Children's Growth:
An Introduction to Nonlinear Modeling

Eva M Tanner, PhD, MPH

Postdoctoral Researcher

Icahn School of Medicine at Mount Sinai

etanner@mssm.edu

https://github.com/evamtanner

Mentor: Chris Gennings

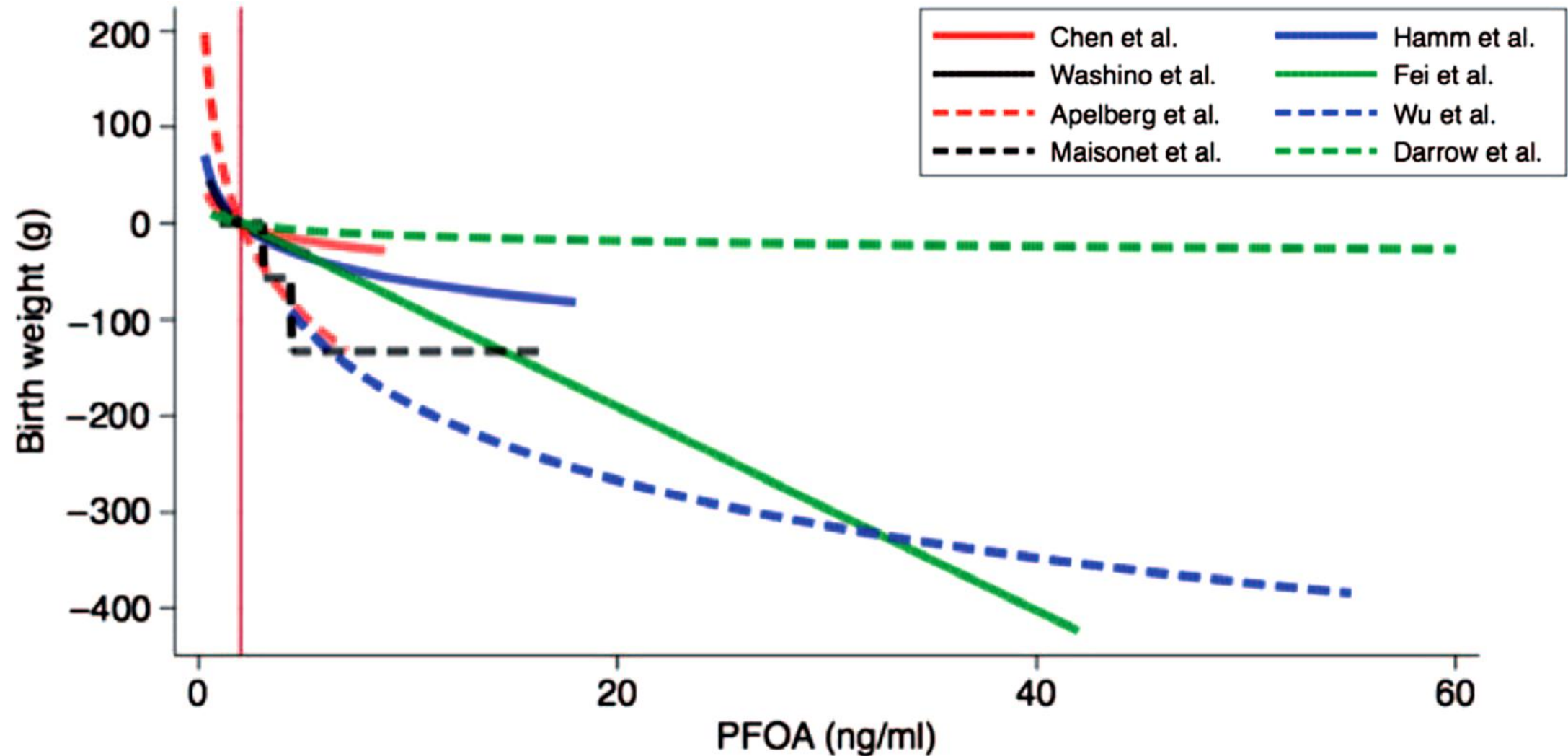Children's Seminar on Prenatal Exposure to Mixtures of Environmental Chemicals and Children's Growth

9/25/19

Mount Sinai

Outline
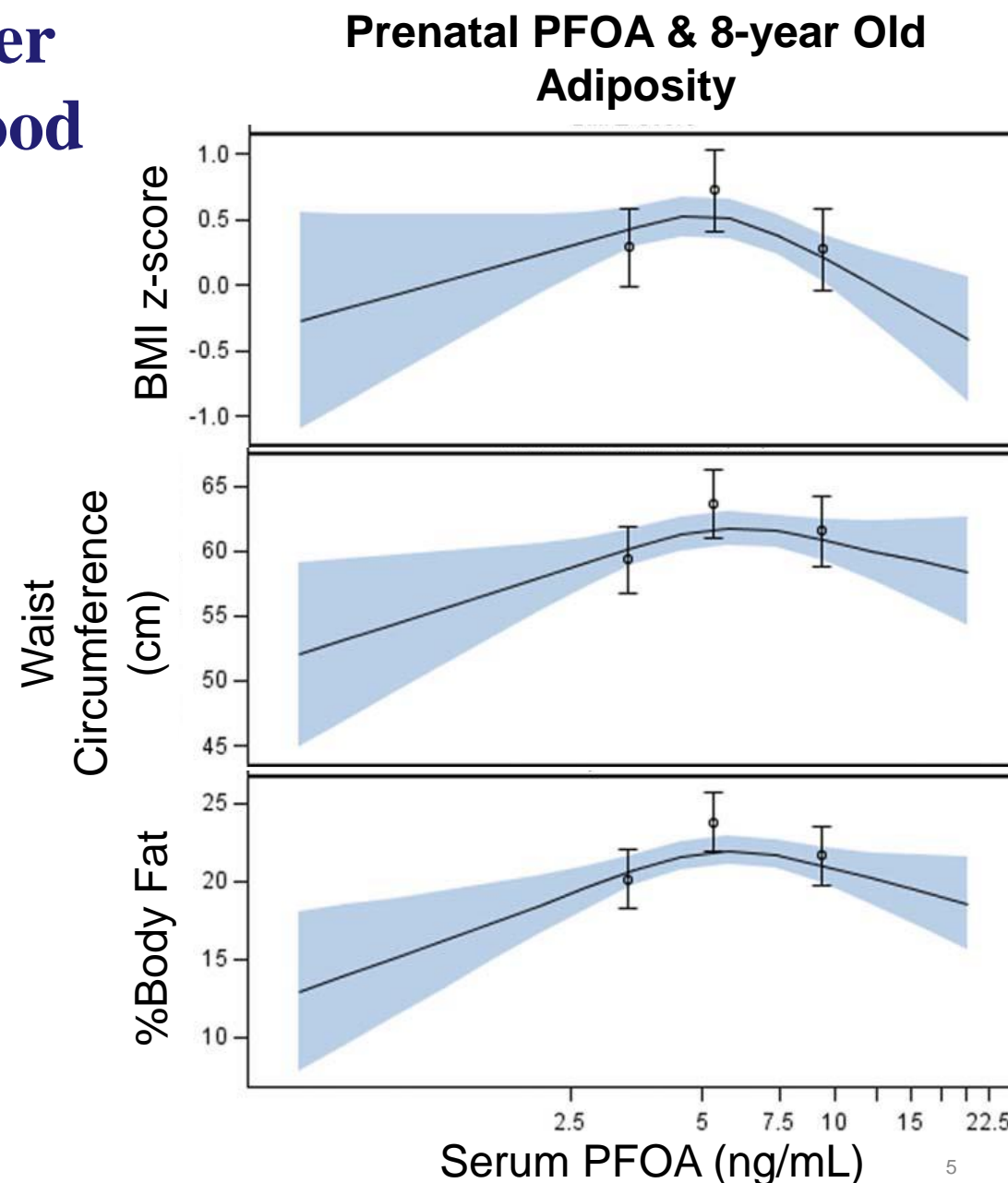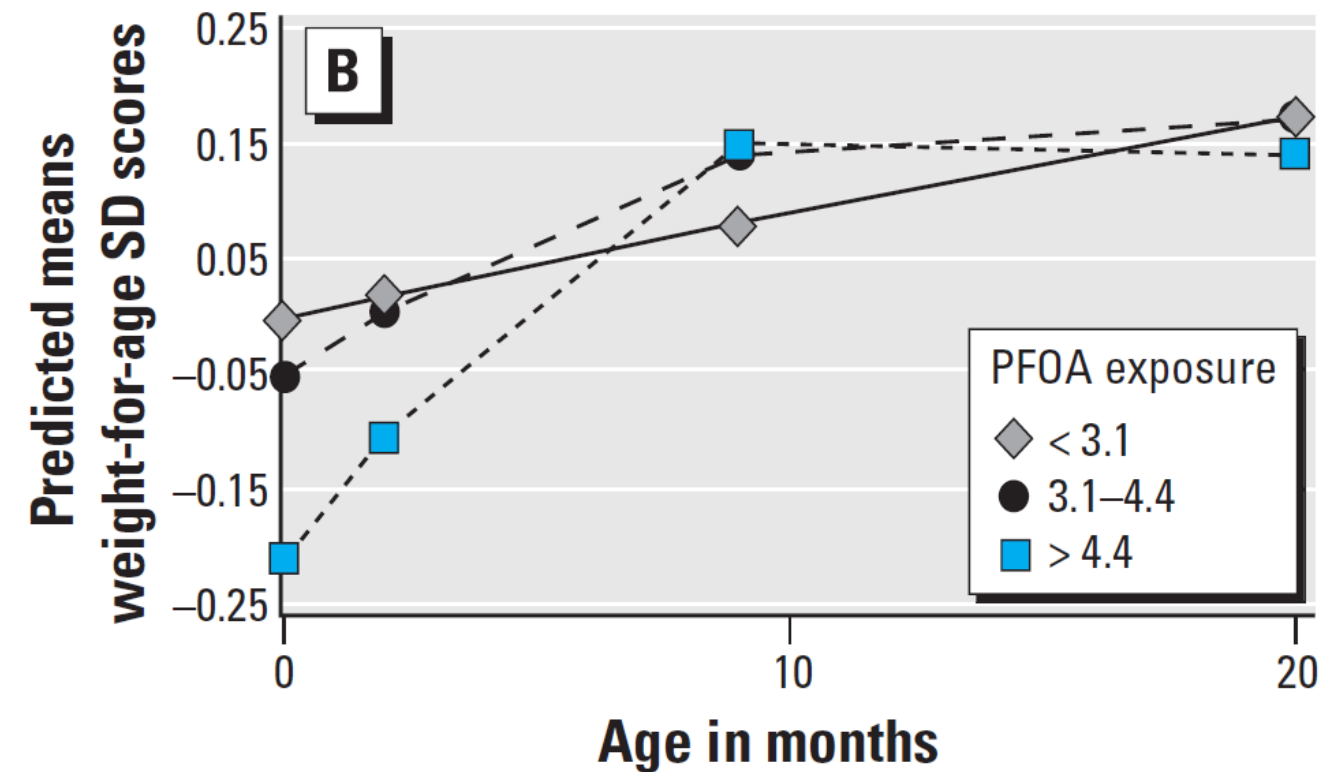
- PFOA Case Study

