Short Title:

Anonymous Data Sharing for Small Bowel MRI

Full Title:

Data sharing with collaborative partners to develop Computer aided detection for the assessment of the small bowel using MRI.

Prof. Stuart Taylor (Chief investigator) [1, 2]

Dr Alex Menys [1,3]

Dr David Atkinson [1,2]

Prof Dean Barratt [4]

Dr Shankar Kumar [2]

Dr Tom Watson [6]

Dr Ruaridh Gollifer [1,2]

Dr Heather Fitzke [1,2]

Dr Jennifer Steeden [6,7]

Dr Stuart Bloom [5]

Dr Anton Emmanuel [5]

[1] Centre for Medical Imaging, University College London, 2nd floor Charles Bell House, 43-45 Foley Street, London W1W 7TY
[2] Imaging Division, University College London Hospital, 3rd Floor East, 250 Euston Road
[3] Motilent Ltd, 69 Wilson St, London, EC2A 2BB
[4] Centre for Medical Imaging Computing, University College London, 90 High Holborn, London, WC1V 6LJ & Charles Bell House, 43-45 Foley Street, London W1W 7TY
[5] Department of Gastroenterology, University College London Hospital, 235 Euston Road, NW1 2BU
[6] Great Ormond Street Children's Hospital, Great Ormond Street, London WC1N 3JH
[7] Great Ormond Street Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH

Chief Investigator contact Dr Stuart Taylor, University College London, 2nd floor Charles Bell House, 43-45 Foley Street, London W1W 7TY Tel 07960 169 321. Email stuart.taylor1@nhs.net

Table of Contents

Definitions

Personal Data: any information relating to an identified or identifiable living individual;

Pseudonymised personal data means:

> *'...**personal data** [that] can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the **personal data** are not attributed to an identified or identifiable natural person'*
> [GDPR, Article 4]

Anonymised data: data which does not relate to an identified or identifiable natural person or personal data that has been rendered anonymous in such a manner that the data subject is not or no longer identifiable.

Data Protection Legislation: all applicable laws and regulations relating to the Processing of Personal Data as the same may be in force from time to time. Including, the Data Protection Act 2018 (DPA) and the General Data Protection Regulation (GDPR).

Data Controller: a person which, alone or jointly with others, determines the purposes and means of the Processing of Personal Data.

Overview

This document describes the protocol for the sharing of anonymised MRI and ultrasound small bowel datasets and associated fully anonymised clinical results with collaborators at UCL Centre for Medical Imaging (CMI) as part of parallel projects to develop computer software to quantify diseases of the small bowel using MRI.

Background

The department of Radiology at UCLH (along with many centres around the UK) has been running a clinical small bowel MRI service since 2005 and have several thousand datasets on its PACS along with a similar number of ultrasound datasets for patients often suspected of having Inflammatory Bowel Disease or other bowel disorders**.** The department of academic Radiology at UCLH has forged academic collaboration with several partners both at UCL and abroad to develop computer software to analyse these Imaging datasets, extracting quantitative information on bowel morphology and function. This document describes the process of anonymous data sharing with these collaborative partners.

Justification for the research

A growing number of diseases are being referred for assessment with Magnetic Resonance Enterography and/or enteric ultrasound including Crohn's disease, constipation, dyspepsia, dysmotility disorders, Irritable Bowel syndrome and a range of neuropathic conditions with gastrointestinal involvement.

By far the best characterised and most commonly referred condition that we routinely investigate is Crohn's disease precipitated by an abnormal immunological response within the bowel wall leading to abnormal wall thickening, stricturing (narrowing), fistulation to adjacent organs and structures, abnormal motility and local sepsis. The incidence is around 10 in 100,000 and in the UK for example there are 6000 new diagnoses of inflammatory bowel disease annually. Crohn's patients experience times of disease quiescence punctuated by acute flares in inflammatory activity requiring medical intervention. Radiological imaging of the small bowel defines diagnosis, disease extent, biological activity and complications and is vital for timely and efficacious clinical management. Several tests can image the small bowel but the conventional tests of barium follow-through and Computerised Tomography impart a significant radiation dose which is concerning since Crohn's disease patients are relatively young and require repeated imaging over several years. The newer technology of small bowel MRI which does not impart ionising radiation is proving to be a safe, well tolerated and robust method of assessing the small bowel and is widely implemented in the UK and Europe. The use of ultrasound is complementary especially where focal disease has been localised with MRI and, like MRI, does not carry a radiation dose for the patient.

MRI evaluates multiple disease related parameters including bowel wall thickness and signal return, contrast enhancement and pattern and bowel motility and is proving increasing reliable for disease

identification, staging, therapeutic guidance and assessment of treatment response.[1, 2] Currently there are no tools that combine these parameters to provide robust and user friendly quantitative prediction of disease activity which severely limits uptake of this powerful tool in clinical practice. We propose to develop computer software to optimise and reliably quantify the information afforded by MRI, for the detection and staging of small bowel pathologies such as Crohn's disease. We aim to provide tools for faster, safer, more accurate patient assessment and these may also aid in the understanding of disease aetiology.

Importantly, MRI is now being clinically used at ULCH and other hospitals to explore gastrointestinal dysfunction (e.g. for abdominal pain, bloating and nausea). MRI in the use of CD is now well disseminated and great strides have been taken to objectively evaluate this data. In other conditions e.g. constipation and dyspepsia, diagnostic techniques are still lacking in clinical practice and automated methods, similar to those developed in CD would be highly advantageous. Furthermore, many observations made using MRI, for example the inverse relationship between motility and inflammatory activity, might be translated across to other imaging methods like ultrasound where dynamic imaging of the bowel structure and movement is easily performed and recorded. Using existing datasets collected at UCLH and partner hospitals, we could generate robust and compelling pilot data in this area to attract funding and drive larger studies.

Clinical and patient demand

Crohn's Disease:

Treatment of Crohn's disease is divided into medical therapy or surgical intervention. In general biologically active disease is treated by medical therapy whilst surgery is undertaken in those with symptomatic "burnt out" fibrotic disease or in those who fail to adequately respond to medical therapy. Correct identification of these patients is the crux of optimum clinical management. Medical therapy is based largely on immunosuppressive medication. Although relatively effective, these drugs are expensive and not without significant side effects, some of them life threatening, notably sepsis secondary to immunosuppression, and malignancy. Rational use of immunosuppressive therapies in Crohn's disease therefore is reliant on accurate identification of those patients with acute inflammation –so called "active disease" who are most likely to respond to the treatment. Unfortunately there is currently no reliable method to identify such patients. Clinical assessments based on patient symptoms, such as the Crohn's disease activity index (CDAI), are relatively subjective, resource intensive (patient symptom data is collected for a whole week) and patients with inactive disease (such as those with chronic fibrotic strictures) often attract high scores. Biochemical markers such as ESR and CRP are useful adjuncts but again do not in themselves always differentiate reliably between active and chronic disease. Nevertheless, such imperfect standards of reference are the mainstay of both clinical and drug trial assessment of disease activity.

MRI has the ability to non-invasively assess disease extent and activity. Specifically several parameters including wall thickness, T2 signal, contrast enhancement and enhancement pattern have all been linked to disease activity. Indeed our group has provided some of the most robust data to date.[3] Furthermore, Crohn's afflicted bowel shows abnormal motility (peristalsis). One major advantage of MRI is its ability to acquire real time "cine" style imaging based on multiple image acquisitions at a

fixed anatomical point, enabling visualisation of motility.[4] To date, assessment using MRI largely relies on subjective assessment by the reporting radiologists with poor inter and intra-observer agreement.[5] Extraction of quantitative information is very time consuming with little in the way of software automation, and thus is essentially limited to the research arena only. Enteric US is now increasingly used in the same way as MRI, providing information on bowel structure and function.[6, 7]

We have consulted widely amongst user groups for our proposal including clinical and academic gastroenterologists (locally, and via the British society of Gastroenterology and European Crohn's and colitis organisation [ECCO]), surgeons, clinical radiologists (locally and via the British Society of Gastrointestinal and Abdominal Radiology), Industry (Philips Medical Systems) and patient groups (patient forum of the national association of Crohn's and colitis). **We have identified a strong clinical need for a tool to reliably define the extent of Crohn's disease, evaluate biological activity and facilitate safe and non-invasive assessment of therapeutic response**. Several validated indices of disease activity are now available for the assessment of Crohn's disease,[8-11] but they are still too time consuming to use clinically.

Functional gastrointestinal disease:

A growing clinical demand exists for diagnostic tests in functional gut disorders. Up to 20% of the population may be classified as having irritable bowel syndrome (IBS) and as much as 50% of the gastroenterology workload presents with functional or unexplainable symptoms. This is 1) unsatisfactory for patients, 2) unsatisfactory for the clinician and 3) inefficient for the healthcare provider who invariably must request various tests. Based on recent developments in CD with CAD it is possible to extract a great deal more data from MRI scans of these patients. As MR has become more routine at UCLH, and many other hospitals we have seen an increase in 'MR Physiology' scans requested by clinical teams (a 20min MRI consisting of motility, anatomical and diffusion imaging) with no IV contrast. Since 2014, around 800 of these scans have been performed in mainly non-Crohn's subjects, and development of quantitative technology to better evaluate functional bowel disease would be advantageous.

Clinical Impact

Development of this robust computer aided diagnosis (CAD) system for assessing Crohn's and other gastrointestinal disease extent and activity using medical imaging will have many meaningful impacts, the most important of which are:

- Provide a diagnostic aid to radiologist, increasing accuracy and workflow efficiency.

- Provide quantitative data on disease activity, facilitating use in clinical triage of patients, assessment of therapeutic response and use as a biomarker, or surrogate endpoint, in clinical trials of therapeutic agents.

- Form the basis of software solutions applicable to other disease states such as disorders of gut motility including constipation, dyspepsia, post-surgical ileus, autonomic dysfunction, food intolerance and delayed gastric emptying.

- Strengthen the role of MRI as a safe, well tolerated and effective method of assessing small bowel Crohn's disease, obviating some of the need for invasive and potentially dangerous endoscopic procedures

- Provide Insight into the mechanism of complex conditions using MRI that might be translated to other modalities like US, meaning greater availability for patients and potential cost savings for healthcare providers.

- Through adding new collaborating sites (for example Great Ormond Street Hospital) observations made in adults might be replicated in children where the need for non-invasive, objective tests of gastrointestinal dysfunction are needed.

Summary of Proposed Technology and Development plan

We have forged academic collaborative partnerships with

- The Centre for Medical Imaging (CMI) and several European Countries with whom we have ongoing collaborative arrangements (Department of Radiology, AMC, Netherlands) << ONGOING >>

- European centres in a recently awarded European FP7 grant award to develop this software << THIS PROJECT WAS COMPLETED IN JANUARY 2015 >>

No	Name	Short name	Country
1	TECHNISCHE UNIVERSITEIT DELFT	TU Delft	Netherlands
2	UNIVERSITY COLLEGE LONDON	UCL	United Kingdom
3	Eidgenössische Technische Hochschule Zürich	ETH Zurich	Switzerland
4	Konrad-Zuse-Zentrum für Informationstechnik Berlin	ZIB	Germany
5	BIOTRONICS 3D LTD	B3D	United Kingdom
6	Academisch Medisch Centrum bij de Universiteit van Amsterdam	AMC	Netherlands
7	VODERA LIMITED	VODERA	United Kingdom

Full details of the developmental protocols with these partners are provided in Appendix 1 (CMI); Appendix 2 (FP7 partners)

In brief, the aims are too develop computer software to extract the bowel from the MRI dataset, measure various relevant parameters such as wall thickening, signal etc which reflect disease activity, create models of those parameters which best reflect disease activity and then validate these models against current clinical standards of reference (notably blood markers of inflammation such as CRP, endoscopic scores of disease activity, biopsy scores of disease activity and clinical questionnaire scoring system such as the Crohn's disease activity index. We also developed accurate quantification of small bowel motility[12-18] which may have clinical uses in other disease states, notably autonomic dysfunction and ileus.

Data Collection and Management

This standard operating procedure (SOP) applies to all NHS hospitals sharing data. Presently this is

i) UCLH
ii) Great Ormond Street Hospital, London

Each site will give permission for data sharing as per this SOP via their usual regulatory/ data protection, research and development pathways and will appoint a local PI who will have responsibility for its implementation

The development of the software will require access to imaging datasets with concurrent clinical reference standards of disease activity such as endoscopy findings, histology results, blood tests and patient symptom questionnaires.

Anonymised datasets acquired as part of an ethically approved research project 'RESEARCH DATASETS':

We have two ongoing ethically approved UCLH studies investigating the use of MRI in small bowel Crohn's disease and comparison with clinical standards of reference, notably endoscopic biopsy, blood test data and clinical symptom diaries. As part of these projects, patients agree to their anonymised data to be used for future work.

Ethics ref: 05/Q0502/124
Enteric and extra-enteric MRI manifestations of small bowel Crohn's disease: qualitative and quantitative histopathological correlation and assessment of disease activity with reference to surgical resection specimens

Ethics ref: 09/H0714/62 (committee A) Defining the role of MRI as a marker of Crohn's disease activity-Prospective Comparison to a clinical reference standard

Ethical approval has been granted for both retrospective and prospective data sharing with our collaborators.

<< THESE TWO PROJECTS COMPLETED IN JANUARY 2016 >>

A third multisite study, METRIC (MR Enterography or ulTRasound In Crohn's disease): Diagnostic accuracy for the extent and activity of newly diagnosed and relapsed Crohn's disease: a multi-center prospective comparison of magnetic resonance enterography and small bowel ultrasound compared to a reference standard in those aged 16 and over, was completed in 2018. Funding and ethical permission has been received for an extended follow-up of a subset of METRIC patients (METRIC-EF), which is currently ongoing. Patients give permission for use of their anonymised data and imaging for future research (METRIC REC Ref: 13/SC/0394; METRIC-EF REC Ref: 18/LO/1930).

A fourth multisite study, MOTILITY (Small bowel motility quantified by cine MRI as a predictor of long-term response in patients with Crohn's disease commencing biological therapy; REC Ref: 17/WM/0106) is also ongoing. Patients aged 16 and over commencing biological therapy are scanned at week 0 (baseline); 20-28 weeks (short term) and 1-year (long term) post-treatment. These patients can give permission to use of their anonymised data and imaging for future research at the time of consent.

A fifth single site study, SB motility (Post-hoc analysis of dynamic magnetic resonance sequences to establish descriptive metrics for small bowel motility in vivo; REC Ref 11/LO/1634) is also ongoing at UCLH. Healthy participants and patients with a condition where dysmotility is postulated are scanned at one or more time-points to assess changes over time (e.g. following drug infusions, food ingestion or treatment). These participants can give permission to use of their anonymised data and imaging for future research at the time of consent.

Anonymised datasets acquired as part of clinical practice 'CLINICAL DATASETS':

Many patients undergoing small bowel MRI or USS at UCH and other collaborating hospitals often also undergo additional tests as part of their usual clinical care which are recognised as good standards of reference against which we can validate our imaging findings. Notable examples are blood tests (eg. CRP), endoscopy and biopsy, and symptom questionnaires. Furthermore, many patients have normal examinations and these datasets are also very useful in software development to define a standard of normality. Suitable datasets will be found as follows:

- Search of the PACS database to identify all small bowel examinations performed at collaborating hospitals

- Use clinical sources freely available to hospital clinical staff via the CDR web system at collaborating hospitals to triage these patients into relevant clinical groups notably those who have normal small bowel examinations, and those with abnormal studies who have a relevant clinical standard of reference performed within 6-12 weeks (CRP level, endoscopy, biopsy, questionnaire)

- Select a sample of relevant datasets for use in software development. The total number to be data shared with the FP7 consortium listed above will not exceed 75 (<< THIS DATA SHARING PROJECT IS NOW COMPLETED>>). The total number of datasets to be data shared with UCL will not exceed 1,500 across collaborating hospital sites. The larger number shared with UCL reflects their need for a large database of normal examinations to train and test new algorithms and assess changes in imaging parameters over time.

Handling of datasets

- RESEARCH DATASETS: Only staff on the delegation log for the original research project will have access to any psudeo-anonymised datasets acquired as part of that research. This is consistent with ICH Good Clinical Practice and local Research Governance procedures.

- CLINICAL DATASETS: Only staff with full or honorary contracts and part of the clinical team at collaborating hospitals will have access to the clinical data and un-anonymised datasets. This is consistent with the situation presently as such staff already can access both the PACS and hospital CDR as part of their usual clinical practice.

- A full list of staff employed in preparing the datasets (and 2 page summary CV) will be kept for internal/external inspection. Only staff meeting the above criteria and approved by the chief investigator (Prof Stuart Taylor), will be permitted to prepare the datasets. At collaborating hospitals, the local PI will give approval

- All chosen datasets will be fully anonymised before transfer using the anonymisation protocol approved by the data controller (i.e. research Sponsor or collaborating hospital) before any analysis or research is performed. No identifiable data (hospital number, DOB, name) will be left visible on the datasets.

- Regions of interest will be placed on the datasets (for example areas of wall thickening) but no further clinical evaluation of the datasets will be undertaken.

- Each dataset will be given a unique identification number (UID). The key to this number will be stored temporarily on a separate standalone password protected Trust computer while the relevant clinical data is collated by a member of the clinical team. This key linking the UID to the pseudo-anonymised (RESEARCH DATA) OR un-anonymised (CLINICAL DATA) held on the Trust system will be **deleted** before the data is transferred. This process will be performed according to Information Commissioners Office guidance in such a manner that the data subject is not or no longer identifiable. For example, through utilisation of hashing or salting; processing data in batches to preserve k-anonymity and re-coding continuous outcomes as binary or categorical such that the subject cannot be identified by a combination of variables.

- The chief investigator will personally approve any researchers who are permitted controlled access to identifiable data (including pseudo-anonymised data). All such staff will hold full or honorary contracts with the research Sponsor organisation or hospital site. Identifiable (including pseudo-anonymised) patient data will never leave the research Sponsor organisation or hospital site. This system is compliant with General Data Protection Regulations and local Research Governance procedures. Local collaborating hospitals will provide similarly secure arrangements for storage of their shared datasets. Data transferred to UCLH from collaborating hospitals will comply with NHS data protection regulations, for example the use of secure NHS email (see below).

- Selected fully anonymised datasets will be stored on a password protected hard drive for transportation from collaborating hospitals. The chief investigator and local PI will approve those staff who will have access to the password. The password will only be released via secure email systems (ie NHS.net email systems) and never physically kept with the hard drive. If possible, secure PACS IEP systems can also be used to transfer the scan data to UCLH for analysis.

- Transposition of MRI datasets on the hard drive will only be via manual hand over or courier services. Standard postal services will not be used

- Correlative clinical data acquired as part of routine clinical practice (notably blood test results, endoscopic findings, questionnaires, histology data) will be collated where relevant. This data will be fully anonymised by collaborators at the donating hospital (members of the clinical team) and thereafter identified to researchers only by the unique study number assigned to each MRI dataset. Relevant data will have been collected within 12 months of the small bowel MRI.

- The key to this number for UCLH data will be kept on a separate standalone password protected UCLH computer in a locked office at UCH (250 Euston Road). Local collaborating hospitals will provide similarly secure arrangements for storage of the key for their clinical data. Of note, a different password will be used than that for the MRI datasets to additional security. The chief investigator or local site PI will personally approve any local researchers who have controlled access. All such staff will hold full or honorary contracts at the donating hospital and be part of the clinical team. This system is compliant with data protection regulations. The source un-anonymised patient data will never leave the donating hospital

- Anonymised clinical data will be sent to collaborative partners via pass word protected datasheets using secured hospital (nhs.net) or university email systems only. The password will only be released by the chief investigator or designated researcher in a separate email, also using secure email systems

Data ownership and storage

- The datasets will remain the property of the donating hospital

- Datasets may be analysed with third party commercial algorithms to aid with research or validation. Examples would include Osirix, Horos and other imaging platforms or specific image analysis tools like GIQuant from Motilent. Under no circumstances will identifiable patient data be transferred to third parties for storage and all data will remain the property of the donating hospital.

- Where third party commercial algorithms that require use of online platforms are utilised - this will be performed with a specific agreement/contract to ensure that data ownership and storage obligations are met. Only fully anonymised datasets - that cannot be linked back to the original data subject - will be analysed online. Although use of fully anonymised data falls outside of the scope of GDPR – appropriate steps will be taken to limit access to data (e.g. platforms hosted on ISO 27100 compliant servers in the UK with end-to-end encryption, 2-way authentication and restricted access; ability to download data restricted by user access level which is reviewed in a regular basis.

- All data sharing (including any commercial aspects) has been agreed by Dr Susan Kerrsion in UCLH R&D. In particular a FP7 consortium agreement will be constructed to govern data sharing with the FP7 consortium. UCLH is formally listed as a subcontractor in the FP7 agreement << THIS PROJECT IS NOW COMPLETED>>

- As part of the FP7 agreement, all datasets supplied to collaborative partners will be subject to the same data protection rules as at UCLH. Notably anonymised electronic data will be stored on password protected computer. As noted above NO un-anonymised data will be released to any collaborator. The FP7 consortium has appointed an external expert (Prof. Andrea Laghi, Rome), who will ensure ethical standards are maintained at all times. In addition an external advisory committee has been developed (see Vigor protocol, Appendix 2) << THIS PROJECT IS NOW COMPLETED>>

- Both projects with CMI and the FP7 consortium (completed) are scheduled to run for 10 years. All shared data will be destroyed or returned to the donating hospital within 6 months of the projects finishing.

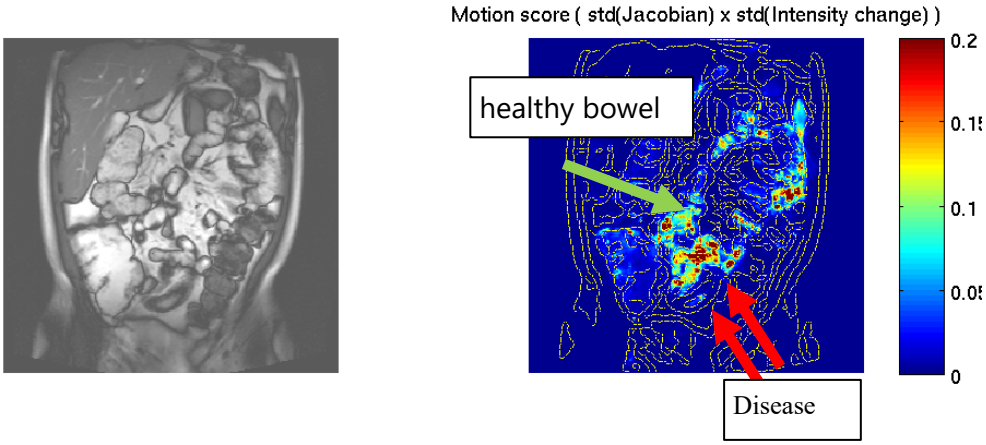
NOW COMPLETE
Appendix 1. - Protocol for software development by CMI, UCL

There are three main aspects to the computational work: data handling and visualisation, image processing to extract parameters including novel assessments of bowel motility, and a model to calculate the disease activity index from these image parameters.

