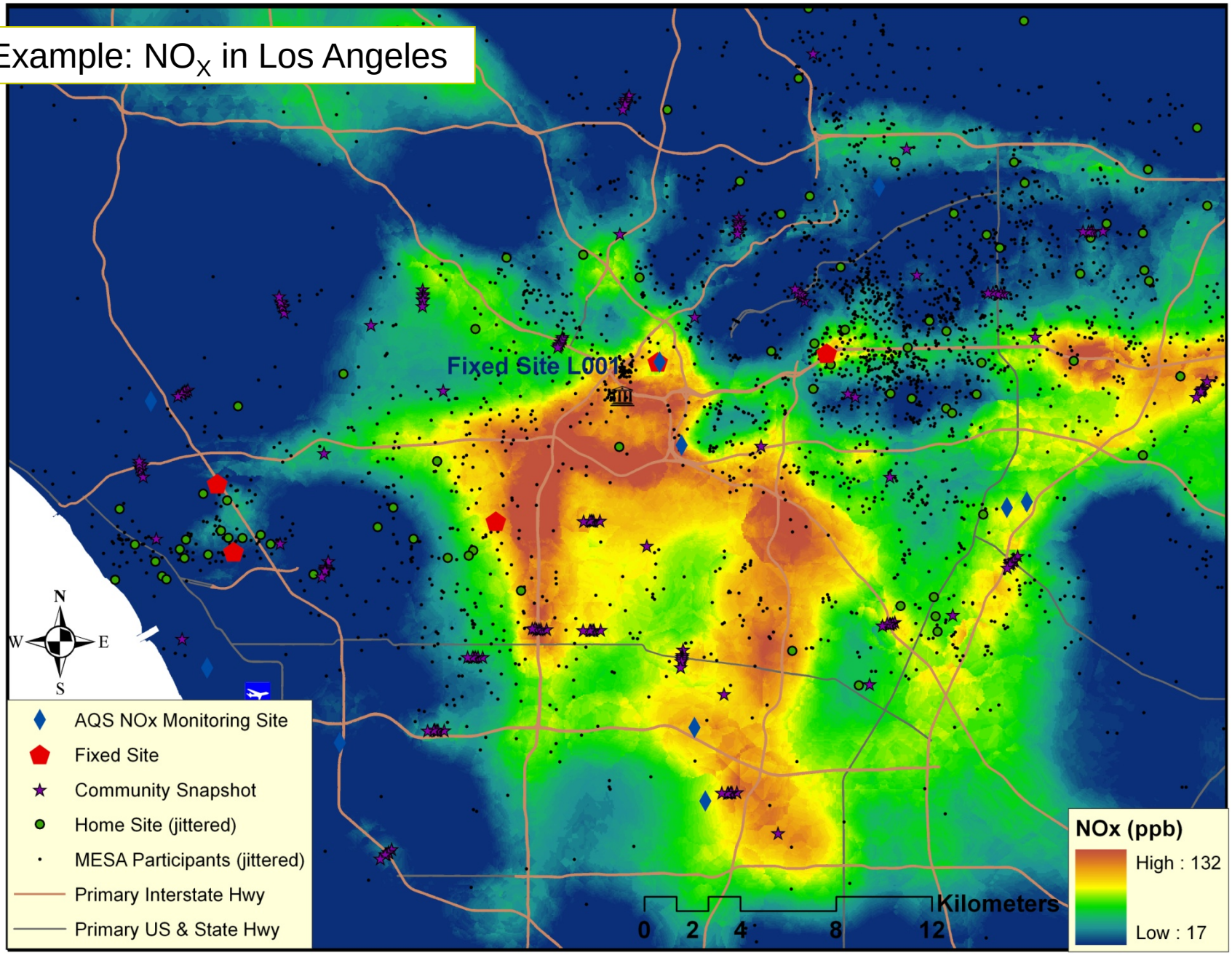
Data Source:

