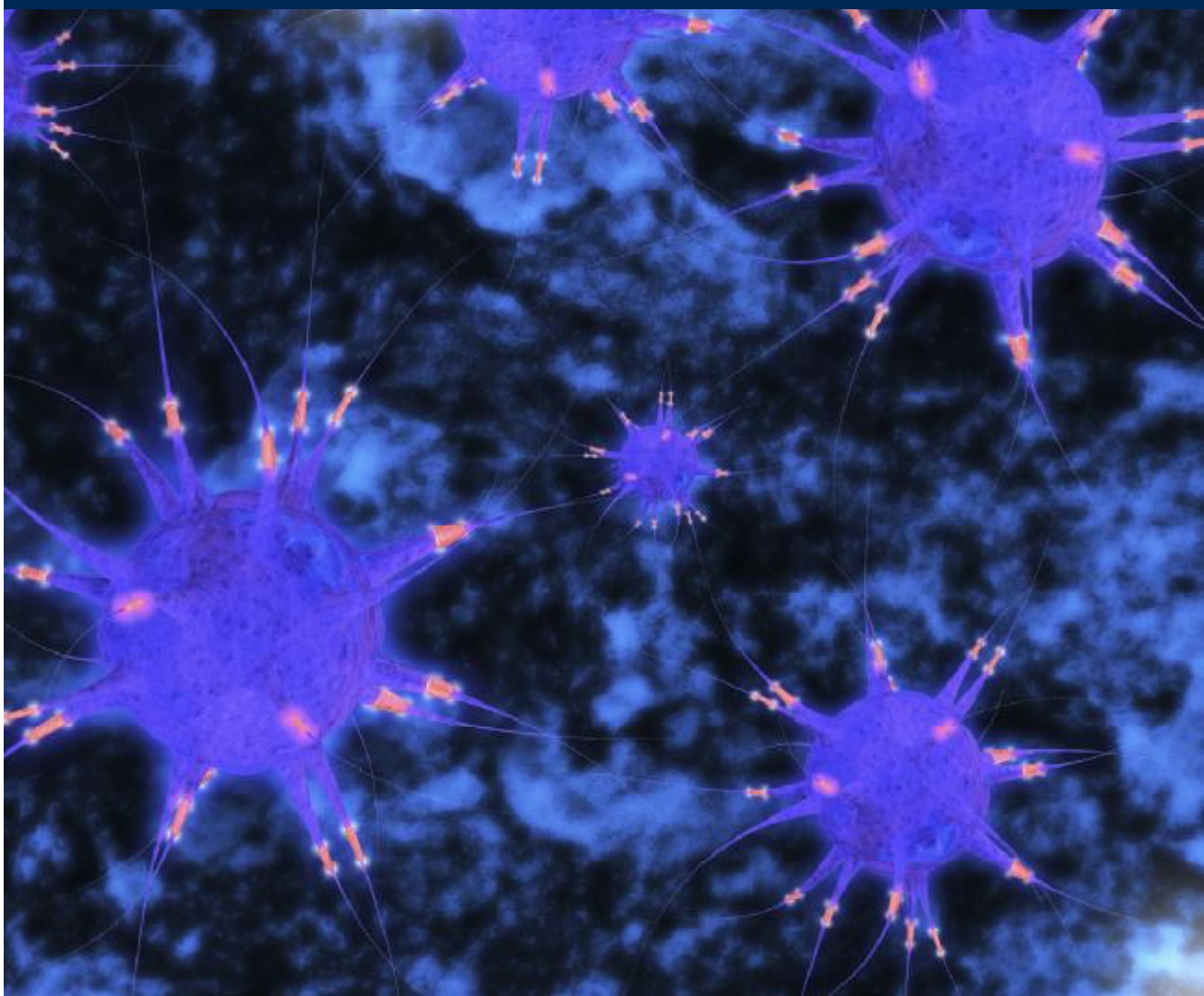
Dagli atomi al cervello

Le Scienze di Base per la comprensione delle funzioni del cervello

POLITECNICO DI MILANO

UNIVERSITÀ
DEGLI STUDI
DI MILANO

Milano, 27 gennaio 2014



Comprendere il funzionamento del cervello è una delle grandi sfide del 21° secolo. «Siamo in grado di identificare galassie lontane milioni di anni luce, sappiamo studiare particelle più piccole dell'atomo, ma ancora non abbiamo svelato i misteri di quelle tre libbre di materia che si trovano tra le nostre orecchie». Con queste parole Barack Obama ha annunciato un investimento di quasi 100 milioni di dollari nell'ambizioso progetto di ricerca sul cervello umano (BRAIN, Brain Research Through Advancing Innovative Neurotechnologies). In Europa quasi contemporaneamente la UE ha finanziato con quasi 1.2 miliardi di euro l'iniziativa di bandiera (flagship) Human Brain Project. Oltre all'avanzamento della conoscenza, le ricadute sociali ed economiche di tali iniziative sono potenzialmente enormi. Una caratteristica comune di questi progetti è di affiancare alle neuroscienze una serie di discipline complementari quali la biologia, la matematica, l'informatica, e la fisica. L'incontro del 27 gennaio 2014 sarà una prima importante occasione per far incontrare il mondo delle scienze di base e quello delle neuroscienze al fine di favorire la conoscenza reciproca e stimolare una progettualità comune in questo importantissimo settore della ricerca.

Comitato organizzativo

Monica Di Luca, Università degli Studi di Milano
Michela Matteoli, Università degli Studi di Milano
Ezio Puppin, Presidente CNISM e Politecnico di Milano
Alessandro Torricelli, Politecnico di Milano

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09:30 - 09:45 Apertura e saluti

Giovanni Azzone Rettore del Politecnico di Milano

Chiara Tonelli Prorettore alla Ricerca dell'Università degli Studi di Milano

Elena Cattaneo Università degli Studi di Milano

09:45 - 10:15 Relazione introduttiva

Egidio D'Angelo Università degli Studi di Pavia

L'emergenza delle funzioni molecolari in modelli di neuroni, circuiti e sistemi integrati

10:15 - 11:45 Le funzioni elementari del cervello - Moderatore: Michela Matteoli

Fabio Benfenati Università degli Studi di Genova

Reti neuronali e interfacce neuro-ibride: nuove tecnologie per lo studio della plasticità neurale

Emilio Carbone Università degli Studi di Torino

Segnali neuronali "visti" attraverso biosensori a base di diamante

Francesco Saverio Pavone Università degli Studi di Firenze

Imaging ottico del Cervello

Mathew E. Diamond SISSA, Trieste

Le basi neuronali della conoscenza

Michele Migliore Istituto di Biofisica del CNR, Palermo

Dalla biofisica al comportamento - Un modello 3D del bulbo olfattivo

Andrea Chincarini INFN, Genova

Biomarkers per l'Alzheimer: metodi di analisi dalla fisica alla medicina

11:45 - 12:15 Special lecture

Giovanni Erbacci CINECA, Bologna

Supercomputers, Modelli e Simulazione: un ponte tra Scienze di base e Neuroscienze

13:30 - 15:00 Il cervello nel suo insieme - Moderatore: Egidio D'Angelo

Gian Luca Romani Università degli Studi di Chieti e Pescara

La MEG per lo studio della dinamica delle reti cerebrali

Marcello Massimini Università degli Studi di Milano

Coscienza e Complessità: dalla Teoria alla Pratica

Luciano Fadiga Università degli Studi di Ferrara

Interfacce cervello-macchina nell'uomo: cosa è fattibile e cosa potrebbe essere utile

Alessandro Torricelli Politecnico di Milano

Neurofotonica: fare luce sul cervello

Alberto Bravin ESRF, Grenoble

Synchrotron radiation: a new tool for the study and the treatment of central nervous system diseases

Alessandra Retico INFN, Pisa

Caratterizzazione delle anomalie strutturali cerebrali nei disturbi dello spettro autistico e tecniche di machine learning

15:00 - 15:30 Special lecture

Tullio Pozzan Direttore del Dipartimento di Scienze Biomediche del CNR

Brain aging and neurodegenerative diseases : a problem of signals

16:00 - 17:30 Applicazioni cliniche - Moderatore: Maria Cristina Messa

Daniela Perani Università Vita-Salute San Raffaele, Milano

Brain Imaging with multimodal PET molecular approaches

Francesca Baglio Fondazione Don Carlo Gnocchi, Milano

Neuroimaging e neuroplasticità in riabilitazione: una finestra sul cervello

Silvana Franceschetti Istituto Neurologico Carlo Besta, Milano

Meccanismi elementari ed espressione clinica delle epilessie

Alberto Priori Università degli Studi di Milano

La stimolazione cerebrale profonda adattativa (aDBS) nella malattia di Parkinson

Sergio Cerutti Politecnico di Milano

Elaborazione dei segnali e delle immagini del Sistema Nervoso Centrale e modelli di interpretazione fisiopatologica

Sommario degli interventi degli oratori in ordine di presentazione

Egidio D'Angelo

Università di Pavia, Dept. Of Brain and Behavioral Sciences;
Brain Connectivity Center, IRCCS C.Mondino, Pavia

L'emergenza delle funzioni molecolari in modelli di neuroni, circuiti e sistemi integrati

Abstract

Il sistema nervoso è costituito da complesse reti cellulari nelle quali i neuroni comunicano tra loro a livello delle sinapsi. I neuroni generano segnali elettrici tramite speciali molecole (canali ionici, recettori e trasportatori) che consentono di regolare i flussi ionici e le differenze di potenziale a livello della membrana cellulare. Questi meccanismi possono essere studiati sperimentalmente a vari livelli, dando informazioni essenziali sulla natura dei processi neurali. Questi meccanismi possono poi essere rappresentati da modelli biofisici e tradotti in modelli matematici generando rappresentazioni accurate delle funzioni neuronali. Tali modelli possono essere connessi in circuiti, che possono a loro volta essere integrati in sistemi di controllo e interfacciati a robots in grado svolgere comportamenti complessi. In tal modo è possibile studiare l'emergenza delle funzioni molecolari, neuronali e circuitali a livello di comportamenti integrati di significato biologico.

Tale procedura modellistica è stata elaborata per la rete neuronale del cervelletto. Un microcircuito cerebellare, o microzona, è costituito da alcune decine di migliaia di neuroni (cellule granularli, cellule del Golgi , cellule del Purkinje, cellule stellate e a canestro, neuroni dei nuclei cerebellari profondi e del nucleo olivare inferiore) connessi tra di loro secondo specifiche regole topografiche. Il circuito cerebellare è stato modellizzato matematicamente ed inserito all'interno di un sistema di controllo robotico. Questo ultimo passaggio è fondamentale per il cervelletto, in quanto tale struttura è al centro del sistema di forward-controller del circuito sensori-motorio.

In questa presentazione viene mostrato come tale sistema modellistico viene costruito sula base dei dati sperimentali ed utilizzato per studiare come i processi di computazione e apprendimento nel sistema cortico-cerebellare.

Reti neuronali e interfacce neuro-ibride: nuove tecnologie per lo studio della plasticità neurale

F. Benfenati
Dipartimento di Neuroscienze e Neurotecnologie, Istituto Italiano di Tecnologia, Genova, Italy

Il cervello è caratterizzato da un'organizzazione altamente complessa, computazione parallela, integrazione delle informazioni afferenti, proprietà emergenti e adattamento funzionale e strutturale. La caratteristica unica, e al momento non imitabile, del sistema nervoso centrale è la sua fenomenale capacità di adattarsi all'ambiente e di migliorare le proprie prestazioni col tempo e con l'esperienza. Le modificazioni indotte dall'esperienza nel sistema nervoso possono persistere per lungo tempo, virtualmente per l'intera esistenza dell'individuo; pertanto, le intrinseche proprietà plastiche potrebbero permettere all'esperienza di plasmare funzionalmente e scolpire strutturalmente il sistema nervoso. L'assemblaggio delle reti nervose è inizialmente guidato da fattori genetici, come la dimensione e la complessità dei bersagli da innervare o la costellazione di segnali chimici di riconoscimento. Tuttavia, dopo questo primo periodo, i circuiti neuronali continuano a essere modificati e plasmati dall'esperienza (fattori epigenetici) per tutta la vita: le connessioni sinaptiche che sono poco utilizzate gradualmente si indeboliscono ed alla fine scompaiono, mentre le sinapsi molto attive vengono potenziate ed aumentano di numero. La trasmissione dell'informazione a livello sinaptico, detta forza sinaptica, può essere finemente regolata ad opera di una combinazione di fattori come l'attività elettrica precedente, la concentrazione di secondi messaggeri e le modificazioni post-traduzionali da essi governate, nonché la regolazione dell'espressione di geni implicati nella crescita, sopravvivenza neuronale e trasmissione sinaptica. Questi fattori sono in grado di regolare la forza sinaptica in distinti domini temporali, da frazioni di secondo o minuti, nel caso della plasticità a breve termine (facilitazione, depressione), ad ore, giorni e mesi nel caso della plasticità a lungo termine (potenziamento o depressione a lungo termine). Queste variazioni transitorie o durature della forza sinaptica hanno un profondo impatto sull'elaborazione, filtraggio e flusso direzionale delle informazioni all'interno delle reti nervose. Queste osservazioni hanno stimolato la creazione di dispositivi ibridi biomimetici in cui i neuroni vengono interfacciati con chip elettronici o con semiconduttori organici per generare interfacce neuro-elettroniche o opto-neurali, o vengono geneticamente modificati ad esprimere attuatori fotoattivabili. Mediante la creazione di queste interfacce è possibile monitorare e modificare l'attività neuronale e creare dispositivi ibridi in grado di regolare l'eccitabilità e la plasticità delle reti nervose.

Segnali neuronali “visti” attraverso biosensori a base di diamante

Emilio Carbone

Department of Drug Science
Nanostructured Interface and Surface Centre
CNISM Unit, Torino, Italy

I “segnali neuronali” regolano il funzionamento di reti nervose complesse che compongono il cervello e sono il risultato di eventi molecolari generati da proteine integrali di membrana (canali ionici, recettori e trasportatori). Canali e recettori di membrana danno origine a “impulsi elettrici” (potenziali d’azione), regolano il rilascio vescicolare di molecole (trasmissione sinaptica) e controllano così il funzionamento di reti neuronali complesse, permettendo per esempio il rapido scambio d’informazioni tra cervello e sistema sensoriale periferico. Misurare accuratamente i segnali neuronali in singoli neuroni o in reti neuronali *in vitro* o *in vivo* è un obiettivo centrale per identificare le basi molecolari del funzionamento del sistema nervoso centrale e individuare i target molecolari delle principali malattie neurodegenerative. Mentre esistono innumerevoli dispositivi multi-elettrodo (MEA; multi-electrode array) capaci di registrare l’attività elettrica di reti neuronali, esistono solo pochi esempi di lab-on-chips in grado di rivelare il rilascio vescicolare da neuroni con alta risoluzione temporale e un buon rapporto segnale/rumore.

Con l’idea di sviluppare nuovi biosensori planari in grado di misurare segnali elettrici, attività sinaptica e segnali ottici in neuroni e cellule neuroendocrine, assieme a Valentina Carabelli e in collaborazione con Ettore Vittone e Paolo Olivero del Dip. di Fisica e Centro NIS di Torino e Alberto Pasquarelli del Dip. di Dispositivi e Circuiti Elettronici di Ulm (Germania), abbiamo iniziato a sviluppare una serie di dispositivi a base di diamante nano- e monocristallino in grado di rivelare potenziali d’azione e rilascio vescicolare di catecolamine (adrenalina, noradrenalina, dopamina) e serotonina. MEA a base di diamante nano-cristallino borato di diverse geometrie e MEA a base di diamante monocristallino con piste micrografitiche singole o multiple sono stati testati con successo. Con i MEA a bassa densità (16 elettrodi di 20 μm di diametro distanti 200 μm) è possibile registrare potenziali d’azione e risolvere il rilascio vescicolare di adrenalina da più cellule cromaffini simultaneamente. Usando MEA ad alta densità (9 elettrodi disposti all’interno di una superficie equivalente alle dimensioni di una cellula) è possibile invece rivelare l’attività neurosecretoria di “microdomini” di membrana e individuare microaree stabili di alta, bassa o no-attività (zone “silenti”) presenti in una singola cellula.

I vantaggi e i limiti di usare MEA di diamante per lo studio di “segnali neuronali” *in vitro* e *in vivo* saranno discussi assieme alle possibili applicazioni future dei dispositivi.

Francesco Pavone

European Laboratory for Non Linear Spectroscopy (LENS)
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Imaging ottico del cervello

Abstract

Quando riusciremo ad esplorare l'intricata rete costituita dai neuroni nello stesso modo in cui navighiamo su Internet, si aprirà una pagina completamente nuova per la scienza, la tecnologia, ed in ultima analisi per l'intera società. La conoscenza dell'architettura del cervello ci permetterà non soltanto di trovare nuove cure per patologie come l'Alzheimer o l'autismo, ma anche di rivoluzionare la tecnologia dell'informazione con nuovi computer ispirati al cervello stesso.

Questa visione ambiziosa non riguarda un futuro irraggiungibile, ma diventerà presto realtà. La Commissione Europea ha infatti deciso di finanziare lo Human Brain Project (HBP), un progetto decennale da oltre un miliardo di euro che riunisce più di 80 istituti di ricerca in Europa e nel mondo intero, ed in cui l'Italia avrà un ruolo fondamentale.

Lo scopo ultimo di HBP è quello di riunire tutta la conoscenza finora accumulata riguardo al cervello umano e di usarla per simulare il cervello stesso usando supercomputer che saranno pronti nei prossimi anni.

Numerosi laboratori avranno il compito di generare dati cruciali per la realizzazione di questo avveniristico progetto. Al Laboratorio Europeo di Spettroscopie Non-lineari (LENS) ed al Dipartimento di Fisica dell'Università di Firenze ci occuperemo di generare una mappatura completa dell'intera rete delle connessioni neurali nel cervello: il cosiddetto "connettoma". Per questo scopo utilizzeremo tecniche innovative di microscopia ottica con risoluzioni molto superiori agli attuali sistemi di immagine (Risonanza Magnetica, TAC, PET, ecc.). I dati raccolti saranno essenziali per capire il legame tra la struttura del cervello ed il suo funzionamento, in modo da poterlo poi simulare, e saranno analizzati insieme a molti altri dati biologici dal centro di supercalcolo CINECA di Bologna.

