LA MEDECINE PERSONNALISEE GRACE AU NUMERIQUE ».

A l'ère du post-génome d'une côte ouest à l'autre!

« Heureux qui comme Ulysse à fait un beau voyage »

Rotary Club Toulouse - Le Belvédère

Prof. Pierre-Antoine Gourraud

UCSF, Neurology Department, San Francisco, USA. & UMR Inserm 1064 -University of Nantes , France&
PHU 11 Pôle Hospitalo-Universitaire 11 : Santé Publique, Nantes University Hospitals, France

PLAN

- 1- Parcours scientifique "d'une côte ouest a l'autre"

  2- La recherche médicale à l’ère numérique

  3- Mon "odyssée" américaine en 5 phrases

UN PARCOURS

Curriculum Vitae – Parcours Académique

- **Emploi Actuel:**
  - Professeur des universités-praticien Hospitalier Université de Nantes

  Ancien Associate Professeur In Residence, Step 3 WOS Neurology School of Medicine; University of California, San Francisco

- **Fonction et Service**
  - 1999-2006 : Elève Normalien – Moniteur Allocation Couplée
  - 2006-2008 : Assistant Hospitalo-Universitaire, CHU-Toulouse
  - 2008 : Création de Methodomics SARL
  - 2009-2011 : Post-doc UCSF, USA
  - 2011- 2015 : Enseignant-chercheur UCSF, USA

- **Cursus Universitaire**

1999 – 2001	UFR Sciences de la vie, Université Lyon-I	Maîtrise	Physiologie – Biol. Cellulaire
1999 – 2003	École Normale Supérieure, Université Lyon-I	Normalien	Biologie
2002 – 2005	Doctorat d'Université, Université-Toulouse III	Doctorat	Biologie
2004 – 2006	Licence de Philosophie, Univ. de Toulouse (I.C.T.)	Licence	Philosophie
2007 – 2010	DU de Pédagogie Médicale, Univ. Toulouse III	DU	Pédagogie médicale
2013 – 2014	Habilitation à Diriger des Recherches, Univ. de Nantes	HDR	Médecine


L'HERMIONE
FRA
1953C

LA RECHERCHE

Introduction

- **La recherche, des chercheurs**
  - Un parcours “collectif et personnel”
- **Des données pour mieux comprendre les maladies complexes** comme la Sclérose en Plaques
  - La variabilité de la maladie
  - 1 - Génétique
  - 2 - Imagerie cérébrale
  - 3 - “Démocratiser” l’accès aux données grâce au numérique
  - 4- Objets connectés

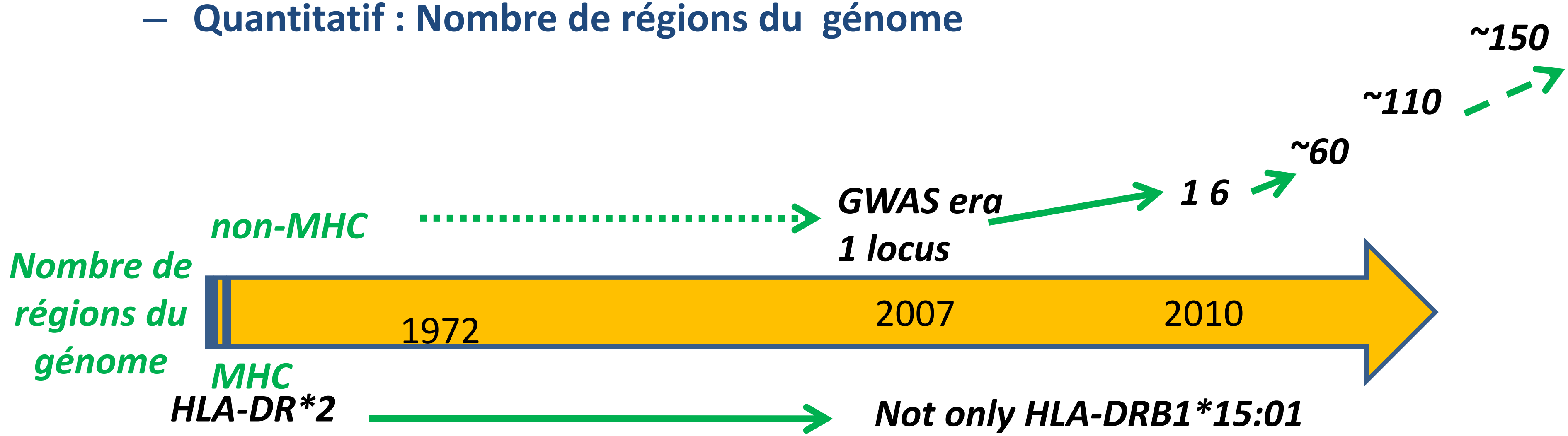
1 – Génétique de la Sclérose en plaques

Cardiff University
Prifysgol Caerdydd
Peninsula Medical School
Universities of Exeter & Plymouth
Karolinska Universitetssjukhuset
National Institute for Health and Welfare
FIMM
Laboratory in Genetics and Genomics Medicine of Inflammation
University of Cambridge
Keele University
Oslo University Hospital
Ullevål University Hospital
Region H
Rigshospitalet
wellcome trust sanger institute
Queen's University Belfast
University of Oslo
University of Copenhagen
KU Leuven
Université de Montréal
Yale University School of Medicine
Charles University Prague
Harvard Medical School
Universitätsklinikum Hamburg-Eppendorf
UCSF University of California San Francisco
advancing health worldwide
Broad Institute
Whitehead Institute for Biomedical Research
Johannes Gutenberg Universität Mainz
Kyushu University
School of Public Health
University of California, Berkeley
BWH Brigham and Women's Hospital
Technische Universität München
CHGR center for human genetics research
University of Miami
Vall d'Hebron Institut de Recerca
Amedeo Avogadro
università degli studi del piemonte orientale
Ospedale San Raffaele
Istituto di Ricovero e Cura a Carattere Scientifico
ASLNuoro
Griffith University
Faculté de médecine Pierre et Marie Curie
University of Otago
New Zealand
The University of Melbourne
The University of Newcastle Australia
UTAS
The University of Sydney
Incidence (per 100,000 inhabitants)
More than 45
Less than 15