MESA Air

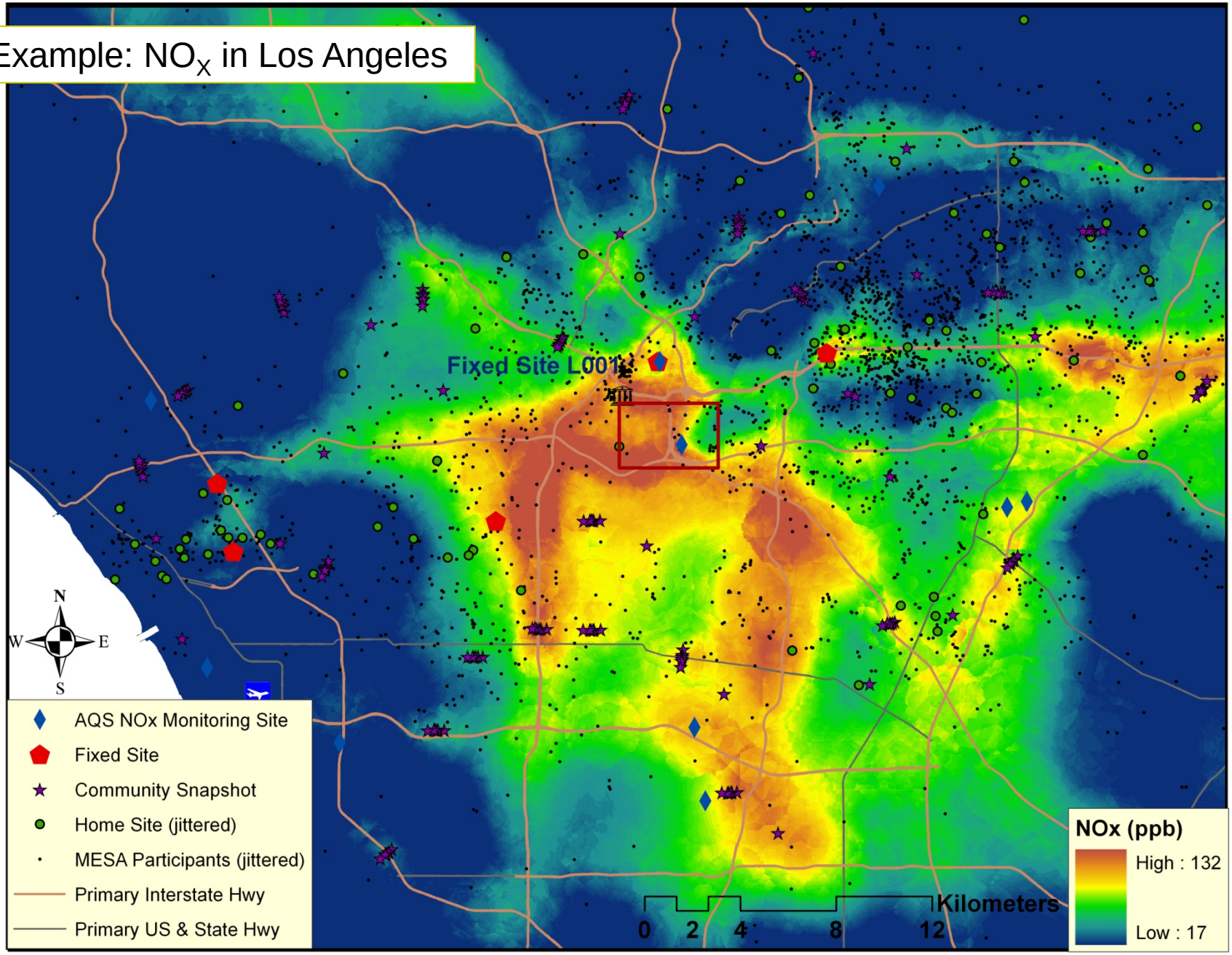
Example: $PM_{2.5}$ in Chicago



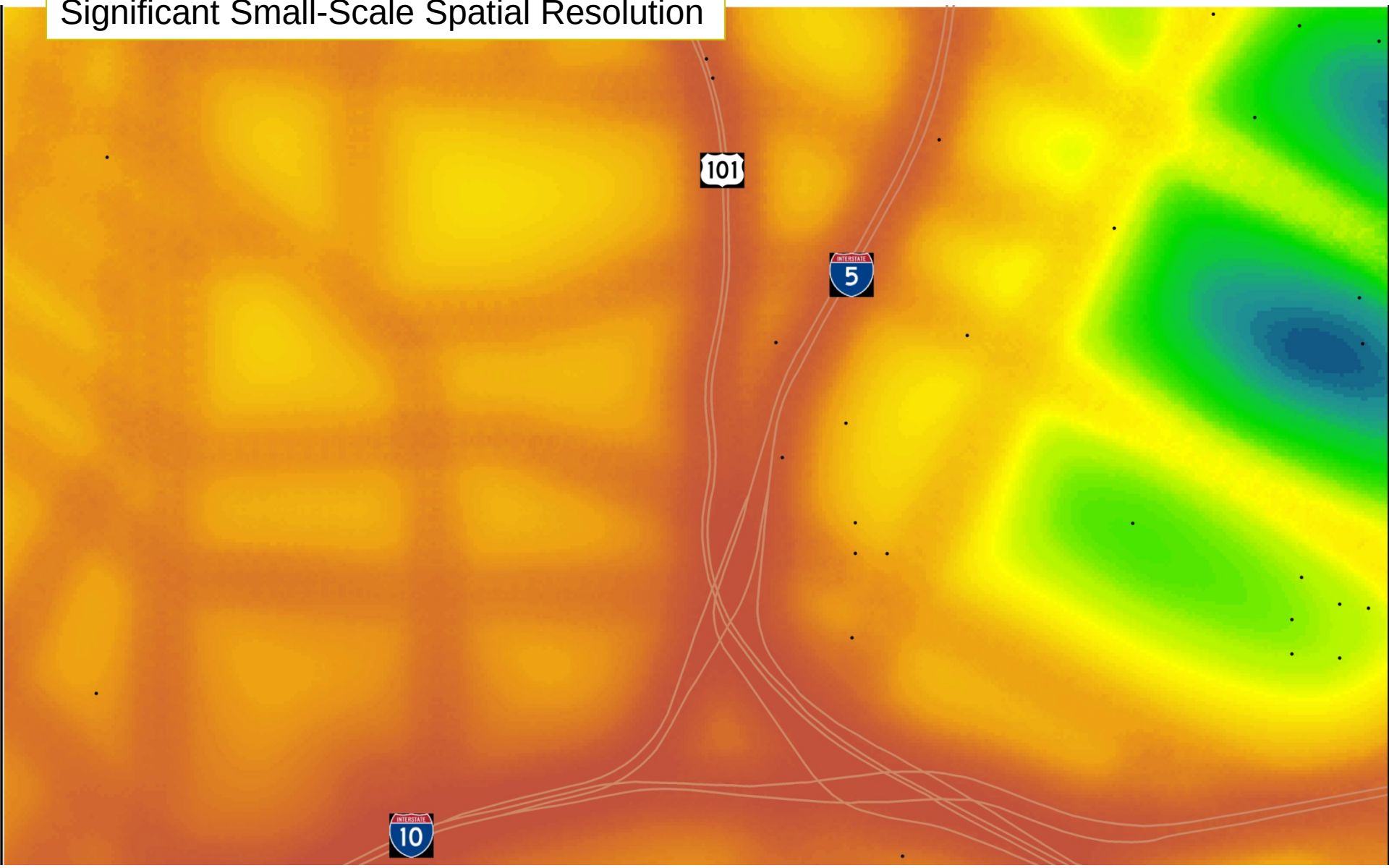
Example: NO_X in Los Angeles



Example: NO_X in Los Angeles



Significant Small-Scale Spatial Resolution



CCAR Project 5

- Aim 1: To build a multi-pollutant exposure model for traffic-derived air pollutants for use in epidemiological analysis
- Aim 2: To develop and validate individual-level exposure estimates for traffic-derived air pollutants, including a determination of the effect of time in transit
- Aim 3: To estimate the effect of individual-level exposure to traffic-derived air pollution on subclinical cardiovascular disease in MESA Air