The UCL/H Comprehensive Biomedical Research Centre (CBRC) is currently funding two software developers within the UCL Centre for Medical Image Computing (CMIC) to produce an Insight Toolkit (ITK) based viewing package. ITK is an open source platform supported by US Federal funds and widely accepted internationally [http://www.itk.org/]. The UCL package is initially intended for neurological imaging but will be extensible to other types of medical images. We will use this framework to develop the tools necessary for loading, viewing and aligning (registering) MR bowel images from a range of different MR sequences. A tool will be implemented within this framework to allow radiologists to select regions of interest that include the Crohn's affected area. Within these regions the bowel wall will be semi-automatically segmented on the different images. <<NOW COMPLETE>>

Using this bowel wall segmentation, image parameters will be calculated, these could include; bowel wall thickness, signal intensity on T2 weighted images, intensity changes following contrast injection (absolute values and curve shape), pattern of enhancement and motility. <<ONGOING>>

Motility in Crohn's and other disorders of the GI tract such as pseudo obstruction, coeliac disease and radiation enteritis is restricted compared to normally functioning bowel and can be visually observed when time series images are played as a 'cine'. Motility imaging combined with manual scoring has been shown to aid in Crohn's detection.[19] We aim to develop a new quantitative assessment of motility as part of our tool. We have used an EPSRC Platform grant to CMIC to pump prime pilot work in extracting motility information from MR cine images. The pilot method uses an adaptation of an optic flow registration algorithm to include intensity changes.[20] Intensity changes are included in an attempt to account for bowel through-plane motion. Our quantitative motility parameter includes both these intensity changes and the local change in volume derived from the registration motion field. Volume change was chosen because it should be insensitive to locally rigid displacements caused by respiratory motion. The figure below shows a single frame from a cine series (left) with the affected thickened bowel wall highlighted by a red arrow. In our pilot quantification map (right), the affected bowel wall appears blue indicating little motion (red arrow) compared to healthier regions showing normal motility (green arrow). This pilot work demonstrates that we can obtain quantitative motility information, though the optimum choice of parameters and their usage remains to be determined. Furthermore the method has been tried on two datasets so far.



The motility and other image-derived parameters need to be combined in the optimum way. We will use linear regression analysis to build a model that can predict disease activity. In the model training and validation, we will use measures of Crohn's activity derived from both the standard CDAI score, histopathological acute inflammatory scores from surgical resections and biopsies and biochemical measures. The application of the technique to other disorders of the small bowel such as dysmotilty syndromes, non-specific abdominal pain, radiation enteritis and coeliac disease etc will also be explored in suitable cohorts undergoing clinically requested MR enterography.

We propose three overlapping development phases. First a software system that uses MRI data acquired on standard, commercially available systems. Second, new MR protocols adapted and optimised for obtaining parameters relating to small bowel disease. Third, extensions to the software to include the capabilities of the new MR protocols and to incorporate feedback from clinical evaluation.

Our goal is a software tool that is easy and effective to use. The less user intervention required the better, but priority will be placed on getting a complete pipeline functioning first, even if this requires more manual interaction than is ideal or subjective visual scoring. The later development phases will be used to refine the software and to adapt MR techniques to give us more relevant or accurate image parameters.

Work Package 1. The viewing tool

A viewing tool currently under development in CMIC will be extended to allow the visualisation of images from multiple MR contrast types simultaneously. This will require standard techniques to handle data with different voxel sizes and slice positions. In addition, the ability to view time series ("cine") images will be incorporated. Functionality will be added to allow the radiologist to select a point in an affected region of bowel in a volume and then reformat so that the image slice is perpendicular to the local axis of the bowel (the bowel wall should then appear approximately circular in the image). Functionality will be added for radiologists to provide scores manually based on observations, e.g. presence or absence of the "comb sign" or abscesses.

Work Package 2. Bowel Wall Segmentation

The disease affects the bowel wall and many of the image based parameters will have to be extracted from this region. Ideally 3D surfaces that define the inner and outer edges of the wall would be found from one volume and copied to the different MR images. Subsequently the image parameters would be extracted from pixels that were located between these surfaces. The challenges are to define the surfaces, select only abnormal bowel and handle the partial volume effects associated with propagating these surfaces to images that may intrinsically have been acquired at a different slice orientation, slice thickness and with a gap between slices. Furthermore, the bowel twists and turns and often does not have a perpendicular intersection with the imaging planes leading to partial volume effects and the appearance of a thicker wall.

The contours overlaid on the figure in the Technical Background section show that a simple edge detection algorithm can find the inner and outer walls, though its reliability and accuracy has yet to be tested. We will use techniques such as edge detection, region growing and thresholding to aid segmentation of the bowel wall on a few slices where, after reformatting, the wall appears approximately circular (WP1). This semi-automatic segmentation will use the MR sequence that shows the best wall contrast and has voxels which are close to isotropic (equal length on all sides). With segmentations on a few adjacent slices, this will enable surfaces to be defined and their intersection with images from other contrast types computed. These intersections will be displayed as 2D ROIs on the other images and the radiologist given the opportunity to make position adjustments.

In summary, at this stage of development, the radiologist has to perform the following steps; locate a point in an abnormal region of bowel wall, rotate the volume to display bowel “end on”, segment on a few slices the inner and outer wall (which will appear approximately circular and thus easy to segment manually or with region growing algorithms), check and adjust 2D ROIs that will then be automatically displayed on the other images.

Work Package 3. Registration and Motility Quantification

We will continue to develop the novel motility assessment outlined in the Technical Background with the aim of providing a quantitative measure which we hypothesise will be a key component in the prediction of disease activity. This motility quantification will be validated by comparison with a radiologist scoring system, e.g. 1 paralysis, 2 hypomotility, 3 normal, 4 hypermotility (see WP 7).

Our use of local volume change in the motility assessment is expected to be independent of respiratory motion. However, the other image parameters are derived from standard MRI protocols including a variety of breath hold image sequences, most commonly Fast Imaging with Steady state Precession, Half Fourier Acquisition Single Shot Turbo spin Echo and Volumetric Interpolated Breath hold Examination before and after intravenous gadolinium injection. Such data suffers from motion artefact, notably from breathing, patient movement and peristalsis of the bowel. In order to reliably collate quantitative data from differing image sequences it is necessary to accurately co-register the datasets. We will apply image registration technology developed by applicants in the UCL CMIC group. In brief these methods include fluid registration[21] and its adaptation to sequences with different image contrasts,[22] and a fast implementation of the B-spline non-rigid registration algorithm that incorporates biomechanics. This is a challenging topic and some residual mis-registration may remain.

For this reason, in WP 1 we have allowed for manual ROI adjustments by the radiologist and we will explore incorporation of biomechanical models of tissue deformation.

Work Package 4. Parameter quantification

Following image registration (WP 3) and identification of region of interest (WP 2) quantitative parameters from the affected bowel wall will be derived Parameters of interest include, bowel wall thickness, motility (WP 3), signal intensity on T2 weighted images, contrast enhancement (absolute value and curve shape) and pattern of enhancement.

Wall Thickness: With the inner and outer wall ROIs already in defined in WP 2, this can be calculated in a straightforward way and an average for the slice provided.

Contrast uptake: Multiple parameters can be calculated from contrast uptake curves (areas, slopes, timings etc). Recent work suggests the early uptake is correlated with disease[23] and we will initially use the slope of enhancement as a parameter.

T2 intensity: As with wall thickness, this is easy to find given the ROIs. It may also be necessary to identify an additional region of normal bowel to act as a reference.

Motility: Described in WP 3.

Pattern of enhancement or "layering": Standard image processing methods of texture analysis will be used to quantify the pattern of enhancement.

Other parameters: Crohn's is associated with multiple characteristics on images. In addition to those above, other characteristics include fistulation, abscesses, luminal stenosis and the "comb sign" (increased mesenteric vascularity). Initially we will provide the facility for these to be manually scored and if necessary, a more quantitative assessment will be performed in WP 9.

Work Package 5. Model interfacing

The software tool will be augmented to output the image derived parameters in a consistent fashion and to enable the organised collection of this data from multiple patients. The statistical modelling will be performed in external software (see WP 6) and the model parameters and weights provided for the viewing software. Modifications to the viewer will be made so that on a given patient the model can be used with the pre-determined weights to display the predicted disease activity score.

Work Package 6. Software evaluation and optimisation

i) We will use MRI datasets from 18 patients undergoing surgical resection for small bowel Crohn's disease.[1] Within this there are 60 regions of interest anatomically exactly matched between the MRI and histopathological sampling of the specimen. A validated transmural score of acute inflammation (AIS) has been assigned to each histological slice. In detail, patients underwent pre-operative MR enterography using a 1.5-T static magnet (Avanto; Siemens, Erlangen, Germany) with the manufacturer's body and spine array coils. Axial and coronal half-Fourier rapid acquisition with relaxation enhancement (RARE) and true fast imaging with steady-state precession (TRUEFISP) images of the small bowel were acquired, together with coronal fat-saturated half-Fourier RARE images. Coronal volumetric Interpolated Breath-hold Examination (VIBE) acquisitions were performed at 30 seconds after injection of 10 mL gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Montville, NJ). The resected bowel was retrospectively identified on the preoperative MR images and multiple regions of interest (median 3, range 1-5 per patient) placed within the bowel, documenting their exact distances to nearby fixed anatomic landmarks (eg ileo caecal valve, fistula opening etc). The surgical specimens were imaged with MRI and regions of interest on the pre-operative MR were co-located on the specimen MRI by reference to the fixed anatomical landmarks. Using the annotated specimen MR as a guide, pathological sampling was taken at sites matched exactly to the MRI regions of interest. A transmural histopathological acute inflammation score (AIS) was ascribed to each of the sample sites by two experienced gastrointestinal pathologists according to the method of et al:[15] This grades AIS with a maximum of 13 based on mucosal ulceration (grade 0-3), oedema (grade 0-3), and quantity (grade 0-3) and depth (grade 0-4) of neutrophilic infiltration.[24] Crucially, these histopathology slices include the whole thickness of the bowel wall and provide full information on cellular inflammation and disease activity - effectively the best standard of reference achievable against which to test the MRI parameter quantification.

ii) We will assemble a sample of up to 75 MRI datasets with correlative terminal ileal endoscopy and biopsy data. Each biopsy will be scored for acute inflammation (from 1 to 5) and matched to the MRI dataset. In detail, all patients will have undergone the small bowel MRI protocol described above and endoscopic terminal ileal biopsy within 4 weeks (median 5 days) of the MRI. The location of the biopsies is recorded with reference to the distance from the ileo-caecal valve-a fixed anatomical land mark identifiable on both endoscopy and MRI datasets. An endoscopic biopsy acute inflammatory score (eAIS) based on typical morphological features of Crohn's disease described in guidelines published by the European Crohn's and Colitis Organization[25] is applied to the biopsy data.

iii) A sample of up to 200 normal small bowel MRI datasets will be assessed to define the range of normality for all parameters.

iv) A prospective study of MRI in the assessment of disease activity has been ethically approved is already underway. 100 MRI datasets validated against contemporary CDAI (i.e.

current clinical standard), CRP (blood marker of inflammation) and calprotectin (stool marker of inflammation) will be collated. In detail, prospectively recruited patients with known Crohn's disease and undergoing small bowel MRI as part of normal clinical practice complete a symptom diary card the week before their MRI for calculation of the CDAI. In addition a blood sample for CRP measurement is taken on the day of the MRI, together with a stool sample for calprotectin level. Calprotectin is a biochemical marker of intestinal inflammation.[26]

v) Ethical permission to perform small bowel MRI in 75 patients with known or highly suspected small bowel Crohn's disease has been obtained. Each patient will have endoscopic and histological scoring of disease activity as described above

We will correlate our software quantified MRI or US scores of inflammation against each subcategory of activity reference individually i.e.

i) Histopathological (surgical specimen and biopsy data)-scored for acute inflammation

ii) Biochemical (CRP and stool calprotectin)-continuous data with higher values reflecting increased activity

iii) Endoscopic inflammation scores

iv) Clinical (Crohn's disease activity index) - a continuous score with score >150 indicating active disease.

The statistical modelling will use external software such as SPSS or MATLAB (Statistics Toolbox). We will perform linear regression to generate the weights for the image parameters, analyse the predictive power of the parameters and perform leave one out cross-validation.

We have multiple possible parameters and multiple standards of reference (histological, biochemical and clinical) to define weights in the statistical modelling. Statistical methods such as back elimination are available for choosing parameters and we will also use our clinical judgement and knowledge of underlying disease mechanisms to identify the optimum combination and weighting of parameters best predicting acute inflammation.

The software will thus be flexible to the variety of markers of disease activity used in clinical practice. Indeed it is anticipated the software modelling will differ depending on the type of reference standard. We will thus provide users with options as to whether the software quantifies according to a clinical (CDAI, biochemical CRP, calprotectin) or histological standard of reference

Work Package 7. Software clinical evaluation

Sections of bowel will be given a clinical score for motility and this will be compared with the numerical values derived in WP 3 (start of year 2). When the complete tool has been built and trained, we will determine the incremental benefit to radiologists of our tool by comparison with non CAD assisted reporting. Notably efficiency will be tested by measuring radiologist reporting times for quantitative evaluation of disease activity in 50 datasets with and without the CAD software. The accuracy of the

interpretation in assessing disease activity with and without CAD will be tested against the defined standards of reference listed above and defined using standard ROC methodology. Usability of the software will be assessed through questionnaires to end users. Indirect evaluation will also take place through monitoring the extent of usage at UCH and the number of external software downloads

Work Package 8 MR Sequence Adaptations

We will investigate protocol modifications that help with the parameter extraction, for example removing any slice gaps or changing resolution.

We will also investigate the use of newer or alternative MR sequences to provide data more specific for Crohn's other enteropathies and provide images better suited to parameter extraction. We will apply MR techniques that can measure motility more directly such as tagging, and methods such as diffusion imaging that are sensitive to changes in water diffusion at the cellular level and flow in the microvasculature. The inflammatory process is linked to changes in blood supply, cell swelling and increased cell count. These all affect the bowel wall diffusion signal and we will adapt sequences and protocols to extract the most useful information for Crohn's patients.

Appendix 2 -VIGOR FP7 Protocol NOW COMPLETE

PART B

COLLABORATIVE PROJECT

Table of Contents

Concept and objectives, progress beyond state-of-the-art, S/T methodology and work plan

Concept and project objective(s)

Gastrointestinal (GI) disorders affect millions of people of all ages.[1] What is more, inflammatory bowel diseases (IBDs) are a huge healthcare problem in the Western World, affecting over 1 million European citizens alone, 700,000 of whom suffer from Crohn's disease[2]. Research in Crohn's disease is particularly challenging due to its nature, which complicates a straightforward assessment of the severity.

In fact, there is a widespread debate on how to extract quantitative, pathology related measures as well as how such measures should be interpreted for many diseases. This complexity has increased the demand for related ICT tools. Physicians require advanced tools to improve the detection and visualisation of abnormalities, to enhance the communication between fellow doctors, and to quantitatively assess the outcome of interventions. Delivering such tools can lead to early diagnosis, improved treatment, reduced clinical risks associated with interventions and eventually, hopefully, prevention of disease.

In this project, we aim to develop a set of ICT tools to fulfil these prospects. The methodological advances this project entails, and the clinical evaluation study we propose, will add to the gaining momentum for a paradigm shift that paves the way for proving the clinical feasibility of new techniques. In order to demonstrate the nature of the tools and their applicability, we chose to drive the development by validating them on the most common type of inflammatory bowel diseases: Crohn's disease.

The VIGOR++ project aims to create a personalised GI tract model, which facilitates improved detection of Crohn's disease and drives an index of Crohn's disease severity.

The proposed technology builds on multiscale information from patients, including laboratory, MRI, colonoscopy and microscopy (histopathology) data. A novel integration of existing models is employed to predict features on the molecular to cellular scale (microscopy/colonoscopy) from descriptive properties at the organ to patient scales (MRI/laboratory).

The benefits are early diagnosis, improved therapy planning and a better quality of life for patient.

The techniques are integrated in the 3Dnet™ Suite environment , to make them immediately available in a clinically usable environment. Notably, tools could be rapidly commercialized and delivered as an optional toolbox to clinical sites.

[1] For example, colorectal cancer is the second most common cancer in Europe. Source: International Agency for Research on Cancer (IARC), http://www.iarc.fr

[2] European Federation of Crohn's & Ulcerative Colitis Association (www.efcca.org).

Concept

The introduction of cross sectional imaging modalities had a dramatic impact on healthcare by facilitating detailed exploration of the human body. In fact, it revolutionised the way in which many conditions are diagnosed and treated. The ability to examine in detail structures inside the body, without resorting to surgery, has allowed clinicians to diagnose problems and plan corrective procedures with a minimum of risk.

Currently, a favoured step forward is to complement the traditional techniques by approaches that integrate observations with models for prediction. Such an approach is also promoted by the European Commission in the eHealth domain striving to promote a shift from population-centred to person-centred systems and from reactive to preventive healthcare. Specifically, it is envisioned that modelling and simulation is adopted to understand the complexity of human physiology and predict human response to therapies. What is more, virtual human organs may be used to understand the impact of patient variability on these predictions.

Virtual Physiological Human

Predictive models have already been successfully applied in the clinical practice, e.g. finite element models to predict the risk of bone fracture and molecular pathway modelling in the design of new drugs. Computer aided detection (CAD) of disease is a comparable, interdisciplinary technology integrating radiological practice into digital image processing and machine learning techniques. CAD systems analyse digital images for typical, physiological appearances and, alternatively, to highlight suspicious sections (potential diseases). Typically, the performance of the predictive models is significantly influenced by the quality of the used images, conditions of the examination, disease subtype and scale. The design of these decision support systems is complex since conventionally a large database with appropriate reference cases is needed to take account of such variations. Unsurprisingly, an evolving trend can be observed towards personalised healthcare, based on computer models that are robust for patient specific circumstances. The computer models effectively extend standard biomedical signal and imaging systems, when invasive measurements are not available, not preferred or not feasible. A crucial challenge to facilitate such extension is to appropriately relate features from observable biological scales to model parameters that accurately predict requested properties of other scales.

The proposed project is part of the Virtual Physiological Human (VPH) framework[3] that aims to investigate the human body as a single complex system. The VPH framework has already delivered extensive descriptive, integrative and predictive knowledge regarding human (patho-)physiology. Still, VPH is the ‘grand challenge’ for many disciplines at the interface between ICT and the biosciences. Effectively, it sustains a system of shared resources formed by federations of disparate but integrated computer models regarding mechanical, physical, and biochemical functions of the human body. The VPH is expected to dramatically alter health knowledge, thereby creating a new basis for research and opening new opportunities for healthcare provision.

[3] STEP Research Roadmap. Seeding the EuroPhysiome: A roadmap to the Virtual Physiological Human, Apr. 2006.

The VIGOR++ project targets a valuable addition to the VPH framework by providing ICT tools for a personalised model of the Gastrointestinal (GI) tract. The models will enhance the understanding of inflammatory bowel diseases, in particular Crohn's disease. The acronym of the project (VIGOR++) reflects the need of patients suffering from diseases of the GI tract to "be lively and active". The term also denotes the energy, capability, and dynamism of the consortium as a whole. It may be noticed that hardly any research focuses on the gastrointestinal tract in the context of the Virtual Physiological Human (VPH) objective, despite the large prevalence of diseases such as IBD[4].

Gastrointestinal Tract

The GI tract (also called digestive tract or alimentary canal) is the system of organs that takes in food, digests it to extract energy and nutrients, and expels the remaining waste. A simplified illustration of the GI tract is given in Figure 1.

The oesophagus is a long muscular tube, which moves food from the mouth to the stomach.

The stomach, situated at the top of the abdomen, can hold up to about 1500 ml of food. In the stomach, acid and other digestive juices are added to the ingested food to facilitate breakdown of proteins, fats and complex carbohydrates into smaller, more absorbable units.

A valve at the entrance to the stomach from the oesophagus allows the food to enter while withholding acid-laden food to "reflux" back into the oesophagus.

The small intestine is about 4.5 to 6 metres in length and is where the majority of the absorption of the nutrients from food takes place. The small intestine is made up of three sections: the duodenum, the jejunum and the ileum.

Another valve separates the small and large intestines to keep the bacteria-loaded colon content from re-enter the small intestine.

In the large intestine, excess fluids are absorbed and firm stool is formed. The colon may absorb a limited amount of nutrients.

GI diseases account for the highest number of bed days for surgical and endoscopic procedures in countries like England, which illustrates their importance.[5]

[4] According to EC briefings for ICT-2009.5.3a:P "The selection of proposals targeting clinical applications other than cancer and cardiovascular diseases will be given preference in case of proposals with tied scores at the evaluation stage".

[5] Source OPCS-4 Intervention Classification Charter in England, 2000/01.

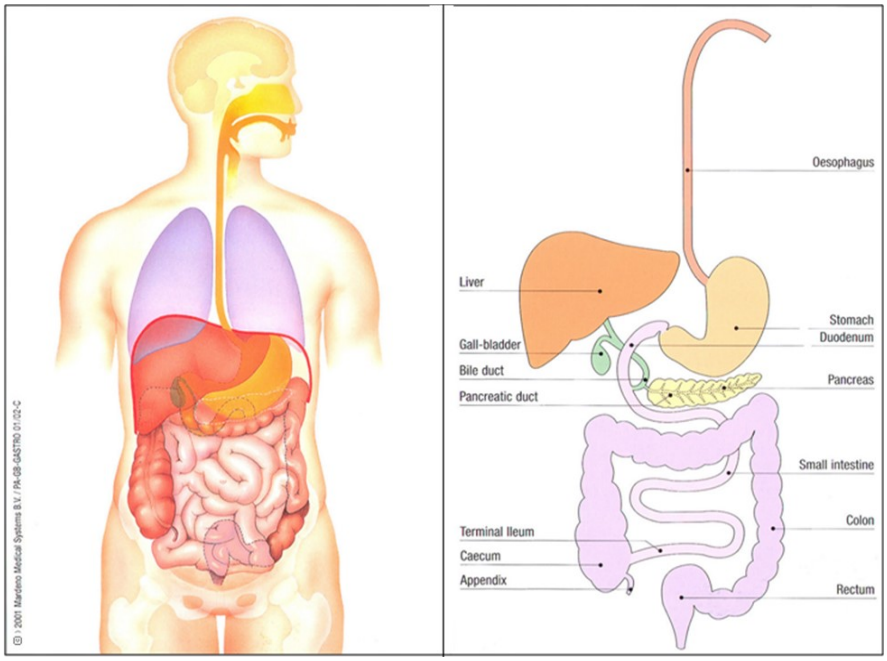


Figure 1 Graphic representation of the GI tract.

Application domain: Crohn's Disease

This project concerns the prediction and early diagnosis of a family of idiopathic and chronic conditions known as Inflammatory Bowel Diseases (IBD), in particular Crohn's disease[6]. The high incidence and prevalence make that IBD are a huge healthcare problem in the Western world. In fact, over 1 million European citizens alone are affected, 700,000 of whom suffer from Crohn's disease. IBD can begin at any age, but adolescents and young adults between the ages of 15 and 35 are most susceptible. The condition affects both men and women equally. Current evidence suggests that both genetic and environmental factors contribute to the aetiology. IBD are characterized by an inflammation of the bowel wall due to an abnormal response in the body's defence mechanism. Several types of IBD are distinguished by distinct genetic profiles, different clinicopathological features, including different locations affected within the GI tract, diverse histological patterns of inflammation and the relative importance of various symptoms such as abdominal cramps, diarrhoea, fever and weight loss. For instance, Crohn's disease can affect any part of the GI tract from mouth to anus whereas ulcerative colitis, another common IBD, is confined to the colon. Also, Crohn's disease may consist of patches of diseased and healthy tissue, whilst ulcerative colitis usually has a more uniform distribution. Crohn's disease can also lead to the development of strictures where the diseased bowel becomes narrowed and to fistulae as a result of severe ulcers breaking through the bowel wall to form abnormal connections with other parts of the body such as the bladder or the skin.