In questo seminario illustreremo alcune delle tecniche sviluppate insieme ad alcune misure utili per la comprensione di alcune patologie come l'autismo o la schizofrenia, o la mappatura delle connessioni cerebrali con un dettaglio ad oggi molto superiore alle tecniche cliniche.

Mathew E. Diamond

Tactile Perception and Learning Lab
SISSA

Neuronal bases of perception

Abstract

We will discuss investigations of how the brain perceives stimuli, stores them in memory, and recalls them. The strategy is to compare the perceptual capacities of rats to those of humans. Each has advantages as an object of study. Human subjects easily give an overt description of the sensory experience, while rats must be trained to give nonverbal responses. On the other hand, in rats we are able to examine the neuronal coding of sensory experience, impossible in humans. The species comparison gives insights into how the simpler brain can carry out complex computations.

We have found that the perceptual and cognitive capacities of rats are surprisingly advanced and, by some measures, rival those of human subjects. Measurements of neuronal activity in the rat brain reveal that in the cerebral cortex the complex task is subdivided into a sequence of computations. The same computations are likely to be the substrate for sensory perception in humans.

Michele Migliore
CNR, Istituto di Biofisica, Palermo; Department of Neurobiology, Yale University, New Haven USA

Titolo:
Dalla biofisica al comportamento: un modello in 3D del bulbo olfattivo

Abstract

I circuiti cerebrali che trasformano un input sensoriale in un segnale neuronale che possa essere immediatamente classificato, codificato, riconosciuto, ed eventualmente memorizzato sono tuttora piuttosto confusi e misteriosi. La maggior parte dei problemi nascono dalle limitazioni tecniche dei metodi sperimentali attualmente utilizzati per studiare il cervello nei suoi vari livelli di integrazione. In particolare, quello che manca in generale è la possibilità di collegare opportunamente le proprietà ed i meccanismi cellulari microscopici a livello di singolo neurone, con le funzioni cerebrali macroscopiche complesse, quali memoria e apprendimento, osservate a livello macroscopico. In questo talk, si discutera' un approccio modellistico bottom-up che potrebbe dare un ausilio fondamentale alla soluzione di questo tipo di problemi, usando tecniche avanzate di simulazione e prendendo ad esempio uno dei sistemi cerebrali piu' studiati sperimentalmente: il bulbo olfattivo.

Con simulazioni e visualizzazioni interattive, verranno illustrati i metodi e le tecniche che permettono di implementare un modello completo in 3D del bulbo olfattivo. Lo scopo principale e' quello di ottenere, a partire dalle informazioni sperimentali disponibili ai vari livelli di integrazione del segnale, un sistema computazionale con il quale studiare i meccanismi cellulari piu importanti utilizzati dal sistema nervoso per la codifica, l'apprendimento, ed il successivo riconoscimento di odori. Utilizzando tutte le informazioni sperimentali disponibili, per esempio la struttura morfologica e topologica delle maggiori popolazioni di neuroni del bulbo olfattivo e le mappe di attivazione degli input in presenza di una varieta' di odori, i risultati del modello saranno direttamente confrontabilii con quelli ottenuti sperimentalmente sia in laboratorio che in vivo. Sara' quindi possibile sfruttare i risultati delle simulazioni non solo per capire in modo piu' dettagliato il funzionamento del cervello, ma anche di predire nuovi sviluppi sperimentali o applicativi.

Biomarkers per l'Alzheimer: metodi di analisi dalla fisica alla medicina.

A. Chincarini

Istituto Nazionale di Fisica Nucleare

Sezione di Genova

Nell'ultimo decennio l'imaging medico ha avuto una rilevanza sempre maggiore, arrivando a essere ormai insostituibile nella ricerca di base e clinica in neuroscienze. In particolare, le immagini di risonanza magnetica strutturale (MRI) e di tomografia ad emissione di positroni (PET) del cervello costituiscono uno strumento diagnostico avanzato per molte patologie neurodegenerative e, in particolare, per la diagnosi della malattia di Alzheimer.

Nonostante l'ampia diffusione delle neuroimmagini morfologiche e funzionali nella diagnostica routinaria delle malattie cerebrali, la fruizione delle informazioni da parte dell'utilizzatore finale - il clinico - rimane ampiamente limitata all'analisi visiva qualitativa. Parte delle informazioni disponibili non vengono utilizzate per la mancanza di sistemi 'user-friendly' capaci di estrarre in maniera automatica dati quantitativi. Probabilmente la ragione principale della scarsa diffusione ed utilizzo di tools automatici per l'analisi quantitativa risiede nei problemi di identificazione, segmentazione e caratterizzazione automatica di regioni clinicamente rilevanti in immagini cerebrali, che, tuttavia, sono potenzialmente molto significative per l'analisi diagnostica.

Durante la relazione verranno illustrati alcuni concetti importanti per analisi avanzate su neuroimmagini, nonché la significatività dei markers da esse ottenuti allo scopo di migliorare l'indagine clinica. Come caso di studio vedremo l'applicazione alle analisi longitudinali delle segmentazioni ippocampali, e accenneremo ad alcune linee di ricerca attuali relativamente all'individuazione di network di correlazione in gruppi clinicamente omogenei.

Si farà inoltre accenno alle grandi infrastrutture internazionali necessarie per la ricerca di base ed agli strumenti comunitari che verranno messi a disposizione del clinico nel prossimo futuro.

Supercomputers, Modelli e Simulazione: un ponte tra Scienze di base e Neuroscienze

Giovanni Erbacci

CINECA – Dipartimento Supercalcolo, Applicazioni & Innovazione

Casalecchio di Reno, Bologna

Abstract

La scienza moderna è caratterizzata da una interazione continua tra teoria ed esperimenti. La complessità della scienza oggi è tale che sia la teoria che gli esperimenti richiedono tecniche computazionali complesse, effettuate su computer ad alte prestazioni; e così la computazione si rivela essere un fattore abilitante universale per la scienza.
Le scienze computazionali, un settore interdisciplinare che coinvolge scienze di base, modelli matematici, tecniche di analisi quantitativa e High Performance Computing (HPC), rappresentano uno strumento indispensabile per affrontare le grandi sfide scientifiche e sociali, quali l'individuazione e il trattamento delle malattie, la modellazione del cervello umano, lo studio di materiali innovativi come il grafene, la previsioni dei cambiamenti climatici, ecc.

Il cervello umano contiene circa 100 miliardi (10^{11}) di neuroni e un milione di miliardi (10^{15}) di connessioni sinaptiche, ciascuno neurone ha poi la propria struttura interna complessa ed in grado di esprimere diverse proteine a livello di membrana cellulare.

Sin dal lavoro pionieristico di Gerstein e Mandelbrot degli anni '60 del secolo scorso, la simulazione del cervello ha richiesto tecniche computazionali innovative e i calcolatori più potenti disponibili al momento. Richiesta che oggi cresce in modo esponenziale se si vogliono indagare settori complessi delle neuroscienze ed arrivare alla simulazione completa del cervello umano.

La matematica e le scienze di base, dalla fisica alla chimica alla biologia, supportate dai metodi computazionali, possono apportare un contributo prezioso a diversi settori delle neuroscienze, dalla modellazione dei processi biologici di basso livello, all'analisi di pattern a larga scala dell'attività cerebrale, contribuendo così a capire e a caratterizzare la complessità del cervello umano. Inoltre, come feedback, si possono sperimentare nuove tecnologie neuromorfiche (hardware ispirato dall'architettura del cervello) che consentono di implementare modelli cerebrali in dispositivi compatti, energeticamente efficienti, e studiare architetture informatiche innovative.

La simulazione multi-livello dell'intero cervello umano, in grado di utilizzare i grandi volumi di dati eterogenei provenienti dalla ricerca e dalla sperimentazione neurologica, richiederà infrastrutture di supercalcolo di classe exascale, caratterizzate da funzionalità innovative in termini di interactive computing, visualizzazione avanzata e big data management.

Affrontare la sfida exascale computing richiede impegni rivoluzionari nei settori chiave delle scienze computazionali che vanno dalla progettazione di architetture energeticamente efficienti di classe exascale (10^{18} Flops, 1000 volte le prestazioni dei supercomputer attuali), allo sviluppo di metodologie matematiche e statistiche avanzate, al disegno di nuovi algoritmi in grado di scalare, con la mole dei dati da analizzare, su miliardi di processi, alla definizione di modelli di programmazione appropriati per queste architetture.

In questa presentazione, viene sottolineato il ruolo delle scienze computazionali nelle neuroscienze, fondamentale per raggiungere una comprensione multi-livello integrata del cervello umano, obiettivo ultimo del Flagship Europeo Human Brain Project (HBP). Viene presentato lo sforzo richiesto a livello europeo per vincere la sfida HBP, in termini computazionali e di evoluzione delle architetture HPC. Infine, viene evidenziata l'azione del programma quadro Horizon 2020 a supporto dell'ecosistema HPC Europeo.

LA MEG PER LO STUDIO DELLA DINAMICA DELLE RETI CEREBRALI

Gian Luca Romani

Dipartimento di Neuroscienze e Imaging e
Istituto di Tecnologie Avanzate Biomediche (ITAB)
Università di Chieti-Pescara

La MagnetoEncefaloGrafia (MEG) è una tecnica di imaging funzionale che si basa sulla misura dei debolissimi segnali magnetici associati alle correnti neuronali legate al funzionamento cerebrale. Si tratta di una tecnica analoga all'elettroencefalografia, in quanto studia segnali elettrofisiologici, dotata, tuttavia, di una risoluzione spaziale assai maggiore (2-3 mm) nella localizzazione delle sorgenti dei segnali stessi. Benché tale risoluzione spaziale sia nettamente inferiore a quella ottenibile con tecniche emodinamiche, quali la risonanza magnetica funzionale (fMRI), la risoluzione temporale della MEG, che è dell'ordine del millisecondo, la rende ineguagliabile da parte della fMRI ed è per questo motivo che oggi le due tecniche sono considerate complementari.

Uno dei temi più rilevanti degli ultimi dieci anni nelle neuroscienze è lo studio delle "reti cerebrali", cioè cercare di comprendere come il cervello si organizza in modo coerente e stabile. Le reti cerebrali sono state individuate non solo durante l'esecuzione di particolari compiti, ma anche durante i periodi in cui il cervello è a riposo, da cui il nome di "reti a riposo" (resting state networks). E' stato recentemente ipotizzato che il funzionamento di tali reti assorba la parte più grande (circa il 70%) del consumo di energia da parte del cervello (da qui la definizione "energia oscura" del cervello, Raichle 2010). Anche se il primo approccio al problema è stata effettuato mediante misure di fMRI, lo studio di questo aspetto dell'attività cerebrale con una tecnica dotata di una grande risoluzione temporale si è dimostrato estremamente efficace. Oggi la MEG è uno strumento indispensabile per indagare ritmi cerebrali spontanei e svelare le complesse dinamiche alla base delle reti a riposo, contribuendo così in modo determinante alla identificazione del "connettoma umano". E' questa la motivazione dell'inserimento del nostro gruppo (ITAB) all'interno del progetto quinquennale Human Connectome Project, finanziato dai NIH, che ha appunto lo scopo di creare un gigantesco archivio di dati strutturali e funzionali relativi al connettoma umano, ottenuti tramite misure di DTI, fMRI e MEG.

Coscienza e Complessità: dalla Teoria alla Pratica

Marcello Massimini
Università degli Studi di Milano

Tipicamente, valutiamo il livello di coscienza di altri individui basandoci sulla loro capacità di interagire con l'ambiente circostante. Tuttavia, sappiamo bene che la coscienza può essere interamente generata all'interno del cervello, in assenza di qualsiasi comunicazione con il modo esterno; ciò accade, quasi ogni notte, quando sogniamo. A causa di questa discrepanza, la presenza di coscienza può essere misconosciuta in pazienti cerebrolesi che non comunicano. Secondo una teoria di recente formulazione, la coscienza di un sistema fisico dipende dalla sua capacità di integrare informazione, ossia da un particolare tipo di complessità. Oggi, misure empiriche, ispirate da questa teoria, ci aiutano di individuare la presenza di coscienza anche all'interno di cervelli che sono completamente isolati dal mondo esterno. Ci aiuteranno, domani, a capire come fa un chilo e mezzo di materia gelatinosa a ospitare l'universo di un sogno?

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Interfacce cervello-macchina nell'uomo: cosa è fattibile e cosa potrebbe essere utile

Abstract

Negli ultimi anni abbiamo assistito ad una crescita esponenziale delle pubblicazioni scientifiche su BMI (Brain-Machine Interfaces). A questo non ha corrisposto una parallela esplosione sul versante applicativo e, nei rari casi in cui ciò è avvenuto, si è trattato di "proofs of concept" più che di interventi che portavano un reale beneficio al paziente. Nella mia esposizione discuterò vantaggi e criticità nel design delle interfacce con il cervello umano trattando in modo specifico l'ottimizzazione della qualità del segnale, il problema della stimolazione elettrica, la biocompatibilità. Tratterò infine il problema dell'utilità: quali scenari possono realmente rappresentare un passo avanti per il miglioramento della qualità di vita di un paziente gravemente inabile?

Neurofotonica: fare luce sul cervello

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Abstract

La nuova disciplina detta Neurofotonica si colloca all'interfaccia tra l'Ottica e le Neuroscienze e racchiude tutti i metodi e le applicazioni basati sulle moderne tecnologie ottiche e fotoniche per l'indagine delle strutture e delle funzioni cerebrali. Questo settore è in rapida crescita e sta guidando profondi progressi nella comprensione dei fenomeni cerebrali sia a livello microscopico che a livello macroscopico.

In questo intervento l'attenzione verrà focalizzata sui metodi ottici impiegati per lo studio non invasivo dell'attività corticale nell'uomo, quali la spettroscopia funzionale nel vicino infrarosso (functional near infrared spectroscopy, fNIRS), la spettroscopia di correlazione in mezzi diffondenti (diffuse correlation spectroscopy, DCS), e l'analisi del segnale ottico veloce (fast optical signal, FOS).

In particolare per queste metodiche verranno brevemente presentati i principi fisici, lo stato dell'arte della tecnologia, le possibilità di integrazione con altre tecniche di indagine, le principali applicazioni cliniche, le limitazioni e alcuni problemi aperti.

Synchrotron radiation: a new tool for the study and the treatment of central nervous system diseases

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Synchrotron radiation facilities are large scale laboratories where extremely intense and highly collimated X-ray beams are made available to researchers for a wide range of applications, among which biology and medicine are constantly increasing of imporance.
These applications are particularly advanced at the European Synchrotron Radiation Facility (ESRF, Grenoble, France) where intense nanometric or homogeneous broad beams are also used to study, analyze and treat pathologies of the central nervous system (CNS).

An endstation, the ID17 biomedical beamline, is fully dedicated to preclinical and clinical studies; research made in house or carried out by the users‘ community focusses on developing novel brain cancer treatments and innovative techniques in radiation therapy and stereotactic radiosurgery. These developments make profit of specific properties of synchrotron radiation like coherence, monochromaticity and high intensity, that make it possible to applying techniques like microbeam radiation therapy (MRT).

The intense, quasi monochromatic beam available at ID17 allowed to develop combined chemo- radio-therapies which exploit the local X-ray dose enhancement achievable by irradiating a tumour previously loaded with a high-Z (chemotherapic) drug. The remarkable curing effect of these combined therapies shown in preclinical tests has paved the way of the clinical application of the novel therapy; in parallel, new optimized drugs-radiation protocols are under preclinical evaluation.

MRT uses multienergy arrays of microscopic beams (from 25 to 600 microns) delivered with submillimetric precision to the CNS. Doses up to hundreds of Grays, delivered in a fraction of a second, can be very well tolerated by the CNS in mammals as shown in several preclinical trials. The potential application of MRT in the treatment of cancers of the CNS is presently under evaluation in veterinarial trials.

MRT has also been applied to obtain the radiosurgical equivalent of multiple subpial transections. Cortical columns are the basic functional units of brain computation. Synchrotron microbeams can generate cortical transections disconnecting adjacent columns and modulating abnormal columnar processing. The hypothesis was verified in epilectic rats. Microradiosurgical transections induced seizure control while motor function was not affected. Also the ability of microbeams to generate hippocampal transections has been recently investigated. This original approach offers an interesting new way to study the hippocampal function and to develop novel treatment avenues for mesiotemporal epilepsy.

More recently, X-ray microbeams have been used to explore the electrophysiological behaviour of neurons contained inside the microbeam-transected primary sensory cortex in experimental models of chronic pain, a widespread invalidating neurological disorder currently orphan of effective medical and surgical treatments. Selected pioneering results of these new research avenues will be presented.

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Caratterizzazione delle anomalie strutturali cerebrali nei disturbi dello spettro autistico mediante tecniche di machine learning

Abstract

Le tecniche di analisi basate su metodi di *machine learning* e *pattern recognition* si stanno affermando come strumenti molto utili sia per l'identificazione che per la caratterizzazione di un gran numero di patologie neurologiche e psichiatriche. Il loro scopo ultimo e quello di fornire dei biomarcatori di patologia, estratti da immagini cerebrali, che possano essere utili nella pratica clinica.

Nell'ambito dei disturbi dello spettro autistico (ASD) siamo ancora lontani dal poter annunciare la scoperta di un biomarcatore valido. Ciononostante, le informazioni derivate dalle immagini cerebrali possono essere di grande aiuto nella caratterizzazione della patologia.