Aim 1: Generate individual-level predictions of outdoor pollutant levels

- Predictions of long-term average multi-pollutant concentration fields achieved by combining the predictions from two seasonal co-kriging models in each city: Baltimore, Winston-Salem, St. Paul, Los Angeles
- Predictions of the impact of traffic patterns and roadway class on pollutant concentrations

Aim 2: Understand in-vehicle exposures

- Recruit 144 participants from Winston-Salem and LA to participate in 2 two-week sampling events
  - Indoor, outdoor, personal, and in-vehicle monitoring
  - NO_X, NO, NO_2, SO_2, O_3, and a suite of up to 11 VOCs

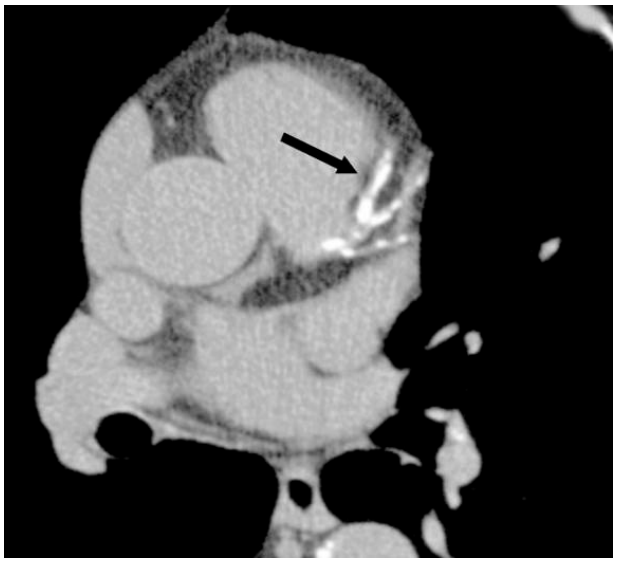

  - GPS data-logging devices to track location

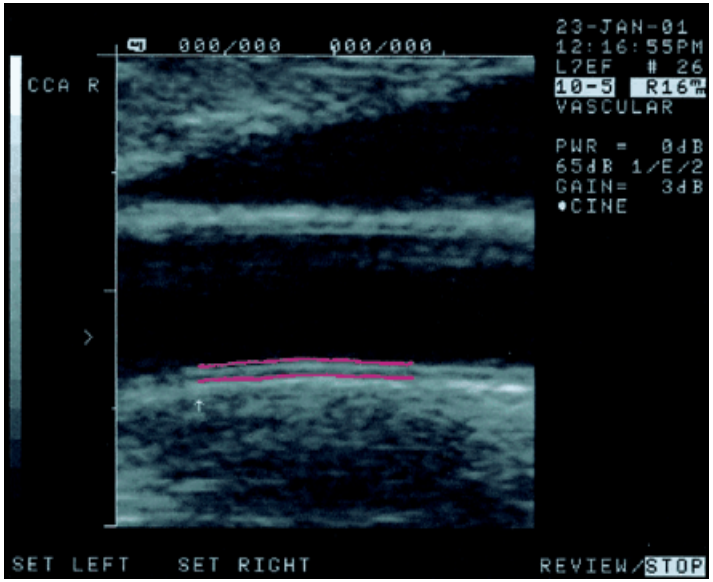
Aim 2, continued

- Information learned from the in-vehicle monitoring study will be applied to all participants, including VOC infiltration efficiency and the relationships between:
  - total personal exposure and in-vehicle exposure
  - reported time-in-transit and measured time-in-transit

Aim 3: Epidemiologic Analysis in the MESA cohort

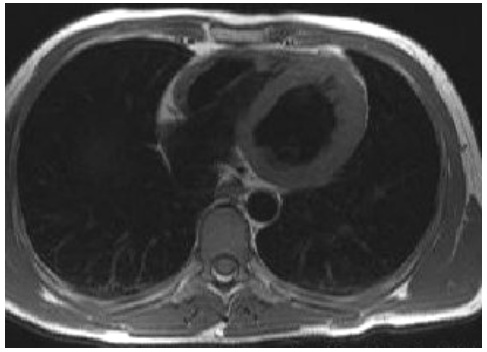
- To understand the relation between exposure to TRAP and changes in CAC and IMT over 10 years, assessed via CT and ultrasound