- Nonlinear Modeling

- SELMA Infant Growth

- PFOA & Infant Growth

- Future Directions

PFOA Case Study

PFOA Consistently Related to Lower Birthweight

4

Prenatal PFOA Also Related to Higher Weight & Adiposity Later in Childhood
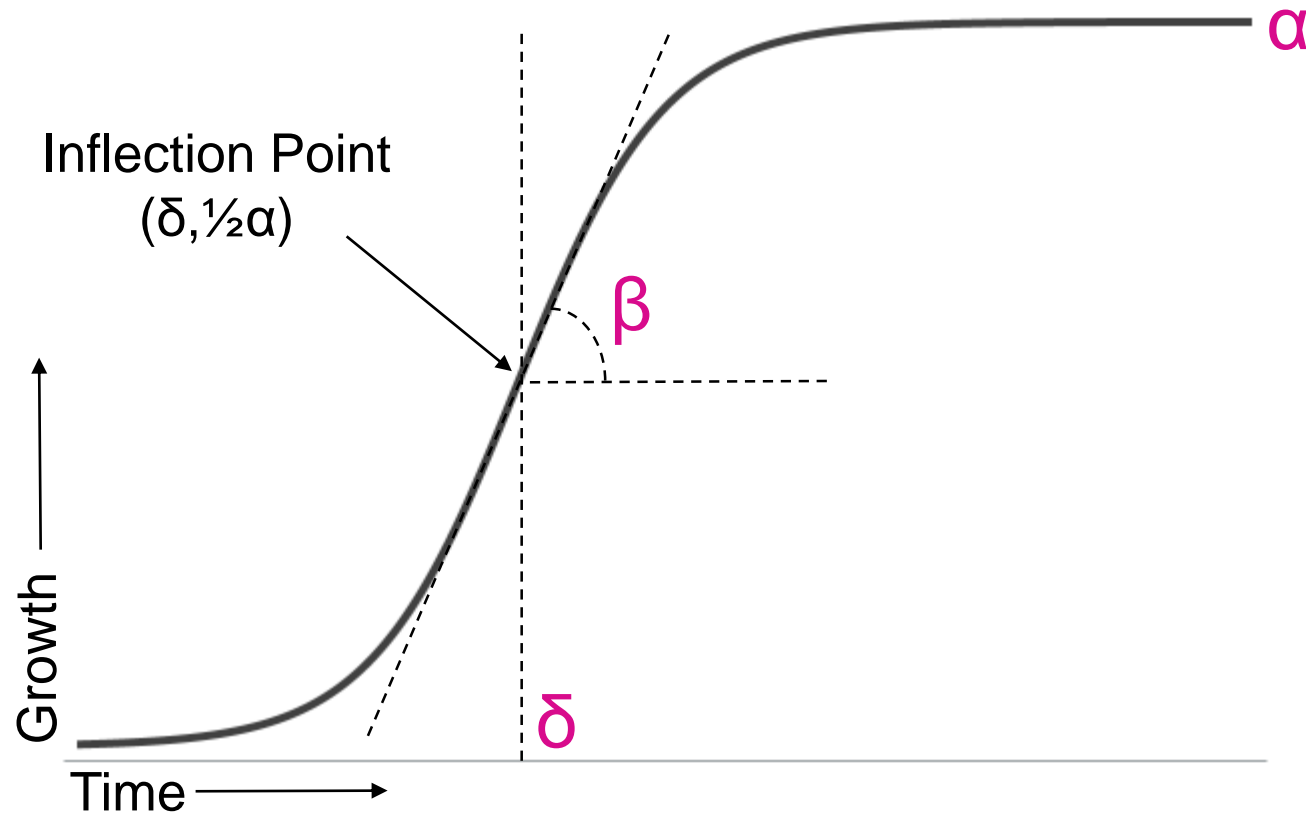
Prenatal PFOA & 8-year Old Adiposity

Limitations & Unresolved Questions

- Prior research uses **cumulative** growth measures
  - Limited insight into rapidly changing growth patterns in early life