In particolare, abbiamo analizzato con un sistema decisionale basato su support vector machines (SVM) le immagini cerebrali acquisite con risonanza magnetica strutturale (MRI) di un gruppo di bambini affetti da ASD allo scopo di identificare eventuali anomalie neuroanatomiche e di evidenziare inoltre possibili differenze morfometriche dovute al genere. Le immagini MRI e i dati clinici dei 152 soggetti analizzati in questo studio sono stati acquisiti e selezionati da parte dell'IRCCS Fondazione Stella Maris (Pisa). In particolare si tratta di un campione di 76 bambini ASD (di età compresa tra 2 e 7 anni) e di un gruppo di controllo di 76 soggetti appaiati per età, genere e quoziente intellettivo non verbale (NV-IQ). Una volta segmentata la materia grigia (GM) cerebrale per ogni soggetto, la stessa è stata analizzata attraverso un classificatore SVM. Il meccanismo di eliminazione ricorsiva delle caratteristiche (SVM-RFE) ha permesso di localizzare le regioni cerebrali dove si focalizzano le differenze neuroanatomiche più rilevanti. L'analisi dei sottogruppi dei 38 bambini e delle 38 bambine separatamente, rispetto ai relativi casi di controllo, ha permesso di studiare la specificità di genere nelle alterazioni cerebrali che caratterizzano la patologia.

Brain aging and neurodegenerative diseases : a problem of signals

Tullio Pozzan
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Ca2+ is an ubiquitous intracellular messenger involved in the control of a variety of cellular functions as diverse as contraction, secretion, fertilization and death. To insure specificity to Ca2+ signalling, a multiplicity of mechanisms have been developed, based on amplitude, duration and subcellular localization of the Ca2+ changes. Compelling evidence has been obtained in the last decade demonstrating the key role of different organelles in shaping cytosolic Ca2+ signals and in controlling its consequences for cell pathophysiology. In this contribution I will concentrate on a few unanswered questions related to cellular and animal models of human diseases, in particular in models of Alzheimer disease due to mutations in Presenilins (PS), key components of the γ secretase complex, i.e. the enzyme responsible for the production of the amiloidogenic peptides from APP. I will discus some recent results suggesting that PS isoforms differently modulate intracellular Ca2+ homeostasis and in particular the ER- mitochondria Ca2+ dependent crosstalk.

BRAIN IMAGING WITH MULTIMODAL PET MOLECULAR APPROACHES

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Positron emission tomography (PET) allows *in vivo* measurements of multiple parameters of regional cerebral physiology, such as blood flow, oxidative and glucose metabolism. In addition, moving to the molecular levels of investigation, PET with adequate radiotracers is unique in the evaluation of the multiple neurotransmitter/neuroreceptor systems of the human brain. These applied studies have increased our understanding of biological and clinical aspects of neurological and psychiatric diseases and have provided information for early diagnosis of dementia conditions

These potentialities are becoming more and more important as the field of research moves to clinical applications. PET techniques have been extensively applied to the study of neurodegenerative diseases, by measuring glucose metabolism and specific targets such as dopaminergic, cholinergic, serotoninergic neurons, reactive glial cells and tau and amyloid deposits.

Main application fields:

a. The study of single cases or comparable group of patients with cognitive deficits, using the tools of cognitive neuropsychology, combined with metabolic imaging methods, such as 18F-FDG PET provided consistent patterns of hypometabolism correlated with the behavioural and cognitive modifications. Due to the very high sensitivity and specificity, PET can be used to predict the cognitive decline and progression to dementia in subjects without a clear-cut clinical diagnosis such as in Mild Cognitive Impairment (MCI). Neuroimaging and genetic testing have aided in the identification of individuals at increased risk for dementia.

   In addition, although [18F]FDG plays a major role, other tracers are becoming available, that could detect the AD pathology in subjects at risk (i.e. tracers for amyloid and tau deposits). PET imaging represents a major tool in the guidelines for the *in vivo* measurements of biomarkers of pathology (amyloid-PET) and neurodegeneration (FDG-PET). The use of PET in dementia is increasing and this is due to various factors, such as the higher accuracy of PET reading through automatic analysis (i.e. SPM) and availability of large data-bases of normal subjects.

b. PET molecular studies of brain functional reserve in groups of probable AD patients and in prodromal AD phase (MCI subjects) have shown that the level of education and occupational activity have a clear-cut neurobiological correlate, namely a functional and molecular reserve capacity probably contrasting the clinical onset and progression of dementia.

c. Neurotransmission studies by PET imaging techniques to measure the distribution of various molecular components that are at the basis of the neuronal communication, like receptors, membrane carriers, neurotransmitters and enzymes. The central nervous system controls behavioural and cognitive processes by modulating the transfer of information through complex neurochemical interaction. These interactions occur through different neurotransmitter systems to maintain homeostasis and to control each different

cognitive or behavioural process in physiological condition or their alteration during pathologies. Molecular PET imaging can be used to *in vivo* measure changes of neurotransmitters interaction in neurological and psychiatric diseases.

Here, I will provide examples from the current literature and personal data on the role of functional and molecular PET neuroimaging.

Neuroimaging e neuroplasticità in riabilitazione: una finestra sul cervello.

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La definizione ed il trattamento della disabilità cognitiva sono di fondamentale importanza in riabilitazione. Il notevole avanzamento informativo delle immagini ottenute con risonanza magnetica strutturale e funzionale consente oggi, una migliore analisi della struttura e della funzione di sistemi complessi, permettendoci di studiare le relazioni, i prima ed i dopo fra i diversi risultati ottenuti utilizzando sia procedure neuroriabilitative classiche, che nuovi percorsi terapeutici riabilitativi. Grazie al *neuroimaging* è infatti attualmente possibile una più precisa definizione della funzionalità neurale residua al danno ed è anche permesso valutare il *remapping* nel tempo come conseguenza di eventuali recuperi, dovuti a meccanismi neuroplastici sviluppati con l'intervento riabilitativo, definendo come neuroplasticità, la capacità del sistema nervoso di rispondere agli stimoli intrinseci o estrinseci riorganizzando struttura, funzione e connettività (Cramer et al, 2011). Questo nuovo approccio valutativo è stato recentemente introdotto nel campo del trattamento riabilitativo delle principali malattie neurologiche (demenze, malattia di Parkinson, Sclerosi Multipla …). Per quanto concerne le demenze, ad esempio, è possibile evidenziare una riorganizzazione post -trattamento nei pattern di attivazione *task*-correlati (Clare et al, 2010; van Paasschen et al, 2013). Anche nel campo della sclerosi multipla evidenze preliminari hanno illustrato come il trattamento riabilitativo migliori la connettività funzionale, promuovendo una miglior *performance* in compiti cognitivi indipendentemente dal carico lesionale (Sastre-Garriga et al, 2010; Prakas et al, 2011, Filippi et al, 2012; Tomassini et al, 2012).

Alla luce di questi recenti dati, si può affermare che l'utilizzo del *neuroimaging*, permettendo una miglior definizione della disabilità cognitiva ed una più precisa valutazione delle possibilità di riorganizzazione cerebrale morfofunzionale post-intervento, si candidi a diventare sempre più, un utile metodo per l'identificazione e la validazione di percorsi di cura in neuroriabilitazione.

Silvana Franceschetti
Istituto Neurologico Carlo Besta

Meccanismi elementari ed espressione clinica delle epilessie.

Nell'uomo, le epilessie sono conseguenza di un'amplissima serie di malattie neurologiche stabili o progressive, ma possono anche presentarsi isolatamente, come unico segno di disfunzione del sistema nervoso centrale; in tal caso è nota o ipotizzabile una "predisposizione" genetica.

E' ben consolidata la nozione che le epilessie, qualsiasi ne siano le cause primarie, sono attribuibili ad uno sbilancio fra eccitabilità e inibizione neuronale, sbilancio che deriva però da meccanismi molto variabili.

Le informazioni concernenti i meccanismi molecolari all'epilessia scaturiscono principalmente da osservazioni sperimentali su modelli, ma le procedure d'indagine che hanno portato a importanti avanzamenti conoscitivi sono state spesso ispirate da osservazioni compiute su patologie spontanee umane.

I campi d'indagine mirati a stabilire con precisione le relazioni fra meccanismi elementari e patologie umane possono essere cosi schematizzati:

- Alterazione di proteine di membrana, soprattutto proteine-canale, che regolano il flusso ionico e quindi le condizioni di base di eccitabilità neuronale;
- Alterazioni di microcircuiti locali conseguenti alla perdita di sottotipi neuronali, al rimaneggiamento di subunità recettoriali sinaptiche, a meccanismi di rigenerazione aberrante, oppure a distorsioni della geometria neuronale.
- Alterazioni gliali e del rapporto fra neuroni e glia
- Distorsione delle relazioni complesse "di sistema". Infatti, le attività di tipo epilettico sono certamente generate dalle strutture corticali, ma macrocircuiti che includono sia aree corticali sia strutture sottocorticali possono essere decisivi nell'espressione "clinica" delle epilessie.

Fra le aree di studio che collegano meccanismi elementari con specifiche condizioni patologiche umane, occorre ricordare:

- La stretta relazione fra maturazione fisiologica pre e post-natale a livello cellulare o circuitale ed epilettogenesi età - dipendente:
- La presenza di meccanismi di plasticità elementare che fisiologicamente governano molte funzioni cerebrali, ma in condizioni d'ipereccitabilità possono divenire abnormi o mal-orientati.

Sulle interazioni fra sviluppo cerebrale, meccanismi di plasticità ed epilettogenesi si basano eventi particolarmente severi nell'uomo che includono sia lo sviluppo di crisi farmacoresistenti che alterazioni globali dello sviluppo cognitivo in molti casi di epilessie infantili.

LA STIMOLAZIONE CEREBRALE PROFONDA ADATTATIVA (aDBS) NELLA MALATTIA DI PARKINSON: DALLA COMPRENSIONE FISIOPATOLOGICA DELLA MALATTIA ALL'INGEGNERIZZAZIONE DI UN DISPOSITIVO ELETTROMEDICALE PER LA CURA DEL PAZIENTE.

Alberto Priori

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La stimolazione cerebrale profonda (Deep Brain Stimulation o DBS) consiste nell'impianto neurochirurgico di elettrodi stimolanti in strutture profonde dell'encefalo (gangli della base) e da circa 20 anni costituisce un trattamento di provata efficacia nella malattia di Parkinson, particolarmente nelle fasi avanzate. Queste ultime tuttavia sono tipicamente caratterizzate dalla fluttuazione rapida delle condizioni cliniche del paziente che in pochi minuti passa dal blocco motorio alla presenza di violenti movimenti involontari. Tali fluttuazioni sono estremamente invalidanti e riducono la qualità della vita, essendo solo parzialmente corrette dalla DBS convenzionale che è erogata in modo costante.
Pertanto il nostro gruppo sin dal 2003 ha ideato, progettato e realizzato un sistema per la stimolazione cerebrale profonda di tipo *closed-loop*: un segnale biologico di controllo rilevato attraverso un apposito sensore nell'elettrodo di stimolazione, viene processato attraverso un circuito controllore che a sua volta modula le caratteristiche di stimolazione adattandole istante per istante allo stato clinico del paziente.
Lo sviluppo di tale idea (oggetto di brevetto in Europa e negli USA) si è articolato in un progetto di ricerca traslazionale che è partito dall'analisi dei meccanismi fisiopatologici alla base delle fluttuazioni tipiche della malattia di Parkinson attraverso lo studio dei segnali derivati per mezzo di elettrodi di profondità nei pazienti, fino alla ingegnerizzazione di un dispositivo prototipo attualmente in corso di sperimentazione clinica autorizzata dal Ministero della Salute. In tale progetto si sono integrate competenze biomediche, cliniche (neurofisiologi, neurologi, neurochirurghi, neuroradiologi, neuropsicologi e tecnici di neurofisiopatologia), informatiche e ingegneristiche (elettronica, bioingegneria, informatica medica) nel dare vita alla Newronika s.r.l., spin-off dell'Università di Milano e della Fondazione IRCCS Ca' Granda che gestisce lo sviluppo industriale del ritrovato della ricerca di base e clinica.

Sergio Cerutti

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Elaborazione dei segnali e delle immagini del Sistema Nervoso Centrale e modelli di interpretazione fisiopatologica

Abstract

Nelle Neuroscienze è oggi possibile ottenere importanti informazioni di tipo anatomico-morfologico e di tipo metabolico-funzionale. Sono oggi disponibili segnali ed immagini con diverse sorgenti e modalità di acquisizione che permettono di eseguire dettagliate analisi, anche su scale diverse, a partire dalla cellula fino ad arrivare a sistemi organicamente più complessi e con forti interazioni con altri sistemi biologici. Elaborare opportunamente queste informazioni, integrarle tra di loro e a varie scale di definizione, appare come un importante approccio di tipo quantitativo nello studio di parecchie funzioni del Sistema Nervoso Centrale. Verranno descritti alcuni parametri ottenuti da queste elaborazioni e verranno confrontati con modelli interpretativi di tipo fisiopatologico per valutare le loro caratteristiche in ambito diagnostico e terapeutico.

Sommario dei poster

Mapping early stage of myelin degradation at nanoscale resolution

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Abstract

To provide insight into the early process of degradation often occurring in severely debilitating diseases with myelin pathology an increased level of spatial structural resolution is needed to bear in the biological realm. Although many observations have connected changes in the periodicity of myelin with illness, few information exist about the microscopic process in the early period of damage of the nerve and how these changes percolate in space. Here we fill this gap by an experimental approach, based on basics spatial statistical approach applied to scanning micro X-ray diffraction data. We have mapped fluctuations in myelin period, membrane packed substructures and axons orientation, with a spatial resolution of 1 μm. Afterwards, the degradation nerve process has been mapped in a physiologically aged sciatic nerve. We identify the first stage of myelin degradation with the period evolving through a bimodal distribution with a spatial phase separation, and evidence that the orientation of axons in the wild sample show fractal fluctuations that are reduced with early degradation.

Neural coding and plasticity in the honeybee brain.

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Marco Paoli (BIOtech center, University of Trento),
Giorgio Vallortigara (Center for Mind/Brain Sciences, University of Trento),
Renzo Antolini (Department of Physics and Center for Mind/Brain Sciences, University of Trento), and
Albrecht Haase (Department of Physics and Center for Mind/Brain Sciences, University of Trento)

Abstract

The western honeybee Apis mellifera was chosen as a model for studying olfactory information coding and memory-formation-related plasticity in a medium-sized brain of about a million neurons with extraordinary learning performance. We focus on the primary centres of the honeybee's olfactory system, the antennal lobes (AL). An imaging platform based on a two-photon microscope allows obtaining both morphological data of the entire AL, as well as time-resolved in-vivo calcium signals of its neuronal activity. The system permits studies on several scales, from imaging the AL structure and its functional centers, the glomeruli, down to single neuron tracing, and synaptic density measurements. Functional imaging allows recording of the glomerular response maps to odour stimuli, highly resolved in space and time. Morphological and functional data are analysed with respect to neuroplastic changes after odour conditioning and possible lateral asymmetries between brain sides due to functional specialization.

Distributed simulation of polychronous and plastic spiking neural networks: strong and weak scaling of a mini-app benchmark

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Abstract

We introduce a natively distributed mini-application benchmark representative of plastic spiking neural network simulators. It can be used to measure performances of existing computing platforms and to drive the development of future parallel/distributed computing systems dedicated to the simulation of plastic spiking networks. The mini-application is designed to generate identical spiking behaviors and network topologies over a varying number of processing nodes, simplifying the quantitative study of scalability on commodity and custom architectures. Here, we present a first set of strong and weak scaling measures of DPSNN-STDP benchmark (Distributed Simulation of Polychronous Spiking Neural Network with synaptic Spiking Timing Dependent Plasticity). In this first test, we used the benchmark to exercise a small scale cluster of commodity processors (varying the number of used physical cores from 1 to 128). The cluster was interconnected through a commodity network. Bidimensional grids of columns composed of Izhikevich neurons projected synapses locally and toward first, second and third neighboring columns. The size of the simulated network varied from 6 Giga synapses down to 200 K synapses. The mini-application has been designed to be easily interfaced with standard and custom software and hardware communication interfaces. It has been designed from its foundation to be natively distributed and parallel, and should not pose major obstacles against distribution and parallelization on several platforms. During 2014, we will further enhance it to enable the description of larger networks, more complex connectomes, and prepare it for distribution to a larger community. The DPSNN-STDP mini-application benchmark is developed in the framework of the EURETILE FET FP7 European project, in cooperation with the CORTICON FET FP7 Project.

Functional Proteomics and Metabolomics of Brain Energy Metabolism in Pathology and Therapy

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Federica Ferrari (Department of Biology and Biotechnology, University of Pavia), Antonella Gorini (Department of Biology and Biotechnology, University of Pavia)

Abstract

In the Laboratory of Pharmacology and Molecular Medicine of Central Nervous System, Department of Biology and Biotechnology, University of Pavia, original research projects are carried out with high intrinsic technology. The fundamental topic is the study of drug actions on CNS and their ability to interact in vivo with the cerebral tissue Bioenergetics and Thermodynamics in various conditions of Physiopathology for Translational Medicine.Through specific programs of ultracentrifugation that allow to obtain definite levels of subcellular fractionations, the technologies comprise: (a) the isolation of peri-karyal mitochondria and intra-synaptic mitochondria; (b) the isolation of different synaptosomal populations deriving from dendro-dendritic and axo-somatic synapses; (c) the isolation of somatic and synaptic plasma membranes. On these subfractions, the catalytic properties of the most representative and regulatory enzymes linked to neuronal energy transduction are assayed (Proteomics e Functional Metabolomics) in various conditions of Experimental Physiopathology and directly on human lymphocytes, evaluating the molecular interactions between Brain Energy Metabolism, CNS Pharmacology and Therapy of Neurological and Psychiatric Diseases.The psysiopathological conditions are referred to animal models of many human Pathologies such as Hypoxia, Ischemia and Psychiatric Diseases, i.e. Depression and Schizophrenia; brain aging is also evaluated to study specific age-linked Neurological Dieseases and Therapy, i.e. Parkinson's Disease and Alzheimer's Disease. In clinical researches, the enzyme activities are evaluated as diagnostic and prognostic markers on lymphocytes obtained from patients affected by the previously mentioned Diseases, several data in the Literature showing that the agreed enzymatic variations in the cerebral tissue correspond qualitatively to those on lymphocytes.Thus, all these different research programs merge to constitute a common integrated picture, a unique wide-spectrum evaluation of the sequential relationships between genome, gene expression, enzyme catalytic activities and energy metabolism, meant to investigate the brain energy availability and its normal and pathologic use.Recent Papers by Villa et al. (2013):· ATP-ases of synaptic plasma membranes in striatum: enzymatic systems for synapses functionality by in vivo administration of L-acetylcarnitine in relation to Parkinson's Disease. Neuroscience. 248:414-26.· Functional proteomics of synaptosomes from different neuronal systems of rat hippocampus during aging. J. Proteome Res. 12:5422-35.· Effect of aging and cerebral ischemia during postischemic recovery on brain energy metabolism: functional proteomics approach to evaluate the responsiveness of ischemic tissue and drug actions. Neurochem. Int. 63:765-81.

