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EPSD (Exemplar Project Strategy Document)

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Executive Summary

This document, the Exemplar Project Strategy Document, or EPSD, details the strategy for targeting the new calls for Exemplars, based on gaps in ToolKit development with respect to intended coverage of vertical and horizontal integration and the intended clinical endpoint. The principal challenge we recognize in development of the VPH ToolKit is establishment of the transversal, or horizontal, connections between the usual domains of investigation. The intention in choosing the EPs (both the seedEPs and future EPs), is to push development in the direction of this transversal integration. We expect this to be one of the main hurdles to success of the collaborative/integrative approach underlying the physiome concept. It must of course rely on the technical resources that will constitute the VPH ToolKit but it represents, in some sense, a change of paradigm, towards a globalization/*mondialisation* of biomedical research.

Thus, whereas the RTAE (Requirements and Technology Assessment Exercise) document analyses the technological requirements and existing resources in a range of VPH task areas, the EPSD focuses on the role of exemplar projects in the challenge of bringing the various scientific disciplines to collaborate towards "*an integrative approach, where biological processes are described from a systems point of view*" (STEP Roadmap, 2007, p.2). It is of course expected that the other projects (i.e., STREPs, IPs) funded under the VPH calls will also work in this direction, but the EPs, which are ongoing projects with independent funding, will receive a budget specifically for this mission directly from the NoE.

In this document, with this underlying goal in mind, we will summarize the existing seedEPs and their expressed technical needs and potential contributions in terms of the WP3 ToolKit development. Our purpose is to target the three calls for new Exemplar Projects by identifying key gaps in both the technological requirements and in coverage of the horizontal and vertical links among the various physiological levels (gene-to-organism) and organ systems.

We also present the practical details of launching the calls, evaluating proposals, and selecting and financing the new EPs.

Section 1. Introduction

The Virtual Physiological Human (VPH) has been previously defined as: “a methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system ... It is a way to share observations, to derive predictive hypotheses from them, and to integrate them into a constantly improving understanding of human physiology/pathology, by regarding it as a single system.” (Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human, STEP Consortium, 2007).

One means towards this long-term goal is the support within the VPH Network of Excellence (NoE) of a small number of Exemplar Projects (or EPs). To cite the NoE Description of Work (DoW):

> *"The concept driving the VPH NoE is integration within the VPH research community, the joint programme of activities (JPA) being designed with service to, and enablement of, this community in mind. Its aims range from the development of tools and infrastructural resources, to* ***the support of Exemplar Research Projects addressing the integration of models and data across the various levels of structural and functional organisation of human physiology****. VPH community building and support in the shape of ‘think tank’ activities, meetings, training and exchange of personnel will be pursued, in the spirit of creating a more coherent VPH working environment. Through the range of its activities,* ***a key feature of the VPH NoE will be that it brings together all VPH-related projects, funded within both FP6 and – more directly – within FP7****. As VPH represents a vast field of endeavour, it is imperative to ensure that projects of high European economic importance have value added by exploitation of the technical and academic infrastructure in which the European Commission has previously invested and will continue to invest, in the future." [from section 3.1 of DoW, emphasis added here]*

The EPs should thus be seen as complementary to a common goal shared by STREPs and IPs funded under the VPH calls.

1-1. The role of Exemplar Projects, their interplay with VPH ToolKit development, and basic principles of the calls for new EPs

Exemplar Projects (EPs) are independently funded projects (National or EU) that accept to enter the VPH "arena" rather than remaining isolated in the usual manner. They commit to interaction with the WP3 team (i.e., VPH ToolKit development) towards the dual goals of horizontal and vertical research integration. They will specify both what they need from the VPH ToolKit (see below) and what they can contribute, such as data (experimental, clinical, benchmark output...), models (subject to validation procedure to be worked out), and resources/software for the ToolKit.

Five research areas exploiting existing expertise of VPH NoE core members were identified during development of the NoE. The VPH NoE allocated 12 person-months to each of these **"seed" EPs** (seedEPs) in the first year of the NoE to enable early feedback for WP3 ToolKit

development in order to ensure that VPH ToolKit development would benefit at an early stage from the input of a number of EPs from core partners.

The present document describes the process for attribution of support to subsequent EPs (2-3 awards of 6-12 person-months in each of years 2, 3 and 4 of the NoE), which will be awarded through a competitive grant mechanism, these funds (500 000 euros total) being held and distributed by CNRS.