- Why does PFOA induce ↓Birthweight, but ↑Weight in Childhood?
- Characteristics of catch-up growth?
- How is PFOA impacting growth trajectories?
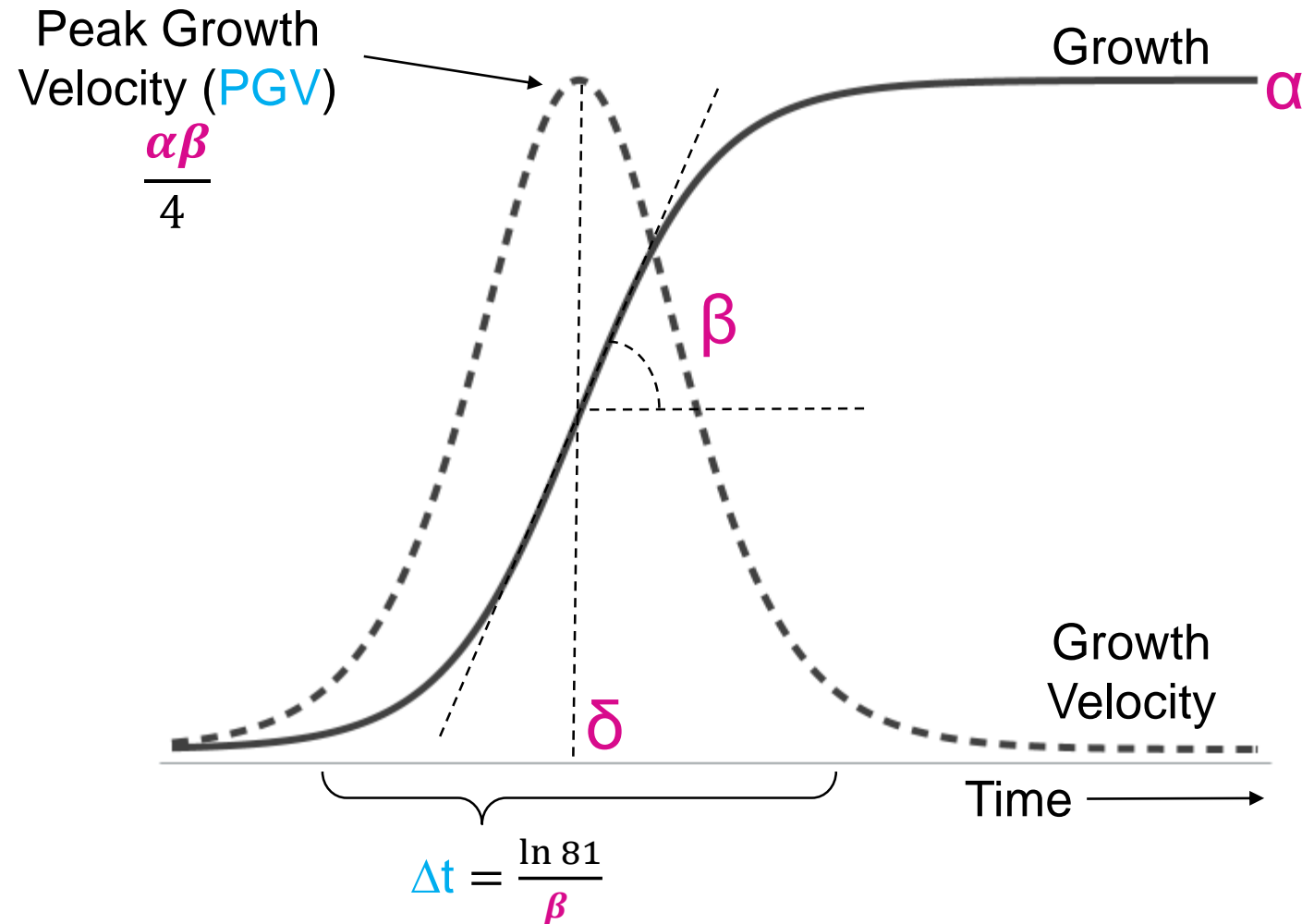
- To answer these questions, alternative methods needed
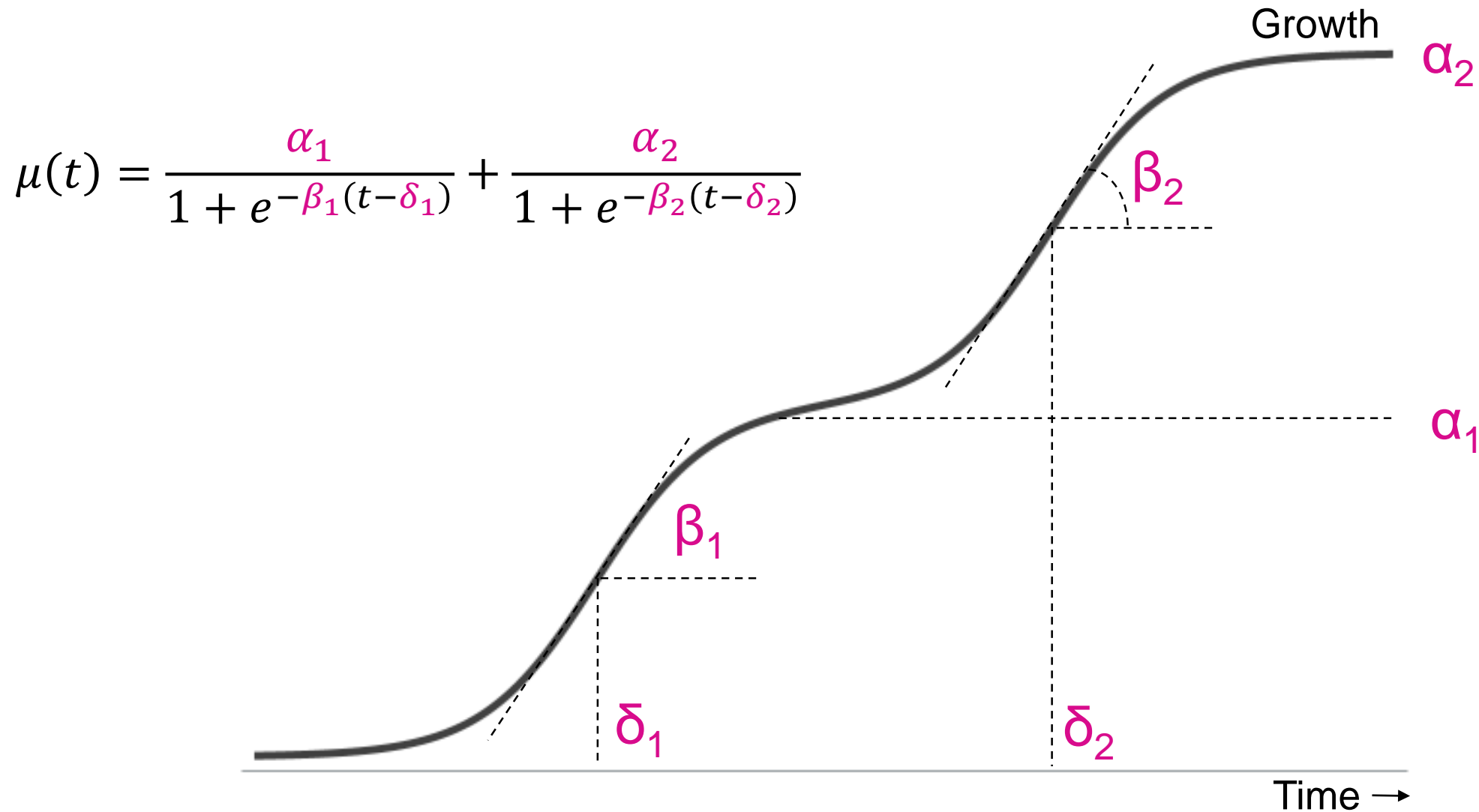
Nonlinear Modeling

Logistic Growth

$$\mu(t) = \frac{\alpha}{1 + e^{-\beta(t-\delta)}}$$

Growth Velocity

Peak Growth Velocity (PGV)
$$\frac{\alpha\beta}{4}$$

Growth α

β

δ

Growth Velocity

Time

$$\Delta t = \frac{\ln 81}{\beta}$$

$$\frac{\partial \mu(t)}{\partial t} = \frac{\alpha\beta e^{-\beta(t-\delta)}}{(1 + e^{-\beta(t-\delta)})^2}$$