Crohn's disease is characterized by a chronic relapsing and remitting course, i.e. periods of exacerbations are alternated by episodes of diminished disease activity. Accordingly, the mere

[6] B. B. Crohn, L. Ginzburg, and G.D. Oppenheimer. Terminal ileitis, 83rd Annual Session of the American Medical Association, 1932.

presence of the disease must be distinguished from active disease, which can occur at varying levels of severity. The changes in disease activity are not necessarily correlated to changes in symptoms[7]. Exactly this complexity makes Crohn's disease a challenging topic for a GI VPH project.

Colonoscopy in combination with the assessment of biopsy samples is considered the reference standard for diagnosis of IBD. However, the procedure is invasive and requires extensive bowel preparation which is poorly tolerated by most patients. Also, the technique primarily gives information on superficial abnormalities (limited to direct visual inspection of the bowel lining or tissue samples from the inner bowel layers only), without much information on the intestinal wall or extra-intestinal disease, both of which are very important in Crohn's disease. As a consequence, radiological imaging techniques have become important for evaluating disease activity in Crohn's disease by providing information about the bowel lumen, bowel wall and extra enteric soft tissues (see section B1.2.1).

Grading of Crohn's disease severity is important to determine treatment strategy and to quantify the response to treatment. Ideally, an activity score should be objective, reproducible, quantifiable, non-invasive and comprehensive. In clinical practice, this assessment can be made by the Crohn's Disease Activity Index (CDAI)[8], laboratory investigations and/or endoscopy (scored in Crohn's Disease Endoscopic Index of Severity (CDEIS)[9]. However, none of these methods are infallible. The CDAI is a clinical index that incorporates subjective elements and therefore partly reflects patients' perception of disease severity. Alternatively, blood markers can be unchanged in the presence of active disease[10]. The CDEIS score requires endoscopy, which is considered a very invasive procedure by most patients. Moreover, none of these indices include aspects of transmural and extra intestinal disease activity. Recently, D'Haens[11] proposed a scoring system for histological abnormalities in biopsy specimens, but that measure focuses solely on microscopic aspects of Crohn's disease.

Table 1 summarizes the limitations for the described disease indices. The complex nature of Crohn's disease hinders the development of an improved index. VIGOR++ aims to set a new standard by

[7] Cellier C, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. Gut. 1994;35(2):231-5.

[8] Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976 Mar;70(3):439-44.

[9] Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989 Jul;30(7):983-9.

[10] Cellier C, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut 1994 Feb;35(2):231-5.

[11] D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998 Feb;114(2):262-7.

delivering a disease index that fulfils all the needs. A clever combination of existing image analysis and pattern recognition drives its development.

Table 1 Synopsis of Crohn's disease indices.

Index\requirement:	Objective	Reproducible	Quantifiable	Noninvasive	Comprehensive
CDAI	-	+/-	-	+	-
CDEIS	+/-	+	-	--	-
D'Haens	+/-	+	-	--	-
VIGOR++	+	+	+	+	+

S&T objectives

The project lies squarely within the remit of the call for proposals by addressing the objective ICT-2009.5.3 "Virtual Physiological Human" (VPH) in the ICT work programme 2009-2010.[12] In particular it addresses the Target Outcome a) which states:

Development of **patient-specific computer based models** and simulation of the physiology of human organs and pathologies. The models should be multiscale by integrating relevant aspects of anatomy and physiology across different levels (from molecular and cellular to tissue and organ levels). The emphasis should be on the integration of existing models rather than on development of new models. The use and benefits of the models must be demonstrated for a specific clinical need covering prediction of disease, prediction of treatment outcome and/or early diagnosis. Any organ or pathology could be targeted as clinical application. Access to existing computing facilities external to the consortium could be supported.

The VIGOR++ project is about research and development of ICT tools for the analysis, modelling and simulation of human physiology and disease processes of the GI tract. It will use the ICT tools to build **patient-specific computer models to sustain personalised healthcare**. Such tools are widely favoured by physicians and other medical disciplines for improved diagnosis and follow-up. The uniqueness of our approach is that it enables quantitative assessment of diseases of the GI tract. Consequently, it is expected that the tools will be very valuable to, for instance, pharmaceutical companies: clinical trials can be much more efficient by having accurate, quantitative descriptors of therapy effect and so reduce the high cost.

Figure 2 graphically depicts the concept on which the project text builds. Crohn's disease patients are the starting point as well as the end point of a working cycle. Multiscale data acquisition including laboratory, MRI, colonoscopy and microscopy data from these patients supports the development of integrated ICT tools. These tools include a normal representation of the GI tract that facilitates detection of abnormalities, ability to grade disease severity, and influence clinical disease

[12] ftp://ftp.cordis.europa.eu/pub/fp7/ict/docs/ict-wp-2009-10_en.pdf

management. The clinical benefit will demonstrated in a study in which the tools are assessed regarding the performance to predict Crohn's disease status: application and validation. Moreover, a preliminary study will be performed in which the effect of therapy will be established. Ultimately, it is expected that the tools can be readily commercialized which we consider a crucial ingredient to dissemination. A more detailed description of the VIGOR++ concept is shown on Figure 4. VIGOR++ aims to predict features on the molecular to cellular scale (microscopy/colonoscopy) from descriptive properties at the organ to patient scales (MRI/laboratory).

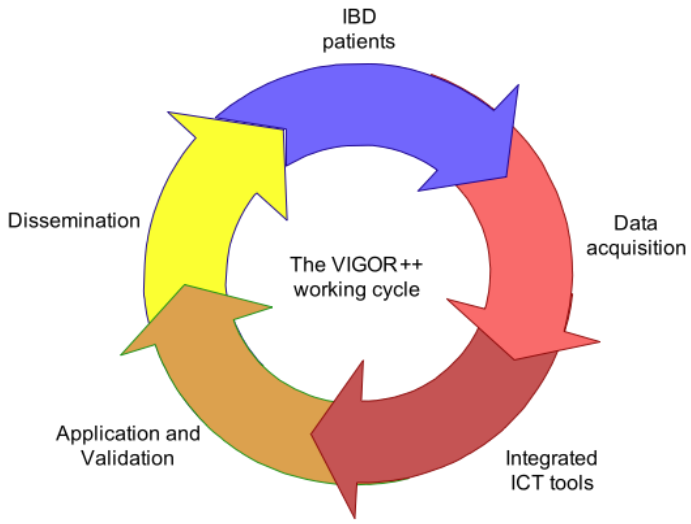


Figure 2 A top level description of the VIGOR++ concept.

The vision of the project is

VIGOR++ will create a 'normal' model of the GI tract that drives accurate detection and grading of Crohn's disease, so that the management of the disease becomes personalized, patient friendly, and effective.

Table 2 defines the key objectives of the project and what drives the consortium that we have assembled. No single country in Europe has the resources and competences required to attempt to satisfy this. It is here that the value of collaboration as part of the Framework Programme becomes directly relevant.

Table 2 S&T objectives, challenges and tangible results for VIGOR++.

S&TObjective	Challenges addressed	Tangible results

1. IMAGE ANALYSIS Adaptation of existing image analysis algorithms to accurately measure descriptive properties of GI wall tissue.	What are the appropriate algorithms for accurate measurement of a wide variety of relevant features in multimodal images?	A toolkit for analysis of all image data. Related Work Package: WP3 (MS4).
2. MODELLING Creation of patient specific instruments to quantitatively assess the status of Crohn's disease.	How can we create a multiscale, 'normal' representation of the gastro-intestinal tract, based upon which clinical decisions can be made? Can of-the-shelf pattern recognition techniques be adopted to sustain classification of disease severity?	A multiscale, 'normal' representation of the GI tract to support detection of abnormalities. A tool to accurately detect and rate abnormalities in a quantitative manner. Related Work Package: WP4 (MS5).
3. VISUALISATION Effective visualisation of the versatile aspects of the GI tract model.	What are the appropriate visualisation techniques to depict the multiscale features of the GI tract?	A computer model of the GI tract that allows easy inspection of descriptive features of Crohn's disease. Related Work Package: WP5 (MS6)..
4. SYSTEM ARCHITECTURE AND INTEGRATION Perform rigorous testing to truly guarantee that a clinically usable system is created.	What are the limits regarding characteristics of the input data with which the system can cope? What are the characteristics of user friendly interfaces that help physicians navigate and inspect abnormalities by means of the designed tools?	A clinically usable software environment in which all the developed ICT tools are appropriately integrated. Related Work Packages: WP6 (MS8, MS9).
5. CLINICAL APPLICATION Establish a care pathway for accurate, non-invasive and cost-effective examination of the GI tract for Crohn's disease.	Do the delivered ICT toolboxes sustain accurate assessment of Crohn's disease? Can the efficacy and efficiency of treatment be improved by introducing ICT tools?	Patient specific guidance recommendations for Crohn's disease care, regarding normative scores, periodic monitoring and treatment. Related Work Packages: WP7 (MS10).

6. KNOWLEDGE DISSEMINATION Disseminate generated knowledge and ICT tools by actively engaging fellow academic disciplines, industry and IBD patient associations across Europe. Identify opportunities for commercial exploitation of developed technology.	How can the results be communicated to create awareness among the different technical and clinical audiences but also the patients? How can the developed techniques be commercially exploited and create successful usable systems?	High quality publications. Trained computer scientists and clinicians. Protected intellectual property. Foundations of exploitation plans for commercially promising products. Related Work Package: WP8 (MS12).

Table 3 Advancing State of the art in VIGOR++

S/T Objective	State-of-the-art	VIGOR++
Adaptation of existing image analysis algorithms to accurately measure descriptive properties of GI wall tissue.	Image analysis techniques are widely available for all sorts of measurement tasks.	Dedicated image analysis algorithms for feature extraction. The features on which we focus are described in Table 5. Related Work Package: WP3 (MS4).
Creation of patient specific instruments to quantitatively assess the status of Crohn's disease.	There are established techniques to statistically model normal variations in data and to recognize certain patterns. We know of no application to IBD.	VIGOR++ will render a multiscale, normal representation of the GI tract upon which abnormality can be established and objectively assessed. Moreover, numerical modelling of disease severity is facilitated. Related Work Package: WP4 (MS5).
Effective visualisation of the versatile aspects of the GI tract model.	Existing techniques based on volume rendering are not suited for MRI data. The field of multiscale visualisation is still in its infancy.	Dedicated visualisation algorithms for diagnosis and treatment planning of GI diseases focused on Crohn's disease. Related Work Package: WP5 (MS6)..

Perform rigorous testing to guarantee that a clinically usable system is created.	There are no clinically usable systems whatsoever to quantitatively assess IBD.	An intuitive, clinically applicable system. Related Work Package: WP6 (MS8,MS9).
Establish a new care pathway for accurate, non-invasive and cost-effective examination of the GI tract for Crohn's disease.	Currently employed diagnostic techniques for GI disorders are either not accurate or very invasive. Early attempts were made by the clinical partners to develop new tools for assessment of Crohn's disease, but a complete, quantitative model was never involved.	VIGOR++ will establish quantitative techniques for diagnosis and management of patients with Crohn's disease. Increased quality of life is facilitated by early prediction of disease, more accurate, non-invasive diagnosis techniques and instruments to measure the effect of treatment. Related Work Package: WP7 (MS10).
Disseminate generated knowledge and ICT tools by actively engaging fellow academic disciplines, industry and IBD patient associations across Europe. Identify opportunities for commercial exploitation of developed technology.	Currently, there are no quantitative techniques for assessment of IBD.	VIGOR++ will deliver tools for objective analysis of Crohn's disease. We expect a large interest in those tools by many parties. Widespread application is foreseen, e.g. pharmaceutical industry will be interested for efficiently conducting trials of GI medication. Related Work Package: WP8 (MS12).

Progress beyond the state of the art

Table 3 summarises the advances that VIGOR++ would bring about and in the subsequent sections we provide more details about the state-of-the-art and the advances proposed. Initially, we will go into methods for assessment of gastrointestinal diseases in order to accurately identify the clinical benefits that VIGOR++ must deliver (B1.2.1). Thereafter, state-of-the-art ICT tools for modelling the GI tract are described, so that the advantages to be gained over traditional techniques and main innovations are made explicit (B1.2.2).

State-of the-art in diagnostic procedures for the GI tract

Assessment of GI diseases conventionally consists of a careful review of a patient's history, laboratory tests, supplementary diagnostic imaging procedures and histopathology.

At present cross sectional imaging techniques (CT, scintigraphy, ultrasonography, MRI and scintigraphy) are routine techniques to assess disease activity in IBD. These methods are replacing conventional barium methods (Barium meal/follow through, enteroclysis, Barium enema). The role of the video capsule is not sufficiently established yet, but availability, costs and other limitations curtail its present use. A synopsis and comparative analysis of imaging techniques for IBD is provided in Table 4:

Table 4 Synopsis of imaging techniques for IBD.

	Invasiveness	Radiation burden	Spatial resolution	Bowel surface visualisation	Bowel wall visualisation	IBD diagnosis sensitivity
Laboratory tests	Low	None	None	None	None	Medium
Barium meal/follow through	Low	High	Good	Medium	Low	Low
Enteroclysis	High	High	Good	Good	Low	Medium
Barium enema	High	High	Good	Good	Low	Low
Ultrasound	None	None	Low to good	Medium	Moderate	Medium to high
Scintigraphy*	Medium	Medium	Low	None	None	Medium to high*
CT enteroclysis	High	Very high	Good	Medium	Good	High
CT enterography (without enteroclysis)	None	Very high	Good	Medium	Good	High
MRI with enteroclysis	High	Low**	Good	Good	Good	High
MRI enterography (without enteroclysis)	None	None	Good	Good	Good	High
Camera Pill***	Low	None	Good	Medium	None	Not established
Optical Colonoscopy	Very High	None	Very good	Very good	None	High
Histopathology	High	None	Very good	None	Good	High

* Only studied in moderate to severe disease.

** Only ionising radiation during positioning of the nasojejunal tube.

*** No systematic investigation.

A systematic review or meta-analysis is considered the best available method for summarising the evidence on a certain topic. Systematic reviews involve searching for all relevant evidence, selecting, critically appraising, and quantitatively summarizing reported outcomes. **Systematic reviews are accepted as the most reliable way by which large volume of research evidence can be managed**.

The medical literature on imaging in IBD has recently been studied in detail by one of the partners[13]. This analysis included 33 studies selected from a search resulting in 1406 articles on CT, scintigraphy, ultrasound, and magnetic resonance imaging. The outcome from endoscopy, barium enteroclysis or small bowel follow-through, surgery and/or histopathology was accepted as the reference standard. Mean sensitivity estimates for the diagnosis of IBD on a per-patient basis were high and did not show significant differences between imaging modalities (89.7% for US, 93.0% for MRI, 87.8% for scintigraphy, and 84.3% for CT, respectively). Mean specificity estimates were 95.6% for US, 92.8% for MRI, 84.5% for scintigraphy and 95.1% for CT respectively; the only significant difference was observed between scintigraphy and US (p=0.009).

The meta-analysis indicates that there were no large differences observed between imaging techniques in terms of sensitivity or specificity. Importantly, a method abstaining from ionising radiation is preferred. Moreover, MRI is preferred over ultrasound because ultrasound has a high observer dependency. Also, it is difficult to quantify ultrasound findings (especially important in evaluating treatment response). MRI is established as the most diagnostically accurate modality in many soft tissue organ systems. However, until recently its role in diseases of the small and large bowel was still developing largely due to technical shortcomings leading to longer procedure times with mediocre image quality. Recent technological developments in MRI (higher magnetic field, new acquisition protocols and coils) have overcome these limitations, resulting in an accurate non-invasive small and large bowel examination technique without radiation exposure.[14]

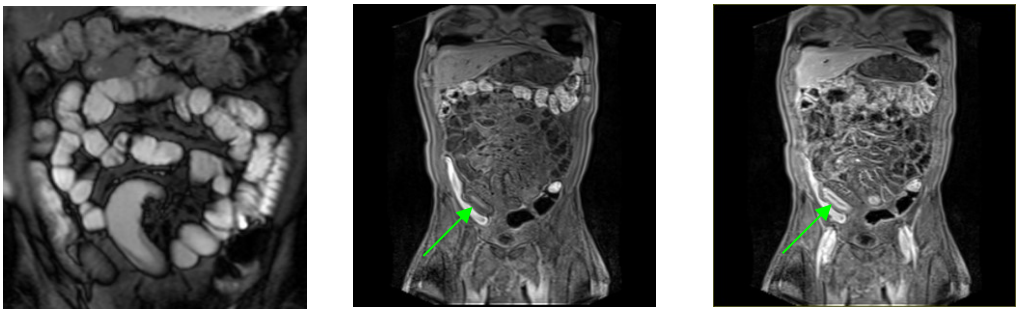


Figure 3 Images of one patient with Crohn's disease: (a) T_2 weighted image showing the distension of the ileum (white); (b,c) T_1 weighted images prior to and after contrast injection; the enhancement in the area of increased wall thickening indicates active disease.

The VIGOR++ project focuses on GI tract modelling on the basis of MRI facilitating a minimally invasive, safe and potentially more accurate approach. Ultimately, it is our objective to accurately predict the colonoscopy and histopathology data and the associated indices of disease severity (e.g.

[13] Horsthuis K, Bipat S, Bennink R, Stoker J. Ultrasonography, Magnetic Resonance Imaging, Scintigraphy, and Computed Tomography for diagnosis of inflammatory bowel disease: a meta-analysis of prospective studies. Radiology 2008; 247:64–79.

[14] Gourtsoyiannis N, Papanikolaou N, Grammatikakis J, Maris T, Prassopoulos P. MR imaging of the small bowel with a true-FISP sequence after enteroclysis with water solution. Invest Radiol 2000;35:707-711.

CDEIS, d'Haens score). This would render the current methods redundant, which is preferred given their invasiveness. Part of the development comprises the creation of a normal representation of the GI tract, as well as ICT tools to detect and rate deviations from normality. VIGOR++ will acquire laboratory, MRI, colonoscopy and microscopy (histopathology) data in order to develop the required ICT tools. Importantly, the colonoscopy and the histopathology data serve for the development of accurate prediction models, but the goal is to predict them from the other modalities (see Figure 4).

`

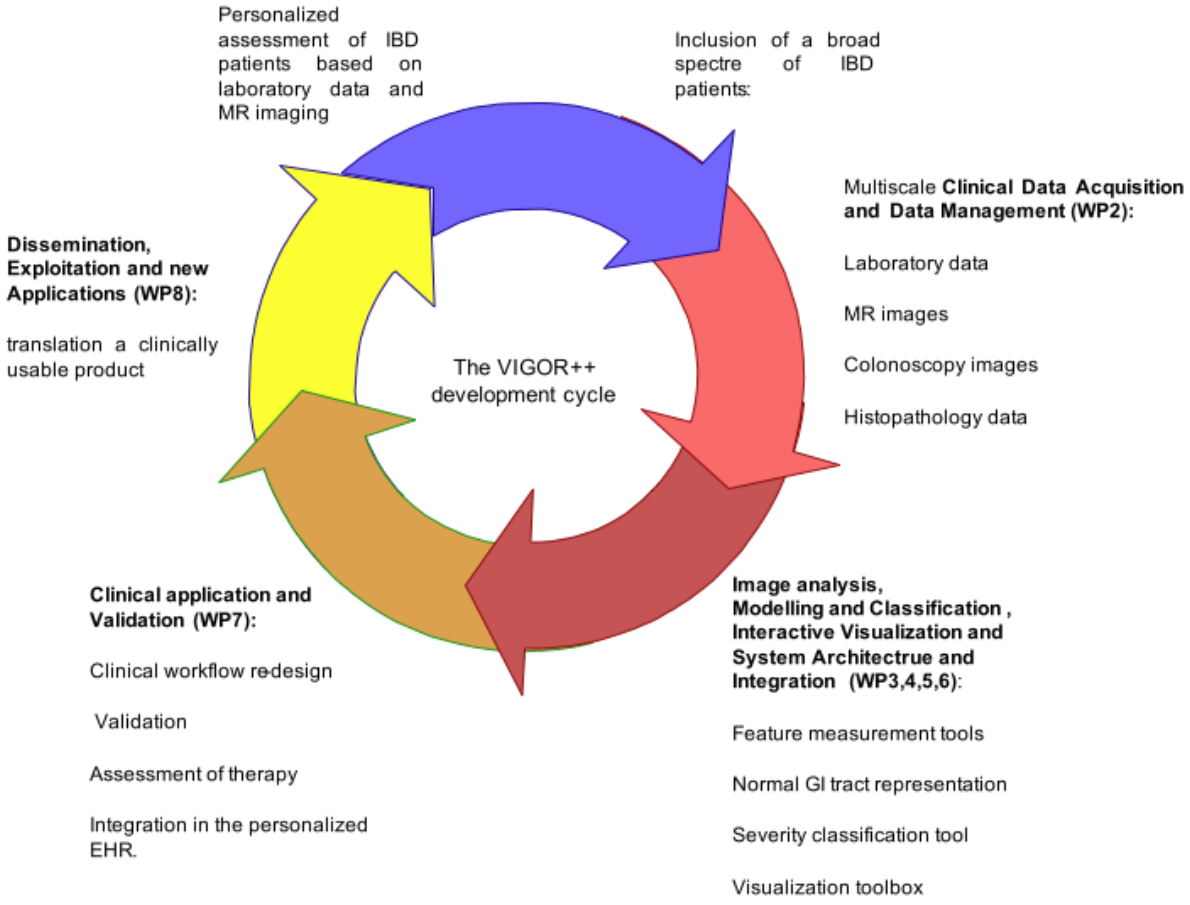


Figure 4 A detailed description of the VIGOR++ concept.

State of-the-art in ICT tools for modelling the GI tract

In the last 15 years, significant efforts have been made to build numerical patient models from multimodal images for surgical planning and image-guided surgery. The components on which the VIGOR++ project will make S&T contributions in relation to the state of the art are described below.

Image analysis

There is a wealth of techniques available in the literature on medical image analysis. Much research was conducted in the context of CT colonography (CTC). This relatively new technique concerns CT

imaging of the colon for the detection of colorectal cancer/polyps. Image analysis algorithms were created to register the scans made of a patient in prone and supine positions[15]. However, research has particularly focussed on the so-called electronic cleansing of CT images, i.e. automated detection of faecal residue in the intestines. Electronic cleansing relies on the patient taking a contrast agent that "highlights" the residue, which may subsequently be detected by means of thresholding. More elaborate techniques were also proposed to cope with noise and contrast non-homogeneity[16]. All this colon segmentation work mainly focused on the inner surface of the colon wall (the lumen-mucosal boundary). Outer wall segmentation from CT images remains an unsolved problem, due to the low contrast between attenuation values of the colon wall and the surrounding fat tissue.