L’emergenza delle funzioni molecolari in modelli di neuroni, circuiti e sistemi integrati

Egidio D'Angelo

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Abstract

Il sistema nervoso è costituito da complesse reti cellulari nelle quali i neuroni comunicano tra loro a livello delle sinapsi. I neuroni generano segnali elettrici tramite speciali molecole (canali ionici, recettori e trasportatori) che consentono di regolare i flussi ionici e le differenze di potenziale a livello della membrana cellulare. Questi meccanismi possono essere studiati sperimentalmente a vari livelli, dando informazioni essenziali sulla natura dei processi neurali. Questi meccanismi possono poi essere rappresentati da modelli biofisici e tradotti in modelli matematici generando rappresentazioni accurate delle funzioni neuronali. Tali modelli possono essere connessi in circuiti, che possono a loro volta essere integrati in sistemi di controllo e interfacciati a robots in grado svolgere comportamenti complessi. In tal modo è possibile studiare l’emergenza delle funzioni molecolari, neuronali e circuitali a livello di comportamenti integrati di significato biologico.Tale procedura modellistica è stata elaborata per la rete neuronale del cervelletto. Un microcircuito cerebellare, o microzona, è costituito da alcune decine di migliaia di neuroni (cellule granularli, cellule del Golgi , cellule del Purkinje, cellule stellate e a canestro, neuroni dei nuclei cerebellari profondi e del nucleo olivare inferiore) connessi tra di loro secondo specifiche regole topografiche. Il circuito cerebellare è stato modellizzato matematicamente ed inserito all’interno di un sistema di controllo robotico. Questo ultimo passaggio è fondamentale per il cervelletto, in quanto tale struttura è al centro del sistema di forward-controller del circuito sensori-motorio.In questa presentazione viene mostrato come tale sistema modellistico viene costruito sula base dei dati sperimentali ed utilizzato per studiare come i processi di computazione e apprendimento nel sistema cortico-cerebellare.

Average synaptic activity and neural networks topology: a global inverse problem

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Abstract

The dynamics of neural networks is often characterized by collective behavior and quasi-synchronous events,where a large fraction of neurons fire in short time intervals, separated by uncorrelated firing activity. These global temporal signals are crucial for brain functioning and they strongly depend on the topology of the network and on the fluctuations of the connectivity. We propose a heterogeneous mean--field approach to neural dynamics on random networks, that explicitly preserves the disorder in the topology at growing network sizes, and leads to a set of self-consistent equations. Within this approach, we provide an effective description of microscopic and large scale temporal signals in a leaky integrate-and-fire modelwith short term plasticity, where quasi-synchronous events arise. Our equations provide a clear analytical picture of the dynamics, evidencing the contributions of both periodic (locked) and aperiodic (unlocked) neurons to the measurable average signal. In particular, we formulate andsolve a global inverse problem of reconstructing the in-degreedistribution from the knowledge of the average activity field. Our method is very general and applies to a large class of dynamical models on massive random networks.

Progettazione e realizzazione di un sistema Continuous Wave fNIRS basato su tecnologia SiPM

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Abstract

La spettroscopia funzionale nel vicino infrarosso fNIRS (functional Near-InfraRed Spectroscopy), è una ben nota tecnica di monitoraggio, di tipo ottico, dei tessuti biologici e dunque non invasiva, applicabile sia su soggetti adulti che neonati, il cui funzionamento si basa sull'uso di radiazioni luminose appartenenti allo spettro del rosso-vicino infrarosso. Grazie alle proprietà ottiche dei tessuti biologici e delle sostanze (cromofori) contenute al loro interno, è possibile determinare lo stato di ossigenazione dei tessuti muscolari e cerebrali. Misurando le variazioni di concentrazione di emoglobina ossigenata (HbO2) e deossigenata (Hb) si riesce a monitorare l'attività cerebrale.Il nostro lavoro consiste nella progettazione e realizzazione di un prototipo di sistema fNIRS, ad onda continua, basato su un particolare tipo di fotomoltiplicatori al silicio, denominati SiPM (Silicon PhotonMultiplier) realizzati dal settore Ricerca & Sviluppo di STMicroelectronics di Catania.Il sistema in esame è stato realizzato a partire da un approfondito studio delle caratteristiche di tali fotomoltiplicatori, effettuato presso i nostri laboratori e dai quali sono emersi i vincoli progettuali necessari alla realizzazione del prototipo.Il sistema embedded è capace di gestire fino a 128 fotorivelatori e fino a 64 LED. Esso si basa su un'architettura scalabile, alimentato a batteria e a basso costo che si compone di:una scheda di alimentazione, in grado di fornire tutte le tensioni necessarie al funzionamento del sistema;una scheda principale su cui si trova un microcontrollore (STM32F4) in grado di gestire il tempo di commutazione dei LED, l'acquisizione dei fotorivelatori e la trasmissione dei dati;8 schede secondarie, nel ruolo di interfaccia tra la scheda principale e ogni singola probe;8 probe modulari e realizzate su supporti flessibili, in grado di ospitare 4 LED bicolore a due diverse lunghezze d'onda (735 e 850 nm) come sorgenti luminose, 16 SiPM come fotorivelatori e un sensore di temperatura.La struttura hardware, inoltre, consente di configurare i parametri via software e, in particolare: la temporizzazione del sistema di misura, la potenza ottica emessa dai LED e la tensione di polarizzazione di ogni SiPM.Infine, è stata realizzata un'interfaccia grafica che permette di visualizzare le variazioni -causate dall'attività cerebrale- dell'emoglobina ossigenata, di quella de-ossigenata e del volume ematico.

Perturbational complexity in chronic patients with disorders of consciousness

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Abstract

The level of consciousness of severely brain–injured patients is assessed clinically from their ability to respond to commands and communicate with the environment. However, both theoretically and practically, consciousness basically depends on the ability of different cortical regions to effectively interact, and does not require a communication with the external world. Electroencephalographic responses (EEG) to transcranial magnetic stimulation (TMS) can directly and non-invasively measure the integrity of different cortical areas and their interconnections, also in patients who are unable to communicate. We have recently observed that the algorithmic complexity of TMS-evoked potentials (Perturbational Complexity Index - PCI) can discriminate the level of consciousness in wakefulness, sleep, anesthesia and coma. In this study we tested the reliability of PCI to evaluate chronic patients with severe brain injury.Sixty chronic in-patients (n=22 in vegetative state – VS, n=25 in minimally conscious state – MCS, n=13 conscious state - CS) with severe brain injury and with stable clinical diagnosis were involed. TMS-evoked potentials were recorded from all patients with a 60-channel EEG during stimulation of the premotor and parietal cortex. Clinical assessment with the Coma Recovery Scale – Revised (CRS-R) was performed on the same day of TMS/EEG recording. After estimation of the cortical sources from scalp recordings, statistical analysis was performed to identify the spatio-temporal distribution of brain activity significantly evoked by TMS pulses, that was used to compute the PCI.The CRS-R score was significantly lower in the VS group as compared to the MCS and CS groups. PCI was able to correctly classify between VS and MCS/CS conditions at the single-patient level. In all MCS and CS patients at least one stimulating target showed a PCI greater than the maximum value previously observed during sleep and anesthesia. In VS patients PCI was overlapping the range of values obtained during sleep and anesthesia. In three VS patients the PCI was higher than expected: in the following months these patients showed a clinical improvement, evolving toward the MCS condition.We conclude that PCI can be considered a promising tool to discriminate VS and MCS/CS chronic patients, who are difficult to evaluate because of a progressive decline of residual sensory and motor abilities. Moreover, PCI might reveal an improvement of the level of consciousness earlier than any behavioral evidence of communication. Future studies should include larger populations of patients to provide a comprehensive validation of PCI for the evaluation of consciousness in chronic patients. Moreover it would be interesting to compare and integrate TMS/EEG results with other brain functional assessments, e.g. event-related potentials, functional magnetic resonance imaging.

Spatial Light Modulator Two Photon Imaging (SLM-2PM) for high-speed detection of Spatiotemporal Neuronal Network activity

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Abstract

The investigation of the spatiotemporal organization of neuronal activity in local microcircuits requires the simultaneous recording from multiple single-neurons. To this aim we have developed an advanced spatial light modulator two-photon microscope (SLM-2PM). A liquid crystal on Silicon-Spatial Light Modulator (LCOS-SLM) was used to arbitrarily generate a plurality of laser beams to scan the sample simultaneously. This method enabled both two-photon image generation and illumination of arbitrarily selected points in the sample. In this approach, the laser wave front is shaped while the number and the location of the laser beams can be dynamically modified. The fluorescence signal elicited by each of the laser beams was collected trough a high speed CMOS camera (1-2 KHz) allowing a high temporal signal resolution. With SLM-2PM, calcium signals could be recorded simultaneously from different network elements in acute cerebellar slices including granule cells, Purkinje cells and molecular layer interneurons. By combining WCR with SLM-2PM, the spike/calcium relationship in granule cells and Purkinje cells could be extrapolated toward the detection of single spikes. Neuronal responses were synaptically evoked with high-frequency trains of action potentials. Granule cell activity depended on the number of spikes in the input mossy fiber bursts. Purkinje cell and molecular layer interneuron activity followed that in the underlying granule cell population revealing the spread of activity through the cerebellar cortical network. Moreover, circuit activity was increased by the GABA-A receptor blocker, gabazine, and reduced by the AMPA and NMDA receptor blockers, NBQX and APV.

The retinal circulation: an open window on the cerebral vasculature

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Abstract

The retina and the brain are highly metabolically active tissues with large metabolic demands via specialized vascular networks. There is a close anatomical correlation between both the macrovascular and the microvascular blood supply to the brain and the retina, and both vascular networks share similar vascular regulatory processes. Assessment of the cerebral vasculature is important in determining an individual's risk of particular cerebrovascular diseases. However, while the assessment of the cerebral microvasculature requires highly specialized and expensive techniques, the potential for using non-invasive clinical assessment of the retinal microvasculature as a marker of the state of the cerebrovasculature offers clear advantages.The present contribution is focused on a multi-scale mathematical model of flow regulation and tissue perfusion and oxygenation in retinal tissue. Transport and diffusion of oxygen is described by advection-diffusion-reaction equations which include sink terms for tissue consumption. Such a model is coupled with an arteriole network, which receives blood and solute from the central retinal artery and then delivers them to the capillary plexi.The healthy situation is first studied, to understand the main features of tissue perfusion and oxygenation under normal conditions. The model is validated using experimental haemodynamic data. Then, various mechanisms are parametrically altered to determine the effect of impaired autoregulatory mechanisms on retinal blood flow. For example, reduced oxygen consumption due to cell death is also simulated to determine if cell death can induce significant haemodynamic alterations, which can suggest whether heamodynamic changes areprimary or secondary to several pathologies.

Alteration of cerebellar functional connectivity in MCI and AD pathologies

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Abstract

Introduction: studies have widely demonstrated that Alzheimer disease (AD) involves alterations in the prefrontal and medial temporal cortex along with changes in functional connectivity (FC) in the default mode network (DMN).1,2 The functional involvement of subcortical structures, like the cerebellum, instead, has been scantily considered. This study aimed to assess using resting state functional MRI (rs-fMRI), which resting state networks (RSNs) are interested by the disease at different stages and whether and how the cerebellum is involved. Methods: 14 AD, 12 mild cognitive impairment (MCI), 16 healthy controls (HC) underwent MRI examination which included a resting state functional MRI (rs-fMRI) FFE-EPI sequence and a high resolution 3D T1 FFE acquisition. For each subject, rs-fMRI images were analysed using the Independent Component Analysis (ICA)3 to characterise the RSNs. A non-parametric permutation test (dual regression)3 was applied to compare group-specific maps (p-value $\leq$0.05). Results and Discussions: ICA analysis resulted in 15 RSNs. rs-fMRI results confirmed a widespread alteration of the RSNs between the patients (MCI and AD) and HC.3 We observed areas of reduced FC in the frontal cortex network (FCN), DMN, salience network (SN) and the cerebellum network (CBLN), with more extended FC reductions in AD than MCI. The largest FC reductions were localized in the prefrontal areas both in AD and MCI. Moreover, MCI compared to HC revealed cerebellar hyper-activation in CBLN and lateral visual network (LVN). Comparing AD to HC we observed cerebellar hyper-activation in the dorsal and right attention networks (DAN and R-VAN). Both AD and MCI showed cerebellar FC increases in the medial visual network (MVN) and in the auditory network (AN). In particular, the largest FC increases were localized in the precuneus, cuneus and in the cerebellum. Conclusions: Results show that, in both AD and MCI, a widespread FC change involved to some extent all the RSNs, not only the DMN, revealing the emergence of alterations in specific nodes including the prefrontal cortex, the medial temporal cortex and the cerebellum. The changes occurring in these networks reflect derangement of functional relationships between multiple areas and could initially represent compensatory mechanisms exploiting the pre-existing neural reserve through plasticity. In particular, RSN changes involving the cerebellum may be explained, at least in part, by abnormal recruitment of neurons caused by a primary cerebro-cortical change. It is also tempting to speculate that increased cerebellar FC takes part in a homeostatic mechanism that aims at limiting the progression of cognitive decline from MCI to AD.References: 1. Wu Xia (2011) Hum Brain Mapp 32(11): 1868-81 2. Koch W (2012) Neurobiol Aging 33(3): 466-78 3. Binnewijzend MA (2012) Neurobiol Aging 33(9): 2018-28

Axon growth in neural development: sensing, transduction and movement

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Abstract

In the embryo, undifferentiated sets of cells form organized patterns following pathways marked by chemical cues. At this small scale, cues are represented by single molecules, displaced from their release location by diffusion. Cells crawl along the positive gradient, towards the direction of increasing chemical signal, from the periphery to the source. This establishes the controlled flow of material needed to build structured tissues. We may ask how far from its birthplace can we hear the metropolitan legend. Analogously, how far from its source can a chemical cue be found? The mathematics of diffusion shows that there exists a characteristic maximum reachable distance, called diffusion length, that depends on the volume (or on the weight) of the diffused molecule and on its activity time. Another aspect that we should consider is the fact that in the embryo, very much like in a noisy square, different cues are present at the same time. Following the chemical gradient cells work out the right direction sensing the chemical cues released in the environment, filtering out noise. To understand this mechanism, it is essential to dig into the process of gradient sensing. Cells try to detect very small differences in molecule concentration across their tiny diameter. With this respect, they behave like an instrument that counts molecules in its surroundings and is allowed only a limited number of probings. The study of the measurement errors of such an instrument can explain the shape of the trajectories. Moreover, we know that repeating the measure can reduce uncertainty, but it requires more time. A mathematical model of the measuring process and of the subsequent cell motion sheds light on the balance between the unevenness of trajectories and the time span of the motion in different conditions. This analysis can explain why neurons grow more slowly when the surrounding environment is morecomplex, for example when they have to perform sharp turns like when they approach the developing spinal cord. The model also suggests that some sort of amplification of the signal must occur inside the cell. This effect stems from a cascade of intracellular biochemical reactions that are only partially known to biologists. Mathematics can predict the magnitude of the amplification needed to separate a weak, but coherent signal, from the background noise and explain how even a couple of molecules in more in a certain direction can make the difference for life.This is a joint work with M. Gozzo, A. Zaghetto , and G. Merlo.

Diamond-based Multi Electrode Array biosensors: towards the systematic detection of exocytosis from chromaffin cells

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Abstract

In this poster we present an overview about the investigation of quantal exocytic events from cultured chromaffin cells carried out with diamond-based Multi Electrode Array (MEA) biosensors.The interest in the use of a diamond-based device in bio-sensing research is motivated by different technological requirements which are not met by conventional bio-materials (silicon, metals and metals oxides, polymers): robustness and reproducibility in performance over repeated bio-sensing cycles, bio-compatibility and long term stability for in vitro measurements, surface selectivity to different cellular and bimolecular bonding, high transparency for optical interfacing.The configuration of the devices allows to record quantal secretory responses from chemically stimulated cells positioned on the graphitic microelectrodes integrated in single-crystal diamond [1].The biosensors are fabricated implanting He+ ions (energy range: 0.8-2 MeV) on high-purity monocrystalline CVD diamond samples. Suitably aligned metal masks and variable-thickness contact masks [2] were employed to define “highly damaged regions”, i.e. converted from sp3 diamond bonds to sp2 graphitic-like bonds, with emerging end-points with micrometric resolution.This technique is extremely versatile, and allows the realization of different geometries of the biosensor for different sensing goals: it is indeed possible to obtain 16-channel multi-cell setups, where a culture of chromaffin cells can be directly grown over the surface of the device, or 16-channel single-cell setups, where all the electrodes are emerging inside a 20×20 µm2 area, thus giving the possibility to study in detail the single-cell secretion of catecholamines. [1] F. Picollo et al., Advanced Materials 25 (2013) 4696[2] F. Picollo et al., New Journal of Physics 14 (2012) 053011

"Multispecies" models to describe large neuronal networks

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Abstract

The set up of computer simulations describing complex networks with a huge number of nodes is a formidable challenge. Higher-level nodes, or interactions, may be affordable given an individual description (e.g., by a system of coupled ordinary differential equations), whenever their number is small to moderate. On the contrary, this approach would be computationally prohibitive for the description of lower-level nodes or interactions, if their number is exceedingly large. Since we assume in complex networks a certain number of neuronal populations exist, a possible alternative to each single cell description may consist in modelling the high-density populations as a continuum, confined in some spatial region, and describing their behaviour by means of a limited number of variables, e.g., submitted to satisfy partial differential equations. On the contrary, each neuron belonging to the low-density populations is described by means of an ODE system. By combining together continuum and discrete approaches we obtain what we call ``multispecies'' model.In order to tackle the presentation and application of the multispecies modelling to a realistic network, we focus on the Golgi-Granular cell network in the Cerebellum. This consists in a network where only two populations are present. Specifically, the multispecies approach consists in the description of the Golgi cell population, the low-density one, by means of an ODE system for each cell combined with only one PDE system for the whole Granular high-density population. Several simulations describing interesting phenomena as synchronization and travelling waves have been done. Finally, biological aspects have also been examined in order to provide our work with scientific completeness and accuracy.