Double-Logistic Growth

$$\mu(t) = \frac{\alpha_1}{1 + e^{-\beta_1(t-\delta_1)}} + \frac{\alpha_2}{1 + e^{-\beta_2(t-\delta_2)}}$$

Growth

α_2

β_2
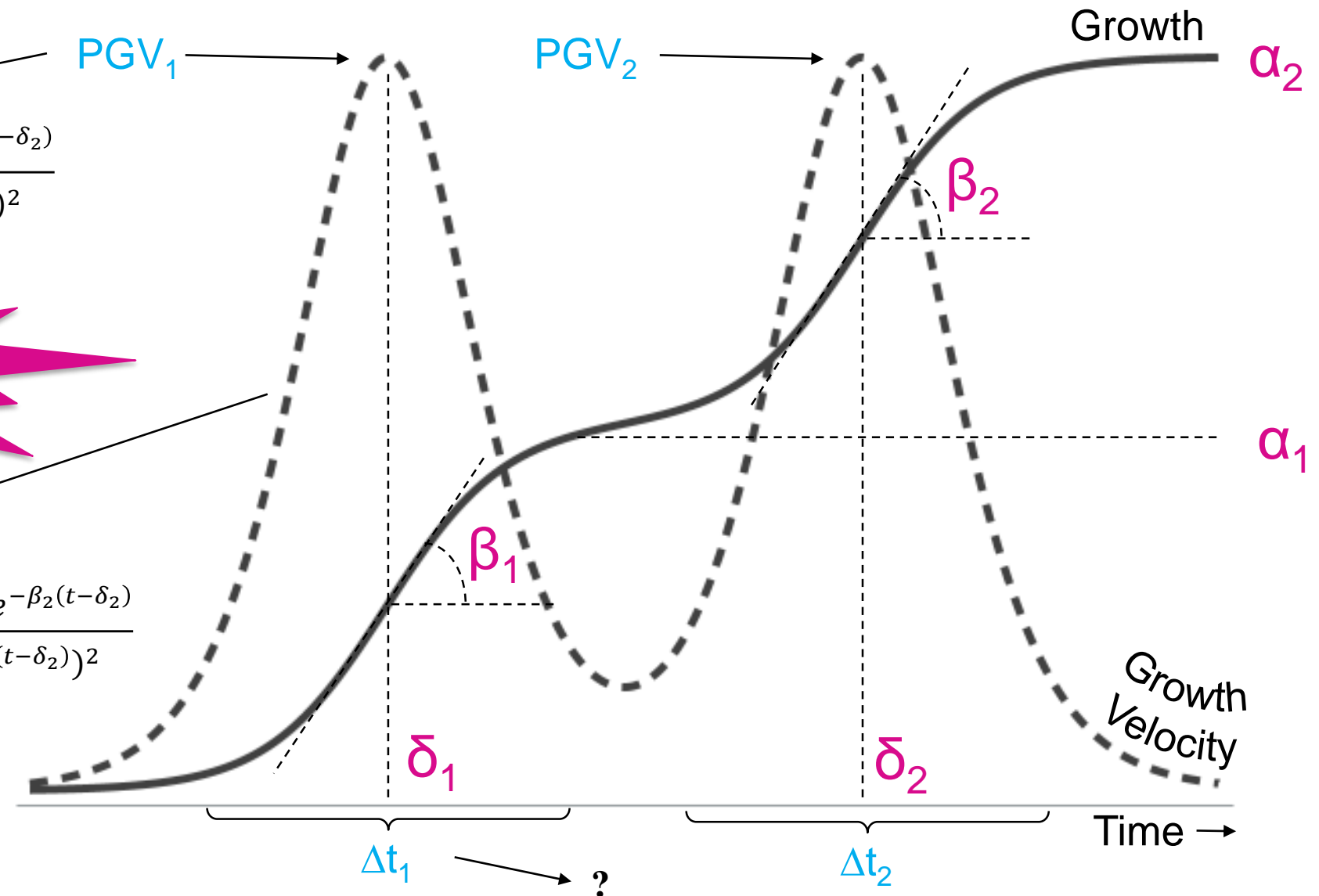
α_1

β_1

δ_1

δ_2

Time →

Double-Logistic Growth Velocity

$$\frac{\mu(\delta_1)}{t} = \frac{\alpha_1\,\beta_1}{4} + \frac{\beta_2(W-\alpha_1)e^{-\beta_2(\delta_1-\delta_2)}}{\left(1+e^{-\beta_2(\delta_1-\delta_2)}\right)^2}$$

Increased complexity of calculations

$$\frac{\partial\mu(t)}{\partial t} = \frac{\alpha_1\,\beta_1 e^{-\beta_1(t-\delta_1)}}{(1+e^{-\beta_1(t-\delta_1)})^2} + \frac{\beta_2(W-\alpha_1)e^{-\beta_2(t-\delta_2)}}{\left(1+e^{-\beta_2(t-\delta_2)}\right)^2}$$

