Pattern and associations of abdominal aortic aneurysm enlargement

PI: Frank Lederle, MD
Co-PI/Project Manager: Brent Taylor, PhD
Programmer: Sean Nugent
Statisticians: Siamak Noorbaloochi PhD, Joe Grill

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Specific Objectives

- To determine whether the use of statins, β-blockers, or ACE inhibitors is associated with slower AAA enlargement.
- To identify the best model for AAA enlargement to improve understanding and prediction

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Outcomes

AAA enlargement is our 1° outcome measure because it

- represents disease progression
- is strongly associated with rupture
- is the main determinant of AAA repair and the only one potentially modifiable by drugs
- was 1° outcome of all trials of medical therapy to date

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Algorithm for finding AAA measurements

- 1995-2009 radiology reports at Mpls, W LA, Seattle VA's
- CPT codes indicating abdominal CT or US
  - *Plus:* no CPT code + procedure name containing 'abdom' + CT or ultrasound (to capture CT of abd & pelvis)
- Include procedure if report contains:

  a) "AAA" or "aneu" or

  b) "aort" if within 60 characters of "mm", "cm", "millimeters", or "centimeters", and does not contain "velocit"
- On any pt who met a or b, also include:
  - Any abd CT/US from Mpls, W LA, Seattle
  - Any abd CT/US that met a or b from any VA

The Reports

- Algorithm identified 19,597 patients with at least one study meeting the search criteria
- 52,962 studies on these patients were imported for further evaluation.
- Double entered by undergrads over 2 summers

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Figure 1. Appli

Study ID: 6184343 Case #: 2853 Exam Date: 10/01/1997 07:57 AM

History Text

Evaluate abdominal aortic aneurysm.

Impression Text

No significant interval change.

Films were read by ERIC WEINBERG, M.D./PAMELA WYMORE, M.D., (Radiologist)

Report Text

Aortic ultrasound.

Comparison: 10/8/96.

Overall, there has been no significant interval change. Again noted is an infrarenal abdominal aortic aneurysm measuring 3.5 cm in greatest diameter. The aneurysm does not appear to involve the iliac bifurcation. The right common iliac and left common iliac arteries measures 1.4 cm in greatest

Is Abdominal aortic measurement provided?

(•) Yes Maximum abominal aortic diameter: ( ) centimeters ( ) millimeters

( ) No

[ ] Note indicates evidence of rupture

[ ] Note indicates evidence of repair

Study Entry Statistics

Total by current user: 25
Total this session: 25
Subject Record #: 3 of 9

Previous Record Next Record

Results

- 6% discrepancies → resolved by 3rd (BT or FL)
- 45.0% had an aortic diameter ≥ 3.0 cm (specificity)
- 4,638 studies not meeting our search criteria were also assessed to estimate sensitivity (= 99.6%).

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Results 2

- Excluded measurements after repair (identified on report or in records)
- Ended up with 5362 patients with AAA (>3cm)
- 2428 patients had ≥ 2 meas over at least 6 mo
- These 2428 patients had 12,397 exams
- Largest single series to date (though not by much)