VIGOR++ will employ MRI to produce robust tissue discrimination and to quantify the features of Crohn's disease. Automated measurement of such features in MRI images has not been investigated, to the best of our knowledge. Signal fluctuations in MRI emanate both from global (bias field) as well as local effects (non-homogeneities in bowel content) and this variation in signal value may preclude simple approaches (e.g. thresholding) for MRI data. Fortunately, sophisticated methods are available cope with those variations, which will be adopted in WP3 (see below).

Radiologists assessing MRI data of patients suffering from Crohn's disease typically look for signs of local bowel wall thickening[17] (see above). The MRI findings of bowel wall thickening are analyzed and classified into several types based on the mural signal patterns[18]. Moreover, the dynamic response of the tissue to the inflow of blood is studied since a marked increase in signal intensity of actively diseased bowel results from enhanced perfusion and vascular permeability in inflammatory tissue[19].

All these aspects will be contained in properties measured on the candidate lesions for Crohn's disease.

---

[15] P. Li, S. Napel,B. Acar, D.S. Paik, R.B. Jeffrey Jr.and C.F. Beaulieu, "Registration of central paths and colonic polyps between supine and prone scans in computed tomography colonography: Pilot study" MED PHYS, 31 (10): 2912-2923 Oct 2004.

[16] Serlie IWO, Vos FM, Truyen R, Post FH, van Vliet LJ. Classifying CT image data into material fractions by a scale and rotation invariant edge model. IEEE Trans Image Process. 2007;16(12):2981–2904.

Serlie IWO, de Vries AH, , Nio Y, Truyen R, Stoker J, van Vliet LJ and Vos FM. Lesion conspicuity and efficiency of CT colonography with electronic cleansing based on a three-material transition model. AJR Am J Roentgenol. 2008;191(11): 1493-1502.

[17] Low RN, Sebrechts CP, Politoske DA, Bennett MT, Flores S, Snyder RJ, Pressman JH. Crohn disease with endoscopic correlation: single-shot fast spin-echo and gadolinium-enhanced fat-suppressed spoiled gradient-echo MR imaging. Radiology. 2002;222(3):652-60.

[18] Choi D, Jin LS, Ah CY, Lim HK, Hoon KS, Jae LW, Hoon LJ, Park H, Rae LY. Bowel wall thickening in patients with Crohn's disease: CT patterns and correlation with inflammatory activity. Clin Radiol. 2003;58(1):68-74.

[19] Brahme F, Lindstrom C. A comparative radiographic and pathological study of intestinal vaso-architecture in Crohn's disease and in ulcerative colitis. Gut. 1970;11(11):928-40.

We intend to **extract morphological (shape), textural (stratification) and structural (vascularisation) features and use a combination of these features for the detection of abnormalities**. In particular the following features will be examined (Table 5):

Table 5 Example features to be examined in the project.

Morphological	Morphology of lumen (diameter, curvature), morphology of wall (average thickness, curvature), granularity of wall surface.
Textural	Layer detection, presence of fat, oedema, haemorrhage in wall and around wall.
Structural	Absolute wall enhancement and enhancement pattern in dynamic contrast enhanced MRI, lymph node enhancements.

Modelling

Automatic detection and classification of abnormalities from medical images by machine learning has received much attention. However, regarding the gastrointestinal tract such computer aided detection is limited to recognition of polyps/colorectal cancer in CT colonography. The most successful techniques[20] are based on local shape features, particularly the local shape index and curvedness, which are computed after segmentation of the colon surface. Although very good results were obtained, these techniques still often fail to differentiate between polyps and residual material. Moreover, they rely on accurate segmentation of the colon surface, which is not always feasible, especially if there is much faecal remains (particularly in patients that did not take laxatives, which is preferred for patient compliance).

The use of dynamic contrast enhanced (DCE) MRI has been advocated by an increasing number of investigators studying physiological processes in the human body. Quantification of DCE MRI data by means of pharmacokinetic models, proposed initially by Tofts and Brix [21], aims at calculating absolute measures that are directly related to the tissue physiology such as vessel permeability, blood flow, blood transit time through a tissue and extracellular volumes. Unfortunately, such compartmental analysis suffers from wide variability in output, which is a consequence of the large variety of models used [22].

An alternative and potentially more robust method is to study the uptake curve shape and to relate this to pathological findings. This approach is based on the utility of qualitative observations of the

[20] Z. Wang, A. Liang, L. Li, X. Li, B. Li, J. Anderson, D. Harrington, Reduction of false positives by internal features for polyp detection in CT-based virtual colonoscopy, Medical Physics, 32: 3602-3615, 2005.

[21] Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E and Knopp MV. Estimating kinetic parameters from dynamic contrast enhanced T1-w MRI of a diffusible tracer: standardized quantities and symbols. J Magn Reson Imaging 1999; 10(3): 223–232.

[22] Harrer JU, Parker GJ, Haroon HA, Buckley DL, Embelton K and Roberts C. Comparative study of methods for determining vascular permeability and blood volume in human gliomas. J Magn Reson Imaging 2004; 20(5): 748–757.

time–intensity curves (TIC) generated from ROI's chosen in lesions by radiologists [23]. Moreover, it is confirmed by the simulations in Tofts et al.[24], that data from curve shape analysis reflect physiological parameters (e.g., the capillary permeability).

We propose to use techniques from **statistical pattern recognition** in order to define an objective score of Crohn's disease severity in WP4.

Initially, a statistical model will be created that mathematically describes the normal variation in the features emanating from patients without active disease. Subsequently, we intend to 'train' a curve shape classifier on manually annotated data to remove the dependency on arbitrary MRI parameter settings. Alternatively, unsupervised techniques, i.e. both principal and independent component analysis will be employed to analyse the prevailing curves shapes. This exploration will enable objective measurement e.g. the prevalence of certain curves shapes in different disease states, that will add to the features described initially (such as wall thickness and stratification pattern).

The combination of multiple imaging features within a classification framework[25] is expected to sustain classification accuracy levels similar to those achieved by trained professionals. A further novel direction in VIGOR++ will be to investigate combining MR data and laboratory data for more reliable and precise diagnostic performance. The combination of imaging and clinical biomarkers of disease activity will draw on the strengths of both methodologies and it is anticipated will add to the robustness of any predictive model. The design of a classifier for quantifying Crohn's disease severity will be treated as a regression problem rather than a traditional classification task. In other words, a weighted probability density function is fit to the feature data in which the weights derive from clinical indices of Crohn's disease activity (CDEIS, CDAI).

Interactive visualisation

A major challenge will be to develop new methods, which allow the examination of GI wall tissue. Conventional volume rendering techniques are applied in CT colonography to visualise the colon's inner surface. The current project requires the **depiction of multiscale, spatially diverse data.** Consequently, novel ways of mapping the data to create an intuitive visual representation are needed. The difficulty to do so particularly lies in depicting clinically important features while mapping onto a two-dimensional display.

---

[23] van Rijswijk CSP, Geirnaerdt MJA, Taminiau AHM, van Coevorden F, Zwinderman AH and Pope TL. Soft-tissue tumours: value of static and dynamic gadopentate dimeglumine-enhanced MR imaging in prediction of malignancy. Radiology 2004, 233293–233502.

[24] Tofts PS, Berkowitz B and Schnall MD. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumours using a permeability model. Magn Reson Med 1995; 33(4): 564–568.

[25] G. T. Papadopoulos, V. Mezaris, I. Kompatsiaris and M. G. Strintzis: "Combining Global and Local Information for Knowledge-Assisted Image Analysis and Classification", EURASIP Journal on Advances in Signal Processing, Special Issue on Knowledge-Assisted Media Analysis for Interactive Multimedia Applications, vol. 2007 (2007), Article ID 45842.

A potential solution to this problem is the concept of importance-driven visualisation[26], which has been successfully employed for the combined visualisation of multi-modal data[27]. Such an approach involves an ordering of features according to a measure of 'importance'. Automatically, a region containing less important features is depicted by means of a less detailed visual representation and/or displaced in order to provide an unobstructed view of a more important region. The ordering to importance will be derived from the classifier to be developed (WP4). The importance information will also be used to guide so-called unfolding techniques to minimize distortions in important areas while allowing for more relaxed conditions in 'contextual' regions.

Clinicians must accurately interpret and integrate findings in order to achieve diagnostic certainty. It is important that uncertainties in the data are made visible. For this recently developed methods[28] [29] will be adapted and extended. Clearly, the goal is to create an integrated visualisation framework which allows intuitive study of the all available information in a unified manner. Techniques for visualising complex anatomies[30] and physiological data in complex anatomies[31] have been studied previously, but a comprehensive solution for the domain addressed here that meets the current clinical demand is certainly not available yet. We hypothesize that the proposed research in this direction offers the prospect of significant progress beyond the state-of-the-art.

Importantly, the consortium regards patient education an obligation that may not be discarded. It is expected that patient education will be supported by the developed visualisation techniques. Patient education is becoming an increasingly important aspect of medical care. Illustrations can be a valuable aid in explaining diagnoses and treatments.[32] Recent progress[33] in the area of illustrative visualisation seeks to reproduce the expressiveness and comprehensibility of traditional illustrations

[26] I. Viola, A. Kanitsar, M. E. Gröller. Importance-Driven Feature Enhancement in Volume Visualisation. IEEE Transactions on Visualisation and Computer Graphics, 11(4):408-418, Jul. 2005.

[27] M. Burns, M. Haidacher, W. Wein, I. Viola, M. E. Gröller. Feature Emphasis and Contextual Cutaways for Multimodal Medical Visualisation. In Proceedings of EuroVis, pp. 275-282, May 2007.

[28] K. Pöthkow and H.-C. Hege, Uncertain Iso-contours, accepted with minor revision for IEEE Trans Visual Comput Graph; available under www.zib.de:/hege/iso_uncertainty.pdf

[29] M. Otto, T. Germer, H.-C. Hege, H. Theisel, Uncertain 2D Vector Field Topology, to appear in Comput Graph Forum, May 2010, available under www.zib.de/hege/ uncertain_vectorfield_topology.pdf

[30] A. Kuß, S. Prohaska, B. Meyer, J. Rybak, H.-C. Hege: Ontology-Based Visualisation of Hierarchical Neuroanatomical Structures, Visual Computing for Biomedicine VCBM 2008, Eurographics, pp. 177-184, October 2008

[31] S. Zachow, P. Muigg, T. Hildebrandt, H. Doleisch, and H.-C. Hege, Visual Analysis of Nasal Air Flow, IEEE Trans. Vis. Comput. Graph., 15:6 (2009), pp. 1407-1414.

[32] P. S. Houtsa, C. C. Doakb, L. G. Doakb, M. J. Loscalzoc. The role of pictures in improving health communication: A review of research on attention, comprehension, recall, and adherence. Patient Education and Counseling, 61(3): 173-190, May 2006.

[33] S. Bruckner, M. E. Gröller. VolumeShop: An Interactive System for Direct Volume Illustration. In Proceedings of IEEE Visualisation, pp. 671-678. Oct. 2005.

using advanced visualisation techniques. Perceptually effective visualisation techniques as well as methods to evaluate their effectiveness[34] and will support this development. Such an approach makes it feasible to generate patient-specific depictions of particular pathologies which are easy to understand for laymen. Similar techniques may also be used to aid medical education and communication.[35]

Advantages over traditional techniques and main innovations

The primary objective of VIGOR++ is to deliver ICT tools for modelling GI tract physiology as well as disease processes. Our research focuses on aspects for which current diagnostic techniques provide no or very limited value:

An appropriate indication of the extent of disease is currently not available. Colonoscopy sustains visualisation of the bowel wall mucosa thereby only allowing identification of superficial disease. Importantly, MRI visualises all bowel wall layers, enabling transmural assessment, including submucosa, muscularis mucosae, serosa.

Similarly, the extent of extraluminal disease is not visualised, such as fistulas, abscesses and their spatial relation to normal anatomy, which is important for surgical planning.

Inspection of the bowel proximally of a stenosis, which is impossible by means of colonosocopy. MRI facilitates robust assessment of the complete bowel, such as presence of prestenotic dilatation and length of the stenosis which impact directly on therapeutic strategy.

A reference standard to quantitatively assess patient specific findings is currently lacking.

Quantifying disease activity is not sustained, which is of utmost importance, however, for clinical management and for monitoring pharmacological studies.

The VIGOR++ tools comprise patient-specific computer models for personalised and predictive healthcare. The novel results of the project include:

1. An improved care pathway for Crohn's disease that will increase accuracy and efficiency of diagnosis, whilst minimising cost and enhancing well-being of patients.

2. Adoption of existing image processing algorithms for segmentation of and feature extraction from MRI datasets of Crohn's patients.

3. Creation of a multiscale normal representation of the GI tract.

4. Automatically detection and quantification of abnormalities in the GI tract

5. Novel visualisation algorithms and user interfaces

[34] A. Kuß, M. Gensel, B. Meyer, V. J. Dercksen, and S. Prohaska, Effective Techniques to Visualize Filament-Surface Relationships, Comput. Graph. Forum. 10 pp., to appear June 2010, available at www.zib.de/hege/…

[35] F. Ritter, C. Hansen, V. Dicken, O. Konrad-Verse, B. Preim, H.-O. Peitgen: Real-Time Illustration of Vascular Structures. IEEE Transactions on Visualisation and Computer Graphics. 12(5): 877-884, Sep. 2006.

6. Techniques to assist doctors for accurate risk assessment and Crohn's disease management.

S/T Methodology and associated work plan

1.3.1 Overall strategy and general description

Work plan strategy

The VIGOR++ work plan defines the execution of activities for the three-year duration of the project. It comprises management and exploitation work packages (WPs) that will act in concordance with technical work packages. The work plan comprises **two** main iterations. The first one is about the prototype development (M1-M22) and the second left for fine tuning (M23-36), see Figure 6.

The work-plan has been broken down according to the following activities:

WP1: Management

WP1 will oversee the smooth running of the VIGOR++ project, ensure that the project objectives are met, take care that all deliverables are presented to the commission on time and, if necessary, corrective actions are made. The management framework is detailed in Section 2.1 of this project.

WP2 Clinical Data Acquisition and Data Management

WP2 will acquire and annotate clinical data from Crohn's disease patients at several biological scales: laboratory, MRI, colonoscopy, microscopy (histopathology) data. The MRI acquisition method will be fine-tuned, liaising with other WPs (particularly WP3, WP4 and WP5). Moreover, a combined, clinical disease severity index will be defined that integrates existing disease indices.

WP3 Image analysis

WP3 combines existing image analysis techniques to identify regions of interest and register the MR images to compensate for patient movement. Moreover, descriptive properties of Crohn's disease activity will be measured in both the MR and the microscopy images. The features thus obtained are at the basis of the classification task in WP4.

WP4 Modelling and classification

WP4 will develop a patient specific instrument to quantitatively assess the status of IBD disease. Of-the-shelf pattern recognition techniques will be adopted to sustain the classification of the disease properties measured in WP3. It will deliver a tool to detect and rate abnormalities, so that the combined, clinical disease severity index created in WP2 can be accurately predicted in quantitative manner.

WP5 Interactive Visualisation

WP5 will develop a visualisation software toolbox to enable interactive visualisation of GI wall tissue properties. The software package will feature established techniques for concurrent visualisation of the multiscale multiscale clinical patient data as well as the mathematical properties measured by WP3 and the classification delivered by WP4.

WP6 System Architecture and Integration

WP6 establishes the overall system architecture and provides a clinically usable software environment in which all the developed ICT tools will be integrated. Moreover, care will be taken that developed system units are continuously tested, so that progress is monitored and proper integration across the WPs is ensured.

WP7 Clinical Application and Validation

WP7 evaluates the accuracy of all developed analysis, modelling and visualisation techniques and serves to demonstrate their clinical benefit. Specifically, the tools for assessing the patient's disease status will be clinically validated, after which the techniques shall be clinically used to quantify the effect of therapy.

WP8: Dissemination, Exploitation and New Applications

WP8 provides the interface between the project and the outside world including academic, clinical, industrial communities, but particularly also the population of patients suffering from Crohn's disease. A dissemination strategy was designed to ensure high visibility of developed ICT tools in the European and International arenas and support the translation of the project's findings into successful products and services.

The components showing their interdependencies

The interaction among the work packages is depicted Figure 5. The main box distinguishes the technical WPs that will be performing the R&D tasks. Central to that are the work packages that generate quantitative, measurable features (WP3); classifiers weighting their relative importance and integrating them in measures of disease severity (WP4); and a GI tract normal representation and techniques for its visualisation (WP5). All development will be performed using data acquired and annotated by WP2. WP6 interacts with the three technical WPs (WP3, 4 and 5) to formulate and reinforce the overall system architecture. The validity of developed techniques will be clinically tested by WP7. The aforementioned work packages are interacting with the management (WP1) and dissemination/exploitation (WP8) work packages to ensure a consistent and effective delivery of the work plan.

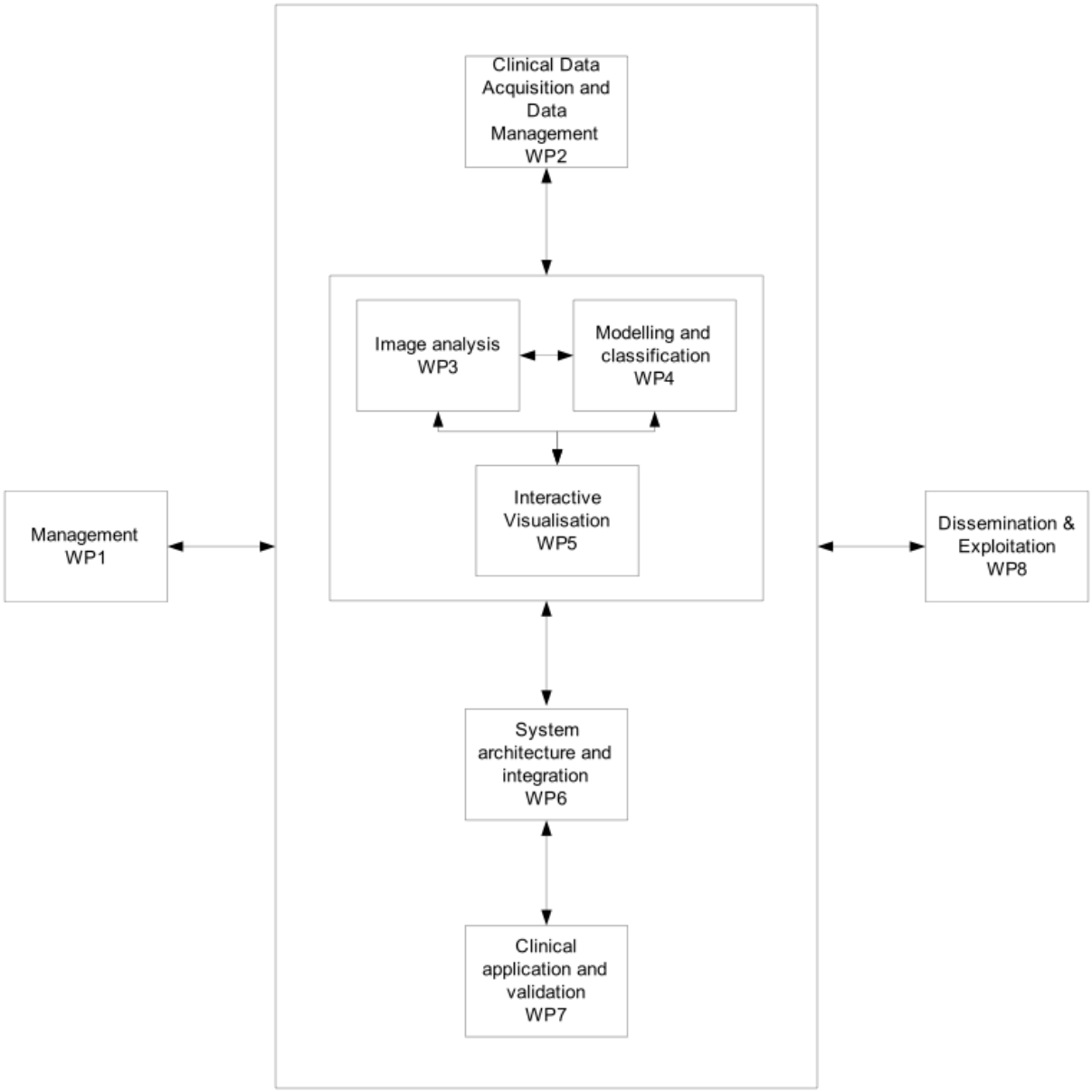


Figure 5 Interactions among the WPs in VIGOR++.

ICT details regarding system architecture and data integration

The VIGOR++ tools will be integrated in the 3Dnet™ Suite[36] environment that has been developed and commercialised by B3D. 3Dnet™ Suite is an open platform for medical image post processing. It represents the latest trends in the ICT market as it is deployed following a paradigm called Platform as a Service (PaaS); the whole delivery mechanism is online, via an advanced and innovative online scripting language dedicated to medical imaging. The platform is a collaborative framework for open innovation, available to academic and commercial developers for application designers to use existing tools (e.g. for data reading, filtering and standard visualisation), or add their own to create

[36] http://www.3dnetsuite.com

new applications. Hence, by making the new tools resulting from VIGOR++ available to the existing community of 3Dnet™ Suite developers the project will stimulate faster adoption.

Risk analysis and associated contingency plans

The main risks for a research project such as VIGOR++ relate to technological and clinical facets. Partner problems and agreement risks are not considered potential threats since there is strong agreement on the objectives and work description among the partners. This stems from the strong collaboration that already exists between several partners. We feel that the small size of the consortium gives the advantage of quick decisions and relatively easily aligned drive in the project. The project plans to actively maintain a risk assessment table so that the Steering Committee (Section B2.1) can take appropriate actions as soon as a potential threat seems to become reality. The risk analysis matrix is given in Table 6.

Table 6 Risk analysis for the VIGOR++ project.

Category	Code	Description	Tasks involved	Probability 1-10	Severity1 -10	Milestone concerned	Contingency plan
Internal Risks							
Clinical	R.I.1	Inappropriate data acquisition (insufficient or incomplete).	T2.1,2,4	1	5	MS2 and MS3	Continued development based on existing data for which ethical approval was already obtained in other projects.
Technical	R.I.2	Performance requirements on ICT tools not met.	Variable (mainly WP3-5)	2	4	MS4, MS5 and MS6	Ensure enhanced performance facilitated by means of user interaction.
Technical	R.I.3	Not enough level of integration or/and incompatibility between components.	Variable (mainly WP6)	1	6	MS9	Initial partial integration complemented by analysis, plans and implementation of complete integration within the defined architecture supervised by WP6.
Management	R.I.4	Partner under performing or leaving the project.	Variable	2	4	Variable	Enforced completion of current responsibilities. Involve project officer and AC. In the short term divide the work among other partners, and in the long term, replace partner.

Management	R.I.5	Lack of appropriate commitment of participants (e.g. delays in deliverables).	Variable	3	6	Variable	WP1 will call attention to the responsibilities of the partners and ensure that appropriate actions are taken.
Management	R.I.6	Ineffective dissemination and exploitation.	Variable	2	3	MS11 and MS12	Coordinated action by the WP-leader to encourage attention to the collaborative project ambitions. Intensified dissemination activities. Ensure that consensus is present about exploitation routes.

