

Polymorbidity, polymedication...

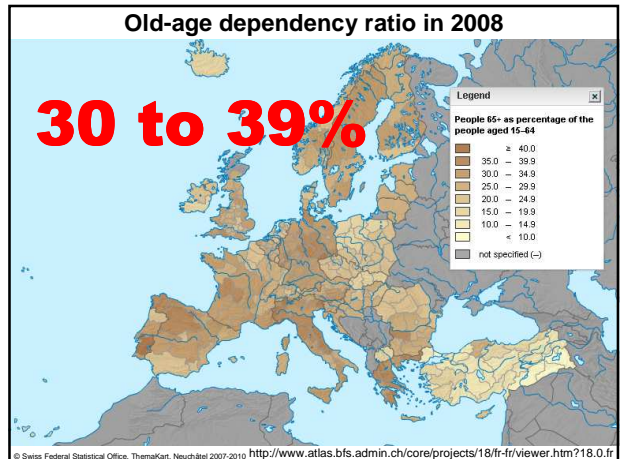
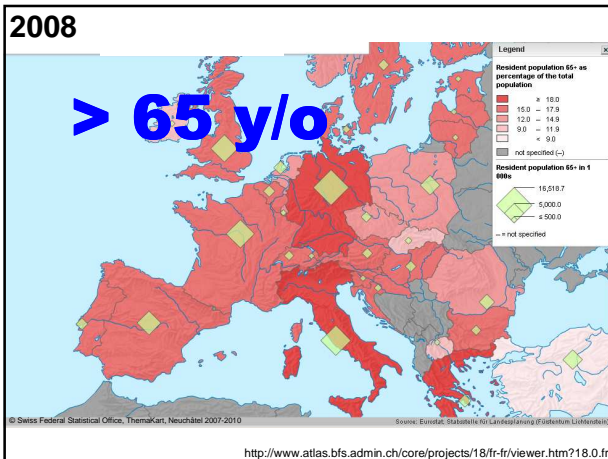
treat everything?

nicole-b.vogt-ferrier@hcuge.ch

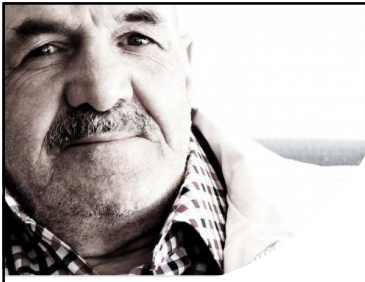


Very very old person

justidm.wordpress.com/2009/04/



- **Frailty: An Emerging Research and Clinical Paradigm—Issues and Controversies**
- Howard Bergman,1 Luigi Ferrucci,2 Jack Guralnik,3 David B. Hogan,4 Silvia Hummel,5 Sathya Karunanathan,5 and Christina Wolfson6
- *Gerontol A Biol Sci Med Sci.* 2007 July; 62(7): 731–737.



What makes geriatric medicine complex?

Frailty
Polymorbidity
Polypharmacy

Frailty



storm ahead

Neurology Chronicle | for | © | Peris Association 2014


Gerontol A Biol Sci Med Sci. 2007 July; 62(7): 731-737.

... Frailty



Gerontol A Biol Sci Med Sci. 2007 July; 62(7): 731-737.

Easy does it



Rockwood K, CMAJ 1994; 150 : 489-495
Bergman J Gerontol A Biol Sci Med Sci 2007; 62(7) : 731-37
Song X, JAGS 2010; 58:681-687

