

The EuroPhysiome, STEP and a roadmap for the virtual physiological human

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Q1 Biomedical science and its allied disciplines are entering a new era in which computational methods and technologies are poised to play a prevalent role in supporting collaborative investigation of the human body. Within Europe, this has its focus in the virtual physiological human (VPH), which is an evolving entity that has emerged from the EuroPhysiome initiative and the strategy for the EuroPhysiome (STEP) consortium. The VPH is intended to be a solution to common infrastructure needs for physiome projects across the globe, providing a unifying architecture that facilitates integration and prediction, ultimately creating a framework capable of describing *Homo sapiens in silico*. The routine reliance of the biomedical industry, biomedical research and clinical practice on information technology (IT) highlights the

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importance of a tailor-made and robust IT infrastructure, but numerous challenges need to be addressed if the VPH is to become a mature technological reality. Appropriate investment will reap considerable rewards, since it is anticipated that the VPH will influence all sectors of society, with implications predominantly for improved healthcare, improved competitiveness in industry and greater understanding of (patho)physiological processes. This paper considers issues pertinent to the development of the VPH, highlighted by the work of the STEP consortium.

Keywords: **physiome; EuroPhysiome; integrative biology; virtual physiological human; strategy for the EuroPhysiome**

1. Introduction

Physiome:

... a comprehensive framework for modelling the human body using computational methods which can incorporate the biochemistry, biophysics and anatomy of cells, tissues and organs. (Hunter *et al.* 2002)

Q2

Q3 The physiome concept (Hunter & Borg 2003; Hunter, P. J. 2006) has been fervently embraced by the European scientific community, which recognizes that the current partitioning of health science endeavour along traditional lines (i.e. scientific discipline, anatomy, physiology, etc.) is artificial and inefficient with respect to such an all-embracing description of human biology. It is argued that a more effective approach must be sought, encompassing cross-boundary disciplines and integrating them according to the focus of the problem in hand, unconstrained by scientific discipline, anatomical subsystem and temporal or Q4 dimensional scale (Boyd & Noble 1993; Welsh *et al.* 2006).

This is a radical approach that deserves to be complemented by a radical framework in which observations in laboratories and hospitals across nations can be collected, catalogued, organized and shared in an accessible way so that clinical and non-clinical experts can collaboratively interpret, model, validate and understand the data. It is a framework of technology and methods, and together they form the virtual physiological human (VPH). This vision is complemented by a community of active protagonists, collectively pursuing Q5 physiome projects across the world (Plasier *et al.* 1998; Bassingthwaighte *et al.* Q6 1999; Kohl *et al.* 2000; Schafer 2000; Hunter *et al.* 2002, 2005; Bro & Nielsen 2004; Crampin *et al.* 2004, <http://www.physiome.org.nz>), and through harmonized action, it may be possible to create a coherent and credible VPH infrastructure in Europe within a decade.

2. Role of strategy for the EuroPhysiome and the VPH roadmap

Strategy for the EuroPhysiome (STEP)¹ refers to a project that is characterized as a European Coordination Action, and was funded to consider and recommend effective strategies that promote the development of the VPH. Its deliberations have recently been published (Spring 2007) in an advisory document entitled

¹ STEP—Strategy for The EuroPhysiome FP6-2004-IST-4-027642.

99 ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological human’
 100 **Q7** (<http://www.europhysiome.org>). This is a policy document that is designed to
 101 advise the EU in respect of VPH funding, emphasizing that the VPH is a
 102 technological framework that aims to be descriptive, integrative and predictive.

103
 104 — *Descriptive.*² The framework should allow observations made in laboratories,
 105 in hospitals and in the field, at a variety of locations situated anywhere in the
 106 world, to be collected, catalogued, organized, shared and combined in any
 107 possible way.

108 — *Integrative.*² The framework should enable experts to analyse these
 109 observations collaboratively, and develop systemic hypotheses that incorpor-
 110 ate the knowledge of multiple scientific disciplines.

111 — *Predictive.*² The framework should facilitate the interconnection of predictive
 112 models defined at different scales, with different methods and with different
 113 levels of detail, producing systemic networks that breathe life into systemic
 114 hypotheses; simultaneously, the framework should enable their validity to be
 115 verified by comparison with other clinical or laboratory observations.

116
 117 These themes (among others) are part of a consultative process within STEP
 118 that involved the discussion of a broad range of groups and lively debate at
 119 conferences, all supported by an advisory board of global physiome experts.
 120 Contributions have come from the academic community, industrial and clinical
 121 users, professional associations, etc.

122 The VPH roadmap begins by defining the scope of the VPH, offering
 123 justification (motivation) for its existence, based on foreseen needs (research,
 124 clinical and industrial). An international perspective is used to give this context,
 125 supported by a series of case studies. The importance of a suitable structure for
 126 the proposed VPH highlights challenges for its implementation, which are
 127 broadly categorized as scientific challenges, challenges in description, challenges
 128 of integration, challenges in IT and their solution. The magnitude of the IT
 129 challenge is considerable in the light of the data flows involved (petabytes), but
 130 carefully evaluated case studies focusing on research, clinical, industrial and
 131 societal impact indicate the value of providing infrastructure support for
 132 EuroPhysiome activity. Other analyses consider matters of exploitation,
 133 dissemination and sustainability, not forgetting political aspects associated
 134 with ethical, legal and gender issues. The final chapter recommends actions
 135 necessary to secure the future of the VPH. This paper presents a brief summary
 136 of the advisory document and allied content.