Individual EPs will be strictly focused on integration of VPH-related research which addresses an area of need (see below), fostering new collaborative links, benefiting from transfer of skills from 'neighboring' VPH activities, with the mandate to make output (models, data repositories) available to the VPH community as widely as possible, and with the expectation that such support will contribute to the ability of the recipients to obtain follow-on funding. The VPH NoE will aim to promote the sharing of data across the VPH community, including the development of appropriate standards and infrastructure to enable this. Furthermore, EPs selected for funding will help to define the needs for the VPH ToolKit and be early adopters of relevant output of the VPH ToolKit development (WP3), thereby contributing to the development of an integrated set of tools for the VPH. The concrete implementation of these tools towards the goals of vertical and horizontal integration will be an essential step in honing them for actual use, and (where appropriate) the EPs should provide a thorough testing ground.

1-2. Summary of VPH ToolKit tasks

As given in the Description of Work (available at www.vph-noe.eu/repository), the path to a workable VPH environment involves the constitution of a number of ICT infrastructure resources. The tasks are outlined in the DoW and more fully examined in the VPH Requirements and Technologies Assessment Exercise (RTAE) document (see www.vph-noe.eu/WP3). **It will be assumed that candidates for EP support will be familiar with the details set forth in the RTAE document.** We give here a list of the classes of technology involved.

However, it must be kept in mind that these technologies are a means to an end, namely, the development of a collaborative and integrative VPH research environment that will eventually enable development and navigation of datasets and mathematical models of physiological function both vertically (i.e., from macro to molecular scales within an organ system) and horizontally (i.e., across tissues and organ systems). While multi-scale vertical integration is a challenging enterprise, it is already a recognized area that involves many established projects, whereas horizontal integration is a largely open challenge. One of the key aims of the VPH NoE in supporting Exemplar Projects is to make a concerted effort towards workable solutions to the problem of horizontal integration. The technologies summarized here are thus to be seen as a means to this end of not only vertical but also horizontal integration.

The tasks specified within WP3 in the Description of Work, and explored further in the RTAE document, are (with numbering from the DoW):

Task 3.2. VPH markup languages for model encapsulation
Task 3.3. VPH markup languages for data encapsulation
Task 3.4. Development and provision of VPH tools
Task 3.5. Adapting and developing workflow environments and middleware
Task 3.6. Development of model repositories and workflow repositories
Task 3.7. Data repositories and data access

Task 3.8. VPH Data Fusion
Task 3.9. Grid Access for Researchers and Clinicians

Work on these tasks has been delegated to a number of working subgroups within WP3.

A new and exciting task emerged at the first WP2/WP3 workshop (Nov. 3-5, 2008, in Paris), proposed by B. de Bono (EMBL/EBI), namely, the cooperation of NoE partners towards the constitution of an ontology of anatomical terms and concepts to be used to establish horizontal and vertical links among models and data. In our judgement, this task represents an outstanding opportunity to unify activities across the research and clinical fields, and special effort will be requested of EPs to contribute to this undertaking. A fuller description of this scenario is given in the Ontologies section of the RTAE document (see also the document "Representing and annotating the anatomy of the Virtual Physiological Human: A key to data and model interoperability." by B. de Bono, EBI).

Interactions underway between the individual seedEPs and WP3 ToolKit development were presented at the first WP2/WP3 workshop. A summary of these interactions can be found in the RTAE for each seedEP. For convenience, a copy of this summary is included as an Annex to the present EPSD.

Additional activities planned, relating to the VPH ToolKit and EPs - coordinated by the VPH NoE - include the establishment **of VPH Data and Standards working groups**. These will act as discussion and strategy development bodies, involve representatives from a range of VPH stakeholders, and will work to establish the strategic foundations to underpin future VPH integrative research. More information will be made available on the groups in due course on the VPH NoE website.

1-3. Plans for showcasing the EPs in the NoE dissemination context

EP Case Studies (submitted as part of the evaluation process, see below) will be published online, with an example included in each VPH NoE newsletter published/disseminated after their completion. This will then be followed, it is hoped, by publication of these reports in review format in special issues of the journal Philosophical Transactions of the Royal Society – A, planned for 2010 and beyond.

Section 2. The 5 seed Exemplars: their needs, their contributions

We give here brief descriptions of the five seedEP projects. A summary of their interactions with ToolKit development, as presented at the workshop in Paris in November 2008, is given in the Annex.