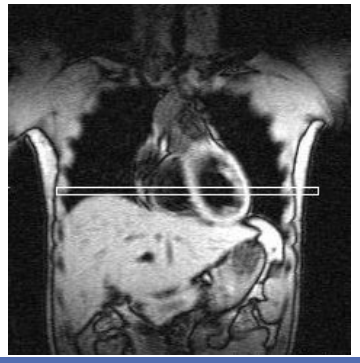


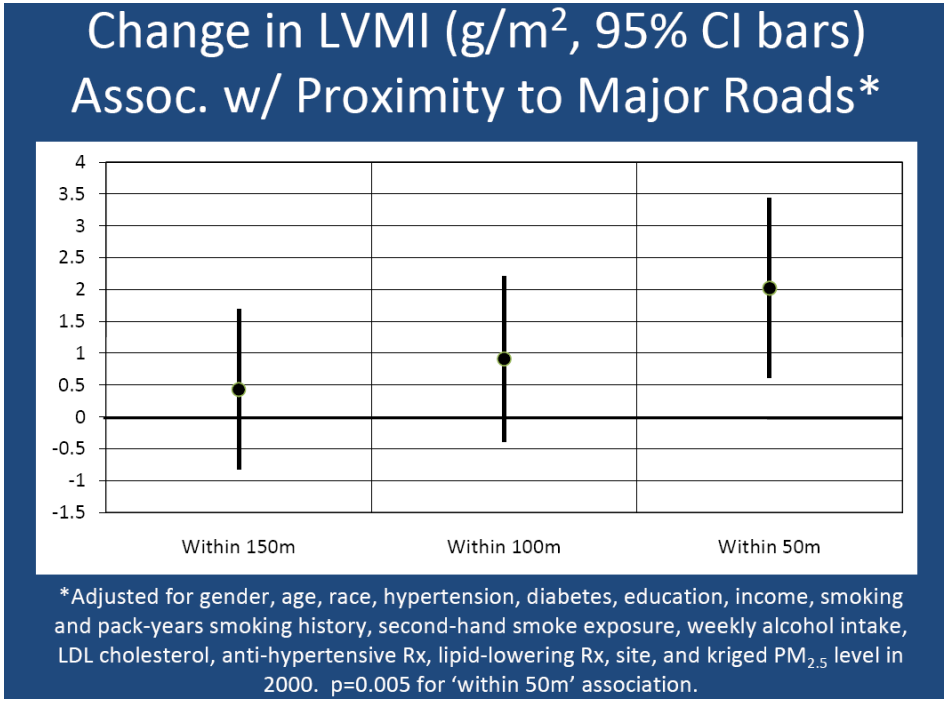


Aim 3: Epidemiologic Analysis in the MESA cohort

- To understand the relation between exposure to TRAP and change in left ventricular myocardial mass over 10 years, assessed via MRI

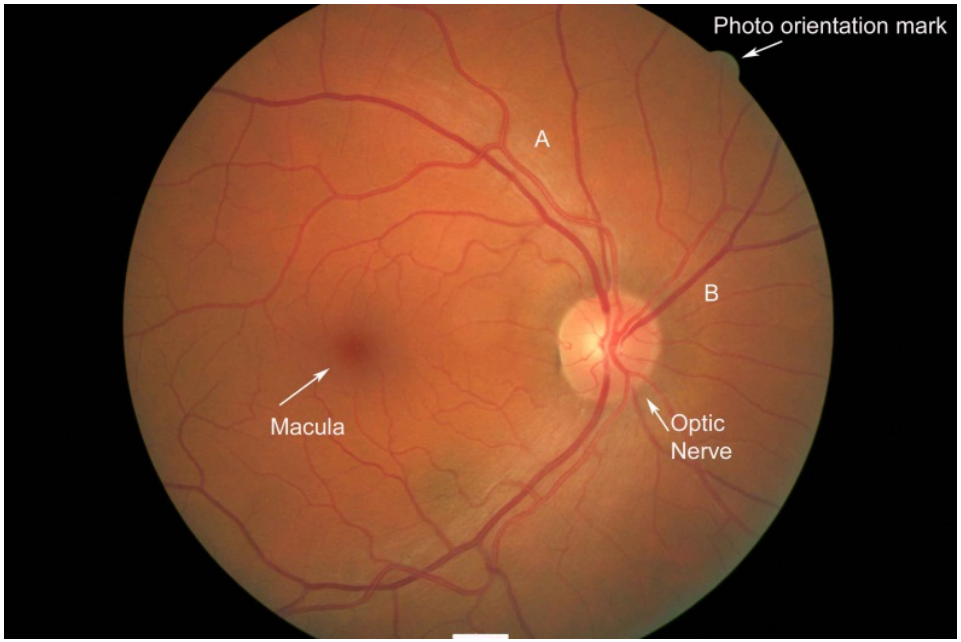


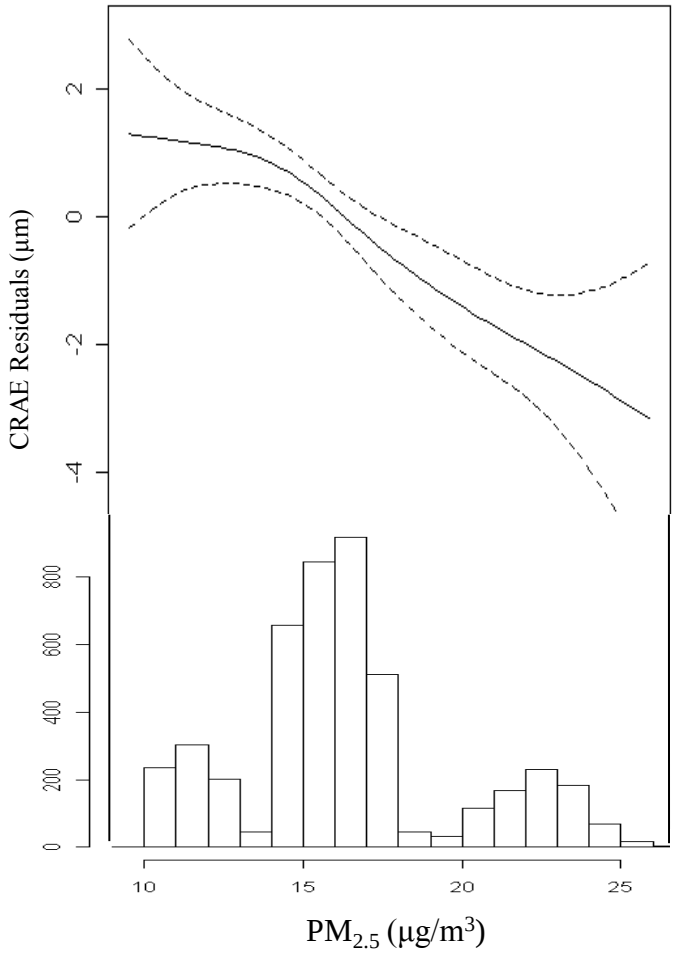




Aim 3: Epidemiologic Analysis in the MESA cohort

- To understand the relation between exposure to TRAP and changes in arteriolar diameters over 8 years, assessed via retinal photography





Aim 3: Epidemiologic Analysis in the MESA cohort

- To explore the impact of exposure to traffic-derived air pollutants on DNA methylation
  - Hypothesis generating
  - Whole-genome epigenetic analysis using a vector of DNA methylation profiles as the outcome
- Due to changes within MESA, participants in Los Angeles are no longer part of the main MESA epigenetics protocol

MESA Air is adding a modified epigenetics protocol at UCLA

- Participants in this region (and especially the new recruits in Riverside LA) experience some of the highest and most heterogeneous concentrations of air pollutants in the MESA Air cohort