137 138 139 **3. The VPH roadmap: motivation**

140 Justification for the existence of the VPH has its roots in anticipated clinical,
 141 industrial and academic needs, underpinned by the conviction that a cross-
 142 discipline approach to medical endeavours is the only credible way forward in the
 143 twenty-first century (Haygarth *et al.* 2005; Hwa *et al.* 2005; McCallin 2006;
 144 Zaenker 2006). Four categories of justification are apparent,

145
 146 ²Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological
 147 human’ (www.europhysiome.org), p. 7.

- 148 (i) *Clinical*. The clinical justification recognizes the way in which clinical
 149 specialization fragments patient management. There are few bridges
 150 between clinical specialties (cardiologist, audiologist, neurologist, etc.)
 151 and patients of an aetiology requiring a multidisciplinary approach are
 152 typically dispatched to various clinical experts for analysis of the
 153 numerous aspects of their disease. A more integrated approach could
 154 yield many benefits, and the VPH is poised to assist the clinician with the
 155 collection, organization, visualization and interpretation of the potentially
 156 vast and rich array of data available.
- 157 (ii) *Academia*. Justification within the realm of biomedical research comes
 158 from the recognition that the expertise of many investigators is quite
 159 narrow. For instance, modellers/engineers do not necessarily understand
 160 the needs of experimentalists, and neither may be aware of the clinical
 161 implications of their work. This is inefficient and impotent in respect of
 162 solving clinical problems that could benefit from state-of-the-art knowl-
 163 edge (perhaps most efficiently addressed in a multidisciplinary manner).
 164 The solution provided by the VPH is an infrastructure that helps to break
 165 down these barriers.
- 166 (iii) *Industry*. Within industry, justification arises from anticipation of
 167 industrial benefit, because the VPH clearly provides a resource for
 168 product design and development. Innovations can be developed more
 169 quickly with reduced risk and cost, and recognition of the VPH by
 170 regulatory authorities may ease product development and decrease time
 171 to market while integrating benefits such as the reduced need for clinical
 172 trials or animal testing. At the point of product delivery, there is the
 173 promise of relevant, easy-to-create simulation-based training and support.
 174 Ultimately, the reward for efforts invested in the VPH is a competitive
 175 edge in a global market.³
- 176 (iv) *Society*. Society plays a vital role in the justification of the VPH, since it is
 177 society that will fuel its development and society that it will serve.
 178 Benefits accrue from industry (*innovation, improved standards, low cost*
 179 *production methods, etc.*), the clinic (*basic science translated to clinical*
 180 *practice, the systemic effects of interventions and side effects, improved*
 181 *decision making*) and cross-disciplinary research. The promise of
 182 improved global competitiveness may have far reaching implications for
 183 quality of life (*unemployment, education, social welfare, etc.*).

184
 185 *Motivation summary*. Cross-disciplinary clinical, industrial and academic
 186 pursuit will benefit society.

187 188 189 **4. The VPH roadmap: international context and common objectives**

190 The advocates of the VPH point to the value of such an infrastructure by noting
 191 the benefits of their own cross-disciplinary, multi-scale activities. Furthermore,
 192 they are plaintiffs for further benefits that could result from harnessing synergies
 193
194

195 ³ Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological
 196 human' (www.europhysiome.org), p. 17.

197 between projects. Such promotion naturally highlights the objectives common to
 198 these apparently disparate activities, which become readily apparent when viewed
 199 as a collection of case studies (Bassingthwaight 2000; Hunter *et al.* 2005).

200 VPH objectives that would benefit all physiome activities include the following:

- 201 — Design of a flexible and logical infrastructure for physiome activities and their
 202 implementation.
- 203 — Data processing and modelling toolkits.
- 204 — Effective access to resources for ontologies and visualization, etc.
- 205 — Computing infrastructures (grid, HPC), knowledge management, back-end
 206 services, etc.

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 208
 209 *Objectives summary.* The VPH infrastructure must support underlying
 210 physiome infrastructure needs.

211 5. The VPH roadmap: observations on research challenges

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 213
 214 Objectives influence architectural design, and the challenges are brought into
 215 sharp focus when the specific needs of participating communities are considered.
 216 The cross-discipline collaborative nature of the VPH is most evident in this
 217 section of the roadmap, since it reflects the diverse opinions of the consultative
 218 process. Clinical, industrial and academic experts were engaged, both through
 219 e-mail and discussion at conferences. A twofold categorization of the research
 220 challenges emerged, identifying broad themes that need to be addressed if the
 221 VPH is to become a reality.

- 222 (a) It is important to clarify the brief of the VPH (i.e. the nature of the scientific
 223 problems and principles to which it relates) and how such issues might
 224 be addressed.
- 225 Q8 (b) It is necessary to identify the information technologies (ITs) that must be
 226 developed to address the challenges raised by the above issues.

227
 228
 229 In respect of item (a) (and in spite of the apparent variety of challenges that
 230 present themselves), it is widely accepted that the true grand challenge lies in
 231 understanding biological function. This requires a wealth of data interpreted by
 232 models that describe and are informed by the underlying biology. In respect of
 233 item (b) it is informative to determine the extent to which (physiome) activities
 234 can be truly integrated. This refers to

- 235 (i) integration of physiological processes across different length and time
 236 scales (multi-scale modelling);
- 237 (ii) integration of descriptive data with predictive models; and
- 238 (iii) integration across disciplines.⁴

239
 240
 241 Complementary and concerted effort is needed (Kohl *et al.* 2000; Gavaghan
 242 *et al.* 2006) to develop the appropriate infrastructure, frameworks and
 243 technologies (computational, organizational and imaging) that can support

244 ⁴Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological
 245 human' (www.europhysiome.org), p. 39.