concept still uncertain



Gerontol A Biol Sci Med Sci. 2007 July; 62(7): 731-737

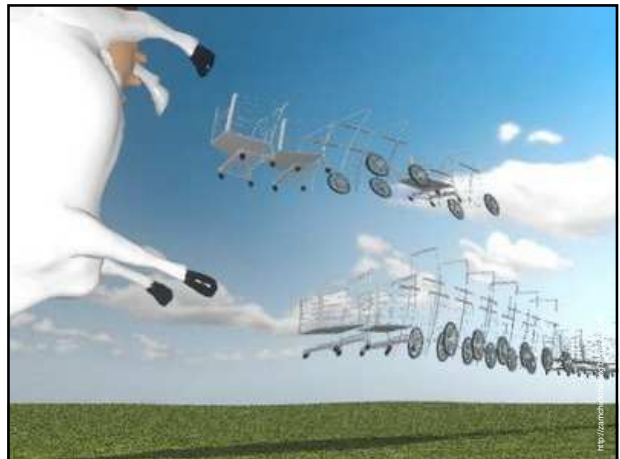
Frailty and mathematic modeling

- « Pour mieux comprendre le concept de fragilité, certains chercheurs essaient de le modéliser.
- L'exercice suivant peut vous faire apprécier la complexité d'un tel procédé.
- Je vais vous fournir des données descriptives.
- Essayer d'imaginer la situation décrite par ces données.

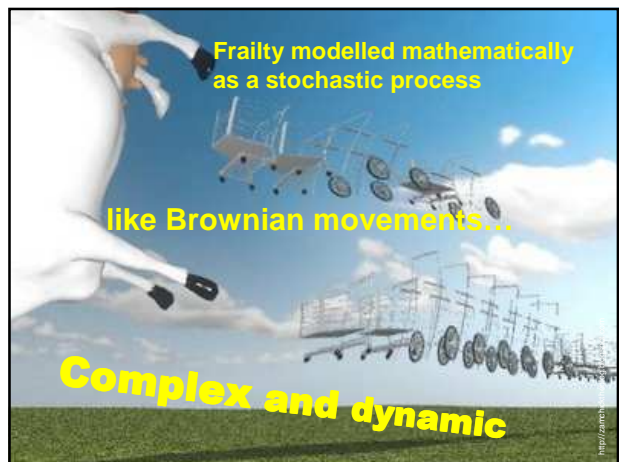
Modelling FRAILITY

- the white cow is facing down.
- the light is 2 feet in front of the cow.
- the column of 6 small shopping carts are 1 foot behind the cow.
- the column is 5 feet above the ground.
- the second column of 12 small shopping carts are 2 feet behind the cow.
- the second column is 2 feet behind the cow.
- the second column is 1.5 feet above the ground.
- it is partly cloudy. the ground is grass.

Gary Zamchick 2009



- Voici ce qu'aurait dû produire votre modélisation mentale du texte lu.
- Etrangement, le concept de fragilité ressemble à des phénomènes aussi différents que
 - le comportement de la bourse de Paris décrite par le mathématicien Bachelier en 1900,
 - la démonstration de nature moléculaire de la matière décrite par Albert Einstein en 1905
 - ou, sur cette image, le déplacement dans le temps et l'espace d'une vache et d'un train de chariots de superette soulevés par l'imagination d'un génial publiciste, [Gary Zamchick](#), en 2009
- Tous ces phénomènes s'apparentent aux mouvements Browniens.



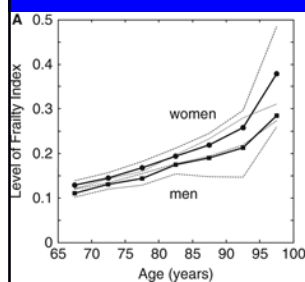
Frailty index (36 items)

- h/o hypertension, heart disease, diabetes mellitus, glaucoma severe enough to cause vision problems so that help was needed with heavy housework
- 6 deficits :
 - 4 diagnoses
 - 1 sensory impairment
 - 1 disability