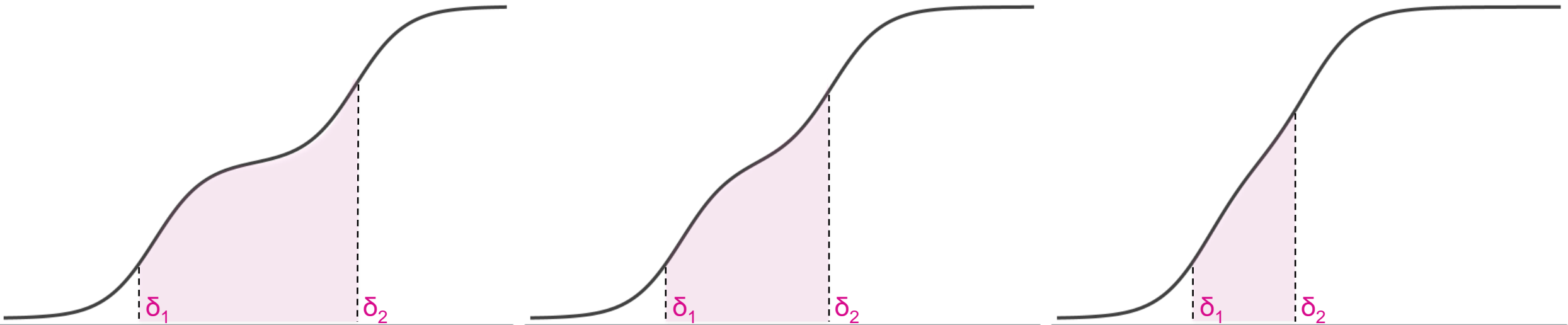PGV$_1$ PGV$_2$ Growth α_2

β_2 α_1 β_1

δ_1 δ_2 Time →

Growth Velocity

Δt_1 ? Δt_2

Overlapping Growth Spurts

$$\text{\%Saturation 2}^\text{nd}\text{ Logistic at time=}\delta_1 = \left(\frac{(Y(\delta_1) - \tfrac{1}{2}\alpha_1)}{(\alpha_2 - \alpha_1)}\right) \times 100\%$$
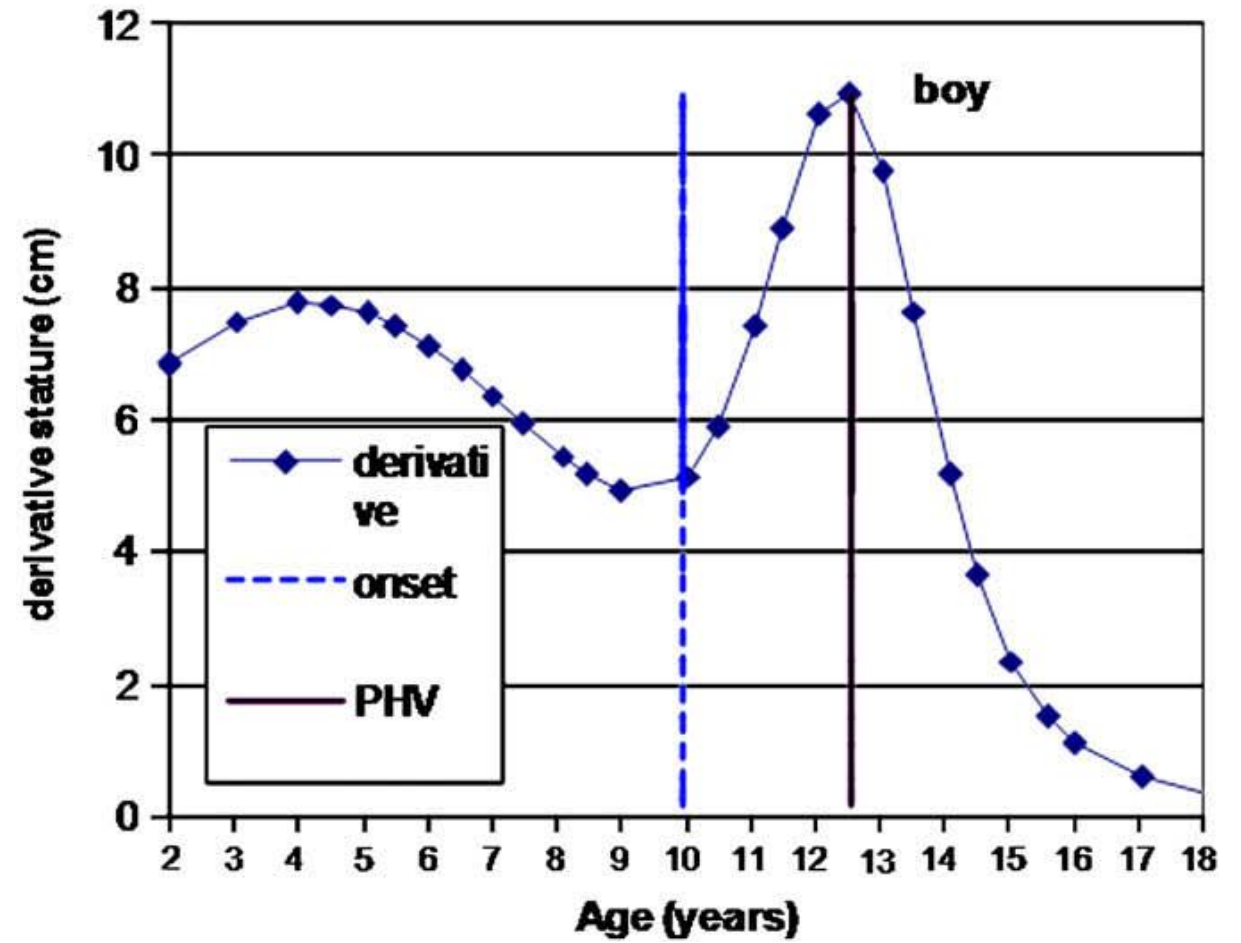
Sequential ⟶ Overlapping

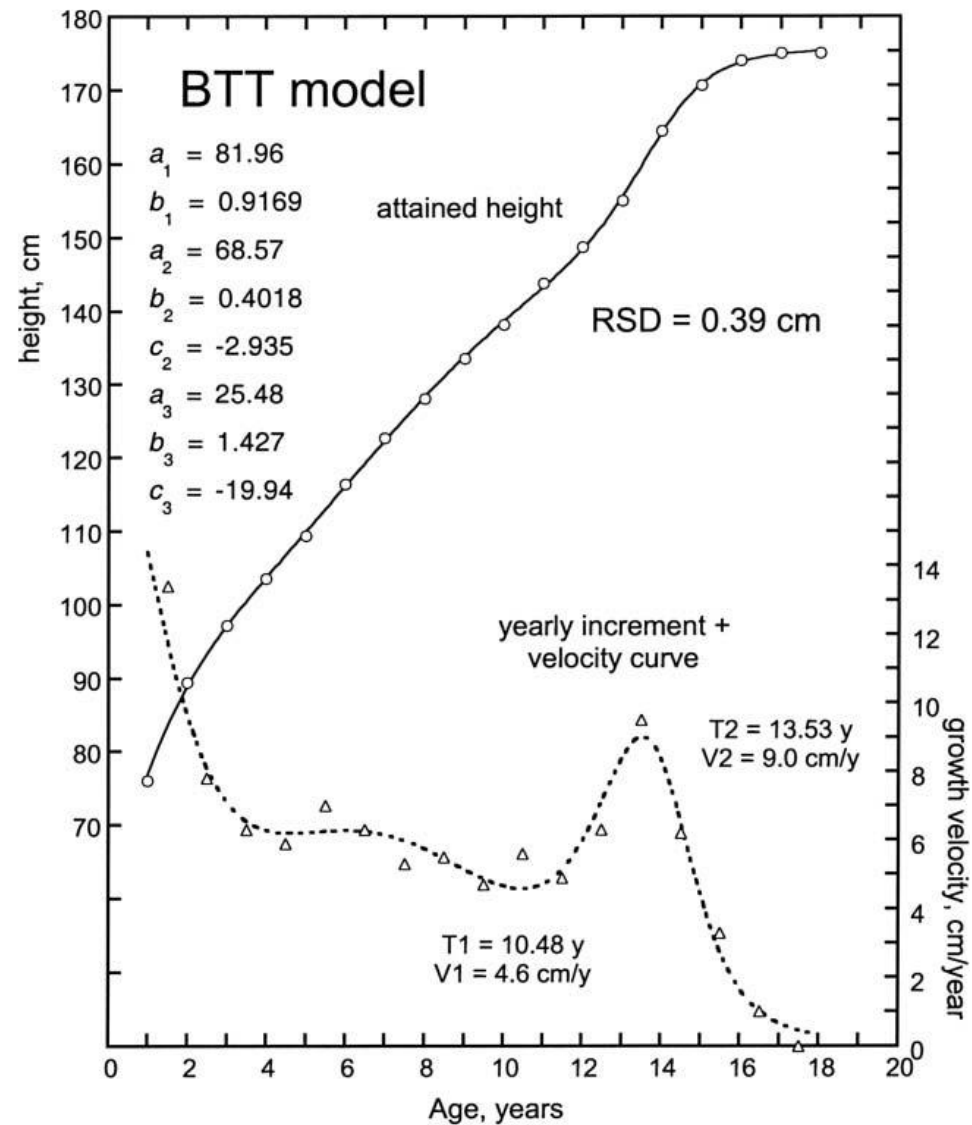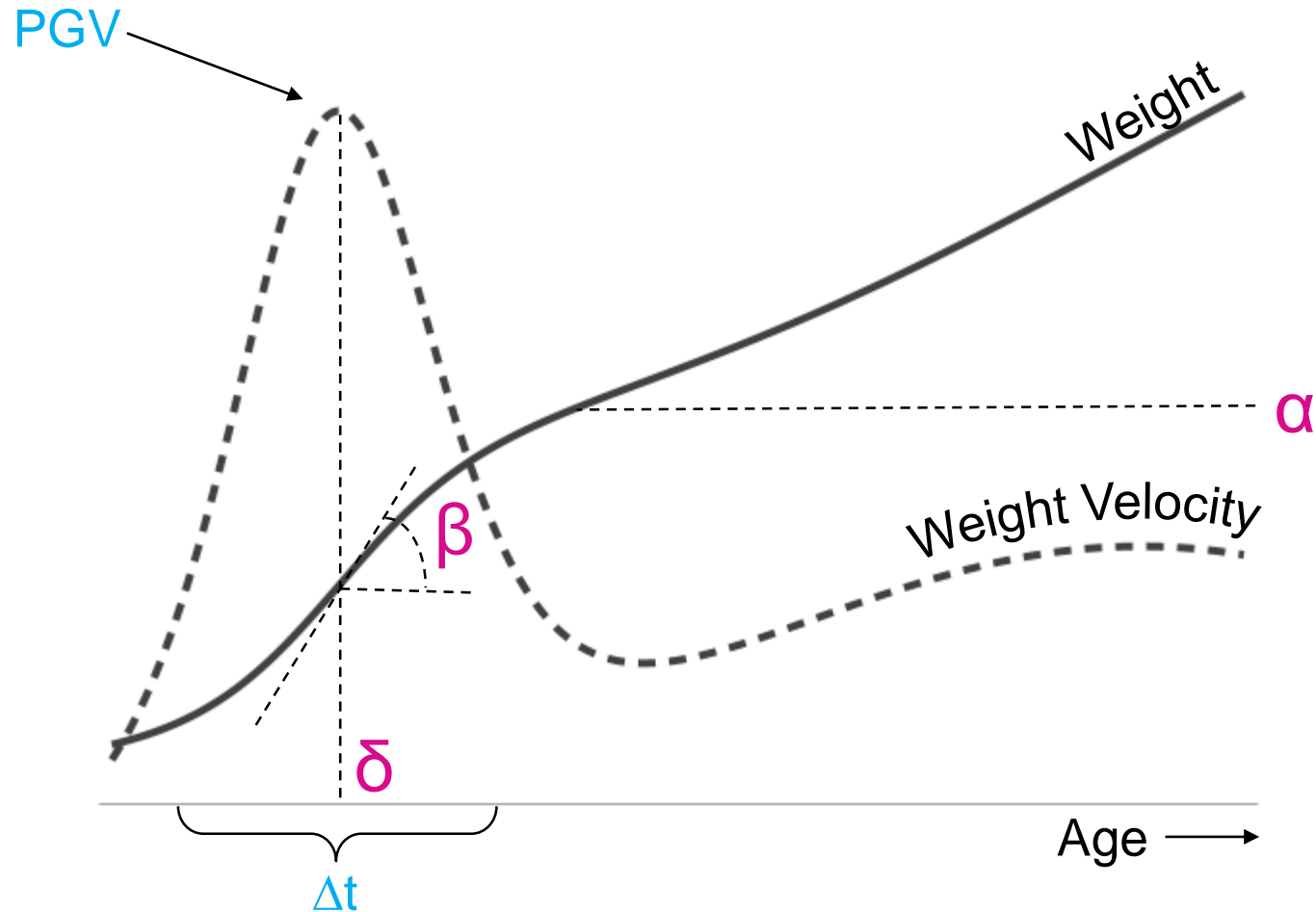Independent logistic curves ⟶ ↑Dependency