Historique de la génétique de la Sclérose en plaques

- **Avertissement sur :**
  - Le rôle limité mais réel de la génétique dans l'explication de la maladie

- **Explosion des connaissances en génétique de la SEP**
  - **Quantitatif : Nombre de régions du génome**



“Big data” La génétique de la SEP

Beaucoup d individus

MS Cases **Controls**

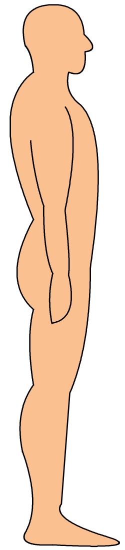
S Single
N Nucleotide
P Polymorphism

Des associations statistiques en population

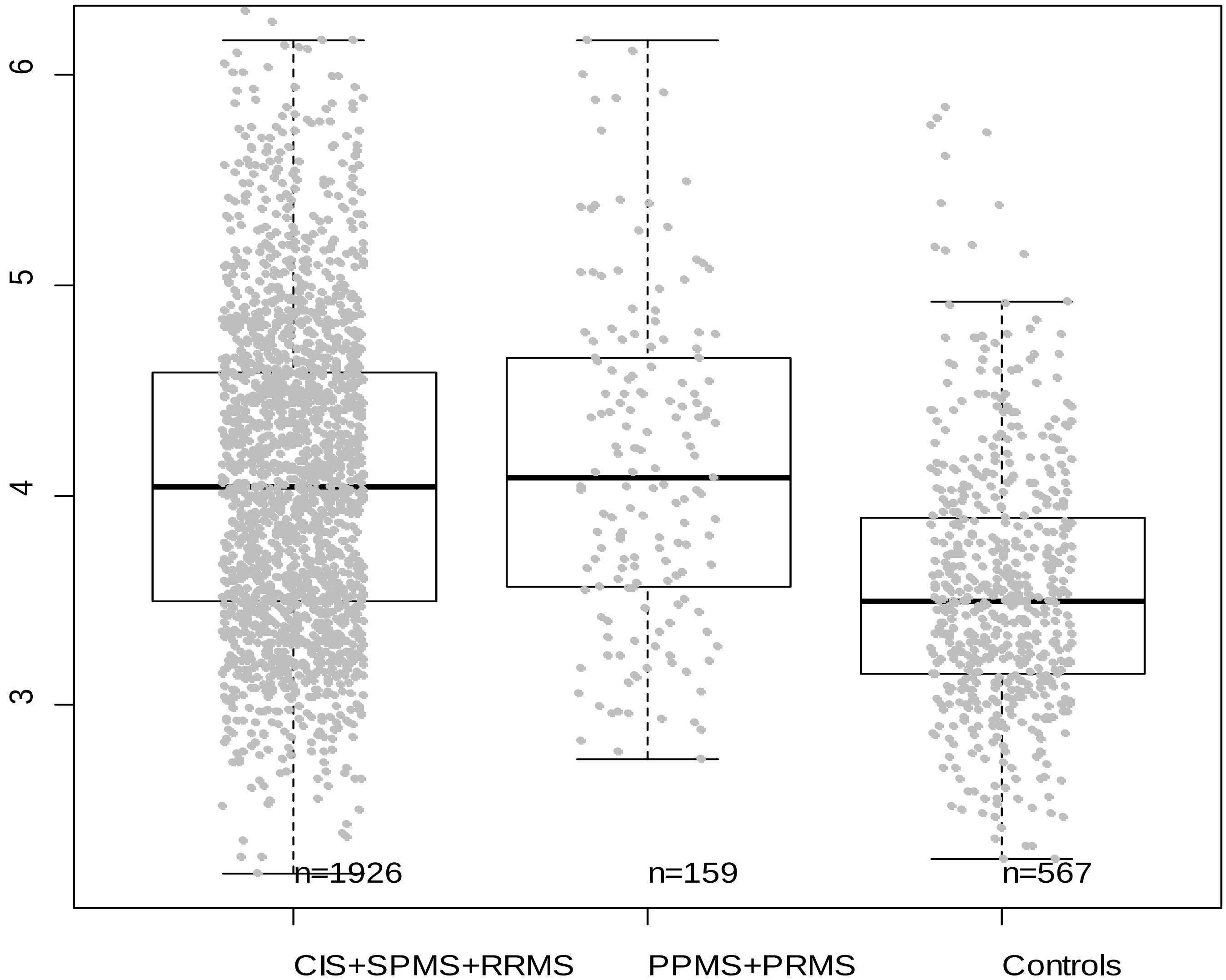
Vers un profil Génétique individuel

MS Cases

Controls



La Variabilité au cœur du vivant…

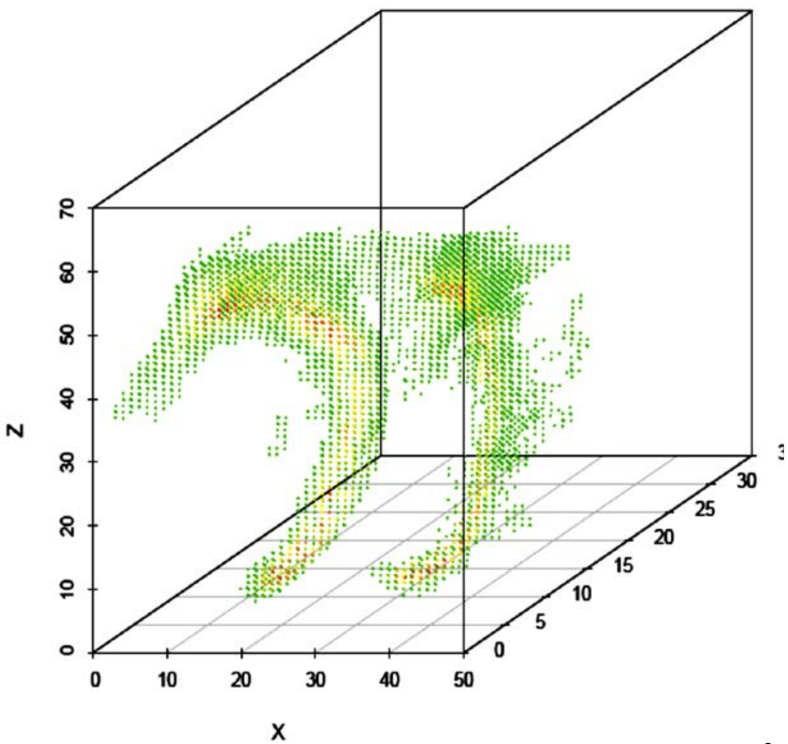


Updated from Gourraud et al. Ann Neurol 2011

2 –Imagerie, la place de la technique et des données

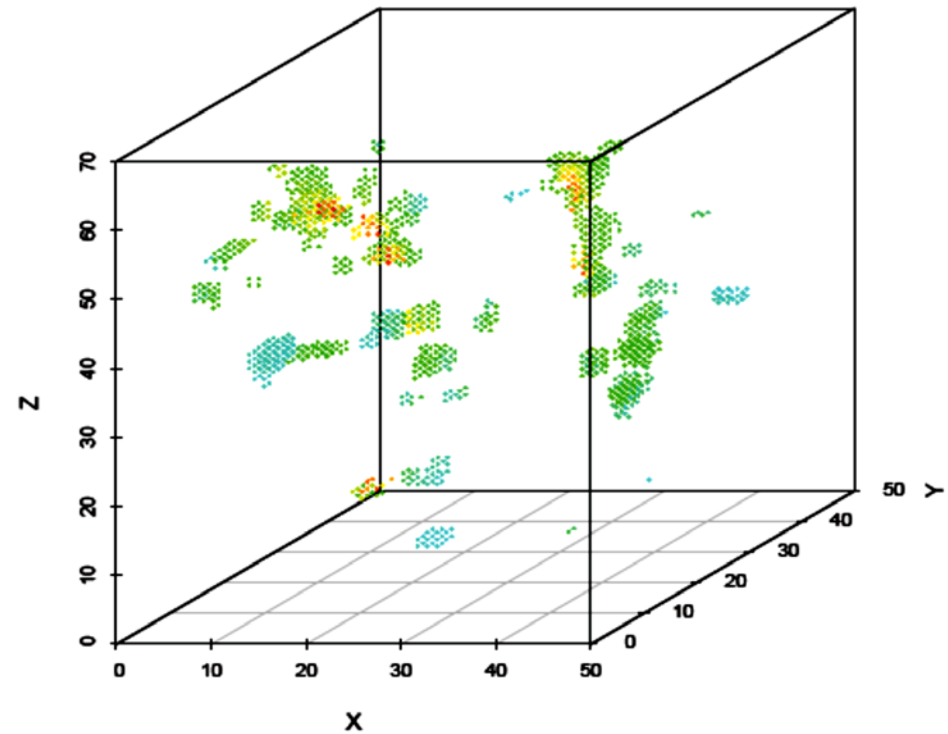
Retourner à l'individu

Niveau de Population



Une carte en moyenne

Niveau de l'individu



Un individu "dans le contexte de donéees en population "

3 – Médecine de précision pour la SEP

Expérience et mémorisation


Power standby light
F1/F2 toggle button
Internal/external input select
Display (2.4cm x 3.6cm)
Default settings for geological, meteorological, and biological data