External Risks							
External	R.E.1	Dramatic change in user requirements	Variable	1	7	Variable	Careful assessment of user needs by WP6 and 7 involving the Interest Group. Adaptation of the project's requirements of ICT tools.
External	R.E.2	Changes in the regulatory framework	Variable (mainly WP2,7)	1	6	MS2,MS3 and MS10	Systematic handling of ethical and legal issues throughout the project by all WP's.
External	R.E.3	Competition risks	Variable	3	2	Variable	A meticulous assessment of the current state of knowledge as well as the markets throughout the project.

Timing of work packages and their components

The tasks are visualised in Figure 6 as part of a Gantt chart. M22 marks the completion of the first iteration of the project. The prototype tools will be subsequently clinically tested and fine tuned. The technical WPs (WP3-5) are front-end loaded. The same applies for the data acquisition WP (WP2). The intensity of tasks in the integration (WP6) and clinical (WP7) is slightly higher towards the second part of the project. Finally, the management (WP1) and dissemination/exploitation (WP8) are balanced reflecting an even distribution over project's lifetime.

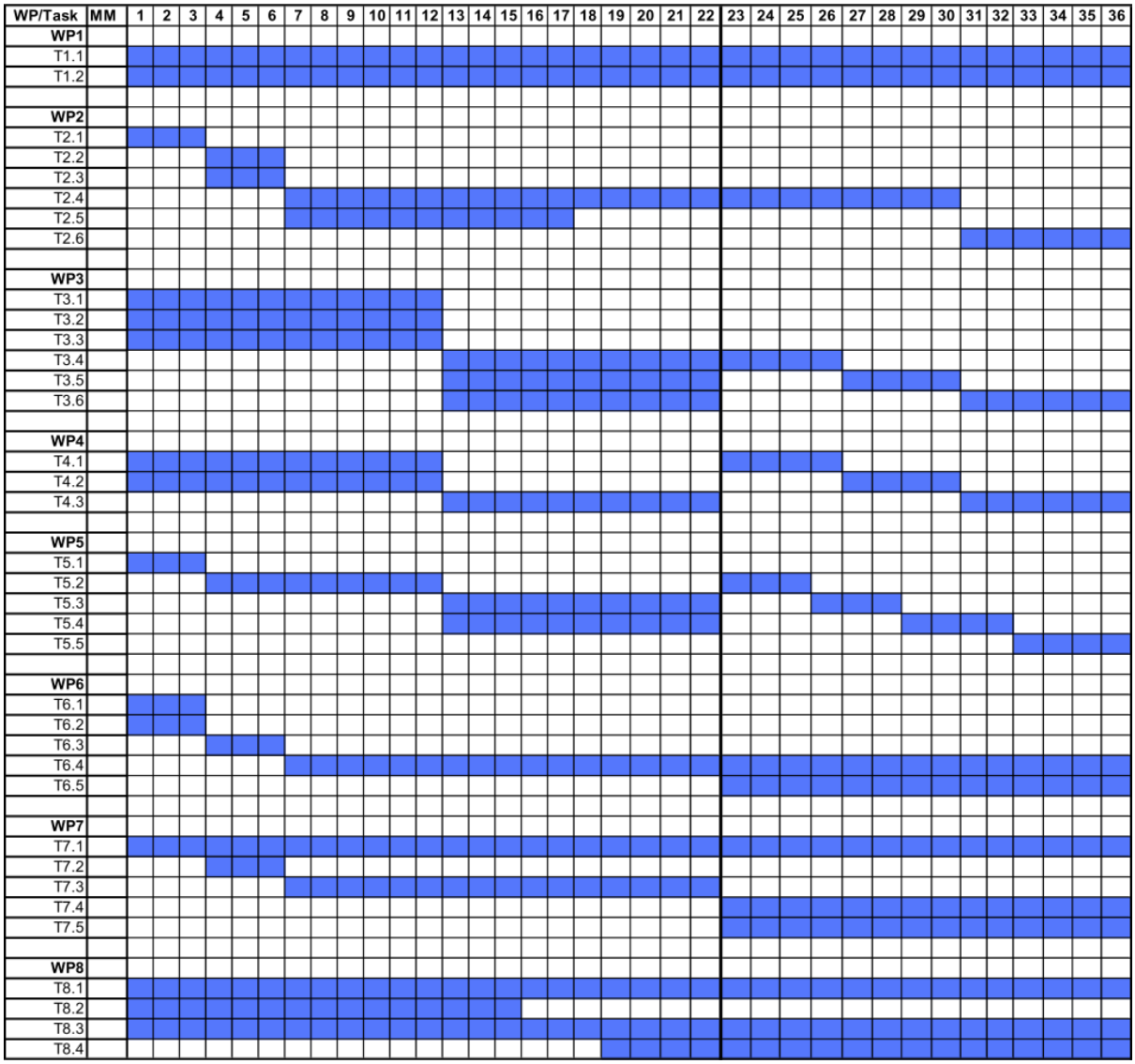


Figure 6 Gantt chart depicting the tasks of each work package during the project. M22 denotes the completion of the first iteration. All work packages start at M1 and finish at M36.

Implementation

Management structure and procedures

The management structure of the VIGOR++ project is designed to be simple, flexible, democratic and efficient in achieving its aims. In fact, it must ensure that all the consortium members work together as a team to undertake an efficient and effective research programme. The management organisation is lean, consisting of a three-layered structure involving a clear assignment of responsibilities at each level (Figure 7):

The work packages

The Steering Committee

The EC

These three levels will operate during the project's lifetime. The coordinator (TU Delft) is responsible for supervising all communication flows between the levels. Decision making is done at all levels. At level one the communication and decision making is done at WP level by WP participants and the WP leader. At level two, the Steering Committee (SC) is the decision making body, gathering representatives of all parties including the coordinator. At level three the communication and decision making is done between Coordinator (representing the SC) and the EC.

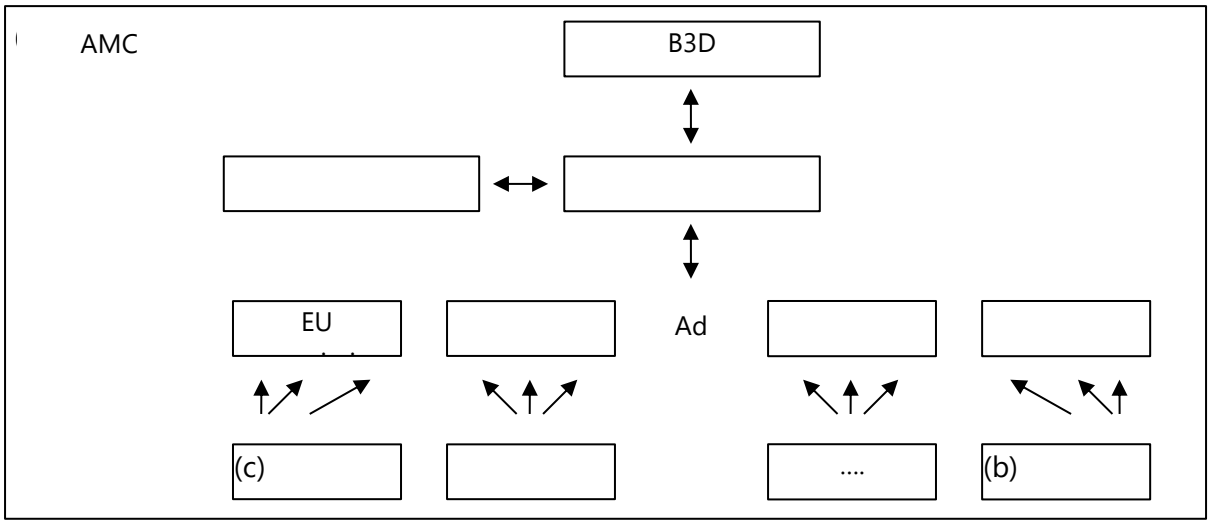


Figure 7: The project management structure.

The management structure layers

Work packages

The individual consortium partners are responsible for executing the tasks as described in this description of work. The coordinator will play a supportive role, maintaining a project-wide overview, promoting synergy, identifying possible inconsistencies and generally overseeing implementation. The coordinator is supported in his work by Work Package Leaders who are

responsible for workflow, coordination and progress of research and development activities and specific project results of the work package, including the contained tasks.

The work package leaders will report to the coordinator every six months for the purpose of efficient monitoring of the progress of the project. Although the consortium partners individually are contractors with the Commission and bound to the Grant Agreement, they also sign a consortium agreement, laying down the rules and obligations to each other. Financial risks such as a bankruptcy of SME contractors in FP projects are covered by a guarantee fund of the Commission, with which the previously collective financial responsibility of partners has been taking over by the Commission. The responsible personnel for the WPs are listed in Table 7.

Table 7 Steering committee

Work package	Allocated to:
WP1 (Coordinator)	Dr. F.M. Vos (TUD)
WP2	Prof.dr. S.A. Taylor (UCLH)
WP3	Prof.dr.ir. L.J. van Vliet (TUD)
WP4	Prof.dr. J. Buhman (ETHZ)
WP5	Prof. dr. H.C. Hege (ZIB)
WP6	Dr. H. Hatzakis (B3D)
WP7	Prof.dr. J. Stoker (AMC)
WP8	Dr C. Kompis (VOD)

Steering committee

The Steering Committee (SC) consists of one representative of each consortium partner (see table) and is chaired by the coordinator. The SC takes the following types of decisions:

Decisions related to the entry of new participants, the exit of existing ones and major shifts in tasks

After quality assurance (QA) check of technical coordinator, decision to accept/reject deliverables

Other decisions related to alterations in contract and budget

Planned publications and other dissemination actions

IPR issues

Conflict resolution as detailed in the consortium agreement

All other decisions affecting the project as a whole

Decisions can only be taken by means of a simple majority provided that at least 4 of the 7 partners are present and in case of a tie the coordinator will have a casting vote. Decisions concerning individual partners (default or acceding or leaving the consortium) can only be taken unanimously. All meetings shall produce minutes and include a list of formal decisions taken.

Coordinator

The project coordination performed by TU Delft is realised by two different entities and persons:

1. The technical and overall coordinator of the project will be Dr. F.M. Vos, whose main responsibility is to ensure that the main goals of the project are pursued and to verify the quality of all deliverables resulting from the project.

2. The non-technical project management is realised by Ms. T. Twickler of TUD's Valorisation Centre who is responsible for the following tasks:

    Liaison with European Commission

    Submission of deliverables and annual progress reports

    Budget control, financial management and declarations/payments from/to consortium partners

    Progress control (deadlines, deliverables, milestones, MM efforts and expenditures etc.)

    Co-organisation of project meetings (together with host partner), making minutes of meetings

    Preparing and implementing SC decisions on an administrative level

    Liaison with other European research projects (at the project management level)

This division in tasks will take away the administrative tasks from the technical coordinator who on his turn can dedicate himself fully to the scientific and technological content development of the project.

Participants will report man-hour expenditures and costs periodically to the project manager while maintaining a registration of same based on their own accounting principles within their own organisation. This information will be recorded in the administration system under responsibility of the project manager.

Advisory Committee

The Advisory Committee (AC) consists of high profile, senior external reviewers who give advice on the strategy and policy of the VIGOR++ project. The Committee has at least four members, appointed by the SC. The members will be experts in the fields that VIGOR++ covers and thus originate from industry, academia (EU based), investors and Government (national or EC). The Advisory Committee will be asked to provide input regarding the project's progress and milestones. Table 8 collates the experts that have been invited to join the project's Advisory Committee.

Table 8 Advisory committee members

Name	Organisation	Country	Expertise
Sir Muir Gray	National Knowledge Service	UK	Health databases.
Chayim Bell	EFCCA	Belgium	Patient representative
Prof. Maria Petrou	Informatics and Telematics Institute	Greece	Image Analysis and Pattern Recognition
Prof. Eduard Gröller	Technical University of Vienna	Austria	Computer graphics and Visualisation
Dr. Michael Grahn	Enteric	UK	Implementation of Medical Technology

Sir Muir Gray has worked in public health for 35 years. He helped pioneer Britain's breast and cervical cancer screening programmes and was knighted in 2005 for the development of the foetal, maternal and child screening programme and the creation of the National Library for Health. He is former director of the National Knowledge Service for the NHS and responsible for the National Library for Health.

Mr Chyim Bell is secretary of EFCCA and himself IBD patient. EFCCA's aim is to improve the well being of patients with inflammatory bowel disease by (1) working with and for the EFCCA Member National Associations and others throughout all of Europe; (2) facilitating the exchange of information and the promotion of cross-frontier activities; (3) effecting regular contact with the European authorities, doctors, health professionals and organisations and with others world-wide; (4) the encouragement of scientific research into Crohn's and Colitis (IBD) causes and treatment.

Prof. Maria Petrou is the Director of the Informatics and Telematics Institute in the Centre for Research and Development, Hellas, in Thessaloniki, Greece. Her research interests include many topics on Image Processing, Computer Vision and Pattern Recognition, with applications (amongst others) in Biomedicine. She has more than 350 publications and numerous articles of journalistic nature, like book reviews and conference reports and co-authored two books. She has served in the Editorial board of several high impact journals and was a member of many (inter)national committees in her field.

Prof.dr. Eduard Gröller's research interests include computer graphics, flow visualisation, volume visualisation, and medical visualisation. He is heading the visualisation group at the Institute of Computer Graphics and Algorithms. He co-authored more than 140 scientific publications and serves on various program and paper committees, such as Computers&Graphics, IEEE Transactions on Visualisation and Graphics, EuroVis, IEEE Visualisation conference, Eurographics conference. He was paper-co chair of Volume Graphics 2005, IEEE Visualisation 2005 and 2006, and Eurographics 2006.

Dr. Michael Grahn is Operations Director with Enteric, The Bowel Function Healthcare Technology Co-operative. Additionally, he is a Senior Lecturer in Biochemistry and has been working with the Academic Surgical Unit, Royal London Hospital, since 1987. His particular interests lie in the

development and implementation of complex medical technologies in the treatment of colorectal disorders. He also acts as a consultant to the European Commission and the UK Technology Strategy Board and has contributed to several medical publications.

Methods of monitoring and reporting progress

Communication

At the kickoff meeting a number of slots will be dedicated to tutorials on the different technologies and clinical knowledge involved in the project. This ensures knowledge sharing and agreement on the terminology at the beginning of the project among the partners on top of our previous interactions and collaborations. Each partner will be responsible for maintaining particular topics in the fields of their competence and ensure knowledge sharing in those fields, within and across the relevant work packages.

The internal communication will be straightforward and informal since all project partners know each other very well and they have met several times during proposal preparation. All project partners are or have been partners in framework projects before, and are well known with the procedures of communication and reporting. Information sheets, deadline recall, minutes of meetings and reports elements will be exchanged via Internet on a regular basis to reduce dead time. Moreover, the project's (web-based) collaboration space will also be used for internal dissemination of documents and knowledge.

Project meetings

A number of physical meetings is also envisaged, although the majority of the decisions may be taken after due consultation by phone or email. The levels, again, reflect the organisational structure:

WP meetings target specific technique or co-operation issues arising from the particular tasks. WP meetings are held in small groups. The WP leaders will give a short summary of past work and then each group member will give a presentation of his achievements if necessary. WP meetings involving more than one participant will usually take place along with the general project meetings in order to save the consortium resources.

General project meetings will be hold at the commencement and completion of the project, every six months during the project, and at the request of more than two project partners. All meetings will be minuted and formally structured around the previous minutes, matters arising, and actions. It will be the coordinator's responsibility to chair or to delegate chairing to another partner, depending on topic. The meeting agenda will be dispatched to all participants from the appointed Chairman one month in advance of the meeting. The most crucial meetings will be held face-to-face, but where it will not impinge on our success we will make use of phone conference facilities. Informal communication between these meetings will be supported using the project‘s web pages and mailing lists.

The general project meetings will be once a year attended by the Advisory Committee.

Steering Committee meetings take place twice every year and will coincide with the general project meetings. Such meetings will ensure that the project outcomes are verified and take into account the latest technological, clinical and market developments. Reports reaching the SC from WP's via the PC will include deliverables, milestone reports and risk-related reports. The SC will also monitor the ethical issues within the project.

Decision-making structure

Decision-making shall be devolved to the appropriate organisational level, so that three categories of decisions are distinguished:

Local decisions concerning day-to-day responsibilities of a work package are taken by the WP Leaders and participants with back up from coordinator. These decisions concern progress, quality and problems that are related to a particular WP and do not influence the project aim and plan, so they can be made within corresponding WP's through local discussions and meetings organised by the WPL's.

Co-ordinated decisions affecting more than one work package shall be referred to the coordinator. The coordinator will then initiate a discussion among the leaders of the involved WP's to reach a solution. Eventually, if a solution cannot be found through discussion, the problem will to be reported to the SC and the SC will make a final decision.

Ultimate decisions related to strategic issues impacting on the project aims and overall progress planning and control are taken at the level of the SC. The EC Project Officer shall be notified and may request participation in the decision-making. This includes resolution of conflicts that cannot be dealt with by the Project Co-ordinator.

Reviews and quality assurance

Each WP leader will have to provide an intermediate progress report every 6 months to the coordinator. The report will be written on the basis of a regularly updated detailed plan. It will contain information about the technical progress, results obtained and compliance with the work program. These reports will be combined into one report which will be the basis for discussions at the Steering Committee meetings. Progress reports will include specific management accounting by the project manager that will show the budgeted, used and remaining personnel effort and costs. Progress on dissemination will be also included as a separate chapter in the annual progress reports.

The progress of each WP and the outlook of the exploitation of the results will be critically reviewed and compared to the planning and criteria described in the work program. The coordinator is responsible for a first quality check of all deliverables and outcomes of the project. Drafts will be submitted to the SC for final approval. The assessment ensures that deliverables meet the project's requirements and are of high technical quality. Ultimate approval is done at EC level, through annual review meetings. A list and database of all deliverables and publications will be kept and updated by the coordinator and can be submitted to the Commission upon request.

Any participant who encounters a problem which may cause a delay in the program will have to inform the coordinator and the corresponding WP manager immediately. The coordinator proposes solutions at the SC, or in case of urgency to hold a virtual SC meeting by email or telephone

conference. Any occurrence or conflict that could seriously affect the work will be reported to the Commission in order to have timely feedback on alternatives and solutions.

Conflict resolution procedures

The organisational structure **is appropriate for the complexity and scale of the VIGOR++ project**. Effectively, it provides built-in escalation and transparent conflict-resolution procedures. WP1 will maintain an archive of all project-external and internal technical documents and discussions. This will be used as a base for resolving any conflicts. **Ultimate decisions** about issues impacting on the project aims and overall progress planning and control are taken at the level of the Steering Committee. The EC Project Officer shall be notified and may request participation in the decision-making. This includes resolution of conflicts that cannot be dealt with by the coordinator.

Beneficiaries

Delft University of Technology (TUD)

Department carrying out the work:	Image Sciences and Technology/Valorisation Centre
Role in the project:	Leader of WP1 (Project Management), leader of WP3 (Image analysis) and contributor to most other WP's.

Delft University of Technology, founded in 1842, is the oldest, largest and most comprehensive university of technology in The Netherlands. It offers a wide variety of education in Science, Engineering and Design. A total of 16.000 students are enrolled in one of its 14 bachelor programs (10.500 students) or in one of its 41 master programs (5500 students) including several Erasmus Mundus Masters. TU Delft has showed its responsibility towards society by focusing its research on four global themes: Energy, Environment, Infrastructures, and Health. It is partner in two recently granted KIC's (Knowledge and Innovation Community) Environment and ICT. The Delft Health Initiative combines all health research at the TU Delft, spread over various faculties and departments. It holds a strong position in developing technology for healthcare in collaboration with partners in industry and academia. It focuses on imaging technologies from nano to macro, molecular technologies for diagnosis and treatment, computer modelling and digital image analysis, measurement techniques, as well as the engineering and design of new surgical instrumentation and implants.

Key Personnel

Dr. Frans M. Vos (1969) obtained Masters Degrees in medical informatics as well as in computer science at the University of Amsterdam, The Netherlands, in 1993. He performed his graduation work at Yale University (USA). In 1998 he obtained the Ph.D. degree at the Vrije Universiteit Amsterdam and subsequently he was a research fellow with the Department of Applied Physics of Delft University of Technology. He became assistant professor with Delft University of Technology in 2003. Since 2000 he is also a staff member with the Department of Radiology at the Academic Medical Centre Amsterdam. Dr Vos is past treasurer of the Dutch Society for Pattern Recognition and Image Processing (2000-2007). Since 2007 he is a member of the education board of the

Master's program on Biomedical Engineering. His main research interests are in medical image processing and visualisation, particularly focussing on virtual colonoscopy, diffusion tensor imaging. He was able to acquire many research Grants from the Dutch Foundation for Scientific Research, Dutch Foundation for Technology and Philips Healthcare. He has been responsible for the development of many tools for CT colonography in Philips' ViewForum workstation. He has supervised 10 Ph.D. students and 40 graduate students and authored and co-authored over 70 peer-reviewed publications in the field of medical imaging.

Professor Dr Ir Lucas J. van Vliet is Professor of Image Analysis at the Delft University of Technology, Director of the Delft Health Initiative, Chairman of the Department Imaging Science & technology, and Head of the Quantitative Imaging group. He obtained his Ph.D. degree cum laude in 1993 and was awarded a prestigious talent research fellowship from the Royal Dutch Academy of Arts and Sciences (KNAW) in 1996. In 1999 he was appointed Antoni van Leeuwenhoek professor. Professor van Vliet is past president (2003-2009) of the Dutch Society for Pattern Recognition and Image Processing (NVPHBV) and sits on the board of the International Association for Pattern Recognition (IAPR) and The Netherlands Advanced School for Computing and Imaging (ASCI). He is (co)author of more than 200 peer reviewed research papers, supervised 20 Ph.D. theses and is currently supervising another 12 Ph.D. students. He was visiting scientist at Lawrence Livermore National Laboratories (1987), University of California San Francisco (1988), Monash University Melbourne (1996), and Lawrence Berkeley National Laboratories (1996). He has initiated and acquired numerous competitive research grants through various funding agencies and public-private partnerships.

Theresia Twickler, MSc, is Senior Project Manager in the Valorisation Centre. She has been managing projects with EU funding since the Third Framework Programme onwards together with supporting staff of assistants and financial officers at TU Delft. Her present portfolio contains an FP6 project (15 partners), two FP7 projects (8 partners each), an Asia Switch project (with 7 partners from Asia including UNEP and UNIDO). She is involved as Liaison Officer on behalf of TU Delft in the Dutch Association of Universities, taking part in member state discussions on the preparation and evaluation of EU Framework Programmes. She is co-founder of the Dutch association of EU project managers (EUPMAN).

University College London Hospitals

Department carrying out the work:	Department of Gastroenterology
Role in the project:	Leader of WP2 (Clinical Data Acquisition and Data Management) and contributor particularly to WP7 (Clinical application) as well as several other WP's.