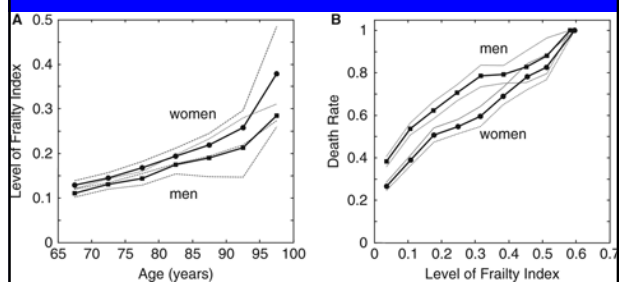
$$\text{Frailty index} = 6/36 = 0.17$$

Song X et al. JAGS 2010; 58:681-687

Frailty increases w/ age



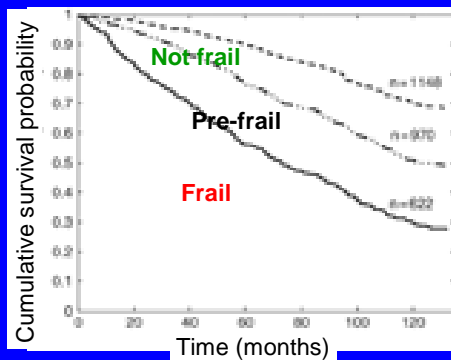
10-year death rate and frailty



JAGS 2010; 58 :681-687

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Frailty and survival



JAGS 2010; 58 :681-687



Diabetes Mellitus in Nursing Homes USA 1995-2004

	1995	2004
DM prevalence	%	%
Men	16.9	26.4
Women	16.1	22.2
Cardiovasc dz		
Men	59.6	75.4
Women	68.1	78.7

all P < .05

Zhang et al. JAGS 2010; 58:724-730

CKD Comorbidity

↓ cognitive function

↑ prevalence of

- DM
- HTA,
- high cholesterol level
- CAD
- CHF
- Cerebrovasc dis
- Peripheral vasc dis
- Cancer

Yaffe K et al. JAGS 2010; 58: 338-45
Stevens LA et al. Am J Kidney Dis 2010;55(3 Suppl 2) : S23-33

Complications CKD

- hyperparathyroidism 30 to 50%
- anemia 20 to 30%
- Ca, PO₄ abnormalities > 6%

Yaffe K et al. JAGS 2010; 58: 338-45
Stevens LA et al. Am J Kidney Dis 2010;55(3 Suppl 2) : S23-33

image julien kisa 2010

Complications

- 20 to 30% anemia
- 30 to 50% hyperparathyroidism
- > 6% biochemical abnormalities

Stevens LA et al. Am J Kidney Dis 2010;55(3 Suppl 2) : S23-33

image julien kisa 2010

Polypharmacy

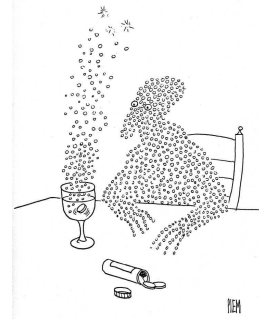


> 5 ?

GETTY IMAGES

*Man who take
sleeping pill and
laxative on same
night will wake up in
deep shit*

Geriatrician's proverb



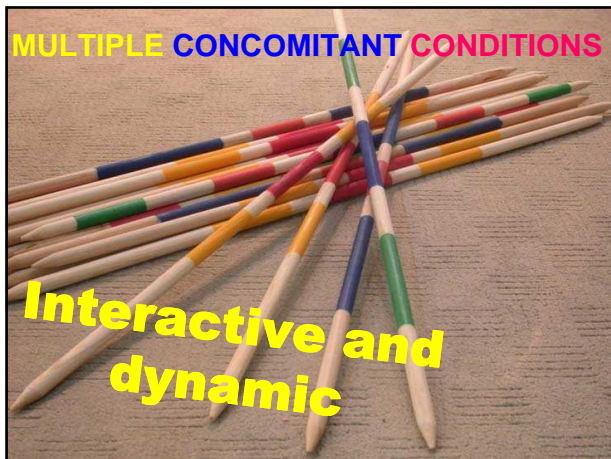
Guidelines

« Good quality guideline »

- ✓ Well defined target population
- ✓ Quality of the evidence used to elaborate the recommendations has been appraised
- ✓ Explicit therapeutic objectives
- ✓ Quality of life also considered
- ✓ Patient preferences included
 - ✓ Competing risks considered
 - ✓ Burden of the treatment for the patient and care-givers considered
 - ✓ Good balance between short- and long-term goals