Emergency data dump button
Data activity indicators
Read/write chip selector
Touchpad for user identification


CHARGER

RCA
Mural TV

Des outils

ECG

Séquençage
des tumeurs

Une opportunité

3- Réalité dans la Sclérose en Plaques

- **Une application “Ipad” le MS Bioscreen**
  - **“Precision” → “Personalized”** Medicine

Comment le numérique va nous permettre de mieux comprendre et traiter les maladies chroniques ?


NEUROLOGY GRAND ROUNDS

Precision Medicine in Chronic Disease Management: The Multiple Sclerosis BioScreen

Pierre-Antoine Gourraud, PhD,[1] Roland G. Henry, PhD,[1] Bruce A. C. Cree, MD, PhD, MAS,[1] Jason C. Crane, PhD,[2] Antoine Lizee, MS,[1] Marram P. Olson, BS,[2] Adam V. Santaniello, BSc,[1] Esha Datta, MS,[1] Alyssa H. Zhu, MSc,[1] Carolyn J. Bevan, MD, MS,[1] Jeffrey M. Gelfand, MD, MAS,[1] Jennifer S. Graves, MD, PhD,[1] Douglas S. Goodin, MD,[1] Ari J. Green, MD, MCR,[1] H.-Christian von Büdingen, MD,[1] Emmanuelle Waubant, MD, PhD,[1] Scott S. Zamvil, MD, PhD,[1] Elizabeth Crabtree-Hartman, MD,[1] Sarah Nelson, PhD,[2] Sergio E. Baranzini, PhD,[1] and Stephen L. Hauser, MD[1]