Prior Applications - Pubescent Height Velocity

Bock (1973) https://www.jstor.org/stable/41459847; Bock and Thissen (1980) doi: 10.1007/978-1-4684-6994-3_16; Hauspie and Molinari (2009) doi: 10.1017/CBO9780511542411.009; Sun (2009) doi: 10.1016/j.jpeds.2009.04.050 13

Characterizing Infant Weight Growth

PGV

Weight

α

Weight Velocity

β

δ

Δt

Age →

- ▶ **Many well-child visits in first years of life**
- ▶ **Opportunity to study early childhood weight growth**

δ_1 δ_2
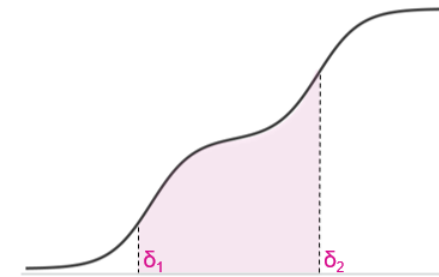
- ▶ **If sequential - can simplify approximations**

SELMA Growth Trajectories

Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA)

Chemical exposures measured in blood & urine (N=2325)

Birth outcomes recorded

Participants followed through mid-childhood
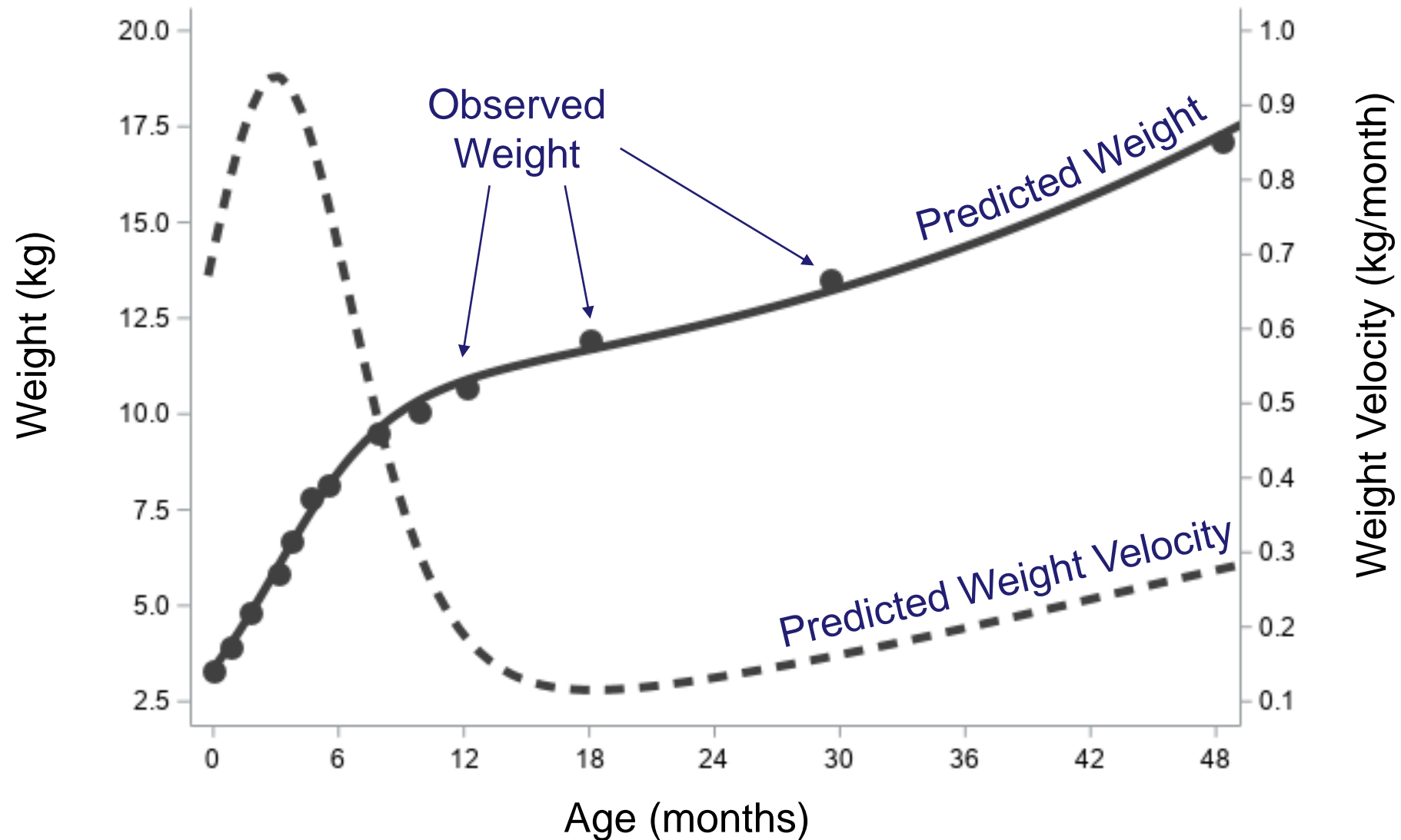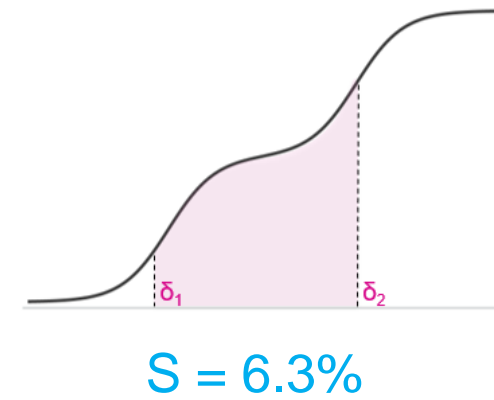
Conception