UCL is one of the UK's top 4 medical schools whatever criteria are adopted. The associated hospital group is a dynamic foundation trust, and is one of only 5 in England to be awarded Comprehensive Biomedical Research Centre status by the National Health Service. It was recently designated as one of the UK's first academic health science centres (based on demonstrating excellence in research, education and patient care). UCL is Europe's second most productive partnership for biomedical science research (according to The Partnership for Science & Technology Studies), which accounts

for 65 per cent of all University activity. The Department of Gastroenterology at UCL and UCH is one of the biggest in the UK and has a very substantial research output as well as an impressive clinical reputation. Specifically in the field of inflammatory bowel disease there are more than 1000 current patients with the condition. There is excellent GI pathology back-up, and imaging support in the hospital is second to none in the UK. The institution has an extremely strong track record and international reputation in medical imaging. By way of illustration, a recent RAND Europe review of the UK (Thed van Leeuwen, Jonathan Grant. Report WR-368-68; April 2006) UCL was the only critical mass contributor to the field "Radiology, Nuclear Medicine, and Medical Imaging ", contributing 18% of HCPs in that field. It holds EPSRC/CRUK Imaging in Cancer Centre status. The Department of Imaging has attracted £16.9M grant funding (£4.4M principal applicants and £12.5M as co-applicants) in the last 7 years and has published over full 120 peer-reviewed publications in the last 5 years. A research 3T MRI facility is currently being installed. Prof Steve Halligan (dept chair) is NIHR senior faculty and the only Radiologist PI to date awarded a NIHR program grant. Important collaborations with pre-clinical partners particularly Centre for Medical Image computing (Prof Dave Hawkes) and Centre for biomedical imaging (Dr Mark Lythgoe) form an integral part of the research program of the unit.

Key Personnel

Prof. Alastair Forbes is professor of Gastroenterology at University College London and University College Hospital. He is Head of the Centre for Gastroenterology and Theme Leader for Research and Development. He was Medical Director of Core (the Digestive Disorders Foundation) and is now Chairman of the Education Committee of the European Society for Nutrition and Metabolism (ESPEN). He was previously consultant at St. Mark's Hospital (1992-2005), Dean of the St. Mark's Academic Institute, Honorary Secretary of the British Society of Gastroenterology, and Chairman of the British Association for Parenteral and Enteral Nutrition (2002-5). His interests lie mainly in inflammatory bowel disease and nutrition, including laboratory work on intestinal regeneration. He has written more than 140 original papers, over 80 review articles, together with books, videos and CD-ROMs.

Dr Stuart Taylor is one of just two HEFCE funded academic Radiologists in the UK. He is a Reader in ClinicalRadiology, University of London and honorary Consultant Radiologist, University College London NHS Foundation Trust. He currently sits on the NCRI Colorectal Surgical Subgroup, is Research Officer for British Society of Gastrointestinal and Abdominal Radiology, and is a member of the Royal College of Radiologists Research Committee and European Society of Gastrointestinal and Abdominal Radiology CT colonography and Educations Committees. He is the chairman of the Abdominal Imaging Section for the European Congress of Radiology (ECR) 2012. He leads the Department of Health Radiological Academic Clinical Fellows and Academic Clinical Lecturer Programme at UCLH/UCL. He was recipient of Radiology Editor's Award for 'reviewing with distinction' 2007-2009, awarded to less than 10% of reviewers. He is the current Royal College of Radiologists travelling Roentgen Professor. He has published 20 book Chapters, invited reviews, guidelines and letters: and has 90 full peer review publications with an H index of 19. He has attracted over £3M Euros grant income as principal or co-applicant, including grants from the National Institute of Health Research and Health Technology Assessment Board. He currently heads the functional MRI research program at UCH and is lead for a new 3T MRI research facility. Current

research interests include the use of MRI, CT and ultrasound in the prediction of histological markers of disease activity in Crohn's disease. He has published widely on the use of computer aided detection software in CT colonography.

Eldgenössische Technische Hochschule Zürich (ETHZ)

Department carrying out the work:	Computer Science
Role in the project:	Leader of WP4 (Modelling) and contributor to several other WP's.

ETH Zurich is the study, research and work place of 20,000 people from 80 nations. About 370 professors in 16 departments teach mainly in the engineering sciences and architecture, system-oriented sciences, mathematics and natural sciences areas and carry out research that is highly valued worldwide. As an internationally oriented institution of higher education and a nationally grounded one this forward-looking task is fulfilled in service to the Swiss nation. Twenty-one Nobel Laureates are connected with ETH Zurich. Maintaining and developing its top standing in the international competition among top universities is an important task of ETH Zurich.

Key Personnel

Prof. Dr Joachim M. Buhmann leads the "Machine Learning Laboratory" in the Department of Computer Science at ETH Zurich. He has been a full professor of Information Science and Engineering (Informatik) since October 2003.

Born in 1959 in Friedrichshafen, Germany, he studied Physics at the Technical University Munich and obtained his PhD in Theoretical Physics with Professor Klaus Schulten. His doctoral thesis investigated pattern recognition problems in neural networks. He then spent three years as a research associate and as a research assistant professor at the University of Southern California, Los Angeles. In 1991, he joined the Lawrence Livermore National Laboratory in California. From 1992 to 2003, he held a professorship of applied Computer Science (praktische Informatik) at the University of Bonn, Germany.

His research interests spans the areas of pattern recognition and data analysis, including machine learning, statistical learning theory and applied statistics. Application areas of his research include image analysis, medical imaging, information security and bioinformatics. He is currently the president of the German Pattern Recognition Society (Deutschen Arbeitsgemeinschaft für Mustererkennung). He has been associate editor for IEEE Transactions on Neural Networks (1998-2004), IEEE Transactions on Image Processing (2003-05) and IEEE Transactions on Pattern Analysis and Machine Intelligence (2004-08).

Dr. Cheng Soon Ong is a research associate at the Machine Learning Laboratory of the Department of Computer Science at ETH Zurich. He completed his PhD titled "Kernels: Regularization and Optimization", at the Australian National University in 2005. He shortly held a postdoc position at the Statistical Machine Learning Group, in NICTA, Canberra, followed by longer ones at both the Max Planck Institute of Biological Cybernetics and the Friedrich Miescher Laboratory. Prior to his PhD, he

researched and built a search engine at Bahasa Malaysia Technologies at Mimos Berhad, Malaysia. He obtained his B.E. (Information Systems, 1999) and B.Sc. (Computer Science, 1997) from the University of Sydney, Australia. Since 2007, he has been action editor at the Journal of Machine Learning Research and advocates open source software through mloss.org. He is currently working on kernel methods and computational biology.

Zuse Institute Berlin (ZIB)

Department carrying out the work:	Visualisation and Data Analysis Department (VDAD)
Role in the project:	Leader of WP5 (Interactive Visualisation).

The Visualisation and Data Analysis Department (VDAD) of the Zuse Institute Berlin (ZIB), Berlin, Germany, currently consists of 4 research groups with about 25 researchers and 21 master students. The main research areas of the VDAD are interactive visualisation, geometry reconstruction and data analysis, especially for biomedical applications. Currently there are several ongoing research projects funded by the European Union, the DFG (German Research Foundation), BMBF (Federal Ministry of Education and Research), three Max Planck Institutes and companies. VDAD produces about 30 reviewed publications per year in journals and international conferences and is quite active in the international research community on graphics and visualisation. Such activities include paper reviewing and conference chairing, program committee memberships for numerous international conferences, and conference organization. For example, EuroVis 2009 – Eurographics/IEEE Symposium on Visualisation, the largest European conference on data visualisation, was organised by the VDAD in Berlin. The ZIB is co-initiator and partner of the DFG Research Center Matheon which develops mathematics for key technologies, including visualisation, and which supports partners in industry, economy and science. VDAD has established four spin-off companies, all in the field of visualisation.

Key Personnel

Prof. Hans-Christian Hege is head of the Visualisation and Data Analysis Department at Zuse Institute Berlin (ZIB). After studying physics and mathematics, he performed research in computational physics and quantum field theory at Freie Universität Berlin (1984-1989). Then, he joined ZIB, initially as a scientific consultant for high-performance computing and subsequently as head of the Scientific Visualisation Department, which he started in 1991. His group performs research in visual data analysis and develops visualisation software such as Amira and Biosphere3D. He is cofounder of Mental Images (1986), Indeed—Visual Concepts (1999) (now Visage Imaging) and Lenné3D (2005). He teached as guest professor at Universitat Pompeu Fabra, Barcelona, as honorary professor at the German Film School (University for Digital Media Production), and as lecturer at the Freie Universität Berlin. His research interests include many branches in visual computing and applications in natural sciences, life sciences, and engineering. Hege co-authored more then 220 scientific publications and acted as a reviewer for numerous conferences and journals in the field. He also served at more then 40 international program committees (like IEEE Transactions on Visualizaton and Graphics, Computers & Graphics, ACM Siggraph, EuroVis symposium, IEEE Visualisation conference, Eurographics conference). He was

paper co-chair of VMLS 2009, EuroVis 2009, Volume Graphics 2008 and 2007, TopoInVis 2007, VisMath 2002, 1997 and 1995. He is member of Advisory Board of the SciDAC Institute on Ultrascale Visualisation, Davis, USA; the Advisory Board, AFI/TFI, Sendai, Japan; the steering committee of section Graphical Data Processing of GI; and the steering group of Eurographics on Visual Computing for Biology and Medicine. Furthermore he serves as vice-speaker of the working group Visual Computing in Medicine of the German Association of Computer Science (GI). He is member of IEEE Computer Society, ACM (Association of Computing Machinery), GI (Gesellschaft für Informatik), DPG (German Physical Society), and CURAC (German Society for Computer- and Roboter-assisted Surgery).

Dr. Steffen Prohaska is deputy head of the Visualisation and Data Analysis Department and is leading the Visualisation Systems group. He received his PhD in Computer Science from the Universität Potsdam in 2007. He also holds a diploma in physics from the Technische Universität Darmstadt. His main research interests are visualisation systems and the visual analysis of image and flow data. He published several refereed articles in these areas. He contributed to the scientific community as a member of the internal program committee of the Eurographics/IEEE Symposium on Visualisation. Dr. Prohaska is also leading the development of the visual data analysis system Amira/Avizo, which ZIB and two companies have been jointly developing. Together with the project managers at the companies, he is steering the system architecture and the integration of code contributed by approximately fifty researchers and software developers.

Vincent Dercksen received his M.Sc. degree in technical informatics from Delft University of Technology, Netherlands, in 2003. Since then, he has been a research scientist and PhD student in the Visualisation and Data Analysis Department at the Zuse Institute Berlin (ZIB). His research topics include 3D geometry reconstruction and biomedical image analysis.

Biotronics3D Limited

Department carrying out the work:	R&D
Role in the project:	Leader of WP6 (System Architecture and Integration), and contributor to several other WP's.

Biotronics3D Ltd was established in 2004 in London and opened an R&D centre in Cambridge in 2009. The company develops and markets innovative components and complete medical software systems for the diagnostic imaging industry. Biotronics3D core technology known as 3Dnet™ Suite[37] offers fast distribution of images across the medical enterprise and has received FDA 510K market clearance and is CE marked. This servicing platform has allowed the company to enjoy a significant position in the international market of advanced medical imaging spanning Europe, North America, Japan and Africa and to sustain substantial growth. The company closed its first round of institutional investment in August 2008 (Longbow Capital).

[37] http://www.3dnetsuite.com

Key Personnel

Dr Harry Hatzakis is co-founder and CEO of Biotronics3D. He has spent all his professional working years in medical technologies in Europe and North America, progressing from R&D through Product Management to Strategic Global Marketing of Diagnostic Imaging Solutions. He has ample experience in global markets having successfully introduced several new lines of products. Harry studied Electrical Engineering as well as Medicine in Greece and Electrical Engineering at Imperial College, London. His current main research is in the field of the management, analysis and visualisation of medical images and their interface to Electronic Health Records. Examples of the recent projects he has been responsible for include a CONNECT project in 2005 from the London Development agency, a SMART R&D award from the UK department of Trade and Industry during 2005-7, a CASE Award by EPSRC to support post graduate research in medical imaging during 2005-7, the usability work package in FP6 MUTED and the MODiMaS project co-funded by EEDA (2009-2011) developing subsystems to support clinical, administrative, research and patient services related to breast cancer.

Dr Soeren Grimm is co-founder and CTO of Biotronics3D with more than 10 years of experience in devising and developing innovative products for the medical imaging market. He has contributed to the development of many start-ups in Europe and USA, including Tiani MedGraph AG, Austria and Viatronix Inc., USA. He holds a Ph.D. in Computer Science from Vienna University of Technology, Austria, and an MSc in Computer Science from the University of Tübingen, Germany. His interests include web technologies, computer graphics, scientific visualisation, computer architecture and especially medical visualisation. He has co-authored numerous scientific articles, is co-inventor of one issued and two pending patents, and acts as reviewer for many conferences and journals in the field.

Rado Andriantsimiavona is a Senior Software Engineer at Biotronics3D. He has over 10 years experience in medical imaging, healthcare and science, in various positions from software engineering, academic research to business development for top tier institutions. In particular, he held positions at Renishaw (UK), SecureRAD (USA), Apple Europe (UK), Guy's & St Thomas Hospitals, (UK), Philips Healthcare (Netherlands) and Metrovision (France). He has an MPhil in Interventional Cardiac MR Imaging, from King's College London, an MSc in Digital Signal & Image Processing from Cranfield University and an Engineering Diploma in Mathematics, Computer Sciences & Biomedical Engineering, Université de Technologies de Compiègne, Compiègne, France.

Laurence Bourn is a Senior Imaging Scientist at Biotronics3D with 12 years of industry experience in 3D medical imaging. He has worked for a variety of European start-up companies in medical imaging including Voxar, 3mensio and Medis. He has a broad range of technical skills including volume visualisation on GPU/CPU, high performance code and cloud computing. Laurence studied Mathematics at Warwick University and has done postgraduate work at Liverpool and Edinburgh computer science departments.

Academic Medical Centre, University of Amsterdam

Department carrying out the work:	Department of Radiology
Role in the project:	Leader of WP7 (Clinical Data Acquisition and Data Management) and contributor particularly to WP2 (Clinical application) as well as several other WP's.

The Academic Medical Centre of the University of Amsterdam is one of the leading medical schools in the Netherlands. GI diseases are one of the spearheads of research and patient care. The department of Radiology of the Academic Medical Centre has extensive experience with the development and evaluation of imaging methods for GI diseases, especially of the small and large bowel (project leader Prof. Dr. J. Stoker). Emphasis is on imaging of (precursors of) colorectal cancer (colonography/virtual colonoscopy; molecular imaging), MRI in IBD, pelvic floor imaging and MR spectroscopy of liver steatosis. The department of Radiology has a close collaboration with the department of Gastroenterology in the development and evaluation of these imaging methods for GI diseases. Approximately 2000 patients with IBD are treated at the AMC. The department of Radiology has an extensive experience with multicenter collaborations.

Key personnel

Prof Dr Jaap Stoker is professor of Radiology with a special interest in abdominal radiology. He is abdominal radiologist, head of research at the department of Radiology, head of the abdominal imaging fellowship and chair of the Abdominal imaging chapter of the Radiological Society of the Netherlands. He has been member of the board of the Radiological Society of the Netherlands (2002-2005) and chair of the Annual Meeting of the Radiological Society of the Netherlands (2002-2005). He is chair of the section Abdominal Radiology of the Radiological Society of the Netherlands (2005-2010). He was/is member (chairing one national guideline) of several national guideline workgroups on gastrointestinal diseases (including on inflammatory bowel diseases). He is author of over 180 peer reviewed papers (H-index 30) and 25 book chapters and is reviewer for several journals including Radiology. He is Editor of the Nederlands Tijdschrift voor Geneeskunde (Dutch Medical Journal) and member of the Signalling Committee Cancer of the Dutch Cancer Society. He has written many granted proposals in the field of development and evaluation of GI imaging (Dutch Organisation for Health Research and Development ZonMw (Dutch Research Council) and Dutch Cancer Society).

Dr Manon Ziech is research fellow MR imaging in Crohn's disease at the department of Radiology. She has performed several studies on MRI of the small and large bowel in Crohn's disease and on MRI of perianal Crohn's disease. The aim of these studies was to develop new methods in MRI in Crohn's disease and evaluate the accuracy and patient acceptance.

Dr Aart Nederveen is MR physicist at the department of Radiology. He is involved in several projects concerning development and evaluation of GI imaging, including MRI in Crohn's disease (primarily at 3T). He has authored and co-authored over 20 peer-reviewed publications in the field of medical physics and bioinformatics and assists several PhD students.

Dr. Cyriel Y. Ponsioen was trained in Internal Medicine and Gastroenterology & Hepatology from 1989-1998. He is currently a senior staff-member of the Department of Gastroenterology & Hepatology at the Academic Medical Centre in Amsterdam. From 1995-2000 he has devoted 40 % of his time to his PhD thesis titled "Etiologic and Clinical Studies in Primary Sclerosing Cholangitis (PSC)", under supervision of Prof. Dr. G.N.J. Tijtgat. In the past five years he has been involved in several large-scale projects concerning Barrett's esophagus research as well as several projects concerning PSC. Since 2006 he is principal investigator of a large scale project covering almost 50 % of the Dutch population (amounting to 8 mln inhabitants) titled: "Epidemiology and Natural History of, as well as Risk Factors for Primary Sclerosing Cholangitis and Primary Biliary Cirrhosis in Central Netherlands". He heads, together with dr. Pieter C. Stokkers, the tertiary referral IBD-centre of the Academic Medical Centre in Amsterdam since 2007. Currently, he is principal investigator of a multicenter epidemiologic project studying the occurrence of intercurrent infectious enterocolitis in IBD. He has published more than 25 articles and has coached several PhD students.

Vodera Limited

Department carrying out the work:	Collaborative R&D
Role in the project:	Leader of WP8 (Dissemination, Exploitation and New applications) and contributor to several other WPs.

Vodera is an innovation accelerator company, specialising in bridging the gap which prevents emerging technologies from making significant contributions to business growth. This gap is often caused by badly defined system requirements, inaccurate estimates of needed resources or poor handling of intellectual property. Vodera was founded in 2006 and assists high-tech start-ups, technology corporations and universities create competitive advantage by rapidly developing new systems and solutions, commercialising technology breakthroughs and transferring knowledge across projects and business units. Vodera maintains close relationships with many experts from academia, industry, and government, who are an invaluable resource when it comes to analysis, scientific dissemination or commercial exploitation activities. Currently, Vodera is engaged in the Framework 7 projects FeedNetBack and RAPPORT, leading work packages related to roadmap development, exploitation and dissemination. The senior staff of the company has also worked in FP6 RUNES, WINNER, MAGNET and FP5 PAMPAS.

Key Personnel

Dr Costis Kompis is the Managing Partner of Vodera specialising in knowledge exchange, technology transfer and research strategy. He has over fifteen years of experience, the first part of which was devoted to ICT research and development and the second part to innovation management and technology commercialisation. He serves as manager of the Wireless Sensing Interest Group (WiSIG), as well as on a number of advisory committees for scientific research, engineering and economic development. He has also helped organise and chaired numerous international workshops and meetings. His work has received several awards, including a Marie Curie Postdoctoral Fellowship, an EPSRC Realising Our Potential Award, a Nokia Invention Award, and the Ericsson First Award of Excellence in Telecommunications. He has a PhD in Computer Science, an MSc in Technology and

Innovation Management and an MEng in Electronic and Computer Engineering. He has also been trained in project management, intellectual property exploitation, technology roadmapping and contract law.

Dr Vaia Sdralia is Partner of Vodera specialising in the design and engineering of communication networks and international market analysis. She has held R&D and product management positions with NEC Europe, Samsung Electronics Research Institute, ARRIS Interactive, the Information Security Group at Royal Holloway University of London and the Aristotle University of Thessaloniki where she worked on medical imaging applications. Vaia has published over forty papers, filed eight patents and sits on various committees and standardisation groups. She holds a PhD in Computer Science, an MSc in Telematics and a BEng in Informatics.

Prateek Sureka is a Research and Innovation Manager of Vodera specialising on technology roadmapping and research commercialisation. He has worked at the University of Sussex as an online search specialist. Prior to that, he worked as computer network specialist. He has helped to organise several technological forums and focus groups. In a short stint of career he has represented the UK in major global business competition and has won other awards in business management and entrepreneurship. He holds an MSc in Technology and Innovation management and a BEng in Electronics and Telecommunication Engineering.

Consortium as a whole

Overview of the consortium

The VIGOR++ consortium is a well balanced and highly interdisciplinary group of academic, clinical, and industrial partners with expertise to carry out novel R&D in the emerging fields of medical diagnosis and disease monitoring. In particular, the consortium comprises partners from medical research (2 Hospitals), ICT experts (3 Universities and 1 SME) and an industrial intermediary (1 SME) coming from all over the European Union. All partners have long experience in research and are used to working in collaborative R&D projects. We have been careful not to make the consortium too large in order to keep the activities focused and the communication overheads low. We want European quality and commitment but not too much internal communication. In fact, we believe that external dissemination is more valuable, than using our energy in disseminating between ourselves. As depicted in Table 9 each of the seven organisations in the consortium has clearly defined and complementary areas of responsibility and proven collaboration experience.

Table 9 Consortium expertises (vertically) and project partners (horizontally); the color of the circles indicates the extend of expertise (black: extensive know-how; white: no know-how).

Research area	TUD	UCLH	ETHZ	ZIB	B3D	AMC	VOD
Abdominal Radiology		●				●	
Image Processing and Analysis	●		◐	○	○		
Pattern Recognition and Machine Learning	◐		●	○	○		◐

Interactive Visualisation and Computer Graphics	●		●	●	●		
System architecture and integration					●		●
Clinical Management of Crohn's Disease		●				●	
Knowledge Exchange and Exploitation					●		●

The formation of the VIGOR++ consortium targeted to ensure a good representation of the entire supply chain for medical imaging solutions. Therefore, we have within the team access to high quality medical data, expertise to generate practically usable models from it as well as expert users defining needs to be addressed. The medical data will be supplied by participants AMC and UCLH (Radiology Departments). The academic participants (TUD, ETHZ, ZIB) bring the necessary know-how regarding development and integration of image analysis, pattern recognition and scientific visualisation methods and have a strong experience in the biomedical field. B3D is experienced in translating academic research, integrating ICT components, creating practically usable systems and bringing these to the market. AMC and UCLH (Gastroenterology Departments) also bring know-how concerning management of Crohn's disease. The planned clinical trials will determine the effectiveness of the resulting system and help the industrial participants (VOD, B3D) establish it as commercially viable option in the healthcare market. Both companies are very close to the target customers and correspondingly aware of their needs, enabling the consortium to spot quickly the opportunities offered by the application of new technology.

Subcontracting

Subcontracting is not envisaged in the project, except for the audit certificates to be provided by externally contracted auditors in case a partner receives more than €375.000 EC contribution.

Other countries

All but one participant are based inside the EU: ETHZ resides in Switzerland.