More than grasping. Toward a cognitive architecture for robotics.

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Abstract

The recent interest in mobile manipulation for robots is reviving the research field of humanoid robotics that has seen already a lot of activities since its inception in 2001. Humanoid robotics has addressed and partially solved many autonomous tasks, as navigation in unknown environments, non repetitive manipulation, human-robot interaction.However the integration of those different skills into a unique "agent" is still obtained through ad-hoc methods, without a unified architecture. For market reasons, most of the attention tends to be devoted in developing the software sub-structures for such a robot, often reducing the problem to a software development and deployment activity. While the integration of well engineered modules may work for specific applications, we could not achieve a real autonomous and adaptive robot without a unified approach that can really integrate body movements, vision, cognition, and social interactions.The proponents' experience in cognitive robotics has grown from research developments in systems as: - a neural model for vision and reaching, modelling the V1 and V2 areas of the cortex (1);- build innovative and compliant arms and legs to try the models (2);- adaptive neural controllers for imitating the reflex control and the adaptation of biological muscles (3);- middle layer architecture for integrating innate and learned skills for sensor-motor agents (4);- high level cognitive system integrating an embodied natural language (5).The next big thing, in our opinion, is to tackle manipulation. The state of the art is still dominated by a study of the kinematics of the device, for the generation of optimal finger placement to obtain a stable grasp, but very little of the psychological aspects of "manipulating" is considered. The result is that specific procedures are developed for a few of tasks (for instance opening a door, or mixing a liquid).The expected use of the object, the environmental and social implications of each possible way of grasping an object, and the body characteristics are all together to interact to determine the optimal and natural grasp (in the "human" sense, in the present research). Findings in Neuro-Psychological fields lead us interesting evidences about the strategy planning and the way to interact. Object manipulation is an interesting test-bench, where higher and lower levels of control must synergistically cooperate, and where it is fundamental considering "boundary conditions" to sustain generalization and to guarantee the effectiveness of the action.

A Novel Approach for Fully Automatic Segmentation of Hippocampus in MRI: Methods and Validation

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Abstract

Hippocampal atrophy is an important clinical biomarker. For this reason there is muchinterest in the accurate, reproducible segmentation of hyppocampus in structural MR im-ages. The proposed approach can be useful for large-scale research studies, in the rstinstance on Alzheimer's disease, where the hippocampal volume is an important biomarker,but also on other brain disorders in which the hippocampus plays a relevant pathogeneticrole. In this study a fully automated pattern recognition system for accurate and repro-ducible segmentation of the hyppocampus in structural Magnetic Resonance Imaging (MRI)is presented. The system has been validated on 56 T1-weighted structural brain MR im-ages, and consists of three processing levels: (a) A volume of interest (VOI) hunter: a novelautomated algorithm, based on Point Distribution Model Theory, was developed for a moreprecise identication of a bounding region containing the hippocampus. (b) Feature extrac-tion: all voxels included in the selected VOI were characterized by 315 features computedfrom local information such as image intensity, voxel positions, Haar-like lters, and se-lected Haralick features. (c) Voxel classication: a Random Forests algorithm was used toclassify voxels as belonging or not belonging to the hippocampus. In order to improve theclassication performance, a training subset was selected through the use of the Pearsonscorrelation coecient between the test image and the training dataset (active learning). Inthe subsequent validation phase, the results were compared with images hand-labeled by anexpert neuroradiologist, and , using a leave-one-out approach, a Dice index of 0.81 0.03was obtained. Finally, this method for hippocampal segmentation was compared with thepublicly available brain segmentation package FreeSurfer.

Systems Neuroscience – University and Politecnico of Turin

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Abstract

The development and the functions of the human brain, including its extraordinary capability to store, retrieve and elaborate information, are determined by the expression of the 'compressed' genetic program stored in the nucleus of cells that compose it. This process is extremely complex, as it involves the expansion of the basic genetic information in the form of multi-dimensional networks. The genes of every cells and their encoded products, such as RNA, proteins and metabolites are organized as complex interaction networks, responsible for establishing the number, the identity and the functional properties of brain cells. On these basis, neurons and other brain cell types self-organize in sophisticated cellular networks, characterized by billions of tunable contacts, from which behaviors emerge. In the past decades molecular, cellular and computational neurosciences have shed much light on the organizing principles underlying the single layers of this multi-dimensional organization. In particular, besides to the established role of transcriptional networks, it is today clear that post-transcriptional regulation dependent on the interaction between mRNAs and micro-RNAs is crucial to the establishment and to the fine-tuning of neuronal networks. The central challenge of modern neuroscience is understanding and modeling how these different layers are integrated. This knowledge will be essential if we want to understand how specific changes in the genetic information may alter the functional properties of the entire brain structure and how the molecular networks of brain cells can be modified in order to obtain favorable changes in brain functions. The aim of the Systems Neuroscience group of the University and of the Politecnico of Torino is to obtain significant breakthroughs in this direction, by promoting the scientific interaction and the exchange between strong research groups involved in computational, molecular, cellular and developmental neuroscience. We will present here in synthesis some of the first results of this cooperation.

Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo

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Abstract

Purpose: In addition to motor functions, growing evidence indicates that the human cerebellum plays a significant role in cognition. This is thought to occur through connections between the superior cerebellar peduncle (SCP) and the contralateral associative cerebral cortex via red nucleus (RN) and thalamus1. While recognizing that tractography provides only an indirect evidence of anatomical connectivity, using advanced diffusion MRI tractography 2 we aimed to characterise the cerebello-thalamo-cortical tract in terms of functional and anatomical areas touched by streamlines. Methods: 15 healthy controls underwent MRI examination including a High Angular Resolution Diffusion Imaging (HARDI) scan. HARDI data were pre-processed in a standard way (FSL3). Cerebello-thalamo-cortical tracts were reconstructed by using an algorithm combining the Constrained Spherical Deconvolution (CSD) technique with probabilistic tractography (MRtrix2) and by tracking the bundle passing through the SCP and the contralateral RN. In order to assess involvement of different cortical regions, cerebral and cerebellar cortices were parcellated according to anatomical and functional basis by referring to Brodmann and SUIT atlases. A new index, “grey matter tract percentage” (T%gm), was introduced to reflect the percentage of grey matter tract volume in one cortical parcellation compared to the overall grey matter tract volume.Results: The use of CSD and probabilistic tractography successfully reconstructed contralateral cerebello-thalamo-cortical tracts. By comparing T%gm values between cerebellar and cerebral cortices in functionally corresponding areas, we found that the cerebellar hemispheres and the cortical associative areas received 79% ± 4% and 80% ± 8% of streamlines while the prefrontal cortex and lateral Crus I-II received 38% ± 11% and 48% ± 4% of streamlines, respectively.Discussion and conclusions: This work shows a characterisation of the cerebello-thalamo-cortical tract in terms of functional and anatomical areas touched by streamlines. Almost 80% of the streamlines reached the cerebellar hemispheres on one side and the associative cerebral cortex on the other, suggesting a prominent connectivity between these areas4. Although tractography cannot distinguish single neuron pathways passing though synaptic connections (like the thalamic relay), it is the only in vivo method for investigating structural connectivity. Moreover, since data were acquired on a clinical scanner, this method has immediate potential in neurological conditions for which a cerebellar origin has been proposed. References: 1. Strick PL et al. Annu Rev Neurosci 2009; 32:413-434; 2. Tournier JD et al. Int J Imaging Syst Technol 2012; 22(1):53-66; 3. FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/; 4. Buckner RL et al. J Neurophysiol 2011; 106:2322–2345.

The effect of covariates on tract-based spatial statistics in Alzheimer disease and Mild Cognitive Impairment.

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Abstract

Purpose: Structural MRI studies have highlighted a severe involvement of specific grey matter (GM) structures in Alzheimer disease (AD) and Mild Cognitive Impairment (MCI) patients1. In this study tract-based spatial statistics (TBSS) was performed to obtain whole-brain maps of the main white matter (WM) tracts, using two diffusion MRI indices such as fractional anisotropy (FA) and mean diffusivity (MD). Furthermore statistical analyses with different type and number of covariates were repeated to investigate the correlation between brain atrophy and microstructural changes and to quantify global aspects of the pathology.Methods: 14 AD and 12 MCI and 16 healthy controls (HC) underwent diffusion scan during an MRI examination. Eddy current correction, brain extraction of the non-diffusion weighted image and creation of FA and MD maps were performed using FSL2. TBSS3 was used to analyse differences among the three groups. Three voxel-wise statistical analyses (5000 permutations, $p<0.01$ TFCE corrected), with different covariates, were performed: 1) age and gender were used as covariates (TBSS-ag); 2) mean FA of the brain (GM and WM) was added to age and gender (TBSS-fa); 3) the brain volume (GM and WM) was added instead of FA (TBSS-vol).Results: Different areas with alterations in AD and MCI were detected using either TBSS-ag or TBSS-fa or TBSS-vol. TBSS-ag showed that the inferior temporal lobe (uncinate fasciculus and fusiform gyrus) and hippocampi were the mainly affected areas. TBSS-fa detected more affected areas, including thalami and frontal lobe (middle/orbito frontal cortex) with reduced FA and increased MD. TBSS-vol and TBSS-fa showed only a few regions in common (cerebellum, insula, uncinate fasciculus and frontal lobe) as well as discrepancies in inferior temporal lobe and thalami. Discussion and conclusions: The main finding is that cerebellar damage is present in MCI and AD and is not correlated with atrophy. Indeed altered cerebellar areas appear both in TBSS-fa and TBSS-vol analyses. In general areas of microstructural changes were evidenced with posterior predominance. The number and the extension of significantly different areas rise by using mean FA value while decrease by using total brain volume as covariate. The fact that TBSS-fa reveals a larger number of significances may reflects that this analysis takes into account damages due to numerous effects. Whereas, TBSS-vol detects fewer alterations because it removes the effect due to brain atrophy. Finally, as a consequence of these results we hypothesize that the use of mean FA as covariate gives a more accurate description of the impairment due to the pathology.References: 1. Serra L et al. J Alzheimers Dis. 2010; 19(1):147-159; 2. FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/;3. Smith SM et al. NeuroImage. 2006;

Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo

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Abstract

Purpose: In addition to motor functions, growing evidence indicates that the human cerebellum plays a significant role in cognition. This is thought to occur through connections between the superior cerebellar peduncle (SCP) and the contralateral associative cerebral cortex via red nucleus (RN) and thalamus1. While recognizing that tractography provides only an indirect evidence of anatomical connectivity, using advanced diffusion MRI tractography 2 we aimed to characterise the cerebello-thalamo-cortical tract in terms of functional and anatomical areas touched by streamlines. Methods: 15 healthy controls underwent MRI examination including a High Angular Resolution Diffusion Imaging (HARDI) scan. HARDI data were pre-processed in a standard way (FSL3). Cerebello-thalamo-cortical tracts were reconstructed by using an algorithm combining the Constrained Spherical Deconvolution (CSD) technique with probabilistic tractography (MRtrix2) and by tracking the bundle passing through the SCP and the contralateral RN. In order to assess involvement of different cortical regions, cerebral and cerebellar cortices were parcellated according to anatomical and functional basis by referring to Brodmann and SUIT atlases. A new index, “grey matter tract percentage” (T%gm), was introduced to reflect the percentage of grey matter tract volume in one cortical parcellation compared to the overall grey matter tract volume.Results: The use of CSD and probabilistic tractography successfully reconstructed contralateral cerebello-thalamo-cortical tracts. By comparing T%gm values between cerebellar and cerebral cortices in functionally corresponding areas, we found that the cerebellar hemispheres and the cortical associative areas received 79% ± 4% and 80% ± 8% of streamlines while the prefrontal cortex and lateral Crus I-II received 38% ± 11% and 48% ± 4% of streamlines, respectively.Discussion and conclusions: This work shows a characterisation of the cerebello-thalamo-cortical tract in terms of functional and anatomical areas touched by streamlines. Almost 80% of the streamlines reached the cerebellar hemispheres on one side and the associative cerebral cortex on the other, suggesting a prominent connectivity between these areas4. Although tractography cannot distinguish single neuron pathways passing though synaptic connections (like the thalamic relay), it is the only in vivo method for investigating structural connectivity. Moreover, since data were acquired on a clinical scanner, this method has immediate potential in neurological conditions for which a cerebellar origin has been proposed. References: 1. Strick PL et al. Annu Rev Neurosci 2009; 32:413-434; 2. Tournier JD et al. Int J Imaging Syst Technol 2012; 22(1):53-66; 3. FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/; 4. Buckner RL et al. J Neurophysiol 2011; 106:2322–2345.

A unifying view of Default Mode Network functional connectivity changes in Autism Spectrum Disorder

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Abstract

Recently several resting state functional Magnetic Resonance Imaging (rs-fMRI) studies have associated ASD (Autism Spectrum Disorder) with disruptions in brain functional connectivity (FC) bringing to the “under-connectivity theories” (1). Conversely, Uddin et al. (2), using Independent Component Analysis (ICA), have detected only enhanced FC in ASD compared to typically developing (TD) children. Therefore, a standard pattern of FC alteration in ASD is not defined. We used ADNI data (3) acquired at 3T GE Signa scanner. We consider a group of 20 ASD (7.9 to 12.9 years) and 19 TD (7.7 to 12.4 years) children in order to investigate the differences in FC focusing on the Default Mode Network (DMN). For each subject, rs-fMRI images were analysed using the ICA computational method in order to characterise resting state networks (RSNs). ICA analyses were carried out using BrainVoyager QX software 2.8 version and the relative plug-in extensions (4, 5). The random effect ANCOVA (RFX ANCOVA), as implemented in BrainVoyager QX, was then applied in order to compare group-specific maps for each independent spatial component. Statistical maps were multiple comparisons corrected using the cluster threshold estimator plugin available in BrainVoyager. A statistical threshold of $p < 0.05$ was considered significant. ICA analysis resulted in 30 independent components (ICs). The DMN was selected visually as the unique cluster generating the typical resting-state pattern of anterior and posterior cingulate cortex (ACC and PCC respectively) and bilateral inferior parietal cortex coactivation.The reduced FC in ASD group involves DMN medial nodes (frontal lobe and PCC) whereas the enhanced FC involved precuneus and lateral DMN nodes (right and left parietal lobe). Our current findings are in agreement with both previously published studies of DMN hypo-connectivity (in adults and adolescents with ASD) and recently published Uddin’s paper. We suppose that the FC enhancement in DMN parietal nodes could nullify or reduce the “extrinsic” parietal cortex normal functions. Within-network hyperconnectivity may also reduce the interaction among networks and could be a barrier for the “normal activity” of neuronal functionally related regions. On the other side, we hypothesize that FC reduction within DMN could be the effect of enhanced activity with others areas outside the network. As a future purpose we would like to investigate, by means of seed-based analysis on an independent sample, the FC of each of the DMN nodes altered in our ICA analysis in order to make a robust interpretation of present results.References: (1)Dichter GS et al. (2012) Dialogues Clin. Neuroscience; 14(3):319-51. (2) Uddin L et al. (2013) Jama psychiatry; 70(8):869-79.(3) http://fcon_1000.projects.nitrc.org/indi/abide/.(4)Hyvarinen A et al. (1999) IEEE Trans Neural Netw; 10:626–634.(5) Esposito F et al. (2005) Neuroimage; 25:193–205.

High-resolution MRI images of the hippocampal region for Alzheimer's disease early diagnosis

renata longo

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Abstract

Purpose:A challenging point in neuroimaging is the early diagnosis of Alzheimer's disease (AD). This research implies the recognition of the Mild Cognitive Impairment (MCI) converter and non converter patients and the possible identification of individuals at high risk of AD in a completely pre-clinical stage. For this purpose powerful techniques [1] have been developed for the analysis of MR images in the hippocampal region [2][3] with promising results. In the present study an MRI acquisition protocol has been developed to obtain higher spatial resolution and higher contrast images in the hippocampal area suitable for automatic analysis.Methods and materials: High-resolution Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequences were optimized to acquire hippocampal regions. A Philips Achieva 1.5 T imager and the SENSE coil with 16 channels were used. The study of the corrections for the inhomogeneity of B1 was dealt and the calibration samples were used during image acquisition to obtain autocalibrated intensity normalization.Results: A new protocol with a voxel size of 0.6x0.6x0.59mm3, a studied volume of 20x20x4 cm3, a scan time of about 14 min was obtained applying the "overcontiguos" option. The acquisition matrix is 336 (Nx) x 278 (Ny), 101 slices are acquired and repetition time (TR) and echo time (TE) are respectively 12,5 ms and 5,9 ms. The flip angle is 8 degand the number of signal averages (NSA) is 3. The SNR is smaller but comparable with whole brain ADNI MPRAGE sequence. More important the reproducibility of the extracted hippocampal volumes is significantly better in our high resolution images (p

Investigating the interplay between intrinsic and evoked activities in cultured neuronal networks by dimensional reduction ..