2-1. seedEP1: (DoW Task 2.1) A multi-organ Core Model of arterial pressure and body fluids homeostasis (CNRS)

Long-term regulation of arterial blood pressure (BP), which necessarily involves several organ systems and regulatory feedback loops, is determined essentially by the balance between fluid and salt intake and their excretion, the latter being characterized by the relation between BP and urinary output, manifested in the renal function curve (RFC). This paradigm serves as the basis not only for understanding normal BP regulation but also for treatment of hypertension (necessarily involving modification of the RFC), and was developed by Arthur Guyton and colleagues based importantly on their quantitative control-theory based models, which were firmly grounded in experimental results (mainly from animal experiments) and several decades of clinical experience.

For the VPH, it is appropriate to build a core modeling environment (CME) inspired by the Guyton models but implemented as a set of basic open source modules for the various functional components (not only organs, such as heart, kidney, lung, and muscle mass, but also the relevant nervous and hormonal regulatory systems), each of which can be replaced as appropriate by higher resolution mechanistic models (or even nested sets of models) allowing the exploration of specific, gene-to-organism predictive scenarios. This is the goal of the SAPHIR project at CNRS, funded by the French ANR (National Research Agency). The ultimate aim is to work towards patient-customization of the generic core model set, which should serve as a valuable aid to the clinician for design of therapeutic regimens.

Within this seed EP, the SAPHIR modeling environment will, first, inform the WP3 ToolKit development team of specific requirements for this type/level of model integration, and, subsequently, be explicitly adapted to the protocols of the VPH ToolKit (WP3) as they become available. In particular, this will involve:

- integration or link-up of the SAPHIR quantitative parameter database (QKDB) with a more generic VPH DB (to be implemented under WP3),
- contribution of the Multiformalism Multilevels Simulation Library® (M2SL, developed at LTSI INSERM, Rennes), to the VPH ToolKit collection of numerical solver packages,
- specification of inter-module I/O connection protocols,
- markup language versions of the various modules (in DAEML and also, in most cases, in CellML)
- cross-discipline ontology integration (and development where necessary).

This EP will thus provide a prototype VPH core modeling environment, along with an example "core model", thus providing a demonstration of an open collaborative working environment. In this way, it will be straightforward for interested laboratories to contribute their detailed mechanistic models at any scale as new sub-modules, thus extending with no *a priori* limit the number of "services" available for customized model construction.

2-2. seedEP2: (DoW Task 2.2) Integrated multi-level modeling of the musculoskeletal system (ULB)

A number of problems met in daily clinical practice relating to the musculoskeletal system still call for the development of new integrative approaches. For example, cerebral palsy requires clinicians to handle and mentally combine numerous types of inhomogeneous data: electromyography, motion data, medical imaging, etc. Furthermore, clinical interventions and observations for this kind of pathology typically occur at the organ level (i.e., injection of Botox in the spastic muscle), while the real problem is located at the cellular level (i.e. spasticity of the muscle fiber, action of the Botox on the neuromuscular junction). Additional complexity arises in the musculoskeletal system due to the interaction of multiple organs (several muscles, several ligaments, the hyaline cartilage) in the overall functioning of the system. Solving this kind of problem will not only require multi-level integration, but will also require the development of multi-organ and multi-tissue modeling based on robust optimization algorithms and advanced visualization tools. Such an approach has been the focus of several EC-funded projects (VAKHUM, Multimod, LHDL), whose main results are the availability of a shared ICT technology, called MAF2, aiming to perform the required integrative research.

Seed EP2 will aim to carefully define the various needs arising in the musculoskeletal field based on the experience of previous projects. These needs will be communicated to the WP3 ToolKit development team to inform it of the specific requirements for this type of model integration. It is expected that the next step within this EP will be the development of an ontology to allow further integration of the musculoskeletal models with other sub-systems (e.g., the nervous system and both cardiac and vascular systems). This EP extends previous work using the Multimod Application Framework (MAF) that already integrates many routines required for MS modelling (data import, visualization, processing, storage and management). MAF will be a contribution of this seedEP to the ToolKit.

2-3. seedEP3: (DoW Task 2.3) The Vertical and Horizontal Atherome (WHAM) (KI)

Coronary artery disease (CAD) is a major (50%) cause of death of the western population. Atherosclerosis is a main driver of CAD and it would be advantageous if the suffering from this disease could be reduced. Due to the western life style there are no indications that atherosclerosis will become less prevalent in the future. Yet, our limited mechanistic understanding of the disease in terms of the identity of the disease-related genes, polymorphisms, proteins, and their interactions, within and between cells and organs, constitutes a severe bottleneck to preventing and developing efficient drugs which can regress the development of atherosclerosis.