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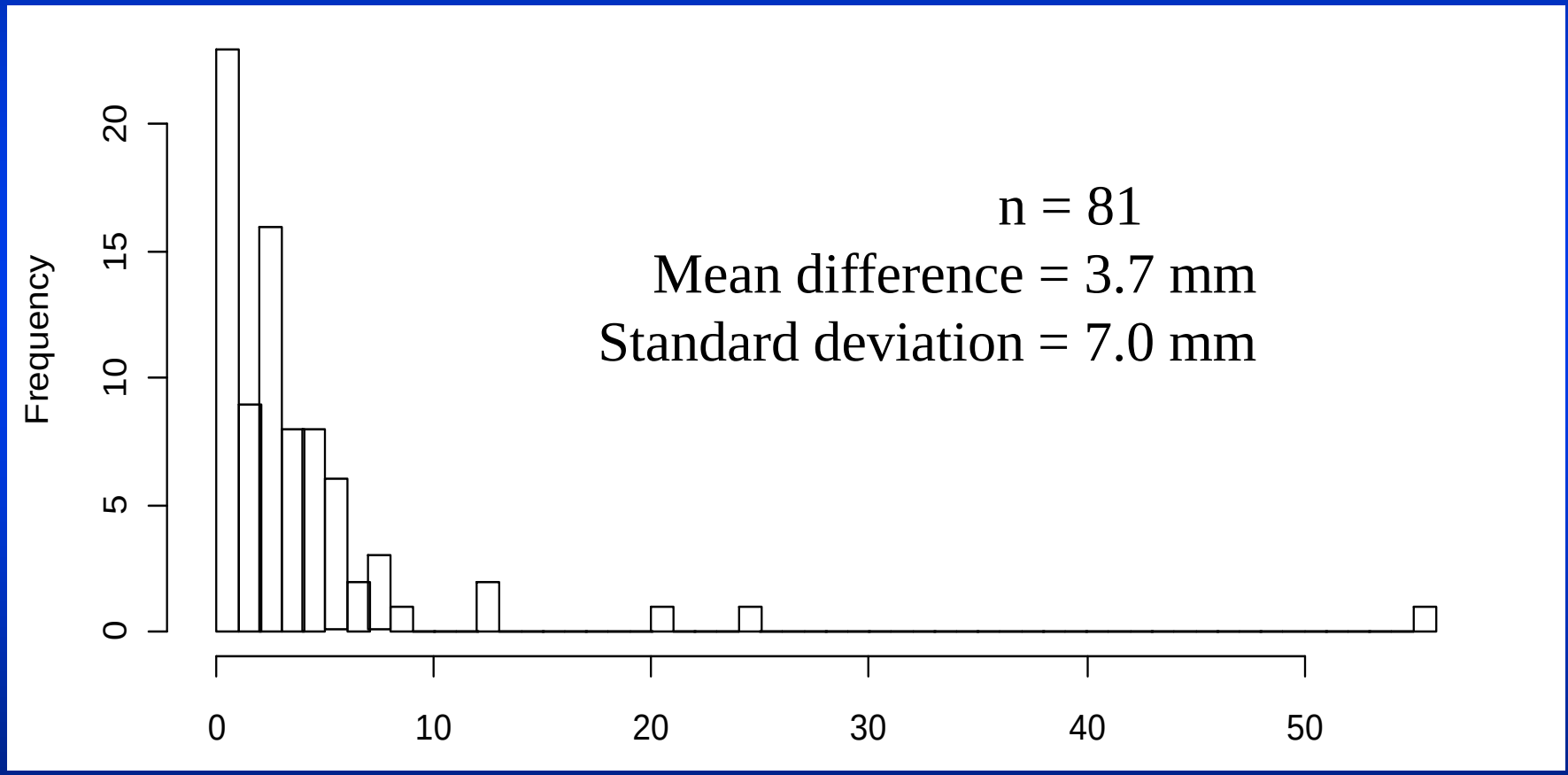
Difference in AAA diameter (mm) between 2 ultrasound exams within 30 days



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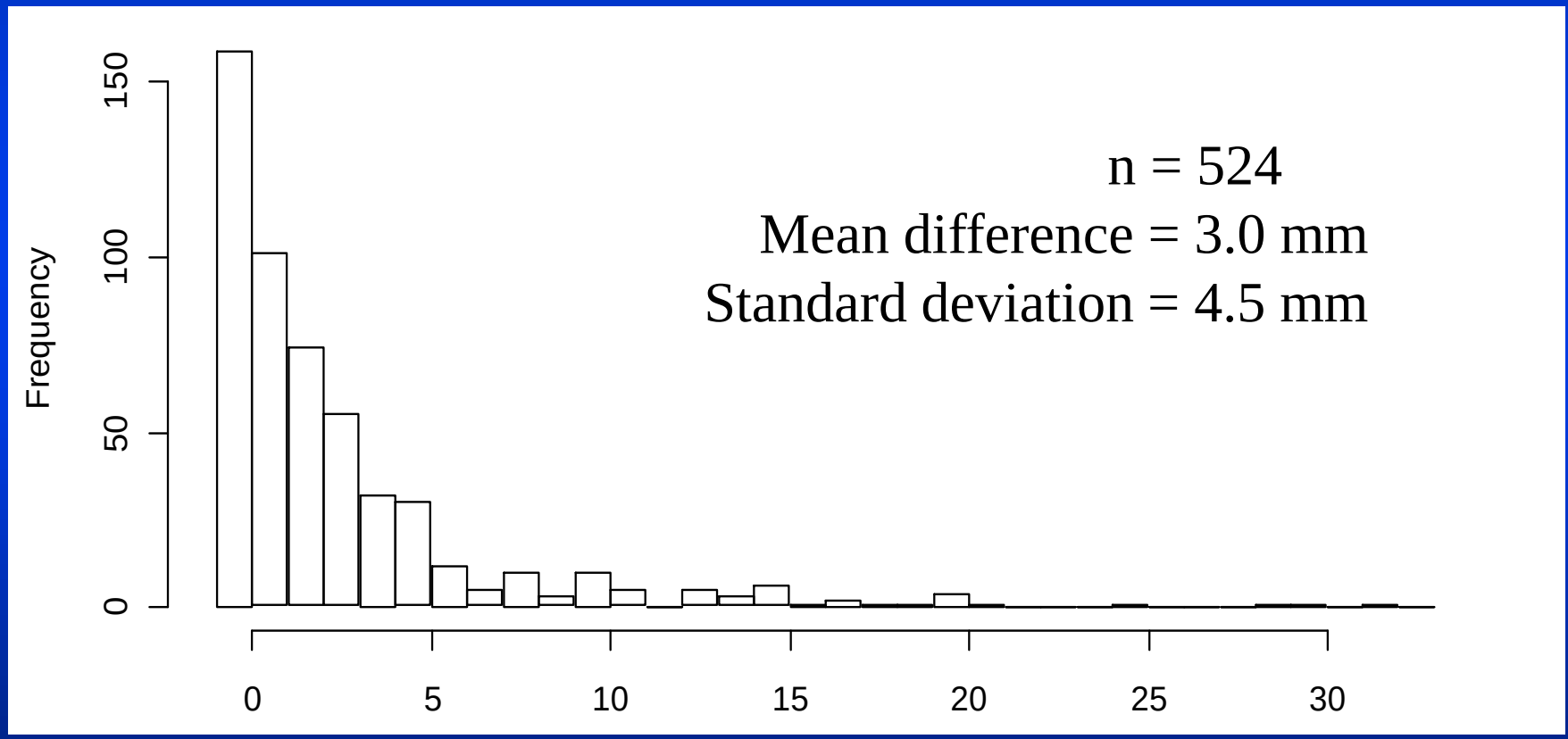
Difference in AAA diameter (mm) between 2 CT scans within 30 days