Boyd, C. M. et al. JAMA 2005;294:716-724

MULTIPLE CONCOMITANT CONDITIONS



Interactive and dynamic

Risk / benefit ratio of drugs

- Quality of life
- Physical disability
- Psychological disorders
- ↑ use health care resources
- Multiple prescribers
- Polymedication
- ↑ risk of adverse events

Interactive and dynamic



Les Guidelines

- Sont conçues en fonction d'une maladie
- Définissent des normes pour la prise en soins de cette maladie
- Visent à améliorer la qualité des soins en établissant des procédures standard
- Ne tiennent généralement pas compte de la possibilité de co-morbidités

Boyd CM et al. Clinical Practice Guidelines & Quality of Care for Older Patients with Multiple Comorbid Diseases JAMA 2005; 294(6): 716-724.

Is this guideline applicable to my patient?

The « killer Bs »

- Burden
- Beliefs
- Bargain
- Barriers

Straus ES et al. Evidence Based Medicine 3rd edit 2005



Is this guideline applicable to my patient?

- Is the **Burden** of illness (our patient's pre-test probability or expected event rate) too low (too different?) to warrant implementation?
- Are my patient's **Beliefs** about the value of the intervention or their consequences incompatible with the guideline?
- Would the opportunity cost of implementing this guideline constitute a bad **Bargain** in the use of our energy or our community's resources?
- Are the **Barriers** (geographical, organizational, traditional, authoritarian, legal or behavioral) so high that it is not worth trying to overcome them?

Straus SE et al. Evidence Based Medicine 3rd edit 2005



Is my patient so different from those included in the studies of the guideline's evidence summary

that this evidence is not applicable?

Straus SE et al. Evidence Based Medicine 3rd edit 2005

Someone who thinks logically



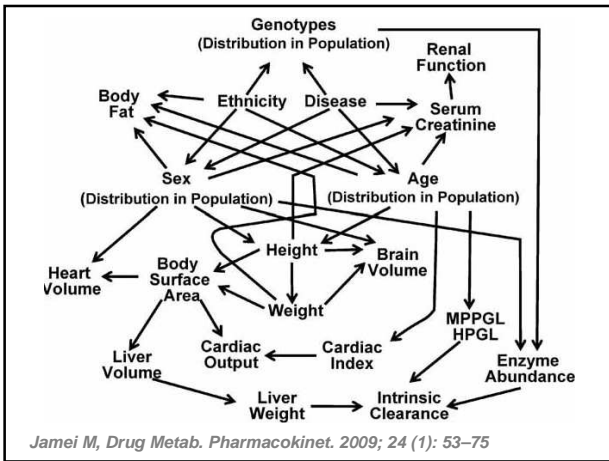
is a nice contrast to reality




Getting to grips with reality





**Pharmacogenetics
Immune response
Organ failure
Comorbidity
Ethnicity
Gender**

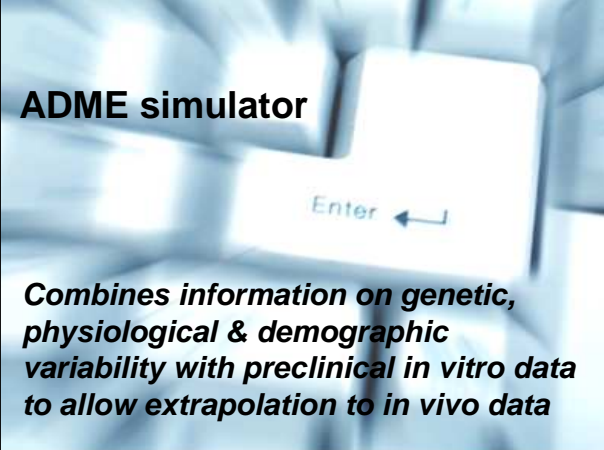
A novel approach to predicting drug metabolism and interactions