246 these requirements. Databases of models and data at many spatial and temporal
247 levels are required if ‘multi-scale’ is to fully embrace everything from molecules
248 to organ systems. Software tools are needed for authoring, visualizing and
249 operating models based on widely adopted modelling standards (Hunter, P. J.
250 2006). There is also a need for the development of ontologies dealing with
251 anatomy, physiology and molecular/cellular biology to uniquely identify and link
252 model components. Finally, data from advances in modelling and imaging should
253 be available to all interested parties through the development of networking
254 databases that keep researchers abreast of relevant progress.⁴

255 *Challenges summary.* Construction of a robust and relevant IT foundation for
256 the VPH.

257 258 259 6. The VPH roadmap: scientific challenges

260 The research challenges above form a backdrop against which specific scientific
261 challenges can be identified. These are categorized as follows: (i) challenges in
262 prediction, (ii) challenges in description, (iii) challenges in integration, and
263 (iv) ICT challenges and their solution.
264

- 265 (i) *Challenges in prediction.* This includes aspects of problem identification,
266 model complexity, understanding interactions (Judex et al. 2006), multi-
267 scale modelling, issues of inhomogeneity and intersubject variation,
268 aspects of validation and identification of gaps in modelling or knowledge,
269 human biology and pathology. There are challenges arising from the
270 coupling of models working at difference scales or in different disciplines
271 (e.g. biology/chemistry to mathematics/physics). Fundamental physio-
272 logical knowledge is also lacking on the effect of genomic information on
273 higher level physiological function.
274 (ii) *Challenges in description.* It is self-evident that the existence of data is
275 necessary for the development of understanding and the validation of
276 models, but the mere presence of data does not mean that it is complete or
277 accurate. The latter is particularly relevant to model validation and data
278 should be interpreted with care. In fact, it is arguable that all data should
279 be accompanied by a classifier that clarifies the confidence of each
280 measurement. Many sources of data exist (obtained from physical measure-
281 ment or simulation), but much of it has its origins in instruments/models
282 that introduce their own assumptions and artefacts into the data. Ideally,
283 data collection protocols would accommodate this, ultimately leading to
284 the creation of generic *in vitro* models (appropriately accounting for data
285 quality) or refined customization of *in vitro* models using patient-specific
286 data (characterizing both normal and pathological behaviours). Auto-
287 mated (or semi-) statistical analysis of the final model may be possible
288 using decision algorithms.⁵ Models that are developed to answer clinical
289 or industrial questions require accurate anatomical and physiological
290 information (imaging, experimental data, etc), and therefore it is important
291
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293 ⁵ Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological
294 human’ (www.europhysiome.org), p. 45.

- 295 to ensure that imaging technology or experimental technique is quality
 296 assured to ensure provision of consistent high-quality data.
- 297 (iii) *Challenges in integration.* Integration refers to the seamless interfacing of
 298 diverse specialties, measurements or models, an obvious example being
 299 integration across multiple scales. Integration between disciplines is also
 300 important. There is merit in explicitly identifying the need for integration
 301 between data that describe biology, and models that can predict and
 302 help with the understanding of function. Often simulations are married
 303 to particular solvers and too easily, these results in the ‘parochialization’
 304 of models. There is benefit in describing models independently of the
 305 numerical solver, separating them from the numerical methods used to
 306 solve them. A flexible arrangement to model implementation or coupling is
 307 required and innovative solutions could include the promotion of mark-up
 308 language development (in the spirit of CELLML, FIELDML, etc.; Hedley *et al.*
 309 2001; Cuellar *et al.* 2003; Hucka *et al.* 2003; Lloyd *et al.* 2004) and the
 310 encapsulation of models as web services.
- 311 (iv) *ICT challenges and their solution.* This concerns the tools needed to address
 312 the scientific challenges discussed above (Hey & Trefethen 2003). A
 313 **Q9** database that collates and classifies models is a core requirement and should
 314 include pointers to other modelling efforts around Europe and beyond, thus
 315 reducing duplication of effort and facilitating collaboration between
 316 researchers (Dao *et al.* 2000; Coyle *et al.* 2003). This could provide a
 317 framework for model communication, and would necessitate the develop-
 318 ment of software tools and standards to facilitate model coupling. Models
 319 with greater detail could be combined with low-resolution models, with a
 320 consequent reduction in the need to set artificial boundary conditions. The
 321 availability of a knowledge management software database could manage
 322 such information and integrate it with data from the literature.

324 The coupling of models is a major challenge in itself and would benefit from a
 325 coherent architecture, relying perhaps on a macroscopically functional scaffold
 326 within which models of greater or lesser detail can operate and communicate. A
 327 federation of predictive services could be used to expose I/O interfaces in a
 328 standardized way. Semantic mediation is needed to support interconnection and
 329 interpret data spaces. The presence of a standardized data format can ease
 330 problems of this kind (e.g. <http://medical.nema.org>, <http://www.hl7.org>,
 331 <http://www.ihe.net>), but a robust solution requires both format translation
 332 and semantic mediation. Data size (typically gigabytes, but ranging from
 333 megabytes to petabytes) needs intelligent strategies for data storage and sharing,
 334 recognizing issues associated with bandwidth, latency, caching, etc. (Rio *et al.*
 335 2003). History indicates that we are unlikely to satiate our appetite for data and
 336 therefore storage/bandwidth issues require a long-term strategy, recognizing that
 337 they are likely to remain perennial problems.