Week 10

Birth

7 years

SELMA Growth Data

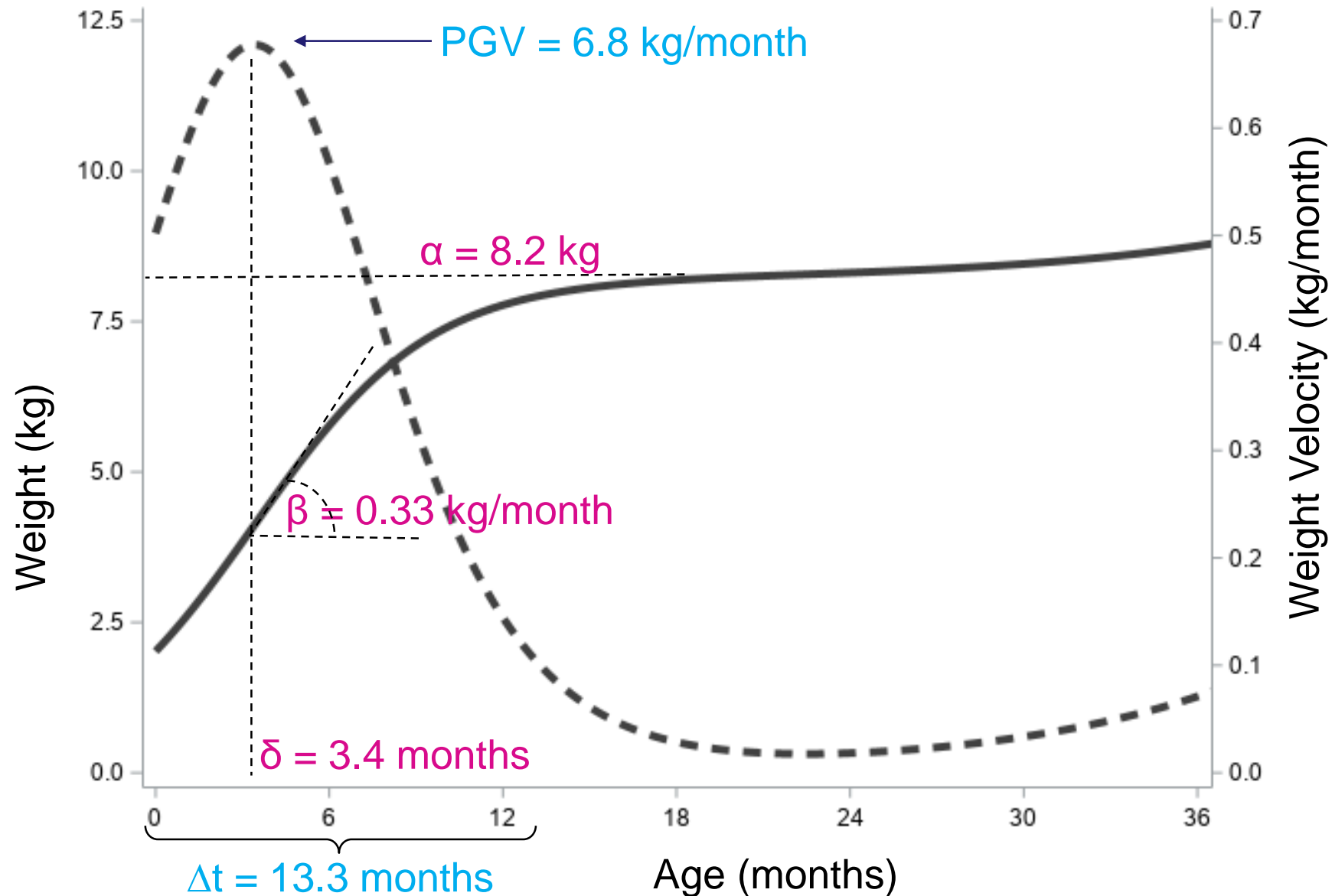- ≤ 15 (mean=12) age and weight measurements from birth to 5.5 years

- Applied double logistic models using nonlinear least squares in SAS

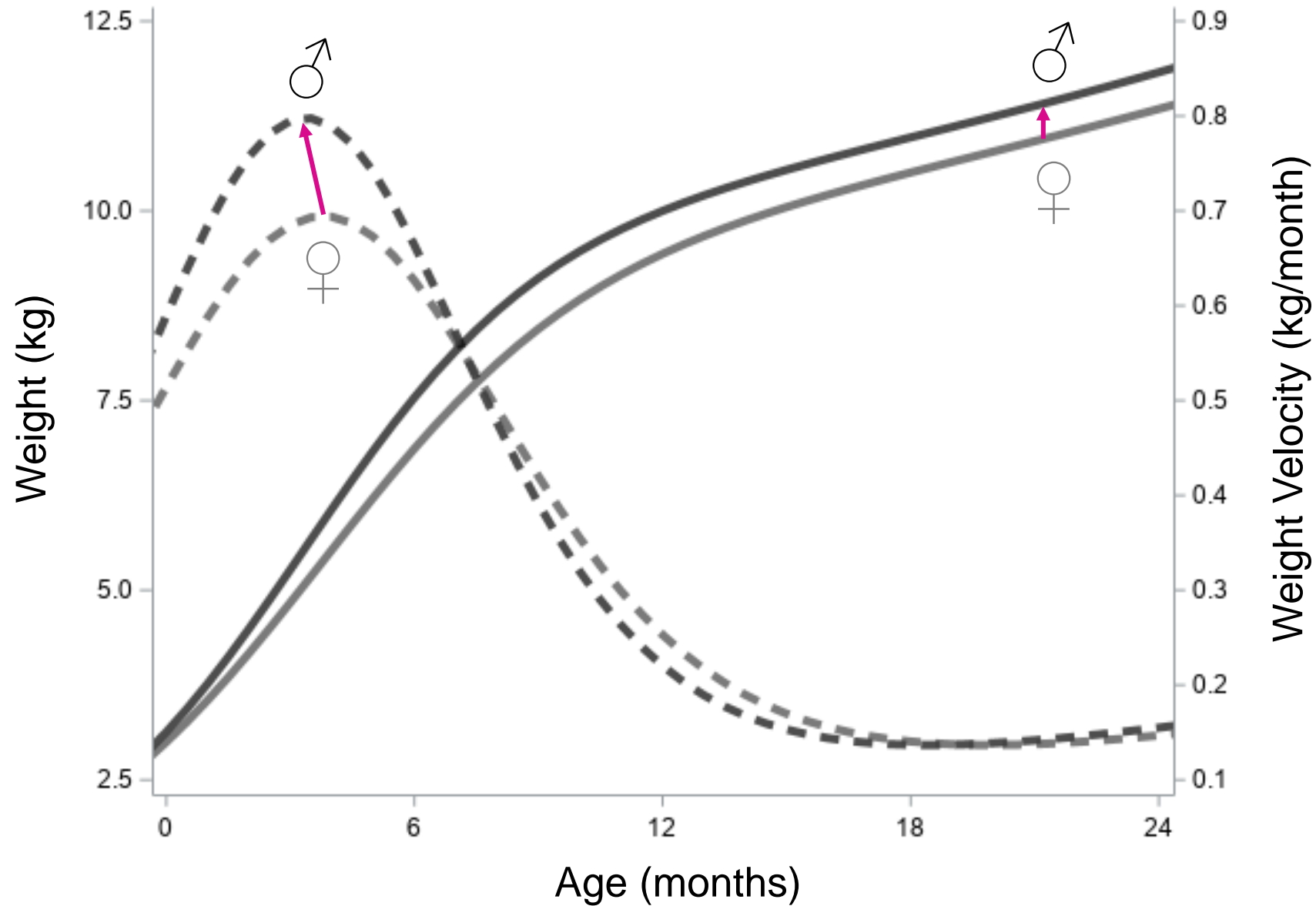- Estimated individual infant growth parameters α_1, β_1, δ_1, PGV_1, Δt_1