The WHAM program requires both a vertical and horizontal integration. Available vertical data ranges from molecular information (gene-expression, protein-protein interactions data) to angiograms (imaging) reflecting the degree of disease from patients undergoing by-pass surgery. Horizontal molecular information is obtained from tissue biopsies (liver, muscle, fat, affected and unaffected aorta). Similar data-types are available from the aorta from a mouse model prone for atherosclerosis. Molecular data from macrophages, a key cell-type involved in atherosclerosis, are also available.

To analyze these data from different organs and model systems of different complexity, a blend of pattern detection techniques (statistics, machine learning), network identification algorithms, and mathematical modeling is required.

This seed EP will aim to harness the development of the VPH ToolKit and accelerate the success of WHAM, since such features have not been developed within the WHAM project itself, this being a clinical and experimental project that was launched and run without these considerations in mind. Therefore, VPH tools enabling "simple" things like storing different types of data (patient descriptions, experimental protocols, expression, SNPs etc) are urgently needed. At the other end of the spectrum, the issue of integrating the molecular information obtained across different model systems and imaging is most likely a central methodological problem for a VPH tool-box addressing clinical needs. This includes visualization but also how molecule X affects the tissue and 3D properties etc, interaction between flow (blood) and expression of various molecules.

2-4. seedEP4: (DoW Task 2.4) Multi-scale simulation and prediction of the drug safety problems related with hERG (IMIM)

An important field of application of the VPH concept is the drug development process, since multi-scale simulations can be extremely useful for the understanding of the physiological mechanisms related to the therapeutic efficacy of the drugs, as well as with their adverse effects (drug safety problems). In order to get useful in-silico predictions of the efficacy and safety of drugs, we require computational models that have to be sensitive to the differential molecular characteristics of the drugs, which, on the other hand, have to be coupled with models simulating the biological system or organ in which the therapeutic effectiveness or adverse events are observed. The hERG-related cardiac adverse effects of drugs are a paradigmatic example of this approach. Although other potential targets for cardiac adverse effects exist, the vast majority of drugs associated with pathological prolongations of the QT segment of the electrocardiogram are known to interact with the hERG potassium channel. The differential interaction of a series of drugs under development with the hERG potassium channel can be simulated at the molecular scale by means of atomistic simulations coupled to drug discovery tools based on quantitative structure-activity relationships. In this way, one will be able to obtain quantitative predictions of the effects of each drug on the electrophysiological parameters of hERG that could be used in both mesoscopic simulations dealing with macromolecular behavior of the channels and, more importantly, in macroscopic electromechanical simulations of the heart with the aim of predicting the change in the QT segment generated by the drugs under study.

This approach is based on tools developed in several projects that are focused on the multiscale processes modeling and their computational implementation (PS3Grid and EC-STREP QosCosGrid) as well as on the translational research aspects of such a multilevel problem (EC-STREP BioBridge). This seed EP will aim at integrating existing software tools dealing with the several levels of complexity of the QT elongation. The expected outcome of the next step will be the standardization of formats for easy integration of simulation scales and the computational implementation of the different levels of detail.

2-5. seedEP5: (DoW Task 2.5) Modeling and visualizing brain function and pathophysiology (ERCIM, Digital Patient Working Group)

The ERCIM project models brain function based on clinical data in order to better understand the causality of brain diseases such as epilepsy, dementia, schizophrenia, and alcoholism. At the first functional level, linear and nonlinear synchronization methods are applied to study neuronal dynamics. The latter have been increasingly recognized to be an important

mechanism by which specialized cortical and sub-cortical regions integrate their activity to form distributed neuronal assemblies that function in a cooperative manner. Synchronous oscillations of certain types of such assemblies in different frequency bands relate to different perceptual, motor or cognitive states and may be indicative of a wider range of cognitive functions or brain pathologies. At a second level, source estimation models and graph theoretic measures are applied to better describe and understand the functional characteristics of brain networks.

The project also investigates brain tumors (especially glioblastoma) and normal brain tissue behavior at the cellular and higher levels of biocomplexity. Such models will be individualized, therefore requiring pertinent image analysis, data processing and visualization techniques in order to extract the necessary information, which will be the input to the cancer simulator. In particular, image analysis tasks (such as image registration fusion, segmentation, etc) will be applied at different scales (e.g. tissue 3DMRI images, microarray data, etc). Most of these activities are already being funded (e.g. ACGT for simulation tasks, BIOPATTERN NoE for Brain Disorders). FORTH is additionally investing its own funds to develop brain network visualization algorithms (and relevant clinical applications), etc. Significant progress has been made in the action lines mentioned both in R&D (cancer simulation has already gained significant attention and respect within ACGT and the EC), as well as in the purely scientific/academic area (e.g., a number of papers demonstrating the clinical value of brain networks to understand and model function, microarray analysis, etc.).