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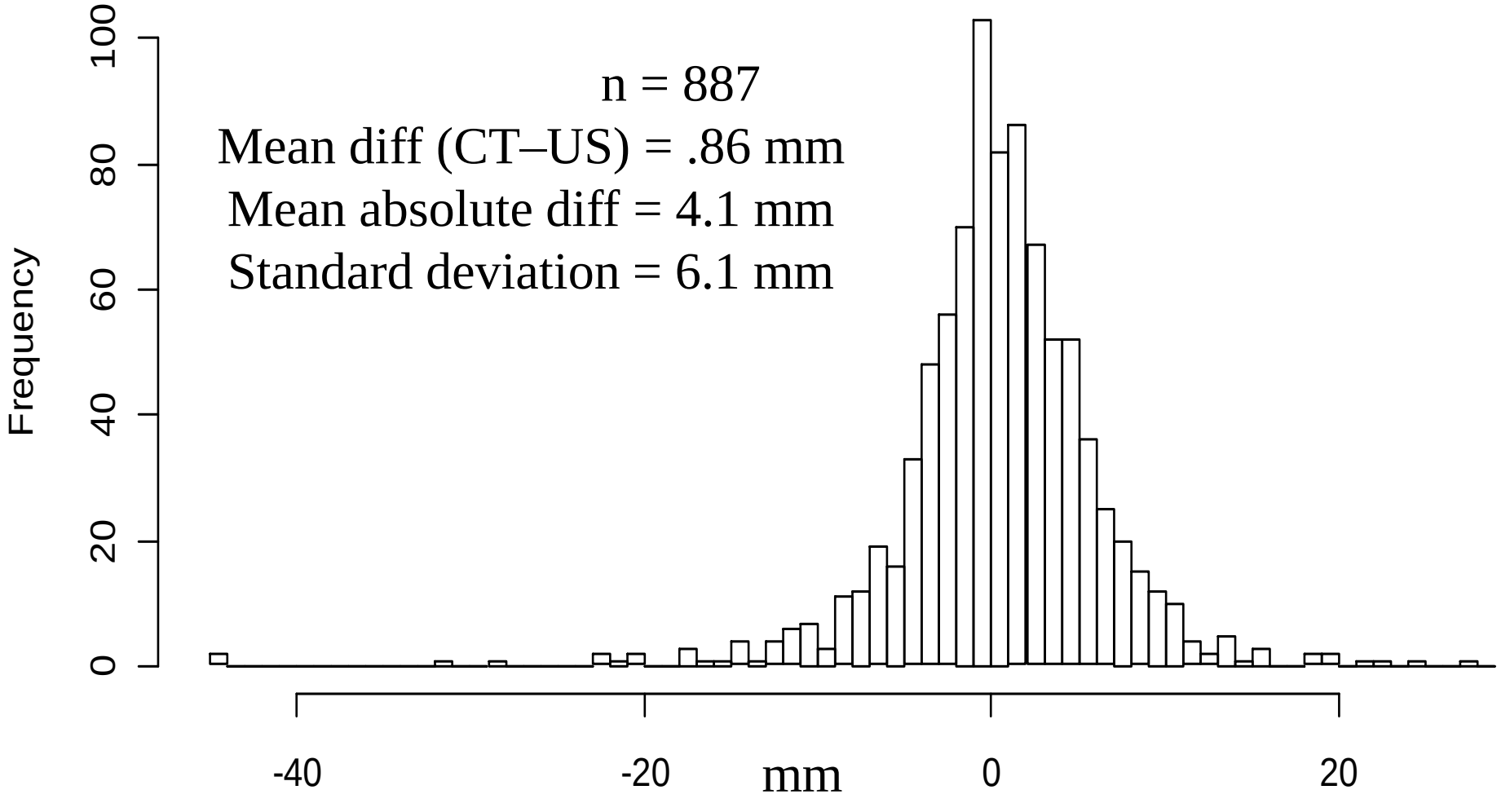
Difference in AAA diameter (mm) between ultrasound & CT exams within 30 days



Preliminary Analysis

- Smoothing
  - for ≥ 2 meas w/i 30d, replace w mean at date of last meas
- Using simple linear model: enlargement rate for the 2428 with at least 2 measurements at least 6 months apart = 2.0 mm/yr