We present a precision medicine application developed for multiple sclerosis (MS): the MS BioScreen. This new tool addresses the challenges of dynamic management of a complex chronic disease; the interaction of clinicians and patients with such a tool illustrates the extent to which translational digital medicine—that is, the application of information technology to medicine—has the potential to radically transform medical practice. We introduce 3 key evolutionary phases in displaying data to health care providers, patients, and researchers: visualization (accessing data), contextualization (understanding the data), and actionable interpretation (real-time use of the data to assist decision making). Together, these form the stepping stones that are expected to accelerate standardization of data across platforms, promote evidence-based medicine, support shared decision making, and ultimately lead to improved outcomes.

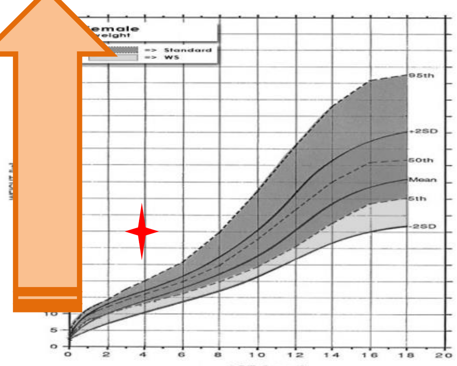
Gourraud et al. 2014 “Precision medicine in chronic disease management: the MS BioScreen
Annals of Neurology Vol 76, Issue 5, 633–642, Nov 2014

De la PRECISION à la PERSONNALISATION

Utiliser les données pour construire les « courbes de croissance » du XXIst siècle

Une « courbe de croissance électronique »

Ex EDSS, Disability score - disease duration



Traditionelle « Courbe de croissance» Ex: Age -poids

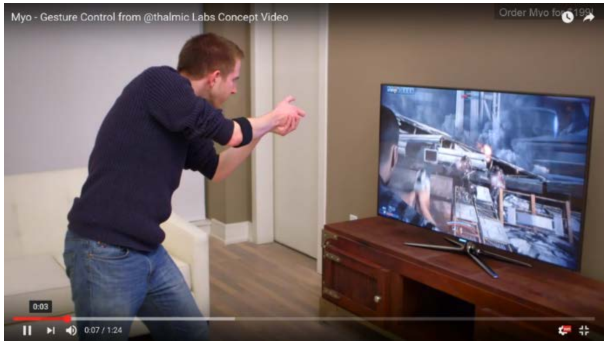
Capacite de modifier la reference

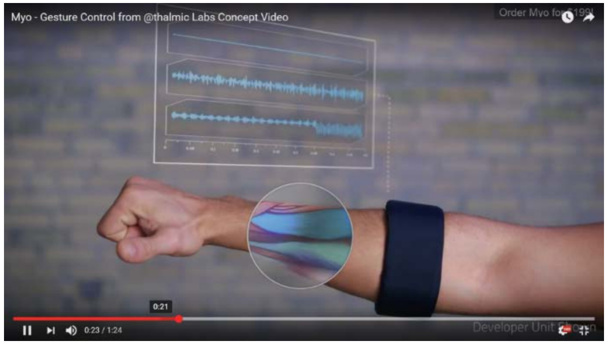
4- LA TRANFORMATION DIGITALE DE LA SANTE – UN EXEMPLE DES OPPORTUNITÉS

Surface au service de la collecte de données

- Examen Neurologique traditionnel
  - Observation : pratique de l’art de la médecine
  - Test de Coordination : système moteur & sensoriel
    - Lesions cérébellesue et/ou vestibulaire

- **Present** : Digitalisation des pratiques





Electro-Myographe de Surface au service de la collecte de données

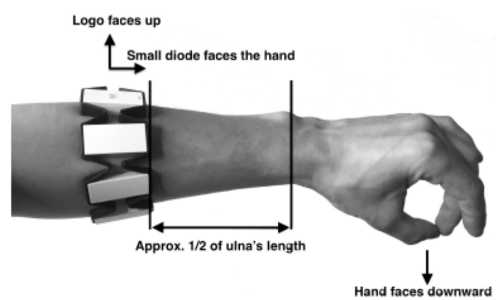


Fig. 2. Armband positioning on the forearm, example shown for finger tapping test.

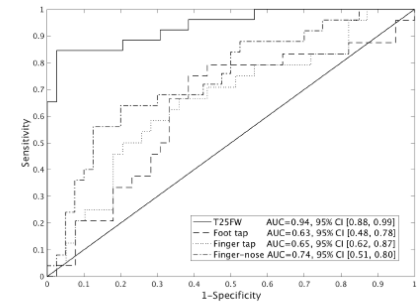
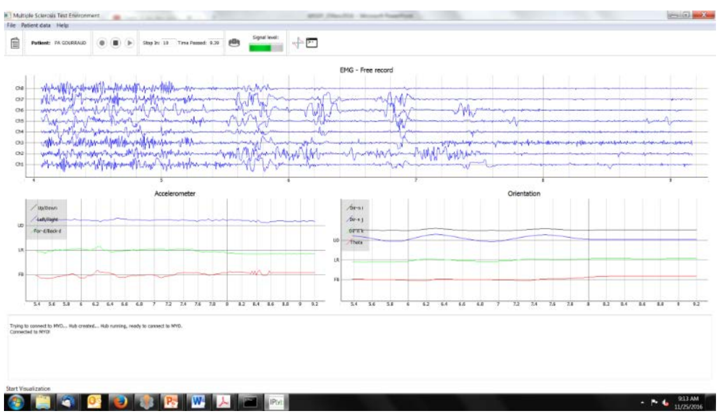


Fig. 4. ROC curves for four motor function tests, T25FW stands for timed 25 foot walk.