As a seed EP, functional modeling of the brain will require certain VPH ToolKit elements that are already generically described in WP3. However, some “fine-tuning” will be needed in order to meet the brain's specific needs. What will be needed from the VPH ToolKit includes:

- web-accessible repositories for data, annotations, patient information etc.;
- model solutions to the inverse or forward brain source localization problems;
- patient-specific customization of models;
- data fitting; and
- GUIs specifically tailored to visualize causal and functional relations between different brain lobes.

Section 3. Gap analysis—Organ systems vs. Levels of organization, and seedEPs vs. WP3 Tasks

Figure 1 displays a matrix containing 11 main organ systems and, within each of these, the span over multiple spatial scales; from molecular to systems level, with further extension to the clinical setting. The symbols and links on the diagram show coverage by the five seed EPs. This figure aims to capture the range of research areas required within the VPH effort in an attempt to highlight areas where research is already being conducted and those where we are currently unaware of VPH-related research. To create a fully integrated collection of models covering the entire organism and the linkage of this with the clinical environment, we must facilitate both horizontal (across organ systems) and vertical (across spatial scales) integration.

Figure 2 illustrates the needs and potential contributions of each seedEP to the WP3 ToolKit tasks specified in the DoW. The entries in the table are not to be taken as strict limits in any sense, but only as an indication of principal involvements, to serve as a guide in the selection of new EPs.

More specifically, concerning Figure 1, EPs funded within WP2 will focus on linking at least two, ideally three, research areas (boxes in Figure 1) to improve generic capability across several areas, or to create new links between areas not currently connected by an integrative research project/initiative. Priority will be given to those proposals that engage at least one currently unlinked ('orphaned') area. The actual research within each box of the matrix should already have committed funding for the duration of the proposed activity, with EP-related activity focusing on VPH-related integration.

It is clear from Figures 1 and 2 that many gaps remain, and these will be priorities for selection of future EPs.