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Abstract

High density microelectrode arrays (MEAs) provide extracellular recordings from thousand of electrodes (www.3brain.com) and offer novel capabilities to investigate electrophysiological signaling in cultured neuronal networks and in ex vivo brain tissues. In this study we report on our recent technological and data analysis advancements to investigate the propagation and the interplay of spontaneous and electrically evoked activities in cultured networks. To do so, a novel high density MEA with on-chip stimulating electrodes was realized. It provides whole-array recordings from 4096 electrodes (pitch of 81 um, active area of 8 mm by 8 mm) and electrical stimulation from 16 electrodes located every 8 recording sites. Here, this device was used to interface hippocampal neuronal networks. From the second week in vitro [1] these cultures display a peculiar intrinsic firing regime characterized by periodic synchronized network-wide bursts. These network bursts originate from specific ignition sites of the cultured network (i.e. characterized by more excitable cells) and can propagate through the entire network. These propagations are informative of the underlying network connectivity and their classification based on their spatiotemporal patterns might elucidate the network's organization and its ongoing dynamic. Previous studies [1] have described the trajectories of these propagations by tracking their center of activity trajectory (CAT). Although CATs provide a good overall description of spatiotemporal patterns, they are not suited for fine studies on these propagations. Here we have adopted a more rigorous approach by applying dimensional reduction techniques that take advantage of the redundancy and of the sparseness of multi-unit recordings. Our results show that by Principal Component Analysis (PCA) we can properly reconstruct the time course of spatiotemporal propagations with a minimal set of three components (i.e. explaining ~90% of the variance of the trajectories). The PCA classification based approach allowed us to characterize both intrinsic and electrically evoked network-wide propagations. Interestingly, our results show that electrical stimulation can evoke (i) distinctive propagations that depend on the specific spatial-temporal properties of the stimulus as well as (ii) propagations that are already expressed in the intrinsic 'repertoire' of network bursts. Here we will discuss these results and our observations on the interplay between intrinsic and electrically evoked network-wide propagations.References:Gandolfo M., Maccione A., Tedesco M., Martinoia S. and Berdondini L. Tracking burst patterns in hippocampal cultures with high-density CMOS-MEAs. J Neural Eng. Oct;7(5) 2010.

Diffusion Kurtosis Imaging: prime applicazioni cliniche in ambito neuroradiologico

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Abstract

L'analisi mediante RM del tensore di diffusione (Diffusion Tensor Imaging, DTI) consente di valutare in vivo e con modalità non invasive il processo di diffusione delle molecole d'acqua nei tessuti biologici. La peculiare organizzazione di alcuni tessuti biologici (per esempio muscoli, sostanza bianca del sistema nervoso centrale e tessuti ad alta cellularità) influenza tale fenomeno rendendolo anisotropo e quindi ben valutabile con tali tecniche di studio. Nonostante i grandi vantaggi di tale tecnica, la DTI è basata su un modello molto semplificato che assume che lo spostamento per diffusione segua un profilo gaussiano il che è molto raro in un ambiente variegato come i tessuti biologici. Per caratterizzare la natura non gaussiana della diffusione dell'acqua nei tessuti è stata sviluppata negli ultimi anni la Diffusion Kurtosis Imaging (DKI) che permette di ottenere ulteriori e più accurate informazioni sulle caratteristiche ultrastrutturali tissutali. La DKI è però una tecnica sperimentale in cui molti parametri, sia relativi all'acquisizione delle immagini sia legati all'analisi delle stesse e all'estrazione delle informazioni diagnostiche, devono ancore essere definiti in maniera più dettagliata non essendo ancora standardizzati per l'applicazione in ambito clinico. La DKI è una tecnica di imaging relativamente recente; ad oggi ci sono solo un numero limitato di studi che utilizzano tale tecnica. L'obiettivo primario di questo lavoro è valutare il ruolo di tale tecnica in ambito clinico per la valutazione di patologie del sistema nervoso centrale quali le ischemie, i tumori e le malattie neurodegenerative.

A network model of dissociated cell cultures: the role of connectivity

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Abstract

How an ensemble of neurons links together to form a functional unit is a fundamental problem in Neuroscience. The architecture of neuronal wiring, in fact, determines how neurons communicate and may be important for information processing performed by neuronal networks. However, the knowledge is limited to networks consisting in a small number of neurons, while the topological structure, which connects thousands of neurons together, remains still unknown.Randomly formed in vitro networks are free of any predefined functional role and enable one to study how a system self-organizes. In in-vitro cell cultures of several different preparations, the spontaneous activity of the network exhibit significant fraction of active cells during given time intervals (e.g. 1 s). The synchrony peaks, characterized by a much larger-than-average fraction of active cells, are referred to as synchronous bursting events (SBEs). Multi electrode array recordings show that the firing pattern, also called motif, of each cell participating in a SBE, is substantially similar across multiple synchrony peaks.We developed a neural network model that mimics qualitatively and quantitatively the behavior of real cell cultures. The network topology, in the model, was determined based on the physiological constraints (i.e. cell density, length of the connections) derived from the observation of immuno-fluorescent cell cultures images. With such minimal structural constraints the network model displayed SBEs similar to the recorded ones. In particular, in the model, the SBEs were reproducible along time and propagated through the network similarly to the experiments. The interest of these results is twofold. First, it shows that a network model without the minimal physiological constraints does not allows to properly reproduce observable phenomena such as propagating SBEs. Second, it suggests that networks without well-organized structures (i.e. scale-free), that involve specialized neurons (i.e. hub/leader neurons), can still elicit physiological responses.In the end, our neural network model replicates most of the salient firing properties observed experimental investigations and it therefore constitutes a ground true for further experimental investigations.

Functional anatomy of sensorimotor integration in chronic stroke patients

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Abstract

BackgroundIncreasing somatosensory input can enhance functionally relevant brain reorganisation after stroke and is a potential mechanism of action of functional electrical stimulation (FES). The site of sensorimotor integration (SMI) is not yet clear, but may be different in controls and patients because of post-stroke brain reorganisation. Here we used fMRI to investigate SMI in the brain during FES.MethodsSubjects were scanned during four conditions in a 2x2 factorial design: (1 & 2) repetitive unilateral active (moved by the subject) ankle dorsiflexion with and without concurrent electrical stimulation, (3 & 4) repetitive passive (moved by the experimenter) ankle dorsiflexion with and without concurrent electrical stimulation. Movements were performed with the affected ankle. FES was superficially applied to peroneal nerve; current was set subject by subject. Analysis was performed with SPM8. Here, we define SMI as the interaction between volitional movement and augmented proprioception.Results10 chronic stroke patients and 16 age-matched healthy controls took part (range 28-72 yrs). In controls, all conditions elicited activity in S1 and M1. FES led to relative overactivity in SII. FES had an additional effect in M1 and S1 during active compared to passive movement. In patients, all conditions elicited activity in a more widely distributed network that included S1 and M1 (Fig. 1). In particular, FES had a greater effect during active compared to passive movement in ipsilesional postcentral and angular gyrus (Fig. 1).ConclusionIn healthy subjects, SMI was seen in primary sensorimotor areas, whereas in patients it was seen in secondary areas (i.e. postcentral gyrus; angular gyrus). Angular gyrus is a recipient of proprioceptive information encoded in the postcentral gyrus. These results suggest that SMI takes place in a more widely distributed network of brain areas after stroke, and that patients may take advantage of secondary areas to support motor learning.

The intrinsic and synaptic responsiveness of a new realistic Purkinje cell model

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Abstract

The latest discoveries on Purkinje cell (PC) physiology suggest that the mechanisms of PCs intrinsic excitability have to be revisited. We have constructed a new PC model in Python-NEURON which, based on the most recent literature, explicitly accounts for the Axon Initial Segment (AIS), for a section of the myelinated axon, including three Nodes of Ranvier (RVN), and an unmyelinated collateral. The sodium channels (Nav1.6) are located in the main trunk of the dendritic tree, in the AIS, soma and RVNs. Two members of the Kv3 subfamily (Kv 3.3 and Kv3.4) which are present, respectively, in the dendrites and in the soma/axon, account for the main potassium entry. Four different channels (Cav2.1 and Cav3.1 to 3.3) have been used in various parts of the cell to account for the massive Ca2+ entry and three different channels have been defined for the Ca2+-dependent potassium currents , including Kca3.1 which has been recently discovery in Purkinje cells. Seen the importance of calcium in this cell, has been introduced an intracellular Ca2+ buffer (calbindin and Paralbumin) with calcium pumps too. The new model configuration now generates simple spike (SS) firing reproducing the experimental input-output curve. SSs initiate in AIS and then back-propagate into the soma decaying sharply inside the dendritic tree. Activation of parallel fiber (pf) generates a short burst followed by a pause caused by Stellate cells. The pause is modulated by the presence of the H-current. Following a complex spike (CS), SS activity is interrupted independently of the inhibitory synaptic input. The unreliable transmission of high speed spikes (pf burst and CS burst) along the axon can be used to test the synaptic transmission to the Deep Cerebellar Nuclei. The pf and granule cell ascending axon (aa) synapses have been modeled using a stochastic release mechanism activating AMPA synaptic receptors. The facilitation and depression profiles of pf and aa synapses faithfully reproduce the experimental data. This model provides a valuable tool to further investigate the Purkinje cell function in cerebellar network models.

Un solutore meshfree per EEG/MEG

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Abstract

L'applicazione di tecniche non invasive di neuroimaging per lo studio dell'attività cerebrale è aumentata considerevolmente negli ultimi anni proponendosi come alternativa alle tecniche di nucleari. La recente disponibilità di sistemi particolarmente sensibili di rilevamento dei campi elettromagnetici generati dall'attività cerebrale, hanno reso la MagnetoEncefaloGrafia (MEG) e la ElettroEncefaloGrafia (EEG) tecniche diagnostiche con notevoli potenzialità, caratterizzate da elevata risoluzione temporale. Tali tecniche si basano sul rilievo del campo magnetico e/o del campo elettrico generati dall'attività neuronale e sulla successiva soluzione di un problema inverso che consente la localizzazione delle loro sorgenti. Attualmente, l'impiego in ambito clinico delle tecniche elettromagnetiche riguarda principalmente l'identificazione e la localizzazione di focolai epilettici per la pianificazione dell'asportazione chirurgica delle aree epilettogeniche. In tale ambito, un'elevata accuratezza di localizzazione è fondamentale per evitare l'insorgere di deficit neurologici dovuti all'asportazione di tessuti sani. Inoltre, recenti studi riguardanti la MEG hanno riportato risultati incoraggianti nella diagnosi di un'ampia gamma di patologie quali sclerosi multipla, Alzheimer, schizofrenia, Asperger, e nella comprensione dei processi cognitivi. Premessa fondamentale per la soluzione del problema inverso è l'efficiente e accurata soluzione del problema diretto, tradizionalmente approcciato mediante metodi numerici grid-based che richiedono una reticolazione preliminare bidimensionale (BEM) o tridimensionale (FEM) del dominio di interesse Al fine di gestire in modo più efficiente la complessità fisico-geometrica del sistema, per la soluzione del problema diretto si propone l'applicazione di un metodo numerico meshfree che non richiede alcuna reticolazione preliminare del dominio di interesse. I risultati di validazioni effettuate su domini geometricamente semplici suggeriscono che il solutore proposto è particolarmente competitivo, permettendo un'economia di risorse computazionali tanto maggiore quanto maggiore è l'accuratezza richiesta. Tale vantaggio riveste un importante ruolo quando il solutore inverso è applicato nel contesto del processo iterativo di soluzione del problema inverso. Inoltre, ulteriori vantaggi derivano dalla notevole semplificazione del setup sperimentale, dal momento che nessun processo di meshing è richiesto in fase di pre-processing. Alla luce dei suoi vantaggi e in relazione ai più recenti studi sperimentali riportati in letteratura, la metodologia proposta, inserita nel contesto di soluzione del problema inverso, potrebbe avere impatto significativo sia in fase diagnostica che in fase di studio dei processi che regolano le funzioni cerebrali.

A multimodal study based on fNIRS-EEG and fMRI-EEG for brain mapping of cortical motor areas on healthy and epileptic subjects

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Abstract

In this work we present a multimodality approach based on coregistration between functional Near Infrared Spectroscopy and Electroencephalography (fNIRS-EEG) and between functional Magnetic Resonance Imaging and EEG (fMRI-EEG) on epileptic patients and healthy volunteers during motor task.Ten right-handed patients with progressive myoclonic epilepsy 1A (EPM1A) patients and twelve right-handed healthy subjects were enrolled. 20s of hand grip (squeezing a soft ball at 2Hz) were executed by alternating 20s of rest (10 repetitions). Three different paradigms were successively executed: right hand vs. rest, left hand vs. rest, left hand vs. right hand.The multichannel dual wavelength medical device for time domain (TD) fNIRS developed at the Department of Physics, (Politecnico di Milano) was used. 15 detection bundles and 8 light sources were positioned over the left and right hemisphere centered on C3 and C4 cerebral motor areas.We found that results of individual and group analyses agree with literature. Functional activation was detected by fNIRS in the contralateral hemisphere in channels close to central area (C3 or C4). fMRI maps and EEG measurements confirmed the activation position.We verified that different neuroimaging techniques can be easily applied and co-applied. All topographic results in volunteers agree with literature and are located within the area of fMRI activation, assumed as gold standard. The measurement campaign on patients with circumscribed diseases shows the feasibility to use time domain NIRS also in the clinical environment. Our data suggested that TD fNIRS could be a useful technique aimed at studying patients with movement disorders being able to disclose changes in hemodynamic not directly revealed by fMRI. Work is in progress to develop new data fusion strategies and to optimize a standard functional imaging procedure.This research has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement HEALTH-F5-2008-201076 (nEUROPt).

Multiscale Modeling and Simulation of Neuro-Electronic Interfaces

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Abstract

In this communication we propose a multiscale approach to modeling and simulation of neuro-electronic interfaces. These latter are bio-hybrid systems in which neuronal cells and material substrates made of inorganic or organic semiconductors are put into intimate contact through a thin layer of ionic solution (electrolyte cleft) [1,2]. Following [3], we start from a fully 3D representation of ion flow in the cleft based on the Poisson-Nernst-Planck (PNP) electro-chemical formulation. Then, to reduce model complexity, we perform a dimensionality reduction by averaging the 3D PNP equations in the direction perpendicular to the cleft (z axis). This leads to a 2D PNP model to determine the spatial distribution of ions and electric field in a plane parallel to the neuron adhesion surface on the underlying substrate (xy plane). Solution behaviour in the z axis is modeled by assuming that current and electric displacement are piecewise constant quantities, from which it follows that potential is a piecewise linear continuous function and ion concentrations are piecewise exponential continuous functions, respectively. The backward Euler method is adopted for temporal semi-discretization of the 2D PNP model and a fixed-point iteration based on Gummel's map is used to decouple the system equations. Spatial discretization is performed using exponentially fitted finite elements on a triangular partition of the 2D computational domain. Preliminary results are in excellent agreement with those obtained in [4] using analytical solutions of the PNP problem in radial coordinates and in [3] using simplified lumped parameter models.References:[1] High-Resolution Multitransistor Array Recording of Electrical Field Potentials in Cultured Brain Slices, M. Hutzler, A. Lambacher, B. Eversmann, M. Jenkner, R. Thewes, P. Fromherz, J Neurophysiol 96: 1638-1645, 2006.[2] A hybrid bioorganic interface for neuronal photoactivation, D. Ghezzi, M. R. Antognazza, M. Dal Maschio, E. Lanzarini, F. Benfenati, G. Lanzani, Nature Communications, 2, 166, http://dx.doi.org/10.1038/ncomms1164, 2011.[3] Field-effect transistor with recombinant potassium channels: fast and slow response by electrical and chemical interactions, M. Brittinger, P. Fromherz, Appl. Phys. A, 81: 439-447, 2005.[4] Solution of the Poisson-Nernst-Planck equations in the cell-substrate interface, M. Pabst, G. Wrobel, S. Ingebrandt, F. Sommerhage, A. Offenhausser, Eur. Phys. J. E 24, 1-8 (2007).

Recurrence of spatio-temporal patterns and neural avalanches at the critical point of a non-equilibrium phase transition.

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Abstract

Recently, many experimental results have supported the idea that the brain operates near a critical point, as reflected by the power laws of avalanche size distributions and maximization of fluctuations. Several models have been proposed as explanations for the power law distributions that emerge in spontaneous cortical activity.However, there are additional features of neuronal avalanches that are not captured in these models, such as the stable recurrence of particular spatiotemporal patterns and the conditions under which these precise and diverse patterns can be retrieved.In many areas of the brain having different brain functionality, both during sleep and in the awake state, repeatable precise spatiotemporal patterns of spikes seem to play a crucial role in the coding and storage of information. Previous studies have separately addressed the topics of phase-coded memory storage and neuronal avalanches, but our work is the first to show how these ideas converge in a single cortical model.We model spontaneous cortical activity with a network of coupled spiking units, with structured connectivity, in which multiple spatio-temporal patterns are stored as dynamical attractors. We introduce an order parameter, which measures the overlap (similarity) between the activity of the network and the stored patterns.We find that, depending on the excitability of the network, different working regimes are possible. For high excitability, the dynamical attractors are stable, and a collective activity that replays one of the stored patterns emerges spontaneously, while for low excitability, no replay is induced. Between these two regimes, there is a critical region in which the dynamical attractors are unstable, and intermittent short replays are induced by noise. At the critical spiking threshold, the order parameter goes from zero to one, and its fluctuations are maximized, as expected for a phase transition (and as observed in recent experimental results in the brain). Notably, in this critical region, the avalanche size and duration distributions follow power laws. In conclusion, our simple model suggests that avalanche power laws in cortical spontaneous activity may be the effect of a network at the critical point between the replay and non-replay of spatio-temporal patterns (S Scarpetta, A de Candia PLOS ONE 8 2013).