- **Nouvelles données nouveaux Outils :**
  - Algorithme d'intelligence artificielle"
  - Traitements des données à grande échelle
  - Classement des patients
- **Modification de notre regard sur la sclérose en plaques**
  - Analyse de la marche

Exemple : Objet Connecté

- La vision d'un progressiste-traditionaliste
  - Passer a la vitesse supérieure – être “data-savy “
  - Ancrage traditionnellement disciplinaire
- **La révolution des TIC crée des opportunité de de collecte de données a bas coûts**
  - acquisition de données <u>Active</u> (avec la participation active du patient)
  - acquisition de données <u>Passive</u> (sans requérir la participation active du patient)
  - <u>Opportunité de transformation</u>
- Traditionnaliste : Qualité des données
  - Signal / Noise
- Traditionaliste : biais et représentativité
  - Une nouvelle épidémiologie des données massives et non intentionnelles

SVM-based Tool to Detect Patients with Multiple Sclerosis Using a Commercial EMG Sensor

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Einar A. Høgestøl‡, Ingerid Tutturen‡, Hanne F. Harbo‡, Steffan D. Bos-Haugen‡,
Jennifer Graves¶, David-Axel Laplaud‖, Pierre-Antoine Gourraud‖

*Université de Nantes, LS2N UMR 6004, Nantes, Frances, Email: konstantin.akhmadeev@ls2n.fr
†Ecole Centrale Nantes, LS2N UMR 6004, Nantes, France
‡Department of Neurology, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
¶Department of Neurology, School of Medicine, University of California San Francisco, San Francisco, CA, USA
‖Université de Nantes, INSERM, Centre de Recherche en Transplantation et Immunologie UMR 1064, Nantes, France

***Abstract*—Multiple sclerosis (MS) is a major auto-immune disease that is the leading cause of non-traumatic impairment of the central nervous system (CNS) in young adults. Successful treatment of MS patients depends on accurate tools for both the MS diagnosis and the disability progression. In current and upcoming studies the authors aim to explore the capabilities of applying a commercial electromyographic and inertial sensor (MYO Armband by Thalmic Labs Inc.), coupled with a multichannel signal processing tool, to standard neurological examination. In this pilot study we formulate a two-class "healthy control" - "having MS" classification problem. A dataset of electromyographic signals and inertial sensor measurements from 71 individuals (31 MS patients and 40 healthy controls) was acquired during standard neurological examination routine. Temporal and spectral features of the signals were extracted in order to train and validate a classification model. Finally, a Support Vector Machine classifier was obtained giving AUROC = 0.94, 95% CI = [0.88, 0.99] and verified using five-fold cross-validation. We propose a set of signal descriptors that correlate with objective components of the neurological examination. The proposed signal acquisition and processing technique, being easy to integrate into the traditional neurological exam, may have high potential for aiding in diagnosing MS and quantifying its progression.**

I. Introduction

Multiple sclerosis (MS) is a chronic debilitating neurological disorder that mainly affects young individuals aged between 20 and 40. As a cause of neurologic disability MS is second only to trauma, having its prevalence estimated at 2.5 million worldwide in 2014. The actual cause of MS is yet to be identified, but a complex interaction between genetic and environmental factors contributes to the risk. To date, there is no reliable method to predict MS onset or progression. Successful managing of the symptoms and attacks for MS patients highly depends on an accurate and timely diagnosis as well as the possibility to measure disability progression.

Diagnostic criteria for multiple sclerosis include a number of clinical and paraclinical laboratory assessments [1], [2]: cerebrospinal fluid analysis, study of visual evoked potentials, electromyography analysis, neuroimaging and motor/sensory/balance function tests. The latter involves various motor tasks to be accomplished by the subject: timed 25-foot walk [3], 9-hole peg test, finger-to-nose test [4], heel-knee-shin test, finger tapping, foot tapping, etc.

The most common motor manifestations of MS are muscle fatigue, spasticity and tremor. Listed symptoms involve abnormal functioning of skeletal muscles and thus affect their activation patterns. In such cases, deviations may be revealed by analysis of limb trajectories and of involved muscles' electromyography (EMG). These measurements are proven to be efficient in different studies of MS progression [5]–[7]. Thus, an EMG recording along with the inertial measurement unit (IMU) data may aid to characterise presence and severity of MS.

Common MS diagnosis and progression study approaches, as those listed above, require specific equipment, procedures and clinical expertise. A lack of them may slow down or make the diagnosis impossible, which is a common case for low populated areas or developing countries. A possible way to overcome these difficulties is to apply a widespread cheap acquisition system, along with unified assessment protocol and automated decision-making. As such an acquisition system we propose the MYO armband (figure 1) developed and commercialised by Thalmic Labs Inc [8]. It comprises eight EMG channels and an IMU giving acceleration, orientation and rotation speed measurements in three axes. This device is wireless, cheap, easy to use, actively supported by community and can be shipped to any location.

MYO armband's default software is capable of recognising five different hand gestures, based on EMG. Also, IMU sensor provides a pointer control. In academic studies, this device was applied in sign language gesture recognition [9] and prosthetic control [10], [11]. Typical signal processing pipeline in these applications consists of the following steps: windowing, feature extraction, dimensionality reduction and classification using machine learning techniques [12], [13]. Such an approach may also be effective in an application to MS diagnostics since there is no strictly defined model of how MS affects surface EMG signals or limb trajectories. Other reasons to use machine learning techniques in this case are the dimensionality of the data and the fact that measurements

Quels enseignements dans ce projet ?