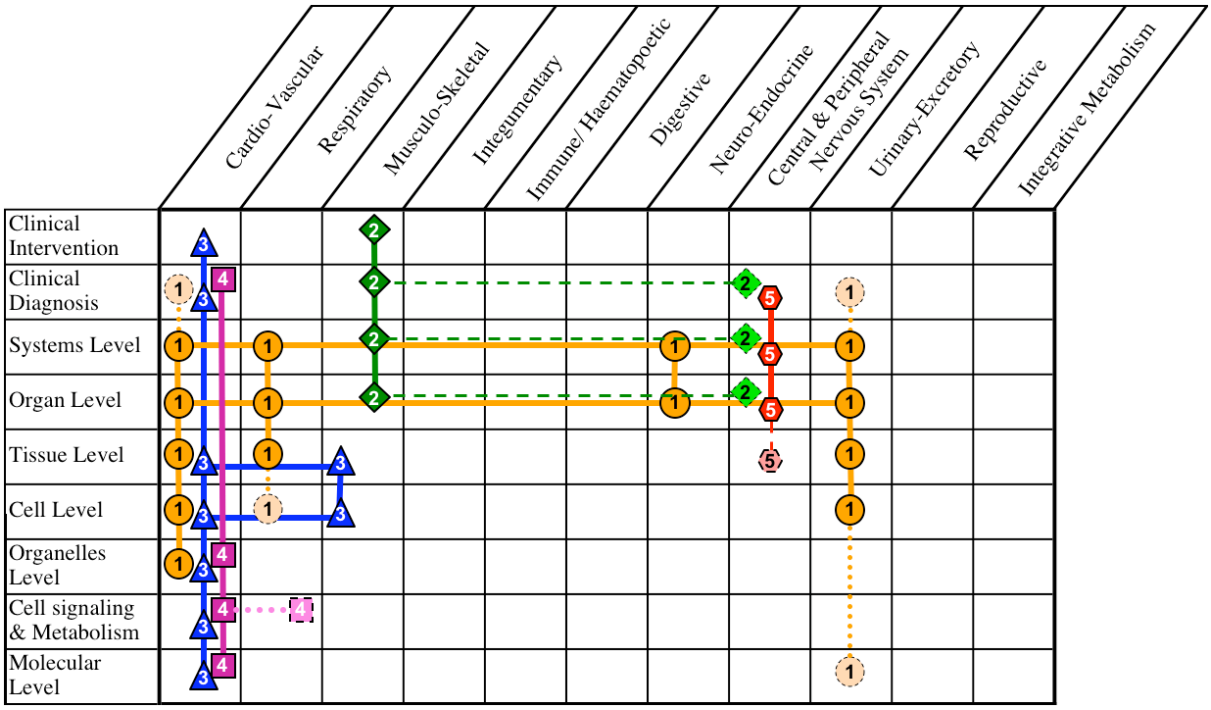

Figure 1. Organ Systems vs. Levels of Organization. The figure shows, for each of the five seedEPs (indicated by the numbered colored symbols), the vertical and horizontal integration activities. Note that emphasis is on the horizontal and vertical links themselves. Dark symbols indicate existing activities; pale symbols represent activities under development. (NB: compared to the similar figure in the Description of Work, this has a new column for Integrative Metabolism)

ToolKit Tasks	CNRS	ULB	KI	IMIM	ERCIM
3.2 - model ML	(n)/c		n	(c)	
3.3 - data ML	n			n	
3.4 - tools/GUI	n	n/c	n	n/c	n/c
3.5 - workflow	n			c	
3.6 - model repositories	n/c	n/c			n
3.7 - data repositories	c	c	n	(c)	n
3.8 - data fusion	n	(n)/(c)	(n)/(c)		n
3.9 - grid access	(n)/(c)			c	

Figure 2. seedEPs vs. WP3 tasks. n="needed", c="contribution".

Section 4. Technical essentials of new EP calls

With an EP budget of 500,000 EUR, the NoE expects to fund a total of 6-8 exemplar projects within these three calls (i.e., 2 or 3 per year).

4-1. Nature, duration, and amount of support provided to selected projects

Individual EP support will be manifest as a grant of 6-12 months duration, to fund personnel (real/direct costs, no overheads). The proposal must specify the cost per person-month at their institution.

4-2. Who can apply

The calls for new EPs will be **open to all VPH NoE Core or General members** and will preferably involve collaboration of two or more VPH NoE institutional members, though this is not a requirement (collaborations with Associate Members are acceptable, provided they are not in receipt of funds).

4-3. Summary of dates and timing for new EP Proposals and Evaluation/Selection

- SD-1 month: Calls to be sent out to all NoE members five months before start dates, and one month before submission deadlines: i.e., in PM8, 19, and 31. **The starting date for the first round of new EPs will be 1 July 2009**.
- SD: Submission Deadlines for new proposals four months before start dates — PM9, 21, 33. Proposals must be sent to WP2 coordinator. A subcommittee [to be constituted] of the EP Evaluation Committee (*EPEC*) will
    - assign reviewers from the members of the Advisory Boards.
    - assign a primary and a secondary rapporteur for each proposal. These rapporteurs are members of the EPEC. The Primary rapporteur will present the proposal at the Selection meeting.
- SD+1week: Proposals sent to reviewers within one week after SD.
- SD+3weeks: Send all the reviews to all EPEC members. The rapporteurs Reviewer/referees will prepare to present their assigned proposals.
- SD+5weeks: Selection committee (i.e., the EPEC) meets for 1 day. Proposals will be presented and pre-classed during morning/early afternoon. EPEC members implicated in a given project will abstain from discussion of said project. Final selection late afternoon.
- Decisions will be sent out on the day following the EPEC meeting. Selected projects will thus have approximately two months before the start date, in order to allow them time to search for candidates for the funded position.

4-4. Monitoring of past and ongoing Exemplars

Once underway, EPs will report to the WP2 coordinator on success of initial startup 6 months after the start date, and will report on tasks accomplished at 12 months. A final report must be compiled and submitted in the form of an 'EP Case Study' to the WP2 coordinator 18 months after the start date. The timing for this monitoring is thus as follows:

- seed EPs: monitoring (PM6, 12) and final report (PM18)
- EP round 1: monitoring (PM19, 25) and final report (PM31)
- EP round 2: monitoring (PM 30, 36) and final report (PM42)
- EP round 3: monitoring (PM 42, 48) and final report (PM54)

4-5. Proposal conditions and format

Applicants/proposals should aim to fit or address the following criteria (full details will be provided in the call text):

- The applicant for funds must be a VPH NoE Core or General member (collaborations with Associate Members accepted, provided they are not in receipt of funds)
- Research to be 'integrated' as part of the proposed EP must be already ongoing and must already have committed funding from other sources for the whole period of EP support
- Research to be 'integrated' as part of the proposed EP must have potential for future clinical uptake/traction
- The proposal should address VPH needs for vertical & horizontal model/data integration and development of technical infrastructure resources, i.e. fit and interconnect empty slots in the "Organs systems vs. Scales" diagram (Figure 1), and propose to adopt relevant ToolKit resources and/or furnish/adapt their tools to the needs of the ToolKit.