- Approved ancillary study modification to allow for the collection, processing, and storage of additional blood samples from ~150 participants in LA

CENTER FOR CLEAN AIR RESEARCH

UNIVERSITY *of* WASHINGTON

Biostatistics Core

PI: Lianne Sheppard
Adam Szpiro
Paul D Sampson

Biostatistics Core Objectives

1. Advise Center projects on data management and compilation
2. Ensure quality statistical design and analysis of Center research
3. Implement novel statistical methods that are required for Center projects (Project 6)
4. Identify additional statistical research that will advance Center projects
5. Communicate and disseminate Center findings

1. Advise Center projects on data management and compilation

- Provide advice on: (i) Database design, (ii) Forms design, (iii) Data entry support, (iv) Data quality review, (v) Data storage and back-up, (vi)Documentation
- Due to resource limitations, the role of the Biostat Core in database management and compilation will be advisory. We will exploit established MESA Air and other ancillary study infrastructure for needed support for these activities.

2. Ensure quality statistical design and analysis of Center research

- Fundamental Core activity conducted at weekly meetings of Core faculty and staff. Consultation addresses:
  - (i) Study design,
  - (ii) Sample size calculations,
  - (iii) Data collection,
  - (iv) Statistical analysis plan (SAP) development,
  - (v) Statistical analysis,
  - (vi) Interpretation of study results.

Statistical Analysis Plan Template

- **Working Title:**
- **Overview/Purpose:**
- **General Scientific Question(s); Specific Scientific Question(s) (e.g. hypotheses):**
- **Outcomes of Interest; Predictors of Interest; Potential Confounders or Adjustment Variables:**
- **Other Data Specifics (e.g. time period, subgroup):**
- **Data request (date, number):**
- **Type of Analysis:** Hypothesis testing Estimation
  - Hypothesis screening Modeling
  - Hypothesis generating/exploratory Method evaluation
  - Descriptive
- **Analysis Approach and Special Issues:**
- **List of Tables:** (or note location of draft tables)
- **Responsibilities and deadlines:**
  - Paper outline
  - Initial analyses
  - Introduction
  - Methods
  - Results
  - Discussion
  - Tables and Figures
  - Follow up analyses
  - Final Draft
- **Names and roles (authors, co-authors, Data Core staff):**
- **Revision History:**

3. Implement novel statistical methods that are required for Center projects

- Incorporating multi-pollutant spatial data from fixed and mobile monitoring in multivariate spatial modeling for exposure prediction
- Modeling disease outcomes with multi-pollutant exposures; computing scientifically meaningful RRs and other effect estimates for air pollutant mixtures
- Multi-pollutant measurement error correction in disease modeling

[These points addressed further by Adam Szpiro.]

4. Identify additional statistical methodological research that will advance Center projects

- Active participation of statisticians enables identification of scientific problems that would benefit from innovative approaches to statistical analysis
- Two-way interaction:
  - => Center scientists providing motivating applications and questions for methods research
  - <= Center scientists responding to Biostat Core suggested enhancements in statistical design and analysis for Center-sponsored research.
- Additional methodological research may not be funded through CCAR, but
  - CCAR will provide platform for methodology research proposals, and
  - Methodological research may provide a focus for cross-center collaboration.

5. Communicate and disseminate Center findings

- Biostat core will bring to bear the most *current perspectives* from the fields of statistics and biostatistics on the *interpretation and communication* of statistical analyses
- Examples from CCAR research can be featured in statistical papers that a) provide new methodological development, or b) demonstrate methods implementation.
- Core will:
  - Support manscript preparation and review
  - Foster understanding of more complex statistical models and methods
  - Engage statisticians in air pollution research.

Summary: General and Specific Connections with other CCAR Projects

The objectives of the Biostatistics Core comprise:

(a) "Routine" consulting and collaboration with all projects on topics of data management, analysis, and report writing

(b) "Out-of-the-box" methodological development (objectives 3, 4), including, for example,

i. Consultation on the mobile monitoring study design and sample size (project 1)

ii. Multivariate characterization of the pollutant compositions that distinguish fresh and aged atmospheres (projects 1, 2, 3 and 4)

iii. Strategies for multi-pollutant exposure modeling and health analyses (project 5)

CENTER FOR CLEAN AIR RESEARCH

UNIVERSITY *of* WASHINGTON

Strategy for Multi-Pollutant Exposure Modeling and Health Analysis "Project 6"

UW CCAR
Scientific Advisor Committee
26 September 2011

Objective

- An integrated statistical methodology for analyzing multi-pollutant health effects in cohort studies
- Connections with other CCAR projects
  - Project 1, Objective 1: Characterize spatial and temporal gradients of selected air pollutants along roadways and within neighborhoods in MESA cities using a mobile platform
  - Project 1, Objective 2: Measure spatial variation in concentrations of selected air pollutants at two-week average fixed sites in coordination with the mobile measurements
  - Project 5, Objective 1: Develop city-wide exposure surfaces for traffic-derived air pollution components for each of four study cities
  - Project 5, Objective 3: Assess the effect of individual-level exposure to traffic-related air pollution, including on-roadway exposures, on vascular outcomes, including left ventricular mass and retinal arteriolar diameter, and epigenetic phenomena in a cohort of over 4,000 MESA Air participants

Statistical Challenges

- As much as possible, we will extend our methods from single-pollutant studies
- Challenges specific to (this) multi-pollutant setting
  - Exposure prediction for multiple correlated pollutants based on data from complex spatio-temporal monitoring campaign
  - Formulation and interpretation of multi-pollutant health effect quantities of interest
  - Accounting for different types and magnitudes of measurement error between pollutants