Cerebellar theta burst stimulation dissociates memory components in eyeblink classical conditioning

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Abstract

The cerebellum plays a critical role in forming precisely timed sensory-motor associations. This process is thought to proceed through two learning phases, one leading to memory acquisition and the other leading more slowly to memory consolidation and saving. It has been proposed that fast acquisition occurs in the cerebellar cortex, while consolidation is dislocated into the deep cerebellar nuclei. However, it was not clear how these two components could be identified in eyeblink classical conditioning (EBCC) in humans, a paradigm commonly used to investigate associative learning. In14 subjects, we show that EBCC proceeds through a fast acquisition phase, returns toward basal levels during extinction and then is consolidated, as it becomes evident from he saving effect observed when re-testing the subjects after one week from initial training. The results were fitted using a two-state multi-rate learning model accounting for both memory acquisition and consolidation. In a subgroup of 7 subjects, transcranial magnetic stimulation was used to apply continuous theta-burst stimulation (cTBS) to the lateral cerebellum just after the first training session. After cTBS, consolidation was unaltered but the extinction process was significantly impaired. These data suggest that cTBS can dissociate EBCC extinction (related to the fast learning process) from consolidation (related to the slow learning process), probably by acting through a selective disruption of plasticity formation in the cerebellar cortex.

Organic Ultra-Thin Film Transistor with Liquid Gate for Extracellular Stimulation and Recording of Neural Networks

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Abstract

Electronic transducers of neuronal cellular activity are important devices in neuroscience and neurology. Organic field-effect transistors (OFETs) offer tailored surface chemistry, mechanical flexibility, and high sensitivity to electrostatic potential changes at device interfaces. These properties make them attractive for interfacing electronics to neural cells and performing extracellular recordings and stimulation of neuronal network activity. In this work we operate pentacene ultra-thin film (9 nm thick) transistors with a liquid gate both as transducer and electrical stimulator of neuronal network activity. These devices are highly sensitive to small potential changes in cell medium and exhibit sufficient stability in standard cell culture conditions for nine days. We show that murine neural stem cells can be adhered on top of functional devices with no need of an additional layer of cell-adhesive molecules, and then differentiated into neuronal networks. OFET response is monitored during the different phases of the neuronal differentiation process up to nine days. Only when stem cells are differentiated into neurons, it was possible to measure electrical signals in the OFET current following the stimulation. Due to the large sensing area of our device, which accommodates from hundreds to thousands interconnected neurons, the OFET electrical signals arise from the collective electrophysiological response of the neuronal population. The maximum extracellular potential change in the cleft region adjacent to the transistor surface amounts to 350 mV. This demonstrates that pentacene ultra-thin film OFETs enable good cellular adhesion and efficient coupling of the ionic currents at the biological-organic semiconductor interface with the OFET current.This work was funded by the EU 7th Framework Programme [FP7/2007-2013] under Grant Agreement No. 280772, Implantable Organic Nanoelectronics (iONE-FP7) project.[1] T. Cramer et al. Phys. Chem. Chem. Phys. 2013, 15, 3897-3905. [2] T. Cramer et al. J. Mater. Chem. B 2013, 1, 3728-3741.

Involvement of Peroxisome Proliferator-activated receptor β/δ (PPAR β/δ) in BDNF signalling during aging and in Alzheimer's Dise

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Abstract

Aging and many neurological disorders are linked to oxidative stress, which is considered as the common effector of the cascade of degenerative events. In this phenomenon, reactive oxygen species play a fundamental role in the oxidative decomposition of polyunsaturated fatty acids resulting in the formation of a complex mixture of aldehydic end-products, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and other alkenals. Interestingly, 4-HNE has been also indicated as an intracellular agonist of peroxisome proliferator-activated receptor β/δ. PPARs, which comprise isotypes α, β/δ and γ, are ligand-activated transcription factors playing important physiological and pathological roles in different tissues, including the nervous tissue, both during development and in the pathogenesis of various disorders. Even though PPARβ/δis the most abundant isotype in the developing and adult central nervous system, its role in neurodegenerative diseases remains unclear. We have previously demonstrated that PPARβ/δis crucial for neuronal maturation and that its expression affects the BDNF signaling pathway. Neurotrophins and their receptors are expressed in brain areas involved in plasticity (i.e. the hippocampus, cerebral cortex) and are considered the mediators of synaptic plasticity. The expression of BDNF and its receptors, the full-length catalytic receptor (TrkB-fl), the truncated isoform (TrkB-t), lacking intracellular tyrosine kinase activity, and the unselective low-affinity p75NGFR receptor has been described during normal brain aging and in Alzheimer's disease.The aim of the present work was to investigate the role of 4-HNE and PPAR β/δ in relation to BDNF signalling during AD progression and in physiological aging. To this purpose, we used the Tg2576 mouse model, as compared to its wild-type counterpart. Differently from other AD mouse models, this strain is characterized by a slowly progressive pathology, offering the opportunity to study even subtle age-dependent alterations. In the present study we focussed on the neocortex, which is more exposed to ROS, compared to other brain regions, owing to its high aerobic metabolism and content in PUFAs and redox-active transition metals. To this purpose, we examined at early and advanced AD stages (3, 9, and 18 months) the pattern of 4-HNE and its catabolic enzyme glutathione S-transferase P1 (GSTP1), in relation to the expression of PPARβ/δ, BDNF and its receptors, as mRNA and protein, as well as on their pathological forms (i.e, precursors or truncated forms).The data obtained indicate a detrimental age-dependent role of PPARβ/δin AD by increasing pro-BDNF and decreasing BDNF/TrkB survival pathway, thus suggesting that a specific PPARβ/δ antagonist may be used to counteract the disease progression.

Novel Microstrip Radio Frequency Coils Technology for Ultra High Field Magnetic Resonance Imaging of the Human Brain

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Abstract

Ultra-High-Field (7-9.4T) human Magnetic Resonance Imaging (MRI) scanners have been developed in the past decade to improve signal to noise ratio and spatial/spectral resolution. It is expected that the increased spatial/spectral resolution obtainable with UHF MRI will provide clinically relevant information in imaging the human brain [1], specifically in the case of neurodegenerative diseases such as Alzheimer, Parkinson [2-3].In the past decade our group has developed a range of novel RF coils specially designed for UHF MRI [4-13]. In this work we report the design, simulation and workbench testing of a novel proton RF surface coil made with microstrip technology suitable for brain/neck MRI applications at 7 T. To optimize the penetration depth of the RF field within the brain/neck a range of geometrical designs were simulated using a numerical EM model. References:[1] Amunts K, et al., Science 340:1472-1475 (2013).[2] Kilsdonk ID, et al, J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp-2013-305601 (2013).[3] Florio T, et al, Behavioural Brain Research 250:326-333 (2013).[4] Alecci M, et al, Magn Reson Med 46:379-385 (2001).[5] Alecci M, et al, Magn Reson Med 48:404-407 (2002).[6] Alecci M, et al, Magn Reson Med 49:363-370 (2003).[7] Alfonsetti M, et al, Meas Sci Technol 17:N53-N59 (2006)[8] Alecci M, et al, Italian Patent RM2007A000585 (2007).[9] Alfonsetti M, et al, Measurement 43:1503–1515 (2010).[10] Vitacolonna A, et al, Italian Patent RM2011A000266, 30 maggio (2011).[11] Vitacolonna A, et al, PCT/IT2012/000159 (2012).[12] Stara R, et al, Progress in Electromagnetics Research M 29:121-136 (2013).[13] Vitacolonna A, et al, Brevetto USA N. 14/115,676, 05 novembre (2013).

Brain-inspired Sensorimotor Robotic Platform: Learning in Cerebellum-driven Movement Tasks through a Cerebellar Realistic Model

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Abstract

Biologically inspired neural mechanisms, coupling internal models and adaptive modules, can be an effective way of constructing a control system that exhibits human-like behavior. A brain-inspired controller has been developed, embedding a cerebellum-like adaptive module based on neurophysiological plasticity mechanisms, in the framework of the EU project REALNET (REAListic real-time NETworks and computation dynamics in the cerebellum).The controller drives in real-time an ad-hoc developed neurorobot, integrating a 3 degrees of freedom serial robotic arm with a motion tracking system. The learning skills have been tried out designing open-loop and closed-loop sensorimotor experimental paradigms: eye blinking classical conditioning (EBCC), which is a stimuli temporal associative task, vestibulo-ocular reflex (VOR) and upper limb multi-joint reaching under external perturbations.The cerebellar model was firstly embedded into the controller in an analog version then in a more realistic spiking version, thus including also encoding and decoding biologically-plausible computations in order to read-out information from the time-dependent spike patterns.The Mossy Fibers receive information related to the actual state of the system, such as the Conditioned Stimulus (CS) for the EBCC, the vestibular signal for the VOR and the desired angular trajectory of the perturbed joint for the reaching. The Inferior Olive carries information related to a sort of "attention" or "error" of the system, which correspond to the Unconditioned Stimulus (US) for the EBCC, the retinal error for the VOR and the angular error for the reaching. The output of the cerebellar module (Deep Cerebellar Nuclei) elicits the Conditioned Response (CR) for the EBCC, generates an eye compensation movement for the VOR and counterbalances the trajectory deviation on the joint perturbed by the force field during reaching task, all in a predictive way thanks to the plasticity occurring along repetitions of each task. The achieved learning behavior was comparable to the human one.In conclusion, the robotic platform with its brain-inspired controller is able to reproduce the human behavior when dealing with different cerebellum-driven tasks and it could be considered a generalized and realistic cerebellar model of learning able to operate in real-time dynamic environments.Acknowledgments. This work was supported by grant of European Union REALNET FP7-ICT270434.

AN EXPERIMENTAL PLATFORM FOR PROLONGED ELECTROPHYSIOLOGICAL INVESTIGATIONS OF NEURONAL CULTURES

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Abstract

The elucidation of physio-pathological mechanisms expressed by a neuronal network throughout an extended time scale is the goal of many neurophysiological and neuropharmacological in vitro studies. Microelectrode Arrays (MEAs) represent a powerful and widespread technology to perform non-invasive, repeated electrophysiological recordings from neuronal cultures in a large variety of applications. Nowadays, standard MEA-based experimental platforms provide well-established setups for several neurobiological applications where short recordings (i.e., from 10 minutes to a couple of hours) are adequate to gather the information of interest. Nevertheless, the possibility to perform longer, continuous investigations of neuronal activity with MEAs helps to throw light on long-term network mechanisms (e.g. long-term plasticity). In this context, a technological requirement is the establishment of an experimental setup able to maintain the cultures under controlled environmental conditions, in order to design truly significant experiments and collect reliable data from prolonged recordings with MEAs. Accordingly, our group has been developing a climate controlled bench-top chamber which merges an effective environmental control and MEA recordings capability, eliminating environmental fluctuations during recordings. By connecting the chamber to environmental control systems (temperature, relative humidity) and multichannel electronic equipment, it is possible to reproduce a physiological environment and gather MEA data over extended periods. The work presented here regards (i) the design and quantitative environmental characterization of the environmental chamber (ii) the design and validation of a custom multichannel front-end for the readout of MEA signals and (iii) preliminary results regarding prolonged recordings with this platform.This system can collect multichannel data from neuronal cultures over long periods, providing an effective solution for long-term studies of neural activity.

Verso l'investigazione di un possibile ruolo funzionale di sorgenti endogene di rumore nell'attività cerebrale.

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Abstract

Il rumore, inteso come fluttuazione casuale di una grandezza fisica, è presente anche all'interno di sistemi neurali. Ne sono la prova sia, a livello del singolo neurone, la distribuzione quasi-Poissoniana di scarica nel caso di stimolo costante, sia, a livello di reti di neuroni, l'indeterminatezza intrinseca nei processi decisionali a risposta forzata ("tertium non datur"). Benché al rumore sia spesso associata una connotazione negativa, un suo ruolo vituoso, attraverso il meccanismo della risonanza stocastica, è stato dimostrato in esperimenti nei quali esso veniva generato esternamente ed "iniettato" nel sistema neurale mediante processi sensoriali.L'investigazione di "generatori di rumore" endogeni e di un loro possibile ruolo funzionale, ad esempio con patologie quali l'autismo o la sindrome ossessivo-compulsiva, costituisce invece un campo di ricerca pressoché inesplorato. Ciò è in gran parte dovuto alla difficoltà di misurare il rumore endogeno, in particolare utilizzando metodi non-invasivi. L'approccio perseguito nella nostra indagine è quello di utilizzare i tracciati EEG al fine di determinarne la componente di rumore stocastico. Tale determinazione è resa complicata dalla presenza nei tracciati di una componente caotica deterministica: se analizzate con tecniche di analisi convenzionali, le componenti stocastica e deterministica risultano infatti indistinguibili. Le due componenti possono essere separate analizzando le serie temporali mediante un'idonea tecnica di "embedding". Verrà illustrato un nuovo metodo di embedding e le sue potenzialità nell'ambito dell'analisi del rumore all'interno dei tracciati EEG.

Automated Hippocampus Segmentation with the Channeler Ant Model

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Abstract

The hippocampus, a central part of the limbic system, belongs to the medial temporal lobe and has a typical bulb-like shape, protruding into the lateral ventricles. Since its conditions are relevant for the diagnosis of many neurological pathologies and psychiatric disorders, the availability of reliable tools for a fully automated segmentation would effectively support the medical community and contribute to the assessment of several pathologies.Ant Colony-based models are powerful segmentation tools that are intrinsically not linear; their application to medical image processing is quite recent, although it already provided some promising results in the analysis of CT and PET scans.The present work discusses a fully automated method for the hippocampal segmentation based on an extension of the Channeler Ant Model: the pheromone deposition rule was modified so as to take into account the expected average shape of the object to be segmented.The results on several clinical datasets, corresponding to patients diagnosed with different diseases and obtained from the comparison to manual segmentations by different subjects and protocols, show an average Dice Index in the $0.71-0.79$ range, depending on the analysed dataset.

Computer-Assisted Detection in FLAIR and DT neuroimages: automatic segmentation and volume assessment of cerebral gliomas

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Abstract

Purpose: tumor cells in cerebral gliomas invade surrounding tissues preferentially along WM tracts, spreading beyond the abnormal area depicted on conventional MR images. Diffusion Tensor Imaging can reveal larger peritumoral abnormalities in gliomas that are not apparent on conventional MRI.We aimed at characterizing pathological vs healthy tissue in FLAIR and DTI datasets by 3D statistical Texture Analysis, developing an automatic segmentation technique for cerebral glioma, hereafter called GlioCAD, especially useful in patient follow-up during chemotherapy, and for preoperative assessment of tumor extension.Methods and materials: thirty-four patients with gliomas were selected. 3T axial 3D-FLAIR, axial 3D-T1w, and DTI (single-shot EPI sequence, b=1000 s/mm2, 32 gradient directions) were acquired. Isotropic and anisotropic maps (FA, MD, p and q) were calculated, and pathological ROIs were manually drawn. 3D texture features were calculated with a sliding window approach in the segmented ROIs and in the contralateral healthy tissue, for CAD-system training. The feature-space dimensionality was reduced by Linear Discriminant Analysis, which allowed tissue classification by simple thresholding.Results: For each map, tumor-classification sensitivity, specificity and ROC curves ($0.90 \leq AUC \leq 0.97$) were calculated, and manual and automatic segmentations were compared by the Jaccard Coefficient, showing good concordance. The CAD system automatically calculated lesion volumes and histograms.With the purpose of allowing remote fruition of GlioCAD, a Graphical User Interface was designed as a plugin for OsiriX, a well-known radiological viewer.Conclusion: GlioCAD is proposed as a new tool, based on statistical textural analysis, for the automatic segmentation and volume assessment of brain gliomas, and for the quantitative analysis of the histograms in the regions of interest.

Formaldehyde Fixation Progression of Whole Mouse Brain By Means of Magnetic Resonance Microscopy

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Abstract

Reference brains are useful tools in neuroscience, enabling integration of multimodal data into an anatomical atlas. Recently a three-dimensional model of a paraffin-embedded human brain, based on thousands of histological sections, was described [1]. Magnetic Resonance Imaging (MRI) of fixed brains has been used to accurately map a number of biophysical parameters such as proton density, relaxation times and diffusion coefficient [2]. Animal models (mice, rats) are widely adopted for basic neuroscience studies, and also to investigate a range of neurodegenerative diseases. Quite often such models require post-mortem MRI to relate the microscopic structure of the tissues with the pathological conditions [3]. However, very little data are available about the fixation process of whole mouse brains [4-7].We report about the use of high resolution MRI (T2 and ADC maps) to investigate the progression of whole mice brain formaldehyde fixation, comparing the immersion and perfusion methods with a non-fixed ex vivo whole brain. We show that the perfused cerebral tissue presents lower T2 and constant ADC values over time, indicating that the perfusion-fixation process is set with a preserved microstructure over time. A maturation process characterizes the infused-fixed tissue within the first hours of observation, and it should be taken into account for subsequent MRI and histological studies. Moreover, the data about the non-fixed whole brain should also be useful to estimate the effect of post-mortem intervals on the MR contrast.References:[1] Amunts K, et al, Science 340:1472-1475 (2013).[2] Tofts P. Quantitative MRI of the Brain, Wiley, 2004.[3] Eltoum I, et al, J Hystotech 24:173-190 (2001).[4] Yong-Hing CJ, et al, MRM 54:324-332 (2005).[5] Dawe RJ,et al, MRM 61:810-818 (2009)[6] Shepherd TM,et al, Neuroimage 44:820-826 (2009)[7] Florio TM,et al, ISMRM Workshop on Diffusion, Podstrana, pg 22 (2013).

Robust gray-level standardization in brain Magnetic-Resonance images

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Abstract

Purpose: it is known that intensities in MRI do not have a fixed tissue-specific numeric meaning, even within the same MRI protocol, for the same body region, or for images of the same patient obtained on the same scanner in different moments. Consequently many problems can arise in large multi-site clinical studies, making the interpretation of results difficult or confused, or affecting post processing phases such as segmentation and registration. In spite of the fact that the lack of a standard and quantifiable interpretation compromises the precision, accuracy, and efficiency of those applications, few papers have explicitly addressed the problems. In this context, we propose a tiSsue-Based Standardization Technique (SBST) of MR brain images.Methods and materials: the system was developed and tested on a large number of images, belonging to healthy people and to patients with different degrees of neurodegenerative pathology, obtained from public databases and the clinical practice. Both histogram and tissue-specific intensity information were used, performing piecewise linear intensity transformations between images, so sharing the simplicity and robustness of landmark techniques, while remaining fully automated and quite light from the computational point of view.Results: the efficacy in minimizing the risk of “mixing” brain tissues during intensity transformations was assessed, and particular attention was devoted to a thorough examination of the benefits comparing SBST with other approaches available in the literature.Conclusion: the technique proved robust in standardizing tissues, giving similar intensities to similar tissues, even across images coming from different sources.