1712 children
25,680 visits

Data cleaning

1549 children
18,740 visits
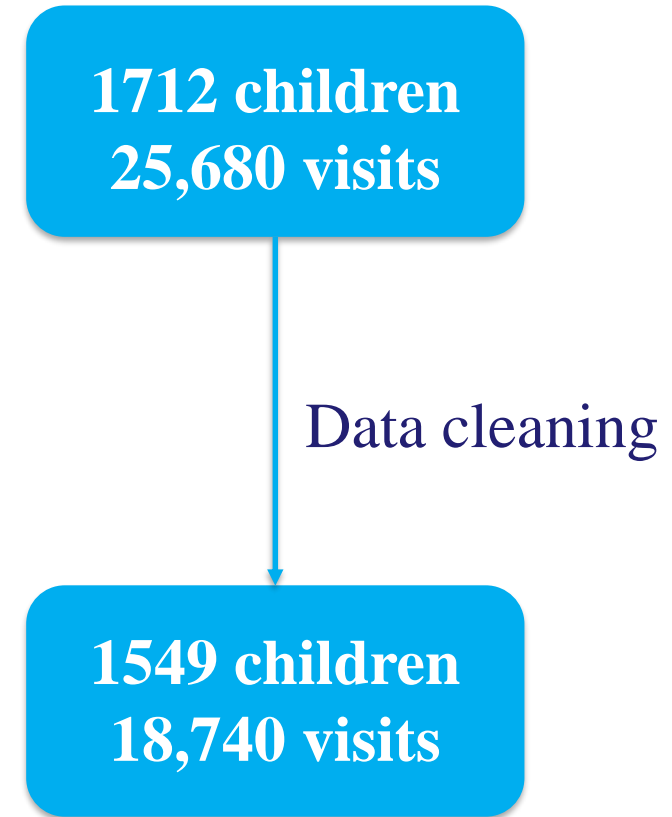
Individual Growth Trajectory for Average Child in SELMA

Average Growth Trajectories in SELMA

PGV = 6.8 kg/month

α = 8.2 kg

β = 0.33 kg/month

δ = 3.4 months

Δt = 13.3 months

S = 6.3%

Weight (kg)

Weight Velocity (kg/month)
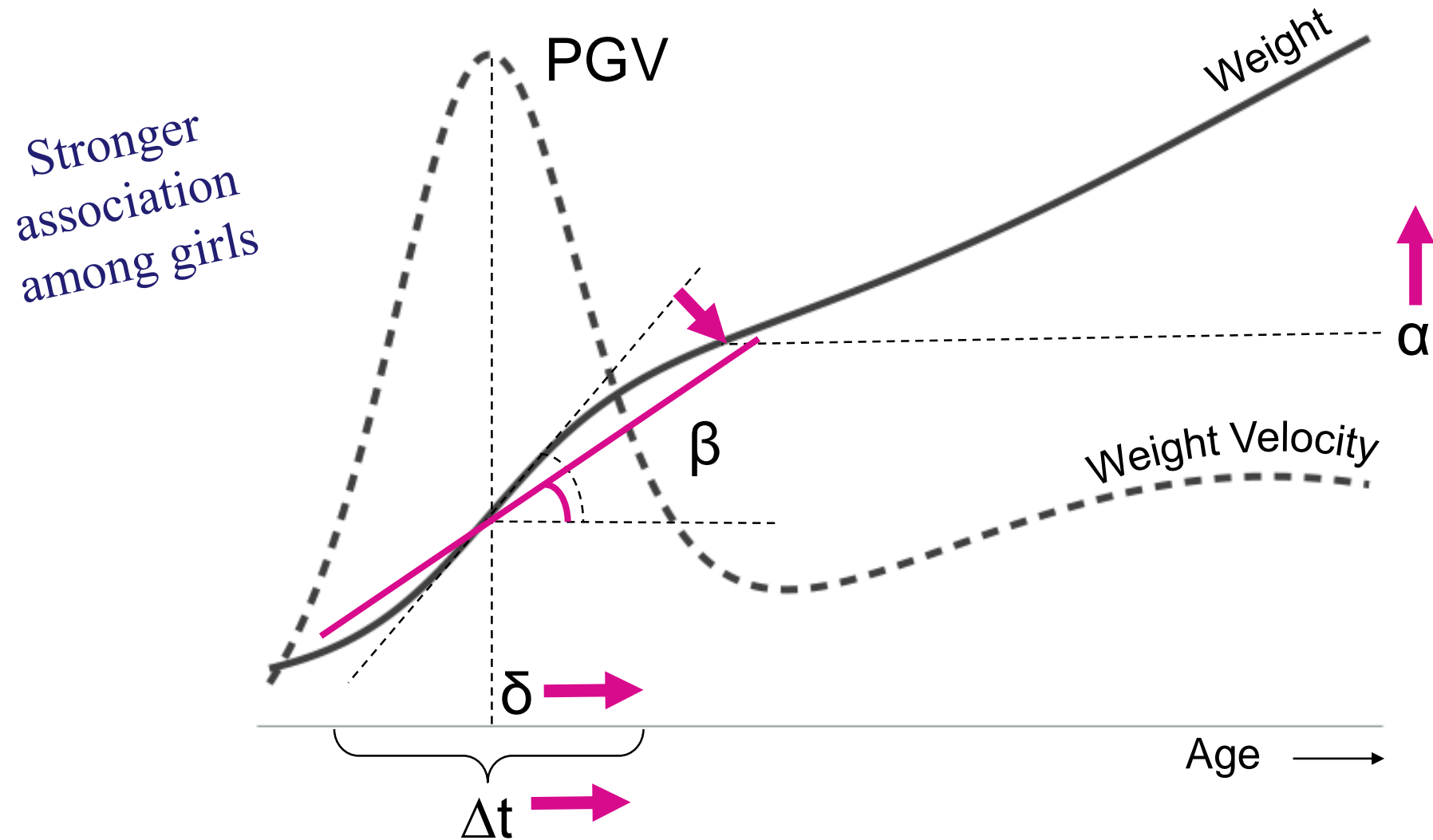
Age (months)

Average Growth Trajectories: Boys vs. Girls

PFOA & Infant Growth

PFOA & Infant Growth Trajectories

Discussion

- PFOA shifted infant growth curves, particularly among girls
    - Delayed tempo
    - Slower, but longer growth spurt
    - Higher post-spurt weight
- Consistent with prior PFOA literature using cumulative metrics
- PGV not impacted
    - Differs from typical catch-up growth

Limitations & Future Directions

Method Limitations

▶ Method requires serial anthropometric measurements with limited measurement error

▶ Metrics are approximations adequate to test association with prenatal exposures – more work need to determine clinical relevance

Future Direction

- Comprehensive growth picture
  - Apply to length, head circumference, BMI
- Additional metrics possible
  - Instantaneous velocities at specific ages of interest
  - Acceleration
  - Higher post-spurt weight
- Applications to exposure mixtures

Acknowledgements

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Questions