An Evaluation Form will be provided for the reviewers that reflects success of proposals at fulfilling the above criteria.

4-6. EC rules that apply to sharing of resources

[from the Consortium Agreement]
"*7.3.6 All payments for supporting Exemplar Projects shall be made directly to the institution concerned by CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE reimbursing, with funds drawn from the Exemplar Project Budget, 100% of real and actual costs incurred with no additional overheads paid to the institution concerned. Reimbursement shall be made for salary and travel and subsistence only. In all cases, reimbursement shall only be made provided that a corresponding active unspent budget is available in the Exemplar Project Budget and it has been allocated for the given expenditure to the concerned institution with decision of the Steering Committee. Payments are subject to the provision of original receipts or invoices and proof of authorization to pay provided by the Steering Committee. CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE shall be responsible for processing these claims in an efficient manner and will enter the amounts as part of its cost claims to the EC.*"

And of course the issues of Intellectual Property, Security, etc. covered in the CA, and which we will not recall here, apply to the EPs.

Annex

[This material in this Annex is copied from the "Seed Exemplar Projects" Section of the RTAE]

Interactions between Seed Exemplar Projects (WP2) and VPH ToolKit development (WP3)

This section describes the links with WP3 as identified at the Paris workshop in November 2008, per EP.

i. Common Threads

The topic of ontologies came up in most of the seed exemplar projects. In many cases the projects have created their own ontologies, perhaps informally, to describe their area of work. As described in the ontology section above, there is a need to consolidate these with common reference terms, to facilitate future integration of systems. Work is beginning to link the efforts of the exemplar projects in this area. One topic being pursued is to analyse where further detail (in the form of additional terms) needs to be added to the FMA (Foundational Model of Anatomy ontology, http://sig.biostr.washington.edu/projects/fm/) in order to address the needs of the VPH community.

All the seed exemplars are also considering the challenges involved in integrative VPH modelling. Data integration, both vertical and horizontal, is a recurring issue, but also one that has many details specific to the particular problem being tackled. Further experience is required to determine where a common approach may provide advantages, but an initial focus on image fusion - particularly fusing medical images - seems appropriate, particularly because this is a neglected area within the systems biology community. Fusing other information with such images is also a highly relevant research area, for example the use of anatomical landmarks and gait analysis to derive a patient-specific model from a generic model in the second seed exemplar project, or fusing EEG readings with MRI brain scans in the fifth exemplar. This area of work is intimately connected with the issue of ontologies and terms for reference. In order to be able to perform vertical and horizontal integration it is necessary that we have tools for referencing across different organs and systems using both images and molecular data. Signal fusion is an important aspect of the problem, and will be taken up later, since it is a much less standardised area than image analysis.

The need for standards also appears several times, both for models and data. Topics such as libraries of available models, algorithms, and simulation results were mentioned. Well-defined and standardised metadata is also important, especially to allow robust searching. Exposing 'silent knowledge' was considered an important goal for the NoE - taking capabilities and expertise buried in VPH projects, and facilitating sharing these with the community. To develop simplified decision tree systems could be one method to expose the silent knowledge thereby facilitate understanding under what conditions a particular method is useful in a given application area. One use case is to support researchers tackling a new problem, by providing the ability to start from a similar working example.

ii. Seed EP 1

The first seed exemplar is both a provider of technology, and involved in driving ToolKit development. The main contributions are a multi-formalism solver environment, M2SL, and a parameter database system, QxDB, which can be used to aggregate parameter information

from publications. An instance of this at http://physiome.ibisc.fr/qkdb/ is used for the renal physiome project.