- Un abaissement formidable du cout de collecte des données
  - Des objets « connectés », des capteurs
- Au centre du développement du numérique la question des <u>usages</u>
  - Pas « disruptif »
  - Que faire de ces « données »? Est-ce qu’on en a trop?
  - Prolonge l’observation et la réflexion ne la remplace pas
- Penser un rapport aux objets techniques
  - Imaginer des opportunités des transformations
  - Etudier les usages
  - Evaluer les conséquences en santé

5- LA FRANCE LES USA, LES VERTUS DU VOYAGE – QUE RAMENER DANS SES BAGGAGES?

Heureux qui comme Ulysse …

1. “What you deliver” – combinaison rapidité et confiance pragmatisme intégral
2. “Today is my last day” – flexibilité réciproque du marche du travail
3. “ You failed that is great “ – culture positive de l’échec
4. « sky is the limit » - American Dream
5. “ I want to do good” Le rôle des fondations – charity

LA MEDECINE PERSONNALISEE GRACE AU NUMERIQUE ».

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Inserm
Institut national de la santé et de la recherche médicale

UNIVERSITÉ DE NANTES

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

UCSF
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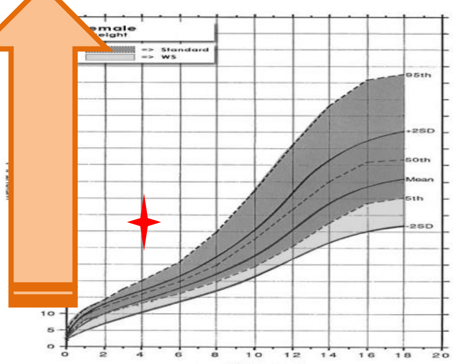
De la PRECISION a la PERSONALISATION

Utiliser les données pour construire les « courbes de croissance » du XXIst siècle

Electronic « growth chart for complex disease »

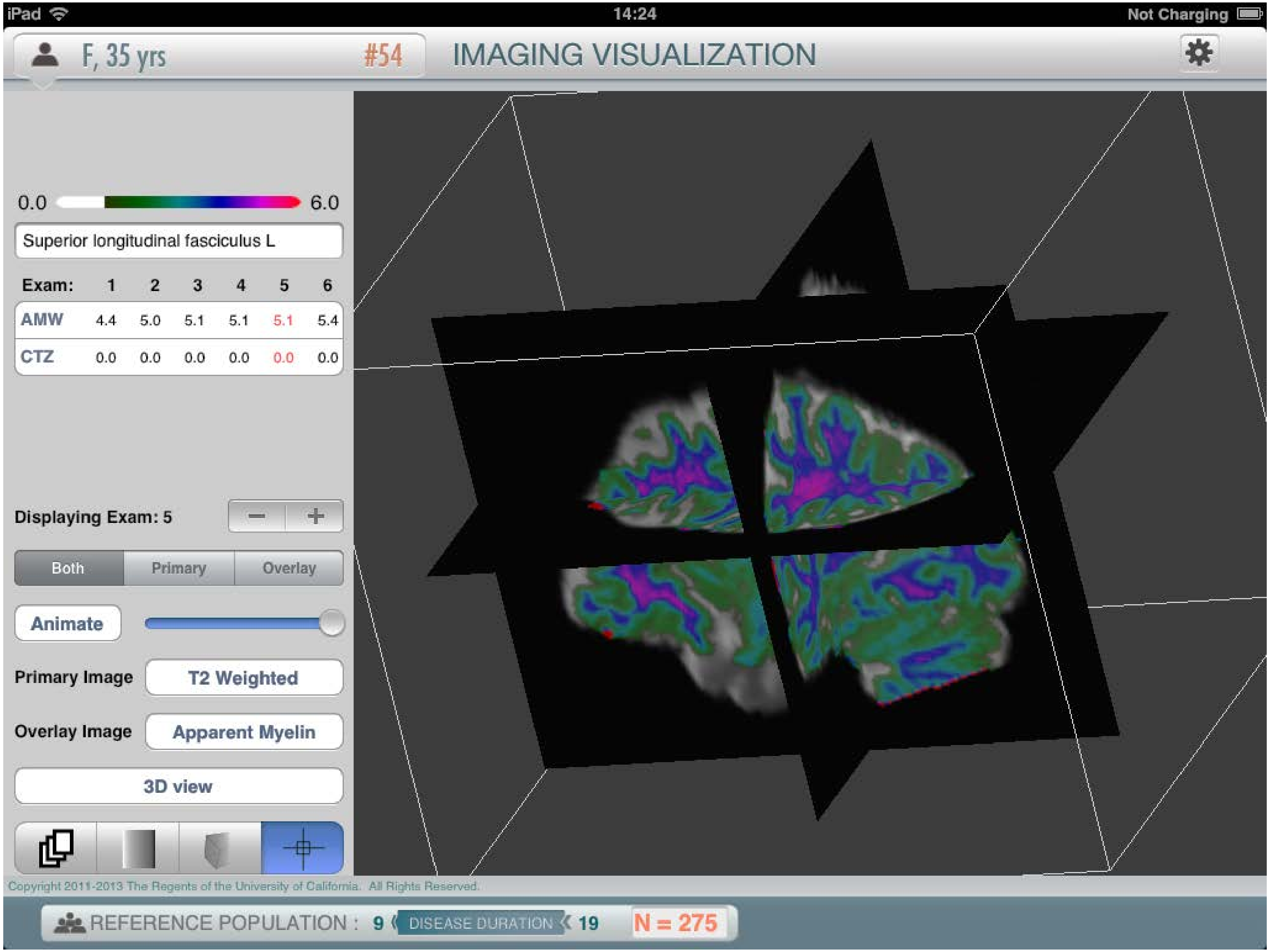
Ex EDSS, Disability score - disease duration