338 Structural functional data used to build and validate models typically come
 339 from the literature or experimental effort. However, data are also generated by
 340 simulation and the infrastructure must support the communication, storage and
 341 processing of vast quantities of such data. Effective curation (Beagrie 2006) is a
 342 core requirement of the VPH. The possibility of distributed computing to solve
 343

344 some of these problems is attractive (Woods *et al.* 2005), and a comprehensive
 345 VPH resource would facilitate the following:

- 346 — Integration of grid computing technologies and middleware into biomedical
- 347 research demonstrators and applications.
- 348 — New architectures and demonstrators for heterogeneous data integration,
- 349 leveraging current efforts and domain standards.⁶
- 350

351 Unfortunately, IT solutions to many of these problems are not immediately
 352 available, but the ongoing development of grid computing projects over recent
 353 years (Coveney 2005) has produced many prototype solutions that are
 354 potentially invaluable (Clery 2006). For instance, the Application Hosting
 355 Q10 Environment (REALITYGRID; Cohen *et al.* 2005) is already available in a first
 356 release and provides a painless means of interacting with federated Grids.
 357 BioSIMGRID (Tai *et al.* 2004) offers a template for a suitable VPH architecture
 358 since it has developed a prototype, which is designed to act as a repository of
 359 simulation data. BIOSPICE (Garvey *et al.* 2003) is another example and provides a
 360 complete molecular infrastructure for life sciences. Through such projects, a
 361 wealth of open source biomedical computing software is available and includes
 362 the following:

- 364 — Middleware/infrastructure resources (<http://www.globus.org>, <http://www.omii.ac.uk>).
- 365 — The National Library of Medicine Insight Segmentation and Registration
- 366 Toolkit (<http://www.itk.org>).
- 367 — The visualization toolkit (<http://www.vtk.org>).
- 368 — The National Biomedical Computation Resource (<http://nbc.r.sdsc.edu/>).
- 369 — The Multimodal Application Framework (<http://openmaf.cineca.it/maf/>).
- 370
- 371

372 *Scientific challenges summary.* Pursuit of integration, description and
 373 prediction through IT solutions that are native to the VPH.
 374

376 7. The VPH roadmap: problem sizing and required resources

378 This section of the roadmap considers the quantity of data associated with multi-
 379 participant dialogue, noting that it will be considerable and will require
 380 exceptional management. Of course the value of the VPH will be measured by
 381 the availability and quality of data that flow to the end-user, but it will also
 382 depend upon a steady influx of predictive concepts and robust data if it is to
 383 continue to meet the needs of the society it serves. Viability is dependent upon an
 384 adaptive infrastructure that can overcome numerous challenges such as the
 385 organization and storage of petabytes of data, sustained communication
 386 bandwidths exceeding terabytes per day, extensive support for data indexing
 387 and data format translation, and all of these embedded within an infrastructure
 388 that guarantees secure and transparent access (Seitz *et al.* 2005). Finally, this has
 389 to be integrated with quality assurance mechanisms that safeguard the quality of

391 ⁶ Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological
 392 human’ (www.europhysiome.org), p. 48.

393 data accessed by the end-user (Montagnat *et al.* 2004; Middleton *et al.* 2005).⁷
394 Overall, the technology must be immune to obsolescence, with sufficient
395 adaptability to match continuing data growth.

396 *Sizing and resources summary.* The VPH requires technology solutions for
397 data storage, data flow and security.

400 8. The VPH roadmap: impact analysis

401
402 The roadmap postulates that the VPH will have significant influence on bio-
403 medical research, clinical practice, sectors of industry and society at large. It is
404 presupposed that the VPH will have profound implications for biomedical research
405 by providing an infrastructure that will enable unprecedented collaboration on an
406 international scale. This will extend classic channels of common participation to
407 include contributions from disparate and distant laboratories and accommodate
408 common resources developed by consortia of international teams. Ideally, this
409 will be accompanied by a new era of defined standards and open-source web tools.
410 Such an infrastructure will ensure practical access to the great body of already
411 published experimental data in ways not possible today.

412 The VPH will impact on clinical practice by facilitating patient-specific
413 tailoring of treatment, better cooperation among the various medical special-
414 izations (e.g. it can benefit patient management through improved clinical
415 decision support) and introducing many other benefits not yet envisaged. For
416 instance, anonymized clinical data and published outcomes of clinical trials are
417 critical components of medical endeavour, and together they can significantly
418 contribute to the cataloguing of the human condition. Follow-up data form an
419 invaluable tool for quantifying the efficacy of treatment strategies, clarifying
420 insights and validating predictions. A requirement to return follow-up data to the
421 VPH will encourage a climate of evidence-based medicine and influence future
422 strategies for patient management.⁸ Eventually, a successful framework might
423 encourage all activities to be VPH compliant.

424 With respect to industry, the impact will be measurable as improved technical
425 excellence, reduced development time or streamlined staff numbers. However,
426 ultimately the yardstick used by industry will be financial, and the financial
427 savings that a European-wide scientific initiative might invoke are reliably
428 calculated to be huge, using, where possible, data supplied by industry itself
429 (PriceWaterhouseCoopers 2005). The impact of the VPH on industry will first
430 be felt in the medical device and pharmaceutical industries, but in time will
431 inevitably spread beyond these key areas.