The project includes researchers working on ontologies and related tools, and has developed an ontology based on the Guyton model. In describing the renal physiome, finer detail of anatomical structure has been needed than is provided by the FMA. An ontology-driven interface to QxDB is also being considered.
This seed exemplar is also involved in the modelling markup languages field. The project has developed DAEML, a language with similar concepts to CellML, but designed to be easier to use in their context. Notably, it allows easier use of XSLT to convert DAEML into other formats, such as input files for M2SL. For CellML, such a task must be accomplished through use of the API. Ideas from DAEML are being fed into CellML development.

iii. Seed EP 2

The second seed exemplar project has a strong clinical focus, and has a focus on the development of a shared technology that would be of help building the necessary infrastructure to improve the current musculoskeletal (MS) modelling state-of-the-art, in order to be able to answer clinical needs and clinical constraints. The main goal of this EP is the definition of the required data processing and data visualization tools. These tools will have to be integrated into a user-friendly interface (GUI) to allow users to access generic models or to build their own models.
This EP extends previous work using the Multimod Application Framework (MAF) that already integrates many routines required for MS modelling (data import, visualization, processing, storage and management) (Van Sint Jan et al., 2006; Viceconti et al., 2007) and hence is likely to be an important contribution to the VPH ToolKit. There is a possibility of further collaboration on data fusion questions.
Looking further ahead, this EP is also an important scientific driver for ensuring the requirements for linking anatomical systems are adequately considered. The MS system is linked particularly to the nervous and cardiovascular systems, and work is beginning to determine how models of these systems might interact (although this is a huge research task, and thus will not be completed within the EP alone). Enabling such research will be a key aim for the VPH ToolKit.

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iv. Seed EP 3

The third seed exemplar project shares many requirements with other high-throughput biology projects. An obvious need is for high performance computing resources, and a list of available resources together with usage guides is considered a valuable asset.

Data integration is a particularly important area. Data for a given system can come from a range of 'omics' technologies (e.g. on DNA, RNA, lipids, proteins), and needs to be integrated both across different organs (for a given organism) and across different species.

There are specific tools available for such tasks, which could be integrated within a VPH approach. A missing link is tools for searching and managing a repository of images (both structural and functional) at different levels of resolution, species, different conditions, etc.

There are also needs in the area of computational modelling, in order to obtain systems understanding. Some are 'basic' requirements, such as a library of available models, and hence markup languages capable of expressing the models in question and easy to use. The capabilities of existing languages appear to be largely sufficient, so focussing on the usability aspect is important to increase take-up. Methods or tools for integrating models in various ways would also be useful, for example for coarse graining, vertical & horizontal integration, and averaging models (at the same vertical and horizontal scale). As a longer term goal, libraries of code or algorithms (e.g. for ensemble modelling, parameter identification, or feature selection) would also be desirable.

A third unexplored area is how to integrate computational models describing molecular events in cells within the arterial wall with models describing the fluid mechanics of the low flow in the arterial vessels. This means integrating kinetics with mechanical models.

v. Seed EP 4

The fourth seed exemplar project is again both a provider and a consumer. The team has extensive experience in molecular-level VPH modelling, with a variety of tools developed specifically for this area, particularly distributed molecular dynamics (e.g. http://www.qoscosgrid.eu/,http://www.ps3grid.net/, http://www.gpugrid.net/) and molecular systems biology (http://cbbl.imim.es/ByoDyn) simulations. The BioBridge portal (http://www.biobridge.eu/) also has much to contribute to the VPH ToolKit by providing an environment for integration of clinical to omics data, being the inclusion of molecular data a relevant new possible task.

The exemplar project is looking at vertical integration, extending this sub-cellular and cellular expertise to multi-cellular investigations. The networking activity of the NoE is being employed to build links between this project and the preDiCT FP7 project (http://vph-predict.eu/) and a first meeting has been already planned with preDiCT partners in December to explore such synergies.

The project has particular needs in the area of modelling markup languages. One requirement is for the elegant description of multi-cellular models which is currently handled by an adaptation of SBML files but that would benefit from the interaction with CellML. A second field of interest is the description of general markup languages for force field definition, already being explored in the IMIM partner in the form of FFML, where links to FieldML will also be considered in the future. Also needed are (metadata) standards for simulation results. An example use case is to enable the sharing of simulations, for example "relaxation of the hERG channel," in the same way the Adun program (http://cbbl.imim.es/Adun) distributes molecular simulations using a P2P network. This could also facilitate comparisons between different simulation methods for the same problem.

vi. Seed EP 5

The fifth seed exemplar project links most closely with the data fusion task in WP3. There is a need for image analysis, data processing and visualisation techniques in order to extract the necessary information, which will be the input to the cancer simulator (from the ACGT project). This work will also need to link with model and data repositories provided through the VPH. A useful service suggested was a categorisation of image processing algorithms, to

aid researchers in selecting the most appropriate algorithm(s) for their problem, and thence tools implementing these.

There is also the possibility of this exemplar project providing to the VPH ToolKit GUIs specifically tailored to visualize causal and functional relations between different brain lobes. In time these could be extended to include source localization algorithms that may be fused with other ToolKit visualization components.