MRI and Switching Ability in a Rat PD Model

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Abstract

The Basal Ganglia (BG) direct and indirect pathways are involved in the capability to perform a behaviourally appropriate response switching from competing alternatives. Parkinson's disease (PD) involves the disruption of striatal loop as a consequence of the degeneration of the dopaminergic nigro-striatal pathway. In saccadic switching ability tasks, PD patients showed an increased striatal activation depending on the dominant/automatic response to switch [1-2]. PD patients show signal increase on T2-weighted MR images, smudging of the hypointensity in the substantia nigra towards the red nucleus or signal loss when using inversion recovery MRI [3]. Additional MRI studies found that non-demented patients with PD had a significant rate of median/global brain volume loss, and these changes correlated with global measures of cognitive decline [4].Recently [5], we developed a cognitive-motor task to perform a behavioural evaluation of the ability to switch from an internally to an externally cued task, and vice versa. As a result, we found that the unilateral dopaminergic striatal depletion enhanced the switch-induced performance differences in favour of the externally guided performance. Dopamine depleted rats were impaired to produce an alternative motion when task switching required to change from an over trained behaviour, towards an alternative self-paced response. We made a comparison of behavioural, histological and high-resolution MRI data. We found a correspondence between visual evaluation of brain MRI scans, used as volumetric measurement in evaluating regional brain atrophy, and the histological section, showing a lesion localized in the striatum with an evident shrinkage of the whole striatum and an enlargement of the ipsilateral ventricle. [1] Cameron IG, et al. Eur J Neurosci. 2009;29(12):2413-25.[2] Cameron IG, et al. Neuropsychologia. 2010;48(7):1948-57.[3] Seppi K, Schocke MF. Curr Opin Neurol 2005;18:370—5.[4] Hu MT, et al. J Neural Transm. 2001;108(5):571-80.[5] Florio TM, et al. Behav Brain Res. 2013;250:326-33.

Stimolazione cerebrale profonda adattativa

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Abstract

La stimolazione cerebrale profonda (DBS) è un trattamento neurochirurgico consolidato per la malattia di Parkinson (MP). Tuttavia la DBS controlla solo parzialmente le fluttuazioni motorie e le variazioni rapide dei sintomi che si manifestano nella MP in fase avanzata e induce effetti collaterali. L'attuale terapia DBS utilizza una stimolazione costituita da un treno di impulsi elettrici ad ampiezza, frequenza e durata invariante nel tempo. L'effetto terapeutico della DBS potrebbe essere ottimizzato mediante una stimolazione adattativa (aDBS) in grado di adattarsi momento per momento allo stato clinico del paziente. Un dispositivo per aDBS è un sistema di controllo in grado di misurare e analizzare una variabile di controllo che riflette la condizione clinica del paziente e, conseguentemente, adattare i parametri di stimolazione.L'analisi dell'attività elettroencefalografica di profondità (biopotenziali) registrata attraverso gli elettrodi impiantati per la DBS direttamente nel nucleo subtalamico (STN) ha permesso negli ultimi 10 anni di studiare la patofisiologia della MP. Da questi è emerso che i biopotenziali sono correlati con lo stato clinico del paziente e modulati dal trattamento farmacologico e la DBS. I biopotenziali rappresentano quindi marker neurofisiologici dello stato clinico del paziente utilizzabili come variabili di controllo per lo sviluppo di sistemi adattativi.Il prototipo del dispositivo per la aDBS brevettato e sviluppato dal nostro centro (PCT/IB2006/002184) è un dispositivo esterno in grado di registrare i biopotenziali durante stimolazione e, grazie ad un sistema di controllo ad anello chiuso, modificare i parametri di stimolazione. Il prototipo dopo essere stato testato in vitro e dopo aver ottenuto i certificati di sicurezza (CEI 60601-1, CEI 60601-1-2) è ora sotto indagine clinica con approvazione ministeriale.L'architettura del dispositivo è stata ideata in modo da permettere prove cliniche flessibili ed ecologiche. In altre parole, si è sviluppato un dispositivo portatile che permetta al paziente di muoversi liberamente. Inoltre, grazie alla possibilità di interfacciarsi ad un programmatore esterno, la terapia è personalizzabile e parametrizzabile sul singolo paziente. I dati raccolti dal dispositivo possono essere trasferiti sul programmatore e infine su personal computer per la memorizzazione ed elaborazione offline. Il sistema così sviluppato permette di valutare contemporaneamente gli effetti clinici della terapia adattativa e la risposta elettrofisiologica delle strutture target neuronali, ponendo le basi per lo sviluppo di una tecnologia impiantabile per la stimolazione cerebrale profonda adattativa.

Organic electrochemical transistor fabricated on resorbable bioscaffold as transducer for bioelectrical signals

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Abstract

Electrical signals govern in large part the functionality of our human body. Interfacing them provides important means for medical diagnosis and therapy and is at the heart of modern electroceutical treatments.1 New generations of implantable electroceuticals have to be developed which combine the bioelectric medical activity with low invasiveness during device implantation, operation and removal.2 In our contribution we present an electrical transducer fabricated on a fully resorbable poly(L-lactic-co-glycolic) (PLGA) thin film. A simple fabrication process is established which allows patterning of active areas of the conducting polymer PEDOT:PSScontacted by gold electrodes on the bioscaffold. Fast and sensible potentiometric sensing of the conformable biodegradable and biocompatible device is demonstrated in physiologic solution. The recording of small bioelectronic signals is demonstrated by measuring cardiomyocytic activity. The electrocardiogram recorded with the device and the obtained signals are comparable to standard potentiometric measurements with Faradaic electrodes. The work paves the way towards simple bioelectronic interfaces processed on implantable bioscaffolds for recording and stimulation nervous tissue. In-vitro experiments for stimulation and sensing of neural cells is a planned activity. Cellular network morphology and electrical stimulation and response will be studied in the perspective of a non-invasive regeneration of injured nerve cord.

A multichannel medical device for brain imaging by time-domain fNIRS

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Abstract

Starting almost 30 years ago with the pioneering work of Jöbsis, non-invasive near-infrared spectroscopy (NIRS) has been used first to investigate brain oxygenation in neonates and adults, and later to assess muscle oxidative metabolism in pathophysiology. The development of compact and portable time-resolved multi-wavelengths multi-distance systems for clinical application would improve the effectiveness of functional brain studies. Recently, the authors reported on the development of a state-of-the-art multi-channel time-resolved tissue oximeter. The system operates with 2 wavelengths, 16 injection points and 16 independent collection points, and acquisition time down to 50 ms.In this work we focus on the development and characterization of an advanced version of this instrument tailored to the clinical use. In the design of the novel prototype we consider four main aspects: fulfillment of safety regulations, modularity of the instrument (i.e. the possibility to substitute an entire section of it without changing all the others), rejection of any electro-magnetic interference with a proper shielding and the possibility to use independently all the couple injection-detection channels with the realization of an independent equalization stage for all the detected signals.

A review of Parkinson's Disease animal model

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta.The current knowledge about the pathogenesis of PD is still limited, and the development of animal models is essential for better understanding the pathogenesis, the mechanism of cell death, and to evaluate therapeutic strategies for PD.Several animal models have been developed to mimic the key symptoms and the slow progression of the disease as accurately as possible. We review the main animal models categories of PD currently known (Toxin-based [1,2], Gene-based [2,3], Viral-based [4], Neuroinflammation-based [5], Multicellular organism-based [6]) with emphasis on their known strong and weak points. We also report the current PD animal models under study in our laboratory at the University of L'Aquila [7]." [1] Blandini F. and Armentero M.T. FEBS J. 2012; 279(7):1156-66.[2] Przedborski et al. J Biomed Biotechnol. 2012; 2012:845618.[3] Terzioglu M. and Galter D. FEBS J. 2008; 275(7):1384-91.[4] Low K. and Aebischer P. Neurobiol Dis. 2012; 48(2):189-201.[5] Liu M. and Bing G. Parkinsons Dis. 2011; 2011:327089.[6] Duty S. and Jenner P. Br J Pharmacol. 2011; 164(4):1357-91.[7] Florio TM, et al. Behav Brain Res. 2013; 250:326-33.

Ultrasensitive Magnetic Array for recording of Neuronal Activity (UMANA) Project

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Abstract

Neurotransmission is the most important mechanism through which neurons communicate thus generating all brain functions, from the simplest ones (reflexes) to the most complex ones such as cognition and behaviour. Understanding brain circuit mechanisms requires to bridge knowledge from single cell level up to large neuronal ensembles. This implies cross-connecting investigations at the cellular and circuiting level.The aim of the UMANA project is to develop an unconventional “magnetic” approach to nanotechnology-based platforms for the in-vitro investigation of neuronal functions, from single neuronal cell to network levels. In particular, strategies for micro-patterning hippocampal neurons will be developed to lay pre-designed neuronal networks onto suitable chips equipped with ultrasensitive magnetoresistive sensors for the detection of the magnetic field associated to synaptic potentials and to the action potentials propagation along neuritis. This platform will permit to combine single cell sensitivity and multiplexing capabilities. This “magnetic” method will be validated by comparison with the standard single-electrode technologies such as patch-clamp recordings, and with other Multi Electrode Arrays platforms.MMA will be used to record propagating spontaneous and evoked network activity in primary cultures of hippocampal neurons and in acute cortico-hippocampal brain slices at unprecedented spatial and temporal resolution, studying physiological and pathological responses of the network to distinct stimulation frequencies applied over different temporal windows.The conclusive goal of the UMANA project will be the use of this platform to characterize physiological and pathological network plasticity in wild-type mice (WT) and transgenic mice, model of human hereditary epilepsy.The proposed Multi Magnetic Sensor Array will literally image neuronal networks activity in cultured neurons and brain slices, through the recordings of extracellular magnetic field, similar to what is done in cell imaging. The ground-breaking nature of the proposed magnetic detection relies on the following advantages: (i) non-invasiveness and (ii) high spatial resolution and sensitivity, which hold promise for recording not only from a single neuron, but also from subcellular compartments.The UMANA project is funded by Cariplo Foundation and will start its activities in April 2014.

Looking for innovative solutions for ultra-high-field brain and body magnetic resonance imaging: the INFN-IMAGO7 collaboration

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Abstract

Investigative techniques based on Magnetic Resonance (MR) have a prominent role in the study of the brain and its function both in healthy and pathological conditions. The research in the MR field is moving towards higher and higher static magnetic field strengths. New diagnostic opportunities come together with many practical challenges.The IMAGO7 Foundation in Pisa constitutes the first Italian research center working on ultra-high-field (UHF) MR whole-body system for human applications operating at 7 Tesla. It is a consortium of partners (Stella Maris Scientific Institute, University of Pisa, Pisa general Hospital on behalf of Tuscany Region government, MEDEA Scientific Institute, Meyer Children Hospital) with research interests in neuroscience.The Istituto Nazionale di Fisica Nucleare (INFN) joins this interdisciplinary research field by collaborating with the IMAGO7 to find appropriate technical solutions to open issues in UHF MR, e.g. signal intensity inhomogeneity and excess in radio-frequency (RF) power deposition in tissues due to the inhomogeneous RF excitation delivered by traditional coil designs.In the attempt to optimize signal transmission and reception at 300 MHz, the design and development of suitable RF coils for specific preclinical/clinical applications is in progress, accounting for the potential hazard due to the interaction between the RF field and the biological tissues. Interesting coil prototypes have already been realized to enable translational studies at 7T and to detect nuclei other than proton (e.g. 31P) in human brain and body applications, whereas appropriate solutions are under investigation to optimize imaging and spectroscopy of particular body districts of great interest in clinical research.

Mathematical Methods for Neurophysiology

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Abstract

In this poster we describe the research activity of the MIDA group (http://mida.dima.unige.it) in the field of neuroimaging and neuroscience.Stochastic Resonance in the Visual System. Stochastic Resonance is a well known model that explains how the presence of noise may help to detect a sub-threshold signal. We investigated whether such phenomenon occurs in the human visual system, by presenting healthy subjects with sub-threshold noisy images of short words, and recording the magnetophysiological responses. We modelled neural responses with current dipoles and studied how dipole strength and latency change with the noise level.Rapid Visual Categorization. We investigate the brain activity elicited in a rapid categorization task. Subjects were asked to categorize images of animals VS non-animals quickly. Half trials were followed by a dynamic noise mask, to block feedback effects. We used MEG to record the magnetic neural activity, and applied both distributed and dipolar source models for localizing in space and time the corresponding sources.EcoG. We addressed the source modelling when the measurements are obtained by subdural strip and grid electrodes. First the lead-field matrix was created using a new function provided by the OpenMEEG software. Then we studied the ill-conditioning of this matrix varying both shape and location of the electrodes' grid positions. Finally we performed the source localization by applying a beamformer to both synthetic data and experimental ElectroCorticoGraphy data.Dynamic Imaging of Dipolar Sources. We developed a novel approach for estimating multiple current dipoles from a time series of M/EEG data. The method assumes that an unknown, time-varying number of sources is active at any time; using a Bayesian model and a sequential Monte Carlo approach, it provides dynamic estimates of the number of sources and of the dipole parameters.Static Imaging of Dipolar Sources. We developed a novel approach for estimating multiple current dipoles from a single topography in M/EEG. A "topography" may be obtained as a single time point, an average over a time window, a single frequency of the Fourier-transformed data , or a single ICA component. The method estimates at the same time the number of dipoles and the dipole parameters.Cortical Constraints. We study the effect of using source orientation constraints in inverse methods in MEG, either when the data fullfill the constraint and when they do not.

Finding Fuzzy Biological and Ecological Aggregations in Spectral Space

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Abstract

In network science, aggregation discovery refers to identifying entities characterized by dense interaction together and few interactions with the rest of the network. Genes, proteins and metabolites as well as individuals in ecological environments show a strong tendency to interact together and form aggregations under certain circumstances. Such relationships play a role in various processes and phenomena in our life, e.g., a subtle biological change may cause disease, such as cancers, or animals death due to ecological instability. Inferring relevant communities can help in revealing the functionality and the relevance of specific macromolecular assemblies or even in discovering possible proteins affecting a specific biological process and hence may aid in drug discovery. Existing community detection methods differ in their stability and accuracy when applied on data living in complex manifolds. In this poster we present the Fuzzy Spectral Modularity (FSM) approach, based on spectral clustering and considering possible fuzziness and sparsity, we applied to discover protein aggregations in Saccharomyces cerevisiae protein-protein interaction network and to infer communities in the dolphin ecological benchmark.

Realistic modeling of cerebellar Unipolar Brush Cell intrinsic excitability

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Abstract

Unipolar brush cells (UBCs) are excitatory glutamatergic interneurons of the cerebellar granular layer receiving both primary and secondary vestibular inputs through mossy fibers (excitatory input) and Golgi cell axon (inhibitory input). When injected with progressively increasing depolarizing currents from a negative membrane potential, the UBC generates a burst sustained by a calcium spike and then a protracted discharge with shorter latency and spike frequency adaptation. The intrinsic excitability of UBCs is determined by an H current and by Low Voltage activated and High Voltage activated calcium currents. Fast inactivating T-type Calcium channels generate low-threshold spikes and L-type Calcium channel sustain tonic firing. The H current (activated between -60mV and -80mV) produces a slow hyperpolarization characterized by a "sag" in response to a hyperpolarizing step and an afterhyperpolarization at the end of a depolarizing step. Here we present a biologically realistic multi-compartmental mathematical model of the UBC realized with the NEURON simulator. According to literature, ionic channels are distributed among compartments (soma, dendrite, initial segmant and axon). The model can reproduce the excitable properties of UBCs in current-clamp and voltage-clamp modes. The response to mossy fiber inputs was reproduced using synaptic models of AMPA and NMDA synaptic receptors. The model is also capable of reproducing the late onset response recently reported for this cellular type by exploiting the interaction between cAMP, TRPC, and H current. This model, in addition to confirm the primary role of the aforementioned currents in UBC's electroresponsiveness, will prove a valuable tool for investigating the UBC's function in the cerebellar network.

An optical neuro-monitor of cerebral oxygen metabolism and blood flow for neonatology

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Abstract

The BabyLux project aims to provide a precise, accurate and robust integrated system to continuously monitoring cerebral oxygen metabolism and blood flow in critically ill newborn babies. Over the last two decades, the percentage of preterm births in the Western hemisphere rose by 20%. During early stages of brain development, injury from lack of blood flow and oxygen delivery may induce cognitive and physical handicaps. In fact, preterm births now account for a significant portion of children with cerebral palsy and cognitive, visual, and hearing impairments. A non-invasive, continuous, cot-side monitor of cerebral oxygen metabolism and blood flow is an unfilled niche in clinical care. The project takes up complete R&D works and extends already tested prototypes to the level of demonstrator, bridging the gap between research products and commercialization. The system uses photonic technologies (diffuse correlation spectroscopy, DCS, and time resolved near-infrared spectroscopy, TRS) to non-invasively and safely measure cerebral oxygen metabolism and blood flow. This innovative combination provides the state-of-the-art in accuracy and robustness in TRS, and introduces, for the first time, DCS in a combined instrument. The instrument will first undergo a demonstration phase in laboratory settings and later an operational phase in real-life settings, conducted in parallel in two public hospitals of two different countries. The advantages of the proposed system will be evaluated by professional end-users during validation tests carried out in conditions fitting in the clinical workflow, protocols and procedures. Dissemination and exploitation activities will promote accelerated acceptance and wider deployment of the proposed biophotonic solution. The BabyLux consortium gathers service content providers (physicists and engineers for biophotonic applications), professional end-users (neonatologists), and SMEs (photonic components producer, medical device manufacturer).