Resources to be committed

The financial plan is tailored specifically to the needs of the project. The person months in the WPs is fitting to complexity of the tasks to be conducted. Together with the equipment and the complementary resources shown here the financial plan is adequate – ensuring project success while not wasting resources and fitting the expected impact. The financial plan is tailored specifically to the needs of the project. The person months in the WPs is fitting to complexity of the tasks to be conducted. Together with the equipment and the complementary resources shown here the financial plan is adequate – ensuring project success while not wasting resources and fitting the expected impact. The overall budget is composed as follows:

VIGOR++		TU Delft	UCLH	ETHZ	ZIB	B3D	AMC	VOD	
		1	5	7	3	2	4	6	TOTAL
RTD activities									
TOTAL Person Months		90	40	76	40	72	40	26	**384,0**
COST MODEL		**AIC**	**SFR**	**SFR**	**SFR**	**SFR**	**SFR**	**SFR**	
BUDGETED COSTS FOR RTD									
	Direct costs Personnel (EUR)	450.000	208.000	433.200	240.000	360.000	212.000	130.000	2.033.200
	Travel/subsistence for meetings	30.000	10.000	20.000	10.000	20.000	10.000	10.000	110.000
	materials	5.000	2.500	5.000	2.500	5.000	2.500	2.500	25.000
	scans		30.000				30.000		
	TOTAL DIRECT COSTS RTD	**485.000**	**250.500**	**458.200**	**252.500**	**385.000**	**254.500**	**142.500**	**2.228.200**
	INDIRECT COSTS	**468.000**	**150.300**	**274.920**	**151.500**	**231.000**	**152.700**	**85.500**	**1.513.920**
TOTAL COST FOR RTD		**953.000**	**400.800**	**733.120**	**404.000**	**616.000**	**407.200**	**228.000**	**3.742.120**
	percentage funding	75%	75%	75%	75%	75%	75%	75%	
TOTAL EU contribution		**714.750**	**300.600**	**549.840**	**303.000**	**462.000**	**305.400**	**171.000**	**2.806.590**
MANAGEMENT activities									
Wp	**WP title**								
1	Project Management (non-scientific)	10							**10,0**
BUDGETED COSTS FOR MANAGEMENT:									
	Direct costs Personnel	77.500	0	0	0	0	0	0	77.500
	Project meetings & travel for management	10.000	0	0	0	0	0	0	10.000
	Dissemination workshops							10.000	10.000
	Advisory Board	18.000							18.000
	DIRECT COSTS MGT	**105.500**	**0**	**0**	**0**	**0**	**0**	**10.000**	**115.500**
	INDIRECT COSTS	**52.000**	**0**	**0**	**0**	**0**	**0**	**6.000**	**58.000**
	Subcontracting (Audits*)	**4.000**	**0**	**2.000**	**0**	**2.000**	**0**	**0**	**8.000**
TOTAL COST MGT		**161.500**	**0**	**2.000**	**0**	**2.000**	**0**	**16.000**	**181.500**
	percentage funding	100%	100%	100%	100%	100%	100%	100%	
TOTAL EU Contribution		**161.500**	**0**	**2.000**	**0**	**2.000**	**0**	**16.000**	**181.500**

TOTAL COSTS PARTICIPANT		**1.114.500**	**400.800**	**735.120**	**404.000**	**618.000**	**407.200**	**244.000**	**3.923.620**
TOTAL EU contribution		**876.250**	**300.600**	**551.840**	**303.000**	**464.000**	**305.400**	**187.000**	**2.988.090**
	percentage project management	4,63%							

Figure 8: Financial overview table.

The total cost of the project is €3.923.620 and the total requested EC contribution is €2.988.090.

Figure 9 depicts the total EU contribution on RTD activities per partner.

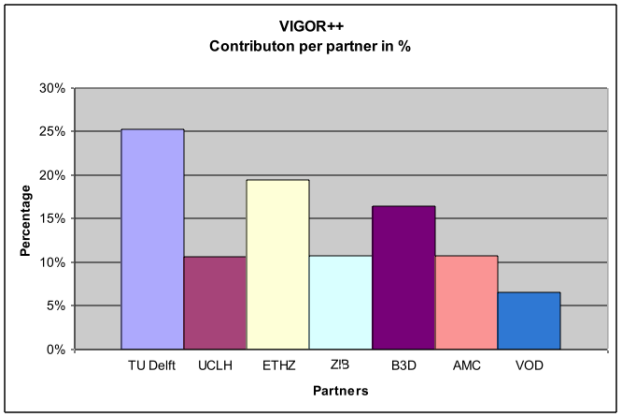


Figure 9: Total EU contribution (%) regarding RTD activities per partner.

RTD

Staff

The participants are both able to invest by means of co-financing the proposed research and to achieve return of the investment through revenue generated by the exploitation of the results in their products and services. The required effort in person-hours for each task was carefully

calculated by the professionals concerned once the detailed work plan was finalized at the tasks level. The partners will mostly employ PhD staff to carry out the work.

Table 10 f effort (in person months) stratified by staff type (vertically) and partners (horizontally).

	TUD	**UCLH**	**ETHZ**	**ZIB**	**B3D**	**AMC**	**VOD**
PHD student/research fellow	72	36	36	36	0	36	0
Postdoc/junior staff	0	0	36	0	41	0	14
Senior staff	18	4	4	4	31	4	10
Administration	10	0	0	0	0	0	0
Total	90	40	76	40	72	40	26

Travel

We have allowed approximately €3,000 per 12 person months to cover the travel costs to attend project meetings and international conferences. Travel cost thus represents 2.94% of the total.

Equipment resources

This project will use conventional of-the-self computer hardware (laptop/desktop computers) and 3rd party application software. As such requirements for equipment resources are limited. We have allowed approximately €2,500 per 36 person months to cover the equipment costs.

Data acquisition

We plan to conduct 150 MRI studies both at UCLH and AMC during the project. Therefore, part of the budget needs to be reserved since such imaging is currently not part of the regular care. MRI scanning cost per subject is estimated to be €250 at UCLH and AMC. The prospective colonoscopy collection at the AMC and UCLH concerns examinations that are performed as part of the patients' regular care and therefore no additional funding will be required. However, the extensive histopathology assessment that is required falls outside regular funding, which cost is budgeted at €100 per subject (both at UCLH and AMC). Additionally, we budget €50 per study for subject recruitment. The total cost will be €30,000 = 75*(250 +100 +50). The generated MRI datasets will be used in addition to the existing studies that AMC and UCLH will supply.

Management

The Management budget is mostly reserved for the non-scientific management of the project. For this, a dedicated project manager is assigned to support the coordinator and the consortium in all non-scientific activities and outputs. The ten person months are reserved based on experience of TU Delft in the management of similar STREP like ICT funded projects: 3 MM per year + one extra MM at the end for final reporting.

Clearly, the partners will be involved in 'scientific' management, e.g. the coordination of research activities. Such scientific management is integrated in the WPs.

A small budget is dedicated to the logistics of the (6) project meetings (€10,000). Furthermore, the costs of the Advisory Committee are set are set to € 1,200 per committee member for 3 meetings, including travel, living allowance and a maximum daily fee (total: €18,000). Moreover, a dedicated budget of €10,000 was planed for the dissemination workshops covering organisation, travel cost of guest speakers and panelists. As such, the total management cost is only 4.63% of the total project cost.

Impact

Strategic impact

VIGOR++ contributes to all 5 expected impacts described for Objective ICT-2009.5.3 Virtual Physiological Human. Below we show how each of these impacts will be realised.

Expected impact I (on patients)

More predictive, individualised, effective and safer healthcare

Inflammatory bowel diseases, such as Crohn's disease, constitute a major burden for society, both in monetary costs and in suffering of patients and their relatives. Crohn's disease can affect any part of the gastrointestinal tract, from the mouth to the anus, but primarily concerns the small bowel and the colon. Symptoms do not necessarily correlate with disease activity, which complicates treatment. What is more, treatment is associated with substantial side effects and cost. Frequent examinations are necessary to monitor response. The ageing society and the altering living habits add to this burden. Currently, approximately 700,000 patients are affected in Europe alone and increasing.

Those patients will be served directly by the project results by integrating detailed, quickly accessible and readily updateable information. The project tools will bring advanced ICT systems to disease management offering to **patients** with Crohn's disease the prospect of a non-invasive, radiation free, low-risk and accurate diagnostic environment. The VIGOR++ tools will not only result in disease management that is less disruptive to patients' day-to-day lives but will also empower the patients via simple portals to play an active role in their care. Consequently, the project will have a significant economic impact by reducing patient's time out of work given that IBD affects many people at a very productive age. At the same time public and private health insurance organisations would face significantly reduced costs.

Expected Impact II (on clinicians)

Accelerated developments of medical knowledge discovery and management, development of devices and procedures using in-silico environments

The associated work plan gives a clear view on the collaboration for knowledge discovery, management and implementation. It is especially designed to allow fast setup of highly interdisciplinary research and to foster the partner's mutual understanding of each other's research area – leading to more multidisciplinary research excellence. Importantly, the developments are

driven by clearly identified clinical needs. Hence, the project will create impact by delivering a plethora of benefits for **clinicians** using the envisaged ICT tools including:

Increased efficiency of diagnosis.

Integrated support for diagnosis and treatment planning

The ability to assess disease progress and predict potential complications both objectively and personally.

Minimisation of the need for optical colonoscopy particularly for vulnerable patients, such as elderly patients, patients with another serious illnesses, and patients who are unable to tolerate sedation or bowel preparation (e.g. due to allergy or psychological reasons).

Automatic identification of results outside acceptable ranges.

Support for 'shared decision' making with patients.

Quantification of medication efficiency (type and doses).

Tools for quantitative assessment of potential drug interactions

Notably, the latter two benefits concern direct VIGOR++ impacts on medication related issues: correct medication is of vital importance because of the high prevalence and the chronic, lifelong nature of IBD.

Expected Impact III (on healthcare systems)

Improved interoperability of biomedical information and knowledge

Many Crohn's patients are diagnosed in their teenage years or early twenties. Patients need life-long support from the health services to enable them to achieve the best quality of life they can within the constraints of their illness since no cure has yet been found. At the same time people are more mobile than ever. Information about an individual's symptoms and treatment must be readily available independent of location. The project will improve the interoperability of medical information and knowledge by overcoming the main difficulties with the Crohn's disease management within healthcare systems which can be summarised as:

1. Management by a multidisciplinary (and geographically distributed) team is required.

2. Self-management requires support by rapid access to specialist services

3. Care needs to be personalised and customised to the individual patient.

4. Treatment moves from hospitals to the community where a 'super' nurse plays a key role.

Increasing complexity of the involved medical imaging.The VIGOR++ system yields new knowledge related to the GI tract by delivering ICT models for personalized assessment of the organ that are combined with clinical evidence and associated information. The project will ensure that all essential information to manage a patient with IBD is easily accessible in a clearly presented form at the point

of care. The integrated presentation of IBD patient information and analyses of such information is what makes the project unique: it is the key to improved care.

Increased cost of healthcare delivery puts pressure on cost reductions.[38]. We expect that the project will have a direct impact on **hospitals** by reducing the cost and disease management (increased throughput, reduction in length of stay) and by improving their return on investment of acquired technology (MRI scanners.). There is also an impact for **national health systems**, as the outcome will help them meet targets set (waiting lists etc.).[39] Finally, **health insurance companies** are expected to benefit by reduced costs which can be passed to clients.

Expected Impact IV (on the pharmaceutical industry)

Increased acceptance and use of realistic and validated models that allow researchers from different disciplines to exploit, share resources and develop new knowledge

Currently, all pharmaceutical companies are in a very competitive race to develop the next generation of medication for IBD and particularly Crohn's, as there is no known cure for the disease. Several promising types of medication are prescribed to treat Crohn's disease (Aminosalicylates, Immunomodulators, Corticosteroids, Cyclosporine and Tacrolimus, Infliximab) but without sufficient long-term medical evidence. Their side effects are not fully known, but some of them even mimic IBD symptoms. The project can **address a frequently acknowledged risk in Crohn's treatment: the mismanagement of drug intervention due to missing data**.

It is expected that the ICT tools produced by VIGOR++ significantly increase the knowledge emanating from clinical trials for Crohn's by offering effective ways to perform early assessment of drug action. For instance, does the new drug do what is expected, and, is there objective, quantitative evidence on its effectiveness? These decisions can have a direct impact on the cost reduction of bringing the new drug to the market. It should be noticed that even small improvements in accuracy in clinical trial outcomes can translate into savings of millions of euro in development and to faster time-to-market. Consider also that pharmaceuticals R&D spending could continue to grow at more than 12% per year. The estimated average cost of bringing a new drug to market is $1.7bn (approx. €1.2bn).[40] The role of medical imaging in clinical trials has increased rapidly in recent years both due to the enormous technical advances in the field and the mounting evidence that it helps answer key questions that arise during the development and evaluation of

[38] Healthcare is already accounting for around 9% of EU GDP,

[39] The cost of IBD to the UK NHS has been estimated at about £720 million per annum, based on the prevalence and an average cost of £3,000 per year per patient. However, half of all annual direct healthcare costs from IBD relate to the inpatient management of a minority of patients who need intensive medical or surgical intervention.

[40] Paul Clewlow, Drugs in transit, Chemistry and Industry, April 2004

medical products.[41] We believe that there is a significant size market for systems like VIGOR++ for IBD in clinical drug trials. A recent market report from Decision Resources found that the market for agents to treat IBD totalled more than £0.6bn (approx. €0.85bn) in 2001 and is expected to increase to £1.2bn (approx. €1.7bn) by 2011. During the course of the VIGOR++ project, factors influencing pharmaceutical sales will include the expanded use of Infliximab and the launch into the market of other biologic agents, which carry a high price tag. We expect that successful outcomes from the VIGOR++ project (including the disease index, the software environment and the technology roadmap) will absolutely appeal to pharmaceutical companies looking to develop or test new drugs in relation to diseases of the GI tract.

Expected Impact V (on the European industry and academic institutions)

Reinforced leadership of European industry and strengthened multidisciplinary research excellence in supporting innovative medical care

To build a verified and validated physiological model of a human organ and an intervention planning system of clinical relevance is without doubt a highly challenging research objective which certainly requires critical mass of knowledge, expertise, man-power, and dedication. VIGOR++ is an example of bringing together European multidisciplinary research excellence, in the fields of medicine (radiology, gastroenterology) and ICT (image analysis, pattern recognition, scientific visualisation).

The envisaged research and VIGOR++ developments are only feasible with extensive European cooperation: the critical mass in terms of skills in this area is simply unavailable at national level. It will certainly help establish know-how beyond the current state of the art in GI diseases and allow participants to leap frog competitive groups outside the EU.

Image processing and visualisation often focuses on extracting more information from acquired images. This is mostly accomplished by processing the images with additional knowledge of an underlying model and jointly visualising registered images with more information, which is especially important for processes that concern multiple scales. The imaging industry is certainly strengthened by providing image processing and visualisation ICT tools that smoothly integrate with biomedical modelling such as developed in VIGOR++.

The research outcome is going to be evident via the application of sophisticated tools for segmentation, feature extraction, classification and visualisation. The research activities will strengthen Europe's technology base and ensure its leadership in ICT, help drive and stimulate product, service and process innovation and creativity through ICT use and ensure that ICT progress is rapidly transformed into benefits for Europe's citizens, businesses, industry and governments in the field of Crohn's disease. The proposed approach which involves an open software architecture with accurately documented and well defined interfaces for the developed tools, creates a strong backbone for attacking other physiologic simulation research questions.

[41] According to Dr. George Mills, Director, Division of Medical Imaging and Radiopharmaceutical Drug Products at the FDA: "Modelling based on imaging is a key technology for assessing, accelerating the development of, and guiding the use of, new therapeutic options."

Relevant European research projects

Numerous prior and ongoing EU projects are relevant to the S&T domain of VIGOR++. Focusing on the topics across the related application domains at EU level, we find at least the next ongoing projects to be relevant.

The VPH concept has a precursor initiative, the **EuroPhysiome**, which reflects a grouping of researchers connected to the International Union of Physiological Sciences (IUPS) at the European level. This grouping represents a wish for a stronger and more co-ordinated representation of European research on the international scene. The STEP Coordination Action developed the VPH roadmap (STEP: a Strategy for the EuroPhysiome). The **GIOME project** is the GI part of the Physiome. The modelling of the anatomy and function of the digestive system has provided a platform for the development of scientific and educational tools, and diagnostic medical devices, for understanding the pathophysiology and pharmacology of symptoms and pain. Success stories from this development are multimodal and functional imaging probes and stimulation techniques that are now being commercialised by European start-up companies and used for clinical drug trials and diagnostic and prognostic clinical studies. The **Renal Physiome** project is a French-led international collaboration that develops a virtual kidney.

VPH related work was undertaken as part of FP6. **@neurIST** (IP) aimed to develop an IT infrastructure for the management of heterogeneous data associated with the diagnosis and treatment of cerebral aneurysms. (Project dates: 02/06 - 01/10) and **ACGT** (IP) Advancing Clinico-genomic trials on cancer: Open Grid services for improving medical knowledge discovery The ACGT project aimed to develop a GRID platform to support and stimulate further exchanges of both clinic and genetic information, with a particular focus on breast cancer treatment. (Project dates: 02/06 - 01/10). The **Living Human Project** simulated the muscles and skeleton needed to animate the virtual body. **ImmunoGrid** is another project that built a computer model of the human immune system using grid technologies. It integrates processes at molecular, cellular and organ levels. The **LHDL** (Living Human Digital Library) project developed interactive digital library services so as to make easier to share and to access collections of complex biomedical data relative to the musculoskeletal system.
Lately, a significant boost for VPH research was given by the VPH Initiative as part of Call FP7-ICT-2007-2.

Although none of the above projects focuses on GI tract or diseases related to Crohn's, VIGOR++ will closely monitor their work and take as much as possible advantage of the knowledge generated by them.

Plan for the use and dissemination of foreground knowledge

Professional management and protection of the results of the project are fundamental, and therefore we have dedicated sufficient effort to Knowledge and IPR management. This is in the form of a separate work package (WP8) that implements these activities. This dedicated work package will assume responsibility for the management of intellectual property and other aspects of innovation, since this requires a co-ordinated approach. The WP8 leader specializes in exploitation of scientific research, is close to the target audiences and aware of their needs, which enables the consortium to

quickly spot the opportunities offered by the application of new technology. The foundation for the proposed strategy is a synthesis of a sophisticated research to deliver relevant ICT tools, a good understanding of the market dynamics, mutually agreed expectations regarding exploitation, and a joint planning.

Dissemination of project results

The dissemination and exploitation of knowledge is a key ingredient for a successful research project. Such transfer of outcomes is not a process which begins when research is complete, but one which runs from the first days of a project to its completion and beyond. Consortia are often unaware of the interests of other stakeholders and often use very different language and concepts. It is the ambition of VIGOR++ to prevent such confusion that hinders knowledge transfer, for instance by a high visibility in media as well as in scientific forums, which will stimulate communication with potential users. VOD brings in VIGOR++ the unique combination of contacts at the cutting edge of technology transfer, research and practical business experience. The target audiences for VIGOR++ dissemination are shown in Table 11. This classification underpins the rationale for different activities to achieve knowledge/technology transfer to different target audiences, such as: annual workshops, the project‘s scientific publications (papers and deliverables) and press releases, the Annual Workshops, Advisory Committee, the technology roadmap, the project’s web portal and the Interest Group.

Table 11 Target audiences for VIGOR++'s dissemination and exploitation activities.

Target audience	Why to them?	What is for them?
Physicians (e.g. radiologists, gastroenterologists, general practitioners).	To obtain feedback so that the design and functionality of the system may be improved.	Increased efficiency of Crohn’s disease management by means of the VIGOR++ tools.
Pharmaceutical industry.	It is the fastest growing market for medical image processing techniques.	Increased efficiency of clinical trials.
Manufacturers of medical imaging equipment such as MRI scanners and post-processing workstations.	Potential mediators to pass the VIGOR++ tools to end users and stimulate adoption of methodology.	A competitive advantage gained by fast support adoption of sophisticated tools.
IBD Patients groups.	The ultimate user.	Improved quality of life, minimally invasive diagnostic procedures, improved treatment, and minimised length of stay in hospitals.
Academics.	Image processing, pattern recognition and scientific visualisation are important research topics in universities.	Extension of research into new fields inspired by novel VIGOR++ technology.

Software engineers.	May give feedback regarding the project's software design.	Acquire knowledge regarding new implementation designs. The opportunity to hear first about new tools.
Students.	The VIGOR++ topics are taught extensively in universities.	Comprehensive knowledge of state-of-the-arts techniques such as delivered by VIGOR++ significantly enhances their career opportunities.
VIGOR++ partners.	To benefit from other partner's expertise and skills.	Knowledge, contacts and tools sharing.

It frequently happens in collaborative projects that so much information is unavailable for everyday use because it is fragmented. Hence, WP8 will handle the information that is distributed, e.g. via mailing lists and made available on the project's external website. It will ensure that such information is readily accessible, updated regularly, and stored appropriately. Specifically, WP8 will keep tract of all project publications, suggest conferences and journals to aim for and keep track of submissions, attend professional events and suggest and support a partner's participation.

The project aims to participate in several conferences, exhibitions and industry fairs to showcase its intermediate and final results and discuss them with interested participants. These occasions will also serve to demonstrate prototype systems, enabling early feedback as well as outreach.

Targeted conferences in which the project partners will be seeking to promote VIGOR++'s results include: Medical Image Computing and Computer Assisted Intervention Conference (MICCAI), IEEE International Conference on Image Processing, International Conference on Pattern Recognition, IEEE Visualisation Conference, and International Symposium on Gastroenterology.

Moreover, we aim to publish the project's results in highly esteemed journals, such as Radiology, IEEE Transactions on Medical Imaging, Medical Image Analysis Journal, IEEE Transactions on Pattern Analysis and Machine Learning, IEEE Transactions on Visualisation and Computer Graphics, Gastroenterology, Computer Graphics and Applications.

To foster a high level of dissemination among the targeted end-user groups VIGOR++ results will be demonstrated in relevant exhibitions and congresses: RSNA - Radiological Society of North America, ECR - European Congress of Radiology, and SIR - Society of Interventional Radiology.

Furthermore, organisations such as the European Crohn's and Colitis Organisation (ECCO), the European Patient Forum, and UK's Health Technologies Knowledge Transfer Network will be approached so as to communicate the aims and results of the project as appropriate. Moreover, the consortium maintains strong links with pharmaceutical companies (e.g. GSK, Pfizer, UCB), clinical research organisations (e.g. Timaq) and manufacturers of medical imaging equipment (e.g. Philips, Siemens). In order to have a more direct impact on practitioners and industry, VIGOR++ will organise four important additional dissemination activities.

Interest Group

It is envisaged that several clinical, academic and industrial representatives will have an ongoing association with the project. VIGOR++ will stimulate such association by creating an Interest Group that will be kept up to date through project e-alerts, and will be consulted on any project issue requiring a broader consensus or set of viewpoints. Interest Group members shall be actively encouraged to input ideas and to comment on the work under development. It is expected that some **members of the Interest group can become early adopters of the VIGOR++ tools.** Clearly, the close involvement into the project makes them well positioned for undertaking the exploitation of the project results. Specifically, we have had close interaction with representatives from Philips Healthcare and GSK who expressed a strong interest in joining the Interest Group during the preparation phase of this project.

Contributions to academic curricula

An increasing number of medical and engineering students have become interested in the topic of medical imaging. Simultaneously, medical imaging problems are posing enormous challenges, so that a high and increasing demand exists now for academically trained, technically skilled personnel. TUD, ETHZ and ZIB have a longstanding scientific and commercial relationship with various industrial participants and are prime providers of qualified staff. The scientific excellence and technical skills built through the VIGOR++ project will be incorporated as case studies in various courses. Moreover, it will influence the university curricula of the academic participants for the benefit of the student communities at those universities, and eventually for the benefit of industries employing those students.