Characteristics of pts with ≥ 2 meas over at least 6 mo

Demographics	
Age, mean (SD)	71.18 (7.94)
CT (vs US), n (%)	1144 (47.12)
White	1990 (81.99)
Married	1229 (50.62)

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Smoking Status, n (%)	
Current Smoker	639 (26.32)
Former Smoker	1128 (46.46)

(Remember this for later)

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Medication Use, mean (SD)	
ARBs	0.04 (0.17)
ACE Inhibitors	0.32 (0.45)
Beta Blockers	0.33 (0.47)
Statins	0.35 (0.45)

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Diagnoses, n (%)	
Arrhythmia	498 (20.51)
Coronary Artery Disease	894 (36.82)
COPD	671 (27.64)
High Cholesterol	552 (22.743
Depression	323 (13.30)
Diabetes	263 (10.83)
Hypertension	1368 (56.34)
Peripheral Vascular Disease	352 (14.50)
Sexual Dysfunction	192 (7.91)
Stroke/TIA	290 (11.94)

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The Propensity Analysis

- Useful when the number of measured potential confounders is large
- For each examined factor (i.e. statins), divide sample into quintiles of likelihood of getting statins given other covariates (demographics, co-morbidities, etc)
- Within each quintile, use generalized linear mixed model logistic regression to assess effect of statins on AAA enlargement
  - Included covariates in logistic regression (doubly adjusted)
- Combine results from the quintiles to get final estimate

Results of propensity analysis using only baseline values

covariate	Group 26		
	c	r1	**r2**
Diabetes	0.000	0.21**	-0.023**
Current Smok	0.004	0.210**	0.005
Ever Smoked	0.016	0.259**	-0.049**
Age > 72 yrs	0.011	0.208**	-0.006
CAD/Angina	0.029*	0.199**	0.014*
COPD	-0.003	0.20**	0.012*
Statin	0.025*	0.195**	0.018*
Beta blocker	0.022*	0.190**	0.024*
Ace Inhib	-0.008	0.198**	0.013*
ARB	-0.028	0.204**	0.022*

explanation coming!

In cm/yr. *p<.05, **p<.01
r1 is subgroup enlargement rate
r2 is change from overall rate.

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Results accounting for change over time

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Statin use

vs first measurement

Stratum	Statin effect (cm/y)	P-value
1 (lowest prop)	-0.053	0.27
2	-0.001	0.97
3	+0.029	0.35
4	-0.039	0.16
5 (highest prop)	+0.031	0.19
Pooled	0.001	0.93

vs last measurement

Stratum	Statin effect (cm/y)	P-value
1 (lowest prop)	0.001	0.98
2	-0.025	0.56
3	-0.017	0.71
4	0.002	0.96
5 (highest prop)	0.05	0.34
Pooled	-0.001	0.97

ACE Inhibitor use

vs first measurement

Stratum	ACEI effect (cm/y)	P-value
1 (lowest prop)	0.014	0.81
2	-0.043	0.26
3	0.004	0.90
4	0.056	0.07
5 (highest prop)	0.052	0.04
Pooled	0.026	0.08

vs last measurement

Stratum	ACEI effect (cm/y)	P-value
1 (lowest prop)	-0.049	0.55
2	-0.007	0.11
3	0.016	0.73
4	0.094	0.04
5 (highest prop)	0.052	0.35
Pooled	0.016	0.48

β blocker use

vs first measurement

Stratum	β blocker effect (cm/y)	P-value
1 (lowest prop)	-0.025	0.66
2	-0.017	0.60
3	0.054	0.11
4	-0.009	0.78
5 (highest prop)	0.011	0.66
Pooled	0.007	0.64

vs last measurement

Stratum	β blocker effect (cm/y)	P-value
1 (lowest prop)	-0.103	0.19
2	0.029	0.54
3	0.062	0.18
4	-0.085	0.09
5 (highest prop)	-0.018	0.75
Pooled	-0.008	0.75

Table 3 Meta-analysis of the influence of patient characteristics on small aneurysm growth rates

		Unadjusted analyses				Adjusted analyses			
	No. of studies	Total no. of patients	Estimate (mm/year)*	*P*	I^2 (%)†	Total no. of patients	Estimate (mm/year)*	*P*	I^2 (%)†
Age at baseline (per year)	18	15 482	−0·004(0·007)	0·559	76	13 966	−0.001(0·006)	0·820	66
Calendar year at baseline (per year)	17	14 432	0·001(0·021)	0·965	86	12 914	0·012(0·022)	0·590	85
Sex (women *versus* men)	11	9262	0·156(0·144)	0·278	78	8472	0·142(0·150)	0·344	78
Smoking (current *versus* ex/never)	12	8196	0·375(0·081)	< 0·001	57	7486	0·354(0·065)	< 0·001	24
Body mass index (per kg/m^2)	5	3756	−0·017(0·008)	0·039	0	3439	−0·008(0·009)	0·348	0
Diabetes	10	6268	−0·596(0·092)	< 0·001	0	5697	−0·505(0·097)	< 0·001	0
Mean arterial blood presume (per 10 mmHg)	8	6723	0·003(0·024)	0·886	74	5957	0·013(0·021)	0·531	62
Pulse pressure (per 10mmHg)	8	6723	−0·040(0·018)	0·024	67	5957	−0·027(0·014)	0·060	46
History of cardiovascular disease	10	6638	−0·177(0·075)	0·017	38	6302	−0·105(0·088)	0·230	46