432 The expected impacts of the VPH on society will be manifold and in general
433 related to interdependent influences. Society will benefit from an improved
434 economy (more turnover and reduced public expenses) and healthier citizens,
435 although societal economic effects due to specific initiatives may be intangible.
436 However, with a large-scaled initiative such as this, several immediate and
437 long-term areas of impact are apparent. At the very least, the VPH will improve
438

439 ⁷ Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual physiological
440 human' (www.europhysiome.org), p. 51.

441 ⁸ Cited from the VPH roadmap, p. 32.

relationships and communication between the industrial, clinical and research communities. This will impact in a number of areas, such as healthcare, industry, research, education and exchange.

Impact analysis summary. A successful VPH will have impact on healthcare, industry and society in general.

9. The VPH roadmap: success stories

Physiome-related activities have contributed significantly to understanding in many areas of the health care sector and there is every expectation that future contributions will be even more significant. A selection of successful physiome projects is listed and potent examples are as follows.

(a) Europe

- LYMFASIM—simulation for modelling lymphatic filariasis and its control (Plaisier *et al.* 1998).
- GEMSS—grid-enabled medical simulation services (<http://www.gemss.de>, Benkner *et al.* 2005).
- SimBio—a generic environment for bio-numerical simulation (<http://www.simbio.de>).
- Q11 — CHARM—comprehensive human animation resource model (<http://ligwww.epfl.ch/~maurel/CHARM/>).
- Q12 — COPHIT—computer-optimized pulmonary delivery in humans of inhaled therapies (http://www-milton.ansys.com/European_Projects//cophit/index.html).
- Q13 — BloodSim—simulation of cardiovascular and other biomedical problems (http://www-milton.ansys.com/European_Projects//bloodsim/bloodsim.htm).
- HUMOS2—development of a set of human models for safety (<http://humos2.inrets.fr/index.php>, Tropiano *et al.* 2004).
- GIOME—integrative modelling of physiological and pathophysiological processes in the gastrointestinal tract (<http://www.giome.com/>, Gregersen 2006).
- LHDL—living human digital library (<http://www.biomedtown.org/lhdl>).
- SAPHIR—a multi-scale, multi-resolution modelling environment targeting blood pressure regulation and fluid homeostasis (<http://saphir.ibisc.fr/>, Thomas *et al.* 2007).

(b) USA

- The visible human server—MRI, CT and anatomical images of the human male and female (<http://www.nlm.nih.gov/research/visible/>).
- BioSim—integrative model of physiology (<http://www.biosim.com/>).
- VSR—virtual soldier research programme—digital humans in real time (<http://www.digital-humans.org/>).
- NRCAM—National Resource for Cell Analysis and Modelling—cell simulation (<http://www.nrcam.uchc.edu/>).

—AHM—active health management (<http://www.activehealthmanagement.com>)—predictive modelling for patient benefit.

Success stories summary. The VPH can support physiome activities and augment their success.

10. The VPH roadmap: ethical, legal and gender issues

It is easy to forget that a scientific resource such as the VPH has a wider impact that extends beyond the boundaries of normal scientific influence. The VPH does indeed offer improved healthcare on an international scale, but it also poses significant ethical dilemmas (Bassingthwaight 2003) that highlight the need for the establishment of intelligent codes of conduct, some of which may require the backing of legislation. In the scientific domain, the promotion of ethical practices is facilitated by key professional groups, and this concept could be rationalized and extended across the entire VPH for the benefit of public confidence and protection.⁹

The ethical dimension includes consideration of the purpose of the VPH and the suitability of the resource to fulfil that purpose. However, ethics does not function in isolation and the VPH should offer opportunities for collaborative sharing of concerns and successes. With respect to intellectual property rights (Maurer *et al.* 2001), a regulatory framework that supports effective data sharing (Q14 and interoperability is required (Ellis & Kalumbi 1998; Charlesworth 2006; Q15 Philippi & Kohler 2006)—this is an important task that deserves dedicated effort. Data storage and processing must comply with data protection legislation (Directive 95/46/CE of the European Parliament 1995; Herveg 2006), but (Q16 legal anomalies are in evidence across Europe (Herveg & Pouillet 2003). The legal component is also necessary to provide guidance in the event of adverse outcomes resulting from inaccurate or incorrectly interpreted VPH data (Q17 liability; Hureau & Hubinois 2005). Gender is relevant to the circumstances in which VPH data should be used (i.e. are VPH data gender specific and is it appropriate to use such data if gender specificity is not present or apparent?; Singleton *et al.* 2005; Berkley *et al.* 2006) and also considers the extent to which the VPH can be a tool to promote social equality across Europe.

Ethical, legal, gender summary. The VPH has the power to deliver political change.

11. The VPH roadmap: dissemination, exploitation and sustainability

The presence of the VPH will generate numerous opportunities, both scientific and social, and its use may require a cultural shift for many, and may even be regarded as a threat by some, to their current practices.

(Q18 It will be important for the rapid and widespread acceptance of this tool so that such perceptions must be reduced as much as possible, both in scale and extent, and that the opportunities provided are seen to be sufficiently rewarding

⁹ Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual physiological human’ (www.europhysiome.org), p. 77.