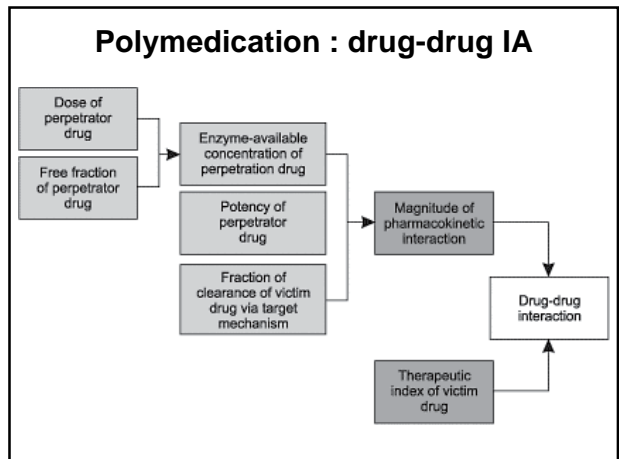
« In-silico » prediction

ADME simulator



Combines information on genetic, physiological & demographic variability with preclinical in vitro data to allow extrapolation to in vivo data



Inter-Individual Variability & mDDI

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Victim substrate metabolised 50% by CYP1A2, 30% by CYP2D6 and is excreted renally (20%)

With complete inhibition of CYP1A2:

- Typical healthy adult may not increase the AUC more than 2 fold,
- An elderly patient with renal failure: 2.7 fold
- An individual who lacks functional CYP2D6 for genetic reasons: 3.5 fold
- A poor CYP2D6 metaboliser with renal failure (25% function): 11 fold

Courtesy Masoud Jamei 2009

Administration of Multiple Inhibitors

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- Only few prospective mDDI studies, evaluating the effect of multiple CYP inhibitors on a single substrate
- Most reports involve HIV drugs and anticancer medications (both for synergistic effects)

Increased Exposure under mDDI:

Substrate	Single Inhibitor (1)	Single Inhibitor (2)	Both Inhibitors Together	Reference
Loperamide	Gemfibrozil 2.2	Itraconazole 3.8	12.6	Niemi M, 2006
Repaglinide	Gemfibrozil 8.1	Itraconazole 1.4	19.3	Niemi M, 2003
Ropivacaine IV	Fluvoxamine 3.7	Erythromycin 1.2	5.5	Jokinen, 2000

Example: Zolpidem is metabolised by:

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
20.93%	36.14%	0.68%	1.41%	40.84%

% enzyme contribution to total hepatic CL_{int} - Average Subject

% enzyme contribution to total hepatic CL_{int} - 2C9 PM

Courtesy Masoud Jamei 2009

Multiple Inhibitors - Hypothetical Examples

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Inhibitors acting on the same enzymes

Zolpidem + Ketoconazole (CYP3A4) $R_{ss}=1.55$

Zolpidem + Itraconazole (CYP3A4) $R_{ss}=1.30$

Zolpidem + Ketoconazole + Itraconazole $R_{ss}=1.58$

Inhibitors acting on different enzymes

Zolpidem + Ketoconazole (CYP3A4) $R_{ss}=1.55$

Zolpidem + Sulfaphenazole (CYP2C9 + CYP2C19) $R_{ss}=1.44$

Zolpidem + Ketoconazole + Sulfaphenazole $R_{ss}=3.18$

Courtesy Masoud Jamei 2009

EBM

Best research evidence

Clinical expertise

Patient's values and circumstances

Straus SE et al. Evidence Based Medicine 3rd edit 2005

Patient values

Unique preferences, concerns and expectations each patient brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve the patient.

Straus SE et al. Evidence Based Medicine 3rd edit 2005

Patient circumstances

Their individual clinical state and the clinical setting



« We are different from the very old of the past »
 Elaine Brody 2010

different

- more education and better health care since early childhood
- Women ... out-of-home work
- Transportation, communication, and technology have exploded in our lifetimes

“We, the very very old, are a new frontier—for ourselves and for you to know and understand.”