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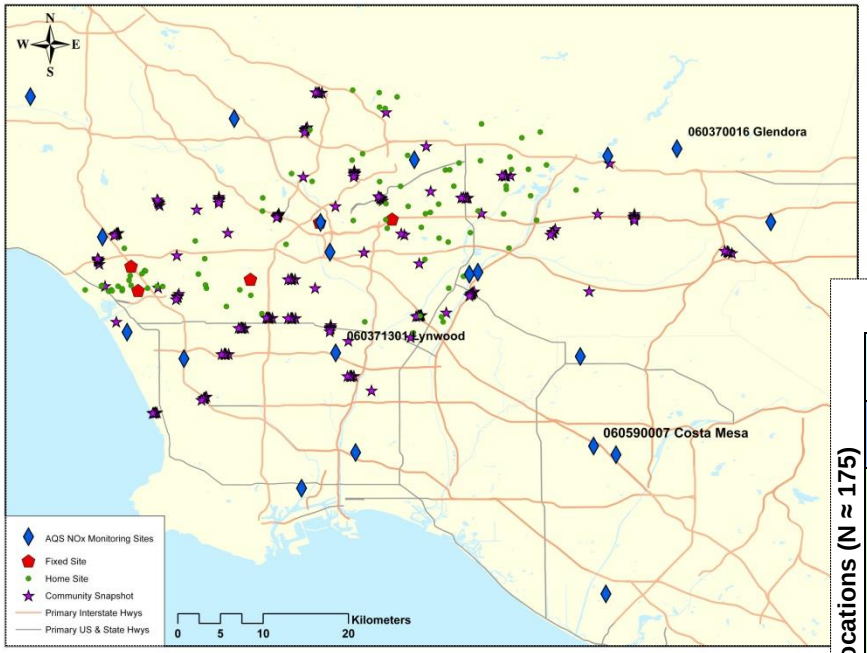
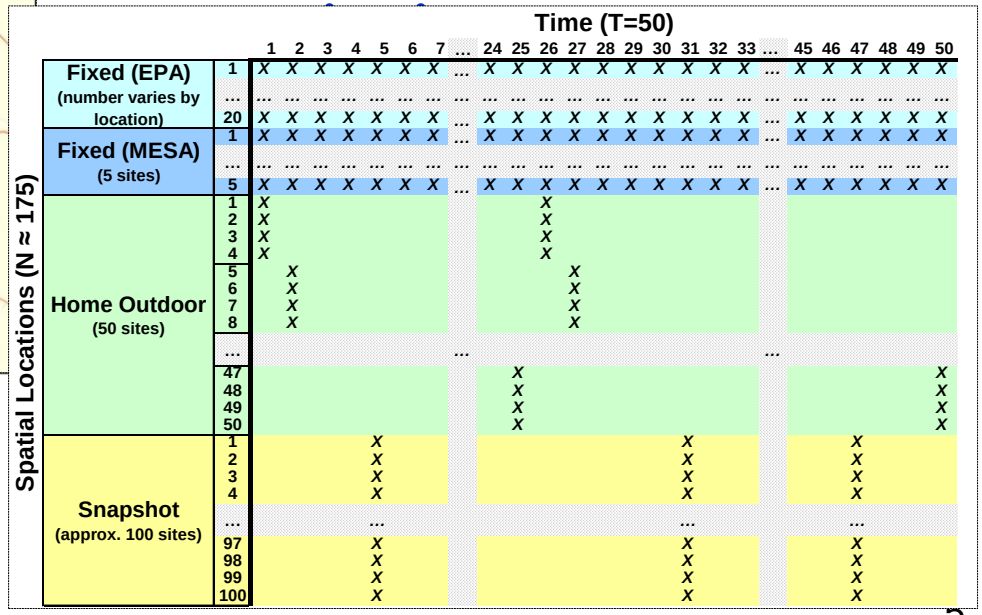
MESA Air and AQS Monitoring Data

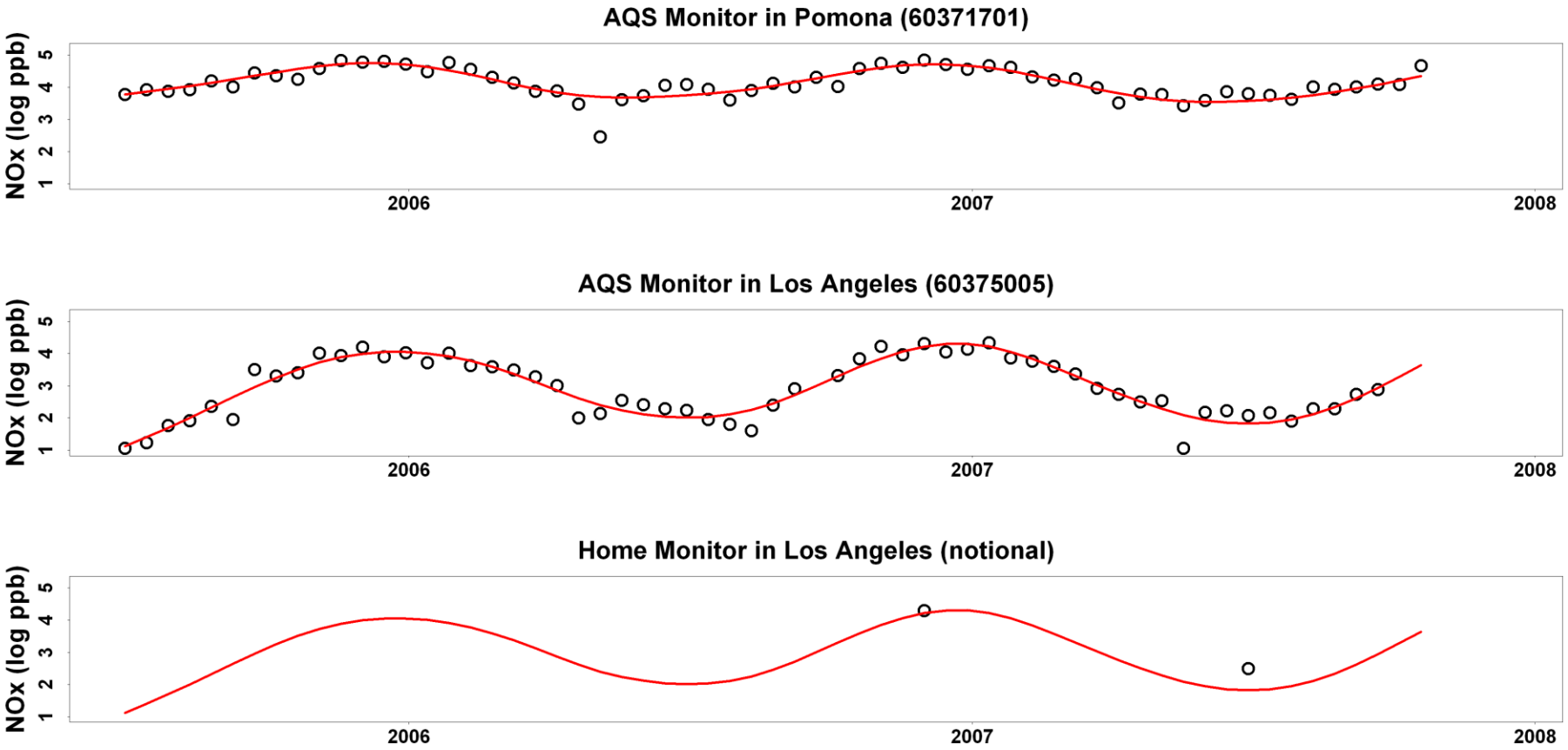
- Air pollution monitoring data at approximately 200 locations in each city with irregular spatio-temporal pattern