Traditional « Growth chart »
Ex: Age -weight

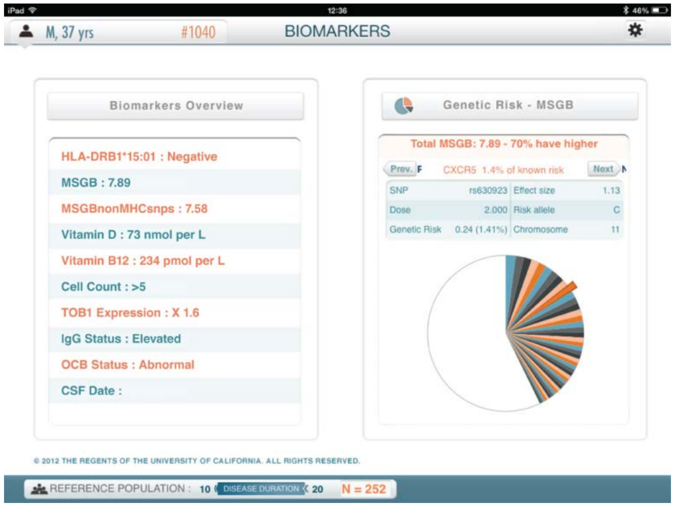
Dynamically tailored reference population empowering physicians & patients

3D serial MR Brain imaging

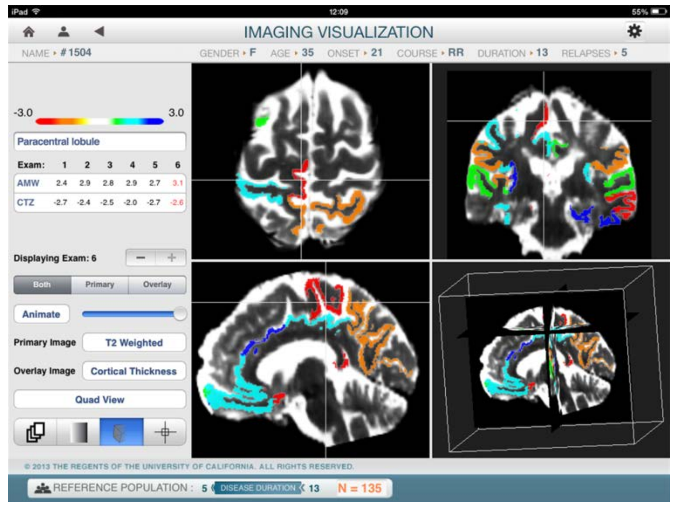


Captures d’écran

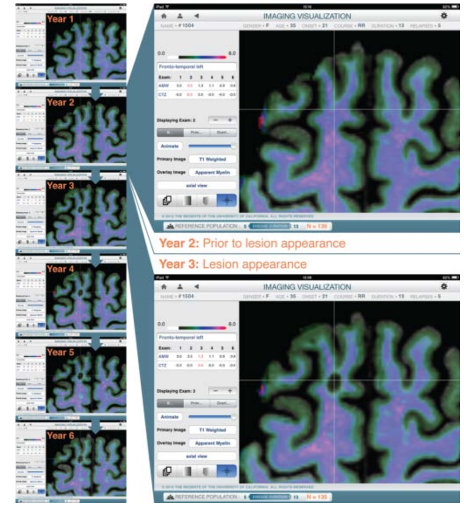
Gourraud et al 2014 Annals of Neurology



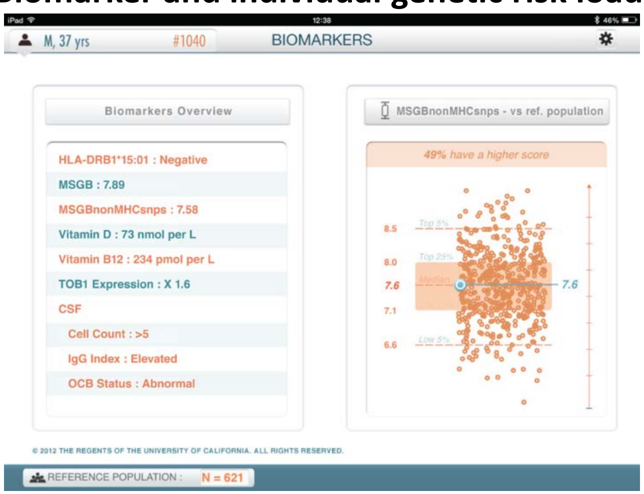
Biomarker and individual genetic risk load



A four panel view of a T2 weighted brain MRI image with cortical thickness z-score overlay.