Elaine Brody 2010



Switzerland 2007

Live in private homes :
 94% of persons 65-79 y/o
 71% of persons over age 80

<http://www.bfs.admin.ch/bfs/portal/fr/index/news/publikationen.Document.129407.pdf>

50% of the total number of unpaid hours spent by the whole population taking care of dependent persons in private homes is provided by persons aged >65



25 Mio hours =
 13'000 full-time jobs

<http://www.bfs.admin.ch/bfs/portal/fr/index/news/publikationen.Document.129407.pdf>



13% of volunteer work hours of the total population are provided by persons aged >65

45 Mio hours =
 24'000 full time jobs

CH, 2007

<http://www.bfs.admin.ch/bfs/portal/fr/index/news/publikationen.Document.129407.pdf>

Child-care

Women

64 to 74 years : 33 hours/month
 > 75 years : 30 h/mo

Men aged 65 to 74 years : 24 h/mo

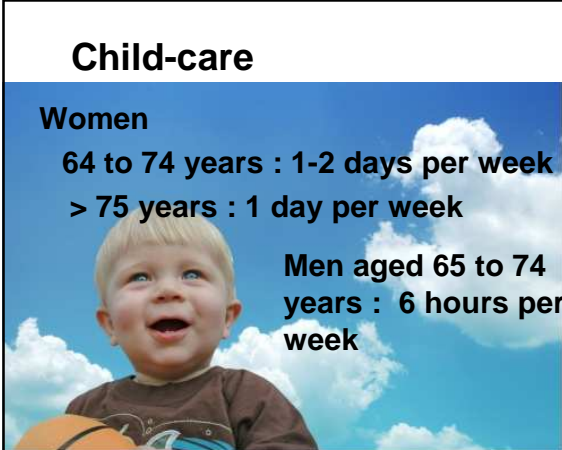
Child-care



Women
 64 to 74 years : 33 hours/month
 > 75 years : 30

Men
 65 to 74 years : 24

Child-care




Women
 64 to 74 years : 1-2 days per week
 > 75 years : 1 day per week

Men aged 65 to 74 years : 6 hours per week


"Many years ago, in a study of older people's day-to-day health concerns, we debriefed the interviewees and asked them, "What is the main piece of advice you can give health professionals?" The interviewees, over and over again, said, "Listen to what older people are really saying ... not only to the words but to cries, whispers and silences. Really listen so that they know their concerns and feelings are being recognized".

Elaine Brody 2010



Brody EM. On being Very, Very Old: An Insider's Perspective. Gerontologist. 2010;50(1):2-10

cries



Cries

- I would like to invite you to pause and listen to the very old patients. Most wish to remain faithful to their true self, to who they've always been. Illness and particularly degenerative diseases such as Alzheimer's are feared because of the loss of identity and autonomy that accompany them. Older persons offer much guidance, explicitly or implicitly, as to whether and what ailments should or should not be treated. Taking such cues into account helps one to tailor down otherwise complicated drug regimens and healthcare. For those who may not be able to express their needs, a holistic approach is required, in which comfort and quality of life is the priority. Coherence lies in the practice of comprehensive geriatric assessments, the integration of social, spiritual and environmental issues in the management of somatic and psychological problems and a balance between short-term and long-term therapeutic objectives. Constraints and restrictions, such as life-expectancy, can also help formulate reasonable treatment plans. (N Vogt)

whispers





silences

YES, YOU'RE RIGHT, I KNOW, BUT...

- Feel the ambivalence
- Explore the silences

- Taking such cues into account helps one to tailor down otherwise complicated drug regimens and healthcare.

(N Vogt)

In summary, treat everything ?

- Frailty, polymorbidity, polymedication
Complex and dynamic
- Guidelines often ignore complexity
- New research, technology and comprehensive geriatric assessments help
- EBM : the third component, patient values & circumstances, help make the right decision
- « It depends... » (E. Brody 2010)
- Tailor made better than one-size-fits all

Listen