- **Some data collected by EPA AQS for regulatory purposes**
- **Additional study-specific**



Need For Spatio-Temporal Model



Space-time interaction and temporally sparse data suggest spatio-temporal model to predict long-term averages

MESA Air Spatio-Temporal Exposure Model

- $X_{s,t} = \mu_{s,t} + \nu_{s,t}$ ← measured concentrations on log scale
- $\mu_{s,t} = \beta_{0,s} + \sum_{i=1}^{m} \beta_{i,s} f_i(t) + \gamma M(s,t)$ ← temporal trend at location s + space-time covariate
  - $f_i(t)$ temporal basis functions derived from data
  - $\beta_{i,s}$ spatial random fields distributed as $N\left(S_i \alpha_i, \Sigma\left(\phi_i, \sigma_i^2\right)\right)$
    - Geostatistical covariance structure with "land use" regression covariates for population, traffic, land use, etc.
- $\nu_{s,t}$ ← variation from temporal trend (mean 0)
  - Geostatistical spatial structure with simple temporal correlation
    - Process noise + measurement error

Szpiro et al. *Environmetrics* (2010), Sampson et al. *Atmos. Env.* (2011)

Spatio-Temporal Modeling in CCAR

- MESA Air spatio-temporal model successfully applied to NOx, NO_2, and $PM_{2.5}$
  - Uses several fixed sites (AQS and study-specific) to create backbone for spatially varying temporal trend model
  - Allows flexible adjustment for seasonality in home monitoring ans snapshot data (irregular in space and time)
- Direct application in CCAR not feasible
  - Extension to multiple pollutants challenging (at least!)
  - Multiple long-term fixed site monitors not available for most pollutants

Removing Seasonality in CCAR

- Primary approach
  - Time trend from single fixed site deployed concurrently with mobile monitoring
- Extension
  - Spatially varying time trends from spatio-temporal predictions of NOx, PM, and other pollutants with sufficiently rich monitoring data

Multi-Pollutant Spatial Prediction

- Don't observed actual exposures X_{ik}
- Monitoring data X_{ik}^{*} for pollutant k at location s_i^{*}
  - There may be some missing data, but for the most part all pollutants measured at all locations
- Use combination of land-use regression and spatial smoothing to predict unobserved X_{ik}
- Two main differences from single-pollutant
  - Want to borrow information between pollutants
  - Want to avoid measurement-error induced confounding

Option 1: Full-Rank Prediction (Co-Kriging)

- Model each pollutant as linear in r geographic covariates with spatially correlated residuals
  - $R_k(s)$: $\mathbb{R}^2 \rightarrow \mathbb{R}^r$ defines the covariate basis for pollutant k
  - $X_{ik}^* = R_k(s_i^*)\gamma_k + \eta_{ik}^*$
  - $X_{ik} = R_k(s_i)\gamma_k + \eta_{ik}$
  - η_{ik}^*, η_{ik} are correlated spatial random effects with a co-kriging, e.g., linear model of coregionalization, structure (many variance parameters)
  - Predict $\hat{X}_{ik}$ as conditional expectation, with ML parameter estimates
- Advantages
  - Allows complex inter-pollutant correlation that induces borrowing of information
  - "Natural" extension of (now) standard universal kriging methods
- Disadvantages
  - Computationally very challenging
  - Possibilities of measurement error confounding not clear

Option 2: Low-Rank Prediction

- Model each pollutant as linear in r geographic covariates with q-dimensional regression splines for spatial smoothing
  - $R_k(s)$: $\mathbb{R}^2 \rightarrow \mathbb{R}^{q+r}$ defines the spline/covariate basis for pollutant k
  - $X^*_{ik} = R_k(s^*_i)\gamma_k + \eta^*_{ik},\ \eta^*_{ik}$ iid
  - $X_{ik} = R_k(s_i)\gamma_k + \eta_{ik},\ \eta_{ik}$ iid
  - Jointly estimate the γ_k from monitoring data by (penalized) OLS/WLS
  - Predict $\hat{X}_{ik} = R_k(s_i)\hat{\gamma}_k$
- Advantages
  - Computationally tractable
  - Preliminary results suggest appropriate choice of $R_k(s)$ avoids measurement error induced confounding
- Disadvantages
  - Not clear how to borrow information between pollutants

Selecting Land-Use Covariates

- Regardless of spatial smoothing technique, land-use covariates are central to prediction
  - Hundreds of covariates available, including traffic density, emissions, population density, land-use, NDVI, etc.
- Variable selection/dimension reduction an especially big challenge for multiple pollutants
  - Process really needs to be automated
  - Not immediately clear whether to use the same covariates for all pollutants