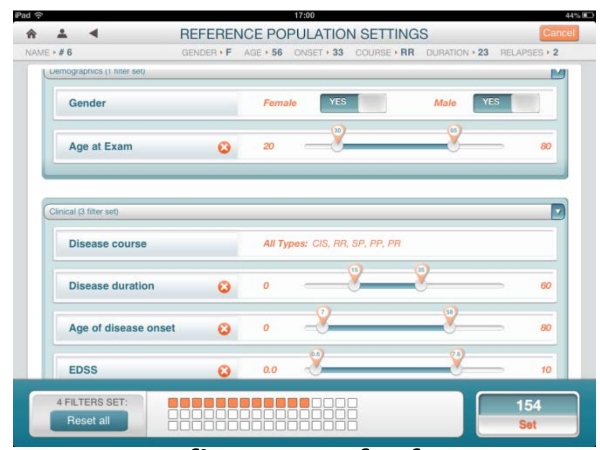


Longitudinal view of MRI data



Individual Genetic risk score in the context of reference population

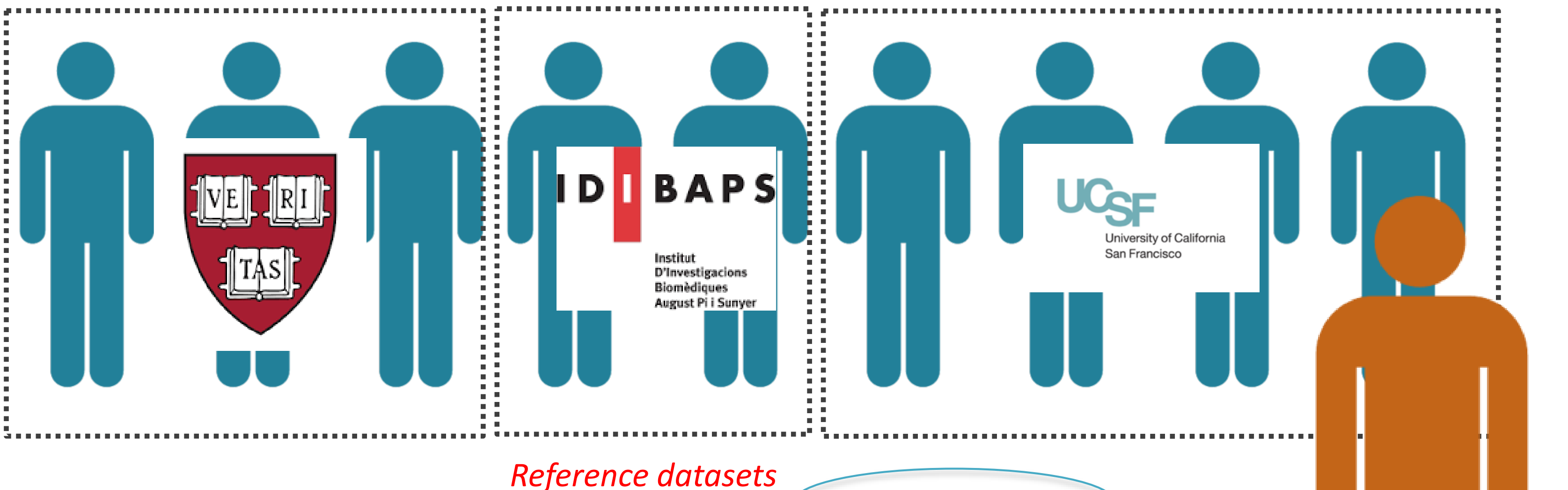
Individual Brain volume change in the context of reference population

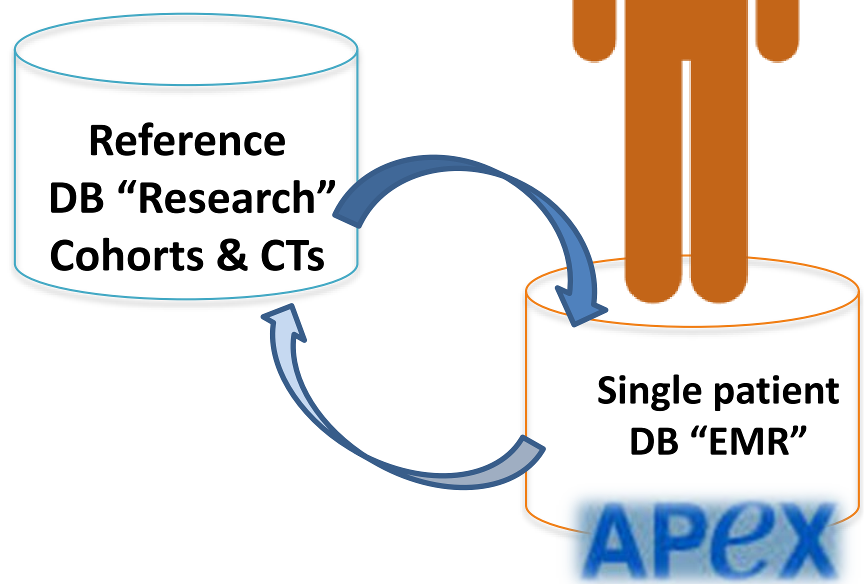


Refinement of reference population selection

Direction 1 : Agrégation des données de référence

*Rôle pivot des algorithmes de **contextualisation***

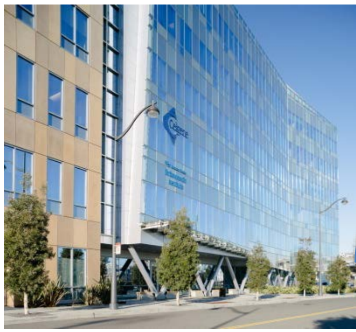




- The **reference dataset** is called on to form the context to which the individual patient is compared.
- The richer, more robust the reference, the more **precise and informed** the contextualization.

Direction 2 : Déploiement

- Cercle Vertueux des données électroniques de sante-



From Clinic to research

Real- life Data at MS Clinic

Research reference data

EMR

APEX

From Research to Clinic

Create structured variables and standardization for key data entry to improve clinical care, quality improvement and also enable this kind of research – **"MS Vital Signs"**

Use EMR-obtained data to regularly update, fuel and validate MS prediction algorithms, make this accessible to clinicians real-time