Table 4 Meta-analysis of the influence of cardiovascular drugs on small aneurysm growth rates

		Unadjusted analyses				Adjusted analyses			
	No. of studies	Total no. of patients	Estimate (mm/year)*	*P*	I^2 (%)†	Total no. of patients	Estimate (mm/year)*	*P*	I^2 (%)†
ACE inhibitors	7	4826	−0·125(0·143)	0·379	61	4269	0·002(0·128)	0·986	42
Beta-blockers	7	4824	−0·189(0·076)	0·013	0	4269	−0·111(0·083)	0·183	0
Calcium channel blockers	6	4124	−0·199(0·082)	0·015	0	3723	−0·081(0·088)	0·358	0
Statins/lipid-lowering drugs	6	4621	−0·341(0·133)	0·010	47	4118	−0·205(0·132)	0·121	32
Antiplatelet agents	6	4137	−0·187(0·101)	0·065	32	3723	−0·125(0·106)	0·241	19
Any antihypertensive drug	7	4826	−0·189(0·064)	0·003	0	4271	−0·108(0·075)	0·149	0

*Values are mean(s.e.m.). †Percentage of total variation across studies due to heterogeneity rather than chance. ACE, angiotensin-converting enzyme.

RESCAN collaborators. Br J Surg 2012;99:655-65

Index Event Bias

Dahabreh & Kent, JAMA 2/23/11;305:822-3

- Arises in observational studies that select patients based on the occurrence of an index event (dx)
- Paradox: risk factor (PFO) for disease (CVA) does not appear to be RF for recurrent CVA
- Explanation: Among those with CVA, those with PFO have less DM & HTN, i.e. it 'compensates' for lack of other RF's
- One CVA 2° PFO, another 2° DM/HTN. All RF's continue, so both pts have same risk for 2nd CVA, but no RF seems to ↑ prob 2nd CVA
- To predict 2nd CVA, a factor must outstrip other factors that led to 1st CVA

Why might enlargement have been less in “ever smokers”?

- Most (2/3) ‘ever smokers’ were ‘former smokers’
- That means the factor (smoking) that got them into the group (AAA) had been removed
- Therefore, they subsequently did better than ‘never smokers’ with AAA whose risk factors (genes, atherosclerosis, etc) continued

My conclusions from spending way too much time on this study

- Observational AAA enlargement studies are of limited value
- Population (and especially screening) studies (AAA vs no AAA) are a better way to learn what factors contribute to AAA development
- The only way to know a drug's effect on AAA enlargement is to do an adequately powered randomized trial
- To find an effective drug, we will probably have to determine AAA etiology and use "intelligent design"