540 so that any short-term inconvenience in embracing the technology will be
541 handsomely compensated in long-term gains. This is a matter of education. The
542 dissemination of accurate information, the number and nature of available VPH
543 resources and how they can be accessed, and the provision of supportive
544 educational materials will be critical for this. Effective communication will
545 encourage the present generation to engage and benefit from emerging develop-
546 ments, but should also provoke consideration of longer term initiatives that
547 can equip the scientific community (especially, the young researcher) with a
548 true, multidisciplinary education. It will be a challenge to develop courses that
549 carefully balance and extend breadth, and yet cover topics in sufficient depth.
550 The most important factor, particularly in the initial stages, is that information is
551 consistent and coherent.¹⁰ VPH exploitability and sustainability are largely
552 dependent on the ability of the VPH to influence the health and well-being
553 of ordinary people for the common good (Maojo & Martin-Sanchez 2004). This
554 will be most evident at the interface with the health care system. Case studies
555 are a useful way of communicating such information to the general public and
556 accessible exemplars can help provide strategic focus. In this manner, the benefits
557 and challenges of integrating models over many scales can be illustrated, with
558 individual components giving visible relevance to the clinical and scientific goals
559 (e.g. infection and immunity could be an exemplar that heightens public
560 awareness, providing advanced systems and population level views of disease).

561 *Sustainability summary.* A short-term high-profile goal (project) may be an
562 effective vehicle for promoting the VPH in society.

563 12. The VPH roadmap: recommendations

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565
566
567 The final section of the roadmap reviews its content and summarizes key points.
568 In particular, it proffers actions that are deemed to be effective responses to the
569 dilemmas presented by the roadmap and raised by the consultation process. The
570 content is intended to be advisory, clarifying the priority of VPH activities that
571 could be funded under the Seventh Framework Programme of the European
572 Commission (http://cordis.europa.eu/fp7/home_en.html). Tables 1 and 2
573 summarize the principal issues that deserve attention if the VPH is to benefit
574 from continued development. The key issues are infrastructure, models and data
575 as briefly described below, noting that nothing is possible without the
576 participation of people willing to invest time and effort into VPH development.

- 577
578 (i) *Infrastructure.* The success of the VPH depends heavily on a robust IT
579 infrastructure. In a broader context, there must be support for a VPH
580 community (perhaps as a physical institute?) with structures that can
581 enforce VPH standards and rules. It should provide an environment that
582 supports the execution of commercial codes while safeguarding the quality
583 and ownership of a multiplicity of data. The greatest legal challenge
584 relates to patient ownership of clinical data. Coherent ethical/legal
585 structures that address such problems must be a priority.

586
587 ¹⁰ Cited from the VPH roadmap 'Seeding the EuroPhysiome: a roadmap to the virtual
588 physiological human' (www.europhysiome.org), p. 83.

Table 1. In order for the VPH to proceed to its next stage of development, the STEP consortium recommends action in particular areas. (The contents of the tables highlight the infrastructure areas that warrant investment.)

Remit of the VPH:

- (a) integration of physiological processes across different length and time scale (multi-scale modelling)
- (b) integration of descriptive data with predictive models
- (c) integration across discipline

<p>ICT infrastructure services</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — A VPH user community — Data object repositories, federation and management — Diffuse knowledge management (ontologies etc.) — Quality assurance of data — Single sign-in access to VPH resources — User friendly environments for grid access and applications — Sharing and distribution of models — Multi-physics, multi-solver, multi-scale coupling — Parallelization and job optimization 	<p>Community infrastructure</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — A recognized central authority that oversees the VPH — A bridging authority in the short term (NoE) — Raising the profile of the VPH with the aim of making it a ubiquitous presence in the biomedical arena — Single sign-on, standardization, interoperability
<p>Physical infrastructure</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — A debate that clarifies whether the VPH should be hosted by few large-scale infrastructures (LSI), or by a loosely coupled, federation of small-to-medium computational resources — Effort to raise the profile of life sciences as a core customer for grid resources (on a par with the high-energy physics community etc.) 	<p>Technology infrastructure</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Middleware development for the VPH — Interoperability and support for effective standards (DICOM, HL7, etc.) — Liaison with other interoperability initiatives (e.g. Integrating the Healthcare Enterprise – www.ihe.net) — Resolution of (grid) security issues, particularly with respect to clinical data
<p>Commercial, Legal and Ethical infrastructure</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — A commercial infrastructure for the VPH that ensures its financial sustainability (e.g. access charges for VPH resources may apply) — Execution of commercial code and resolution of distributed platform licensing issues — Infrastructures that permit data sharing in the context of clearly defined IPR regulations — Data protection and patient confidentiality — VPH promotion of social equality 	

infrastructure

638 Table 2. In order for the VPH to proceed to its next stage of development, the STEP consortium
 639 recommends action in particular areas. (The contents of the tables highlight the modelling, data
 640 and other areas that warrant investment.)