Selecting Land-Use Covariates

- Two approaches we have used for single pollutant models appear promising because they are computationally tractable and automated
  - Partial least squares (similar to principal components)†
  - Lasso followed by exhaustive search of candidate models for varying levels of penalty parameter‡
- Optimize predictions for best health effect inference rather than just exposure prediction accuracy*

† Mercer et al. *Atmos. Env.* (2011), ‡ Sampson et al. *Atmos. Env.* (2011), * Szpiro et al. *Epidemiology (2011)*

Statistical Challenges

- As much as possible, we will extend our methods from single-pollutant studies
- Challenges specific to (this) multi-pollutant setting
  - Exposure prediction for multiple correlated pollutants based on data from complex spatio-temporal monitoring campaign
  - Formulation and interpretation of multi-pollutant health effect quantities of interest
  - Accounting for different types and magnitudes of measurement error between pollutants

Reducing Dimensionality of the Disease Model: A Promising New Paradigm

- General disease model not practical
  - $E(Y_i|X_{i1}, \ldots, X_{iK}) = \psi\left(\beta_0 + \sum_{k=1}^{K} \beta_k X_{ik} + interactions\right)$
  - Expect correlations between pollutant concentrations
  - Too many main effect and interaction coefficients to estimate **or** interpret
    - Leaving out interactions would likely miss important features of health effects
- Alternative paradigm
  - Estimate effect of different ***atmospheric mixtures***, rather than individual pollutant health effects
  - Operationalize this by characterizing the interesting atmospheres with a small number of ***eigenpollutants***

Dimension Reduction Steps

- Step 1: Predict the full set of multi-pollutant concentrations at subject locations $\hat{X}_{ik}$ for $k = 1, \ldots, K$
- Step 2: Perform principal component analysis on the $\hat{X}_{ik}$ and keep the first P (say $P = 2$) eigenpollutants $\hat{X}'_{ip}$
- Step 3: Fit reduced dimension version of disease model with all interactions (linear here for simplicity)
  - $E(Y_i|X'_{i1}, X'_{i2}) = \beta_0 + \beta_1 X'_{i1} + \beta_2 X'_{i2} + \beta_{12} X'_{i1} X'_{i2}$
- Step 4: Compare atmospheres of interest by approximating them using eigenpollutants
  - Compare atmosphere 2 to 1: $(\alpha_{j1}, \ldots, \alpha_{jK}) \Rightarrow (\alpha'_{j1}, \alpha'_{j2})\ j = 1,2$
  - $RR_{21} \approx \hat{\beta}_1(\alpha'_{21} - \alpha'_{11}) + \hat{\beta}_2(\alpha'_{22} - \alpha'_{12}) + \hat{\beta}_{12}(\alpha'_{21}\alpha'_{22} - \alpha'_{12}\alpha'_{12})$
  - $\ldots$

Alternative Strategies

- How to reduce dimension of pollutants to span the interesting range of atmospheres
  - PCA is just a tool, and it may not be the best one
  - Could use PMF, but don't need to interpret in terms of sources
  - Linear model of co-regionalization effectively does PCA (although we also want to capture variability that is predictable with covariates)
- Could do dimension reduction on the monitoring data, **before** multi-pollutant exposure prediction
  - Can exploit additional mobile monitoring data collected en-route

Comments

- **The goal is to evaluate relative health effects of different pollutant mixtures, not to interpret the individual effect estimates**
- Can make policy relevant statements about what would happen if regulations were modified that resulted in some expected change in the aggregate mixture/levels of various pollutants
- This approach will be useful to the extent that the range of possible/interesting atmospheres can be represented by a small number of eigenpollutants

Statistical Challenges

- As much as possible, we will extend our methods from single-pollutant studies
- Challenges specific to (this) multi-pollutant setting
  - Exposure prediction for multiple correlated pollutants based on data from complex spatio-temporal monitoring campaign
  - Formulation and interpretation of multi-pollutant health effect quantities of interest
  - Accounting for different types and magnitudes of measurement error between pollutants

Single Pollutant Measurement Error

- Two components to the measurement error†

$$
\begin{aligned}
U &= X - \hat{X} \\
&= X - E\left(X|X^*;\hat{\gamma},\hat{\theta}_\eta\right) \\
&= \left[X - E\left(X|X^*;\gamma,\theta_\eta\right)\right] + \\
&\quad \left[E\left(X|X^*;\gamma,\theta_\eta\right) - E\left(X|X^*;\hat{\gamma},\hat{\theta}_\eta\right)\right] \\
&= U_{BL} + U_{CL}
\end{aligned}
$$

  - "Berkson-like" component (U_{BL}) from smoothing (inflates standard errors)
  - "Classical-like" component (U_{CL}) from parameter estimation (introduces bias and inflates standard errors)

- Parametric bootstrap effective at correcting bias and variance (parameter bootstrap an efficient approximation)

† Szpiro et al. *Biostatistics (2011)*, Gryparis et al. *Biostatistics (2009)*

Multi-Pollutant Measurement Error Correction

- Parametric bootstrap generalize to multi-pollutant case, at least in principle
  - Need to believe assumptions about correlated spatial random effects are plausible (linear model of coregionalization)
  - Differences in magnitude and type of measurement error can **transfer effects between pollutants** – parametric bootstrap could miss this
    - How much does this matter if we are comparing atmospheric mixtures?
- Alternative paradigm emphasizes fixed exposure surface that is not fully predictable
  - No random effect
  - More consistent conceptually with low-rank prediction
  - Non-parametric bootstrap (and possibly some analytic calculations) can replace parametric bootstrap

Summary

- Reduce spatio-temporal mobile monitoring data to purely spatial by removing temporal trends
  - Single time series or use spatio-temporal results from other pollutants
- Multi-pollutant spatial prediction modeling
  - Land-use regression + co-kriging or low-rank splines
  - Take care to avoid measurement error induced confounding
- Reduce dimension of pollutant space
  - PCA or similar
- Make inference about comparison of different atmospheric mixtures, rather than contribution of individual pollutants
- Correct for exposure measurement error