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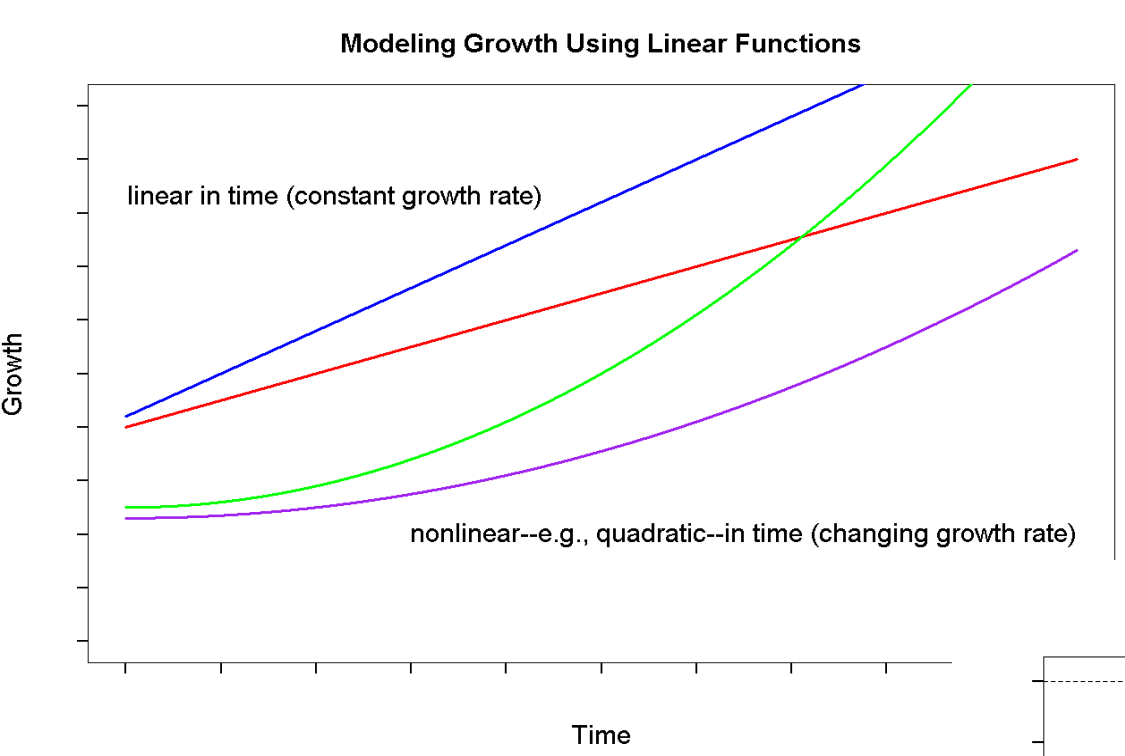
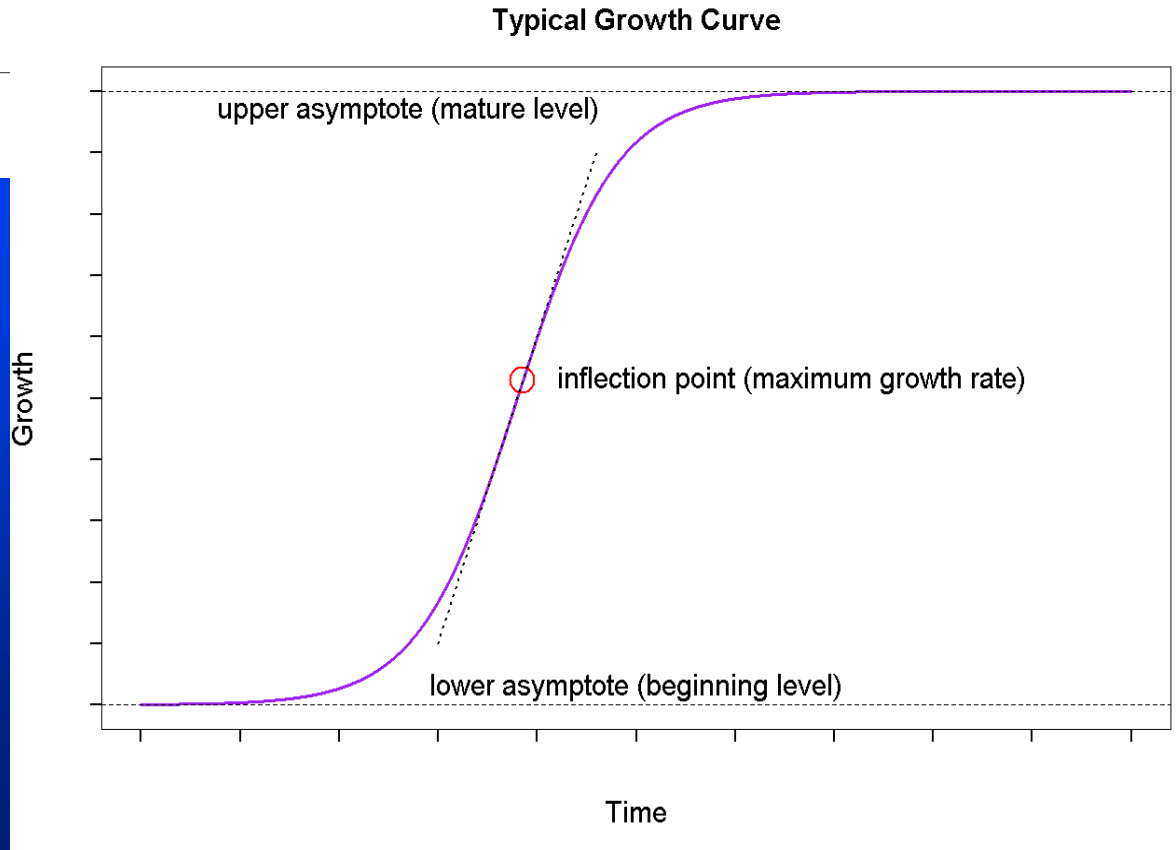


Potential patterns of AAA enlargement



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Linear Growth: $M(t) = \alpha + b(First\ Recorded\ Diameter\ Size) + \beta t + c(Scan)$

Exponential Growth: $M(t) = \left(\alpha + b(First\ Recorded\ Diameter\ Size) + c(Scan)\right)\exp(\beta t)$

Logistic Growth:

$$M(t) = \frac{\alpha + b(First\ Recorded\ Diameter\ Size) + c(Scan)}{1 + Aexp(\beta t)}$$