<p>Clinical Observation</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Widespread clinical participation — Accumulation of clinical, observational data and its organization — Projects that collect relevant experimental data with respect to cell-to-cell and cell-to-tissue interactions 	<p>Model Accumulation</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Developments that enable separation of model definition from the modelling environment — Development of solver-independent modelling formats (e.g. CellML) — The offering of models as encapsulated Web services 	<p>Model Verification</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Methods to quantify model accuracy (i.e. how accurately equations are solved) and verification (i.e. the extent to which the model is an appropriate description of the problem) — Available reference benchmark problems for the quantitative evaluation of simulation code (e.g. speed, accuracy) — Development of adaptive algorithms that can be constrained to deliver solutions to specific accuracy across multiple-scale problems
<p>Data Collection</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Funding to support organized collection, storage etc. of data for the VPH — Data curation (e.g. extension of cultural heritage curation expertise to the scientific domain) — A quality assurance infrastructure that will promote data sharing 	<p>VPH Modelling Challenges</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Model preparation (preprocessing, segmentation, mesh generation, derivation of properties from biological data, missing parameters, etc.) — Model coupling (FSI, lumped parameter and coupled models, changes of dimensionality, boundary conditions etc.) — Methods to overcome limited computational resources 	<p>Model Interconnection</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Development of macroscopic 'supermodels' that describe a functional or metabolic subsystem as scaffolds for organizing lower level, higher detail models — Development of model repositories as a loosely coupled federation of predictive services, exposing an I/O interface that supports model concatenation — I/O interface standardization/data semantics — Data redistribution, latency minimization, I/O overhead reduction — Data standardization and / or format conversion
<p>Validation Issues</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Efforts directed at experimental data collection against simulation results — Model verification in the clinical context — Model certification for clinical use — Methods to accommodate inter-subject variability — A VPH dialogue with regulatory authorities 	<p>Sustainability Issues</p> <p>Support is warranted for:</p> <ul style="list-style-type: none"> — An infrastructure providing a profitable business model that provides a value-for-money resource and yet sustains VPH development (e.g. Barter, E-commerce models, subscription etc.) — Continued infrastructure maintenance and development (funding) 	<p>People Issues</p> <p>Support is warranted for</p> <ul style="list-style-type: none"> — Recruitment (particularly of younger scientists into the multidisciplinary field of the VPH) — VPH career support and incentives
<h1>Miscellaneous</h1>		

- 687 (ii) *Models and data*. The current framework of multi-scale biology has
 688 weaknesses that are best addressed by a research focus at cellular length
 689 scales, although many of the wider modelling challenges are length-scale
 690 independent. These include simulation development, the sharing and
 691 coupling of different models and their verification, data standards and
 692 quality (Hunter, J. 2006), ontological development and semantic mediation,
 693 Q19 etc. Significant issues relating to data curation (Merali & Giles 2005),
 694 storage and data transfer also need to be resolved. Many simulations use
 695 different commercial codes and a suitably flexible licensing model (e.g. pay
 696 per solve) is needed to encourage occasional or short-term developmental
 697 use. The development of models encapsulated as web services may also be
 698 advantageous. The VPH must host a repository of reference benchmark
 699 problems, for which the solutions are known and by which the quality and
 700 performance of emerging simulation tools can be judged.
- 701 Q20 (iii) *People*. A significant barrier to VPH sustainability and consequent reali-
 702 zation of benefits to scientific development and public health leads to the
 703 current lack of attraction of this field to younger scientists. Gifted young
 704 researchers perceive that more promising careers can be found in fields
 705 Q21 such as molecular biology and medicine. Since efforts in interdisciplinary
 706 fields are normally under-rewarded, it will be necessary to redress this
 707 imbalance by developing a comprehensive career support and incentive
 708 system allied to the VPH. Talented young people facing fundamental career
 709 decisions must be satisfied that their scientific development and career
 710 progression will benefit—rather than being compromised—from involve-
 711 ment with VPH-related activities. Such a strategy is essential if the VPH is
 712 to attract the high-quality individuals who are necessary for its rapid and
 713 sustained development.
- 714 (iv) *Miscellaneous*. Intended use of the VPH in clinical practice imposes
 715 numerous responsibilities, including (i) rigour in terms of model design,
 716 explicit recognition of assumptions/limitations and (ii) care in the acquiring
 717 of validation data, with appropriate recognition of errors and acknowl-
 718 edgement of the limitations of measuring equipment. A mechanism for
 719 authorizing clinical application of a model is needed, so that clinical models
 720 can be certified for such use. Industrial use of models faces similar challenges,
 721 since industrial models are intended for human application—FDA and CE
 722 approvals are beginning to acknowledge the value of simulation in the
 723 certification process. A link between these authorities and the VPH could
 724 benefit both parties and accelerate industrial development, safety and
 725 public acceptance of new products.
 726
 727

728 With respect to society, the benefits of the VPH are perhaps best
 729 communicated through concrete examples, and early implementations that
 730 demonstrate significant impact in clinical practice are to be strongly encouraged.
 731 Politically, the VPH must be managed in such a way that success in the short
 732 term guarantees longer term sustainability, independent of contributions from
 733 national and European government.

734 *Recommendations summary*. Infrastructure funding for IT is an immediate
 735 requirement of the VPH.