Contributions to standards

VIGOR++ will deliver methods for objective, comprehensive and quantitative measurement of Crohn's disease severity. Therefore, it will set a new standard for existing disease indices (e.g. CDAI, CDEIS), which are all limited regarding those aspects.

There are also important implications with regards to adopting such disease indices in patient records. For example in UK's NHS, the National Care Records Service (Connecting for Health) aims to create a nationwide computerised store of each person's medical information. However, it is unrealistic to expect this electronic patient record system to contain all the necessary details in the foreseeable future. Creating an IBD Management framework "is a medium-term and future proof solution for the over-worked, repeatedly distracted gastroenterologist. And the patient, their general practitioner and the IBD nurse benefit, too".[42]

The VIGOR++ tools will be integrated in the 3Dnet™ Suite environment that has been developed and commercialised by B3D. 3Dnet™ Suite is an open platform for medical image post processing. It represents the latest trends in the ICT market as it is deployed following a paradigm called Platform as a Service (PaaS); the whole delivery mechanism is online, via an advanced and innovative online scripting language dedicated to medical imaging. The platform is a collaborative framework for open

[42] Rose J, Dunne I, Grainger SL. An electronic patient record for inflammatory bowel disease: helping patients and doctors. Gut 2001;(Suppl 1)48:A87.

innovation, available to academic and commercial developers for application designers to use existing tools (e.g. for data reading, filtering and standard visualisation), or add their own to create new applications. Hence, by making the new tools resulting from VIGOR++ available to the existing community of 3Dnet™ Suite developers the project will stimulate faster adoption.

Dissemination workshops

The knowledge delivered by the project will be disseminated through workshops, to be hosted by a member of the consortium in conjunction with the annual project reviews. The workshops target to broaden the participants' appreciation for and interest in the field of the VPH, and in particular to extend their knowledge of the VIGOR++ tools and their application on Crohn's disease diagnosis and treatment. The target audience of the workshops will include radiologists, gastroenterologists, pharmaceutical industry representatives, specialised nurses, patient group representatives, manufacturers of medical imaging equipment as well as medical imaging software engineers.

Exploitation of project results

The performance of an R&D project such as VIGOR++ can be judged externally based on outcomes such as:

1. Papers (and citations)
2. Prizes
3. Patents
4. Invention disclosures
5. Higher degrees awarded

The nature of the work in VIGOR++, which will result in ICT tools and proof-of-concept medical diagnosis systems for the healthcare and pharmaceutical industry, demands that the research team operate in a commercially responsible way from the outset, aware of the need to respond to the evolution of the external state-of-the-art. There are in fact several commercial reasons for getting the partners involved in this research project. Some of them are:

need to innovate on existing products or develop new ones

need to uptake R&D results in order to give our organisations that competitive edge, increasing our patient care (for the hospitals) or sales (for the companies)

desire to access new customers or new markets

already performing our own internal research in related areas and want to deepen our knowledge and know-how in that particular field of research

value the prestige associated with being part of an important transnational research project

want to build lasting cooperation with other R&D organisations at European level

bring funding to conduct further research and technology development

WP8 will have the responsibility of preparing the project's Technology Roadmap and subsequently Exploitation Plan after reviewing the partners' capability to exploit the results of the project with respect to exploitation rights as outlined in the Consortium Agreement. The Exploitation Plan will define the project's target markets and carry out a thorough analysis in order to identify business conditions and opportunities, and also to establish potential commercial routes for the project's results. Like most key technologies, the above cannot be seen in isolation. We understand the interactions with complementary technologies and we will take into account the complex circumstances (e.g. privacy, safety, user acceptance) in which practitioners operate.

A crucial aspect to ensure exploitation of the project results is the development of all techniques in the 3Dnet™ Suite environment (see above). As such the tools can be straightaway available in a clinically usable environment. In fact, the tool can be readily commercially delivered as an optional toolbox to clinical sites and to the 3DNet resellers internationally.

It is recognised that at the end of the project, we may end up with some results that are not ready for clinical trials. To that end project partners will need to carry out further development work before they can commercially exploit the results in the marketplace. Also, we may need to have the results of the project certified before they can be commercialised. In any case, we will have already looked at the whole issue of certification during the actual project implementation stage.

A market presenting a large opportunity for the output of the project is imaging for clinical trials for drugs and devices. A market report from Decision Resources found that the market for agents to treat IBD totalled more than £0.6 billion in 2001 and is expected to increase to £1.2 billion by 2011. It is clear that new ICT tools will play a key role in the future of drug development and clinical trials by mitigating the cost and risk involved. We believe that there is a significant size market for systems like VIGOR++ in clinical trials, since it offers tools to quantitatively express the effect of therapy

Another route for technology exploitation from the project is for researchers to set up new companies or enter into licensing agreement. Many researchers may be deterred by lack of knowledge of business processes. Where such advice is not provided by the participants' own internal services, participant VOD will provide such advice (e.g. new business planning, from feasibility studies to obtaining finance) to those researchers interested in creating start-ups or in general seeking to commercialise their research results.

Involvement in the exploitation of results

The nature of the work in VIGOR++, which will result in ICT tools and proof-of-concept medical diagnosis systems for the healthcare and pharmaceutical industry, demands that the research team operate in a commercially responsible way from the outset, aware of the need to respond to the evolution of the external state-of-the-art. All partners have clear exploitation plans for their respective work and are therefore highly committed to the project goals.

TUD (1) has a history of many successful applications developed in close cooperation with industry. Amongst these, it has developed methods for CT colonography with Philips Healthcare (Clinical

Science & Advanced Development) and AMC since 2001. These methods were clinically validated and integrated in Philips ViewForum workstation. TU Delft has an active IP policy, with dedicated patent officers and business developers working at the Valorisation Centre offering support to scientists that operate on the brink of research and industrial applications. Currently, the exploitation of results will include the use of the VIGOR++ code to enhance the service offered to collaborating partners and to make TUD more competitive within the VPH research arena. TUD also intends to use the ICT tools in future European Commission funded projects, both as a platform to deliver simulation results, and as starting point for future system concepts.

UCLH (2) has widely studied the use of MRI in the assessment of Crohn's disease activity, both in the small bowel and colon. Also, UCLH has extensive experience in computer aided detection software evaluation of the colon. Additionally, it has been active in creation of national and international guidelines in diagnosis and monitoring of the two main IBDs (Crohn's disease and ulcerative colitis). The principle investigators have had a special interest in the increased risks of cancer complicating long-term Crohn's disease. Its prevention and early detection is currently highly dependent on expert colonoscopy, the acquisition of multiple biopsies and careful histological evaluation. The project has the clear potential to reduce if not to eliminate this expensive and invasive process, and thus to reduce the increased risk of death from colorectal cancer in IBD patients. Further, it would enable UCLH to pioneer the quantitative Crohn's clinical disease severity index.

ETHZ (3) has developed a platform for computational pathology together with the University Hospital Zurich. Machine learning is an integral part of the decision making in this processing pipeline which is primarily used for research purposes in the biomedical context of cancer research. The machine learning algorithms can also be employed in clinical diagnosis as shown in the micro-metastases detection of skin cancer (melanoma) in lymph nodes. Over the last five years the machine learning laboratory has pursued research projects with Roche Diagnostics and with Hoffmann-La Roche AG i.e., on diabetes research. The mixture of industrial contract research and the support of spin-off companies in ETHZ's exploitation strategy ensure that both established industries as well as SMEs and new companies will benefit from the developments of VIGOR++.

ZIB (4) has developed Amira, an advanced framework for visual analysis of data, particularly biomedical data. Since Amira and a derived version Avizo were commercialized, ZIB has continued to develop the academic version ZIBamira. Concurrently, ZIB closely collaborates with Visage Imaging in Berlin, Germany (distributing the Amira software) and the VSG Visualisation Sciences Group in Bordeaux, France (distributing Avizo). Industrial and institutional collaborators of ZIB will benefit from the results generated as a part of VIGOR++. The sophisticated visualisation techniques, including interactive manipulation, cutting, reformatting, and unfolding validated in this project will be especially of interest. Clearly, other projects in ZIB will also benefit from the research project.

B3D (5) has developed 3Dnet™ Suite, an advanced analysis and visualisation technical framework for medical imaging. 3Dnet™ Suite is the outcome of many years research in the optimisation of novel algorithms for medical imaging and has evolved to a mature Software as a Service (SaaS) and cloud computing platform, upon which many medical imaging applications are based. A recent survey within our customer base suggests that 3Dnet™ Suite users realize an average of 12.3% in increased throughput and 17.1% in increased productivity. For example 3Dnet™ Suite has been applied in

diagnostic screening of colonic cancer (Virtual colonoscopy) by examining and classifying morphological abnormalities of the lumen of the colon, indicating the presence of cancerous polyps. The company has now identified and analysed a market niche in creating virtual models of the GI tract and believes that the combination of 3Dnet™ Suite with the knowledge introduced by the other partners will result in a premium technically driven solution.

AMC (6) is one of the leading research groups regarding imaging of Crohn's disease, along with UCLH. It has developed MRI sequences for Crohn's disease and performed several clinical studies on MRI in Crohn's disease. Moreover, it routinely uses such techniques in patient care. AMC also has extensive experience in developing and evaluating other new methods for imaging the GI tract such as CT-colonography (virtual colonoscopy). In the field of MRI in Crohn's disease crucial aspects not addressed until now and topic of the project are quantitative methods for determining all (potential) relevant imaging features of disease activity and extent. The colonoscopy and microscopy (histopathology) data to be acquired will influence the work of the research group and lead to enhanced understanding of the effects on Crohn's disease genesis and treatment.

VOD (7) is an innovation accelerator company with a project portfolio covering various emerging technical fields. Vodera assists high-tech start-ups, technology corporations and universities create competitive advantage by rapidly developing new systems and solutions, commercialising technology breakthroughs and transferring knowledge across projects and business units. The team is working with mature processes, such as technology roadmapping, that have been carefully developed and tested. The proposed project would enable the company to expand its knowledge base in the state of the art medical diagnostics, which is recognised to be one of the fastest growing areas in ICT. VIGOR++ would also allow Vodera to promote the expertise of the company to future clients and establish contacts with experts and suppliers of technologies throughout the EU. In parallel, Vodera's participation in VIGOR++ will enable the consortium members to understand more about the innovation process and influence the research work by market developments.

Management of intellectual property

The Consortium Agreement will be governed by an IPR management cube, in which IPR issues are structured along three dimensions

the type of the asset considered (content or technology)

the point of creation of the asset (pre-existing assets vs. assets created during the project)

the type of intended use (use by consortium partner during the project or after the project, commercial use outside the project, non-commercial use outside the project).

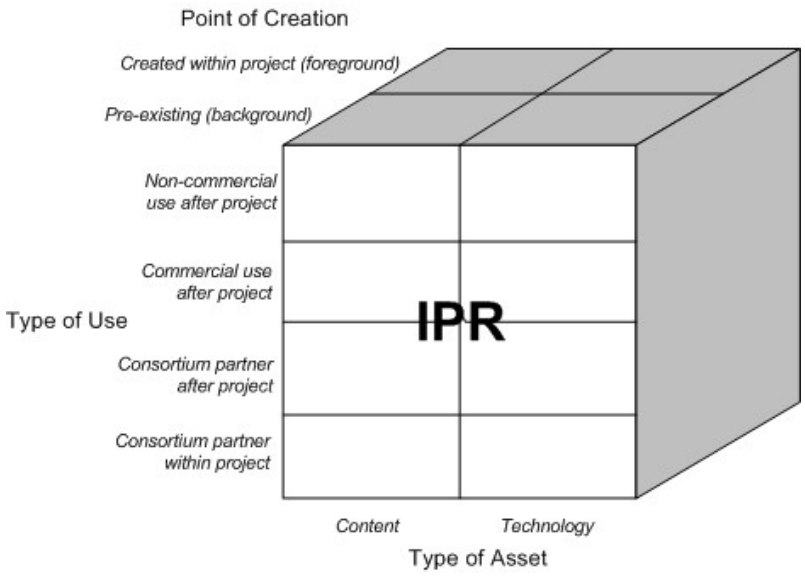


Figure 10 The IPR management cube.The Consortium Agreement will be signed by the consortium partners before the beginning of the project. It will identify potential issues concerning pre-existing IPR rights as well as those generated by the work of the consortium, settlement of internal disputes and commercial exploitation of results. The Consortium Agreement, which will also govern and grant licenses to VIGOR++ consortium members and third party organisations wishing to benefit from VIGOR++ IPR.

Protection of partners' background knowledge will be provided by use of confidentiality clauses in the Consortium Agreement. Pre-existing know-how will be brought in by each partner in order to contribute to the success of the VIGOR++ project. In principal, the IPRs for pre-existing technology stay with its original owners. Naturally, the use of these technologies is free of charge for the consortium partners during the project for purposes of the project. Partners will also be obliged to licence on fair and reasonable terms, any background necessary for exploitation of the foreground IPR developed in VIGOR++.

Intellectual property rights issues will be on the agenda of each project management meeting. A decision will be made case by case after consultation with the Steering Committee if it is most suitable to proceed with a provisional patent application or, alternatively, to prepare a public presentation of the idea. The Project Manager will maintain an archive of all project -external and internal- technical documents and discussions. The archive may be later used as a base for resolving conflicts related to intellectual property rights filings. These procedures ensure that intellectual property will be secured in the interest of project partners.

If it is not possible to determine exactly the ownership of that knowledge i.e. several partners participated in that specific development, ownership will be equally shared by each partner. The Consortium Agreement will state that intellectual property generated during the project can be licensed to the other partners under fair and reasonable terms. This agreement will be in line with the obligations of the EC model contract with regard to protection, use and access rights.

A distinction between licenses for research purposes and licenses for exploitation will be made. It is the goal for most of the technology created as part of the VIGOR++ project to keep non-commercial use free of charge.

Importantly, the Consortium Agreement will take into account the "Guide to Intellectual Property Rights for FP7 projects" Version 28/06/2007, issued by Research DG. The IPR management of the project will also take into account the following published regulations and directives:

Commission regulation (EC) No 772/2004 of 27 April 2004 on the application of Article 81(3) of the Treaty to categories of technology transfer agreements.

Communication from Commission Notice Guidelines on the application of Article 81(3) of the Treaty.

Directive 2004/48/EC of the European Parliament and of the council of 29 April 2004 on enforcement of Intellectual Property Rights.

Ethical issues

The project will comply with national data protection legislation, European Union legislation, respect international conventions and declarations and take into account the Opinions of the European Group on Ethics. A **specific task has been included in the work plan to explicitly address ethical issues.**

The researchers who handle the medical data will ensure that the **data from volunteers will remain anonymous**. The anonymisation will take place at the collection points (AMC,UCLH), i.e. prior to provision for analysis to the ICT project partners. **Informed consent will be required** whenever ICT research involves volunteers in experimentation, and accessing personal medical data records. Before consent is sought, information will be given specifying the risks, and benefits for those involved in a way they understand.

The consortium will follow the Helsinki Declaration, the Charter of Fundamental Rights of the EU, the EU directives related to good clinical practice and other international regulations related to conducting clinical studies involving humans. Local Ethical Committees will be in place to ensure the adequate attention to ethical issues. The partners have broad experience regarding such aspects through previous clinical projects similar to VIGOR++.

Table 12 Ethical Issues Table.

	YES	PAGE
Informed Consent		
• Does the project involve children?		
• Does the project involve patients or persons not able to give consent?		
• Does the project involve adult healthy volunteers?	x	21 WP2 (T2.1 - T2.4)
• Does the project involve Human Genetic Material?		
• Does the project involve Human biological samples?	X	21 WP2 (T2.1 - T2.4)
• Does the project involve Human data collection	x	21 WP2 (T2.1 - T2.4)

	YES	PAGE
Informed Consent		
• Does the project involve children?		
• Does the project involve patients or persons not able to give consent?		
• Does the project involve adult healthy volunteers?	x	21 WP2 (T2.1 - T2.4)
Research on Human embryo/foetus		
• Does the project involve Human Embryos?		
• Does the project involve Human Foetal Tissue / Cells?		
• Does the project involve Human Embryonic Stem Cells?		
Privacy		
• Does the project involve processing of genetic information or personal data (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	x	21 W2 (T2.1 - T2.4)
• Does the project involve tracking the location or observation of people?		
Research on Animals		
• Does the project involve research on animals?		
• Are those animals transgenic small laboratory animals?		
• Are those animals transgenic farm animals?		
• Are those animals cloned farm animals?		
• Are those animals nonhuman primates?		
Research Involving Developing Countries		
• Use of local resources (genetic, animal, plant etc)		
• Benefit to local community (capacity building i.e. access to healthcare, education etc)		
Dual Use		
• Research having direct military application		
• Research having the potential for terrorist abuse		

References

1. Sharman A, Zealley I, Greenhalgh R, Bassett P, Taylor S. MRI of small bowel Crohn's disease: determining the reproducibility of bowel wall gadolinium enhancement measurements. *European radiology*. 2009 Aug 2009;19(8)doi:10.1007/s00330-009-1371-0
2. Taylor S, Punwani S, Rodriguez-Justo M, et al. Mural Crohn disease: correlation of dynamic contrast-enhanced MR imaging findings with angiogenesis and inflammation at histologic examination--pilot study. *Radiology*. 2009 May 2009;251(2)doi:10.1148/radiol.2512081292
3. Punwani S, Rodriguez-Justo M, Bainbridge A, et al. Mural inflammation in Crohn disease: location-matched histologic validation of MR imaging features. *Radiology*. 2009 Sep 2009;252(3)doi:10.1148/radiol.2523082167
4. Froehlich J, Patak M, von Weymarn C, Juli C, Zollikofer C, Wentz K. Small bowel motility assessment with magnetic resonance imaging. *Journal of magnetic resonance imaging : JMRI*. 2005 Apr 2005;21(4)doi:10.1002/jmri.20284
5. Girometti R, Zuiani C, Toso F, et al. MRI scoring system including dynamic motility evaluation in assessing the activity of Crohn's disease of the terminal ileum. *Academic radiology*. 2008 Feb 2008;15(2)doi:10.1016/j.acra.2007.08.010
6. Horsthuis K, Bipat S, Bennink R, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology*. 2008 Apr 2008;247(1)doi:10.1148/radiol.2471070611
7. Horsthuis K, Bipat S, Stokkers P, Stoker J. Magnetic resonance imaging for evaluation of disease activity in Crohn's disease: a systematic review. *European radiology*. 2009 Jun 2009;19(6)doi:10.1007/s00330-008-1287-0
8. Ordas I, Rimola J, Alfaro I, et al. Development and Validation of a Simplified Magnetic Resonance Index of Activity for Crohn's Disease. *Gastroenterology*. Aug 2019;157(2):432-439.e1. doi:10.1053/j.gastro.2019.03.051
9. Rimola J, Rodriguez S, Garcia-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut*. Aug 2009;58(8):1113-20. doi:10.1136/gut.2008.167957
10. Makanyanga J, Pendsé D, Dikaios N, et al. Evaluation of Crohn's disease activity: initial validation of a magnetic resonance enterography global score (MEGS) against faecal calprotectin. *European radiology*. 2014 Feb 2014;24(2)doi:10.1007/s00330-013-3010-z
11. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. *Eur J Radiol*. Sep 2012;81(9):2080-8. doi:10.1016/j.ejrad.2011.07.013
12. Heissam K, Abrehart N, Hoad CL, et al. Measurement of fasted state gastric antral motility before and after a standard bioavailability and bioequivalence 240 mL drink of water: Validation of MRI method against concomitant perfused manometry in healthy participants. *PLOS ONE*. 2020-11-11 2020;15(11):e0241441. doi:10.1371/journal.pone.0241441
13. Gollifer RM, Menys A, Plumb A, et al. Automated versus subjective assessment of spatial and temporal MRI small bowel motility in Crohn's disease. *Clin Radiol*. Oct 2019;74(10):814.e9-814.e19. doi:10.1016/j.crad.2019.06.016
14. Menys A, Hoad C, Spiller R, et al. Spatio-temporal motility MRI analysis of the stomach and colon. *Neurogastroenterol Motil*. Feb 28 2019:e13557. doi:10.1111/nmo.13557

15. Gollifer RM, Menys A, Makanyanga J, et al. Relationship between MRI quantified small bowel motility and abdominal symptoms in Crohn's disease patients—a validation study. *Br J Radiol*. Sep 2018;91(1089)doi:10.1259/bjr.20170914
16. Menys A, Puylaert C, Tutein Nolthenius CE, et al. Quantified Terminal Ileal Motility during MR Enterography as a Biomarker of Crohn Disease Activity: Prospective Multi-Institution Study. *Radiology*. Nov 2018;289(2):428-435. doi:10.1148/radiol.2018180100
17. Menys A, Hoad C, Spiller R, et al. Spatio-Temporal mapping of gastrointestinal motility using MRI and computer post-processing: A proof of concept study. presented at: United European Gastroenterology Week; 2018; Vienna. https://www.ueg.eu/education/document/spatio-temporal-mapping-of-gastrointestinal-motility-using-mri-and-computer-post-processing-a-proof-of-concept-study/181832/
18. Plumb AA, Menys A, Russo E, et al. Magnetic resonance imaging-quantified small bowel motility is a sensitive marker of response to medical therapy in Crohn's disease. *Aliment Pharmacol Ther*. Aug 2015;42(3):343-55. doi:10.1111/apt.13275
19. Froehlich J, Waldherr C, Stoupis C, Erturk S, Patak M. MR motility imaging in Crohn's disease improves lesion detection compared with standard MR imaging. *European radiology*. 2010 Aug 2010;20(8)doi:10.1007/s00330-010-1759-x
20. Gennert MA, Negahdaripour S. Relaxing the Brightness Constancy Assumption in Computing Optical Flow. *MIT Artificial Intelligence*. 1987-06-01 1987;doi:http://hdl.handle.net/1721.1/6477
21. Crum W, Tanner C, Hawkes D. Anisotropic multi-scale fluid registration: evaluation in magnetic resonance breast imaging. *Physics in medicine and biology*. 11/07/2005 2005;50(21)doi:10.1088/0031-9155/50/21/014
22. Melbourne A, Atkinson D, White M, Collins D, Leach M, Hawkes D. Registration of dynamic contrast-enhanced MRI using a progressive principal component registration (PPCR). *Physics in medicine and biology*. 09/07/2007 2007;52(17)doi:10.1088/0031-9155/52/17/003
23. Knuesel P, Kubik R, Crook D, Eigenmann F, Froehlich J. Assessment of dynamic contrast enhancement of the small bowel in active Crohn's disease using 3D MR enterography. *European journal of radiology*. 2010 Mar 2010;73(3)doi:10.1016/j.ejrad.2008.12.001
24. Borley N, Mortensen N, Jewell D, Warren B. The relationship between inflammatory and serosal connective tissue changes in ileal Crohn's disease: evidence for a possible causative link. *The Journal of pathology*. 2000 Feb 2000;190(2)doi:10.1002/(SICI)1096-9896(200002)190:2<196::AID-PATH513>3.0.CO;2-5
25. Stange EF, Travis SP, Vermeire S, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut*. Mar 2006;55 Suppl 1:i1-15. doi:10.1136/gut.2005.081950a
26. Schoepfer A, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflammatory bowel diseases*. 2009 Dec 2009;15(12)doi:10.1002/ibd.20986