Gompertz model:

$$M(t) = (a_0 + b(baseDiam) + c(Scan))\, e^{-\beta_0 \exp(-\beta t)}.$$

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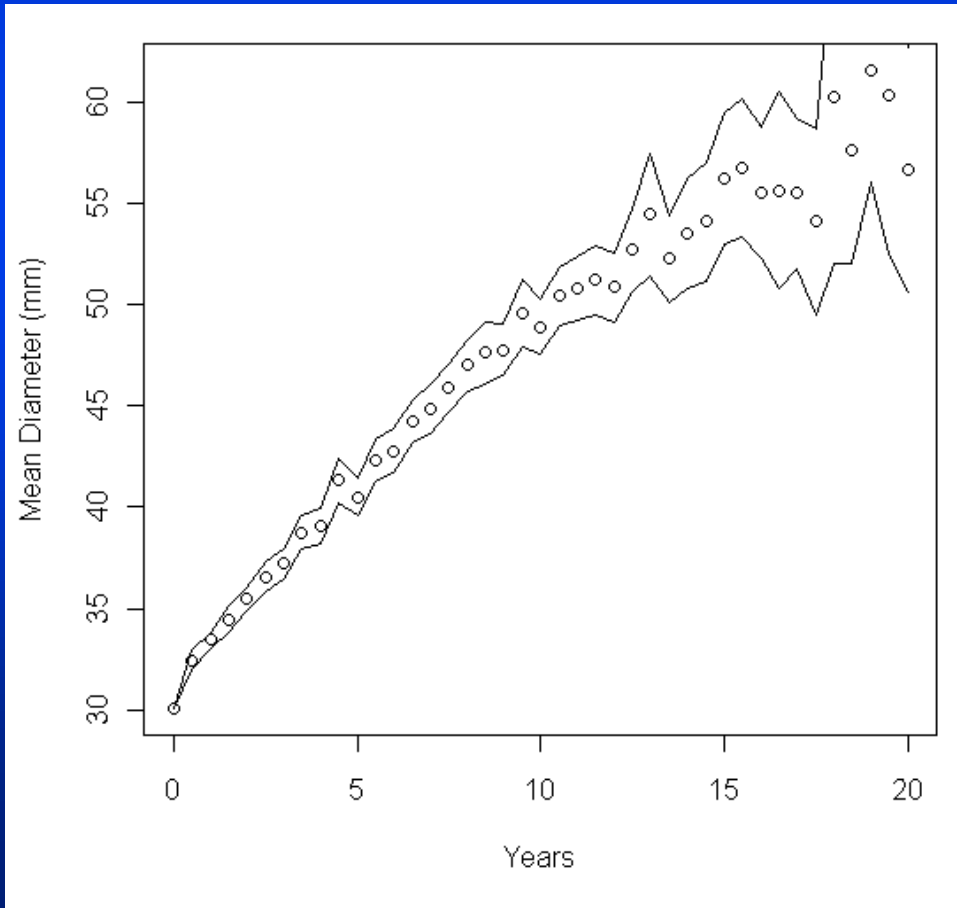
One Random Effect (Gauss)

	Linear	Exponential	Logistic	Gompertz
All				
AIC	5117.2	4780.4	4310.3	7568.1
BIC	5156.7	4819.9	4356.4	7614.2
Cohort5.5	(truncated at 5.5 cm)			
AIC	72.4	623.5	-109.6	4128.3
BIC	111.2	662.4	-64.3	4173.6
cohort26	(≥ 2 meas over at least 6 mo)			
AIC	6767.4	6343.9	6293.0	7944.3
BIC	6802.2	6378.6	6333.5	7984.9

Time alignment with imputation to generate a growth curve

- Round all measures to nearest .25 cm
- 1084 had first measurement of 3.0 cm
- Randomly select from these a time to 3.25 cm and add this time to AAA first measured at 3.25 cm
- Repeat for each .25 cm, adding in pts with that first measurement
- Do 5x and combine results



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An open-ended logistic-based growth function☆

John H.M. Thornley[a,*], James France[b]

1. Introduction

The logistic equation is possibly the best-known simple sigmoidal asymptotic function used to describe the time dependence of biological growth processes (e.g. Verhulst, 1838; Pearl and Reed, 1923; Causton and

A general model for ontogenetic growth

Geoffrey B. West*†, James H. Brown†‡ & Brian J. Enquist§

* *Theoretical Division, MS B285, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA*
† *The Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, New Mexico 87501, USA*