13. Discussion

The physiome is a long-term vision, one in which *Homo sapiens* is ultimately modelled *in silico*. Although currently unattainable, viable elements are beginning to appear within the scientific domain. The most celebrated example is the genome (describing *H. sapiens* at a genetic level; International Human Genome Mapping Consortium 2001; Venter et al. 2001; Little 2005), but many other examples exist, such as the ‘heart physiome’ (*in silico* description of the heart; Smith et al. 2004), the GIOME (*in silico* description of the gastrointestinal tract; Gregersen 2006), the epitheliome (*in silico* description of epithelial cells; Walker et al. 2004), the musculosketome (*in silico* description of the musculoskeletal system; Viceconti et al. 2006; Van Sint Jan et al. 2007), the renal physiome (*in silico* description of the kidneys; Chu et al. in press; Thomas et al. in press), etc. Already these projects are modifying the way we think about human biology, but currently they tend to function as independent entities, operating in isolation from each other. Together, however, they offer the prospect of a grander picture in which information exchange between these *in silico* models enables a description of *H. sapiens* to be formulated (the physiome), based on separate but communicating simulations that describe a whole range of physiological functions across all length scales, from molecules to genes, to cells, to organs to the complete human disposition. An added dimension (with a promise of great reward) is the integration of clinical data, demographics, epidemiology, etc. However, the effective usage of this diversity, usefully augmented by data from modelling, is a challenging exercise, and practical examples, as yet, are few and far between. At the clinical interface, it is perhaps best exemplified by the work of @neurIST (www.aneurist.org), which embraces a rich mixture of data sources (clinical, epidemiological, pharmaceutical, imaging, modelling, etc.) in order to synthesize patient-specific recommendations that are relevant to the clinical management of cerebral aneurysms. This demonstrator is one example of ‘personalized medicine’—a concept that is implicit to the VPH. It is a concept that has spawned numerous projects, addressing the specific multidisciplinary challenges that are critical to the success of patient-specific medicine (e.g. the COAST project has a focus on multi-scale issues, see www.complex-automata.org). In principle, the integrated data/modelling framework could revolutionize understanding of diseases and their treatment, aid clinical decision making, accelerate drug design, etc., offering productivity benefits for industry, health benefits in the clinic, educational benefits in schools, research benefits for the academic and economic benefits for the taxpayer. It is not difficult to see why Europe is embracing this vision at the highest level, but in order for it to become a reality, an infrastructure is needed to facilitate information exchange between projects and support their many overlapping activities. Infrastructure is a critical component of physiome design and ultimately needs to be global in extent. This has been recognized by the European Commission, and recommendations to achieve that end are the primary purpose of STEP. The EC is already committed to investing many tens of millions of Euros to kick-start this process, thereby expediting development of the VPH and availing itself of early benefits.

The STEP VPH roadmap is a vehicle for discussion of issues pertinent to the development of the VPH infrastructure and aims to raise problems and pose solutions as a means of guiding VPH funding within FP7. It has been estimated

785 that development and full deployment of the VPH will require approximately 500
786 million Euros. Approximately 200 million Euros are expected to be invested by
787 national and European research grant agencies, while the remainder is expected
788 to come from the main participants, e.g. industry and medicine. These large
789 figures indicate the magnitude of the challenge to be addressed, pursuing a
790 unifying methodological and technological framework that will allow biomedical
791 scientists from all domains to describe, integrate and predict. The technological
792 component relies on data processing and data modelling tools, storage and
793 computing services, support for community building and collaborative work.
794 This requires the management of knowledge, with innovations that improve
795 access, exploration and understanding of the knowledge accumulated within the
796 VPH by clinical, industrial and societal users. The methodological component
797 involves unified representation of VPH concepts, data and models, development
798 of new processing and modelling methods for the VPH, the development of
799 conceptual frameworks that allow a seamless integration of models, and many
800 other aspects that will emerge during the process. Thus the VPH is manifested as
801 a methodological and technological framework that enables collaborative
802 investigation of the human body as a single complex system.¹¹

803 Europe is not alone in this endeavour, and competing and complementary
804 solutions from the USA and around the world will undoubtedly accelerate
805 Q22 scientific advance (Bassingthwaighte *et al.* 2000; Higgins *et al.* 2001; Hunter &
806 Q23 Nielsen 2005; Oden 2006). Adequate funding is a universal requirement and the
807 Q24 majority of developments can be accommodated within the classic collabor-
808 ative/competitive models, in which scientists organize themselves in transna-
809 tional consortia that compete for funding. However, certain activities would
810 benefit from the coordinating influence of an umbrella organization and Europe
811 may be uniquely placed to provide such a supporting infrastructure, coordinating
812 development of standards, interoperability, semantics, quality assurance, etc.
813 This would give Europe a global presence and the power to influence its emerging
814 direction. This is of consequence, because the VPH has considerable potential as
815 a unifying influence in society—its reach extends far beyond science and touches
816 so many aspects that are held dear by the common citizen, such as education,
817 health, social equality, etc. and provides an imperative for fixing some modern
818 ills such as legal harmonization.

819 Finally, although the VPH might appear to be the offspring of the scientific
820 community, it is important to resist the temptation to think of it purely as a
821 research resource. Close links with industry and the clinic cannot be overempha-
822 sized. Enthusiasm from the industry sector, coupled with demonstrable benefit in
823 the clinic, is its most certain route to success, securing the continued benefit and
824 accelerated development of biomedical science (and all its benefits to the citizen)
825 for the foreseeable future.

826 827 828 14. Conclusion

829 The physiome is a truly global concept that spans many disciplines, involves
830 wide expertise, connects with a diversity of cultures and has the potential to
831

832 ¹¹ Cited from the VPH roadmap ‘Seeding the EuroPhysiome: a roadmap to the virtual
833 physiological human’ (www.europhysiome.org), p. 2.

influence the management of many diseases.¹² It is the kind of grand vision that can be a unifying concept and has been adopted by Europe as the VPH, with priority funding under FP7. The purpose of the STEP project is to advise the funding focus through the provision of a roadmap that considers strategies for achieving the VPH over the next decade. The content of the roadmap has been outlined and its implications discussed in the context of a European vision of the physiome.

15. Uncited references

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