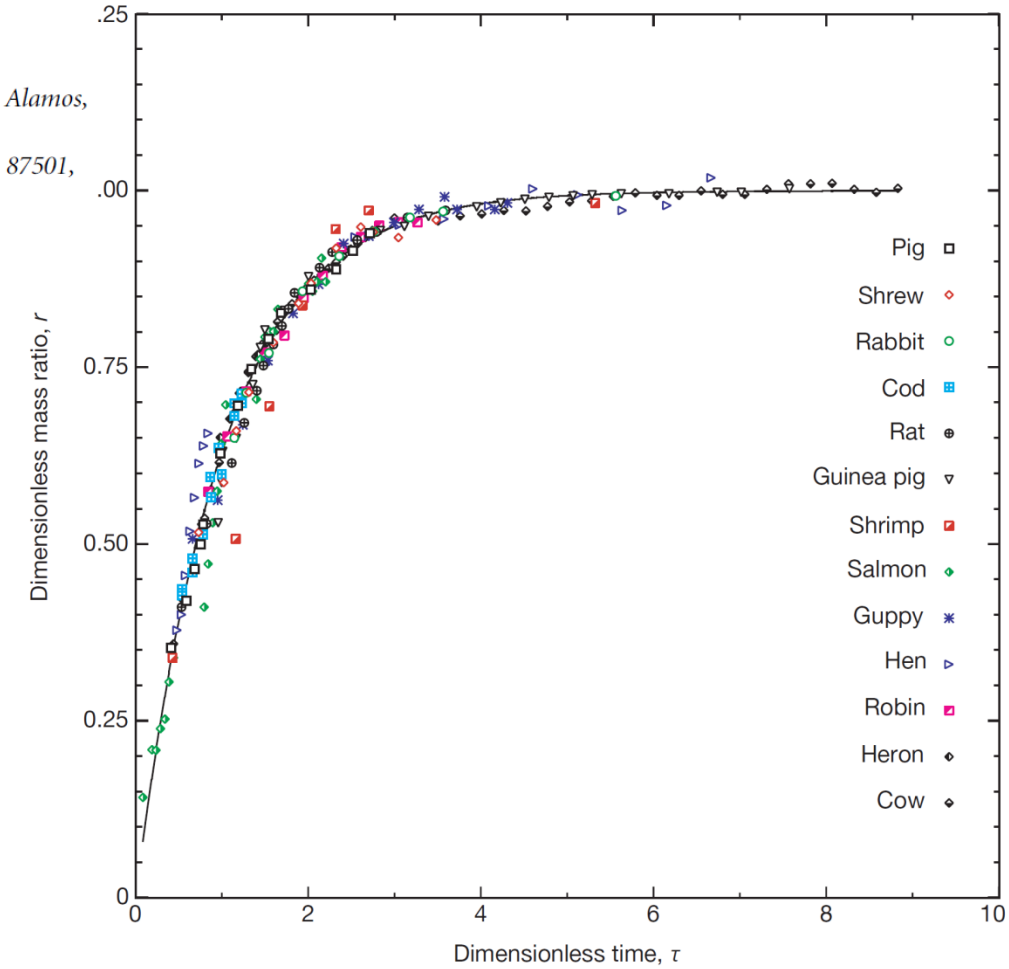

Figure 2 Universal growth curve. A plot of the dimensionless mass ratio, $r = 1 - R \equiv (m/M)^{1/4}$, versus the dimensionless time variable, $\tau = (at/4M^{1/4}) - \ln[1 - (m_0/M)^{1/4}]$, for a wide variety of determinate and indeterminate species. When plotted in this way, our model predicts that growth curves for all organisms should fall on the same universal parameterless curve $1 - e^{-\tau}$ (shown as a solid line). The model identifies r as the proportion of total lifetime metabolic power used for maintenance and other activities.

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Does tumor growth follow a "universal law"?

Caterina Guiot[a,b,*], Piero Giorgio Degiorgis[b], Pier Paolo Delsanto[b,c], Pietro Gabriele[d], Thomas S. Deisboeck[e,f]

[a] *Dip. Neuroscience, Universita di Torino, C. Raffaello 30, 10125, Torino, Italy*
[b] *INFM, sezioni di Torino Università e Politecnico, Italy*
[c] *Dip. Fisica, Politecnico di Torino, Italy*
[d] *IRCC Candiolo, Torino, Italy*
[e] *Complex Biosystems Modeling Laboratory, Harvard-MIT (HST) Athinoula A. Martinos Center for HST-Biomedical Engineering Center, Massachusetts Institute of Technology, Cambridge, MA*
[f] *Molecular Neuro-Oncology Laboratory, Harvard Medical School, Massachusetts General Hospital, Char*

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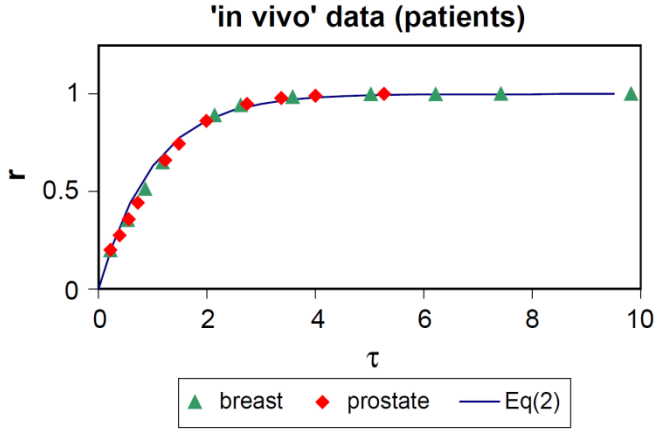

Abstract

A general model for the ontogenetic growth of living organisms has been recently proposed. Here we investigate the extension of this model to the growth of solid malignant tumors. A variety of in vitro and in vivo data are analysed and compared with the prediction of a "universal" law, relating properly rescaled tumor masses and tumor growth times. The results support the notion that tumor growth follows such a universal law. Several important implications of this finding are discussed, including its relevance for tumor metastasis and recurrence, cell turnover rates, angiogenesis and invasion.