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QxDB: a generic database to support mathematical modelling in biology

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QxDB (quantitative x -modelling database) is a web-based generic database package designed especially to house quantitative and structural information. Its development was motivated by the need for centralized access to such results for development of mathematical models, but its usefulness extends to the general research community of both modellers and experimentalists. Written in PHP (Hyper Preprocessor) and MySQL, the database is easily adapted to new fields of research and ported to Apache-based web servers. Unlike most existing databases, experimental and observational results curated in QxDB are supplemented by comments from the experts who contribute input to the database, giving their evaluations of experimental techniques, breadth of validity of results, experimental conditions, and the like, thus providing the visitor with a basis for gauging the quality (or appropriateness) of each item for his/her needs. QxDB can be easily customized by adapting the contents of the database table containing the descriptors that characterize each data record according to an informal ontology of the research domain. We will illustrate this adaptability of QxDB by presenting two examples, the first dealing with modelling in oncology and the second with mechanical properties of cells and tissues.

Keywords: web-based database; generic tool; PHP and MySQL; knowledge engineering and management; modelling in physiology

1. Introduction

Hypothesis-based modelling studies in physiology and pathophysiology require reliable parameter values, usually culled from the experimental literature spanning several decades. Particularly in pathophysiology, the amount of knowledge is growing exponentially in domains such as cancer. Thus, those involved in modelling such processes are faced with the difficulty of compiling from the literature and managing a very large amount of heterogeneous data.

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The search for these often represents a major part of the development time for new modelling studies, because one must usually return to the original articles to extract relevant information that may have been collected with other aims in mind. Furthermore, a significant portion of such quantitative results has a wider domain of application than just that of the original study. This is the case, for instance, with ion permeabilities across membranes, kinetic parameters of ion channels and coupled membrane transporters expressed in multiple tissues, kinetic descriptions of enzyme reactions participating in ubiquitous metabolic pathways, and characterizations of signalling pathways, to name only a few. Finally, each collected item must be checked, compared to others, and carefully analysed in its experimental and observational settings in order to assess its variability and strength of evidence.

To facilitate the dissemination and optimize accessibility of such quantitative data, and to leverage the effort spent by diverse groups in culling these parameter values, Dzodic *et al.* (2004) developed a database for quantitative modelling in renal physiology (QKDB: quantitative kidney database; <http://srthomas.free.fr/qkdb>; login and password 'guest'). A central criterion during the development of the entity-relation data model for the QKDB data model was extensibility and flexibility while minimizing actual programming changes in the case of adaptation of the QKDB and its interface to other domains of research.

In the present article, we present a generic version derived from QKDB called Q x DB (quantitative x -modelling database). Q x DB has been designed by stripping QKDB of features particular to kidney physiology, in order to render it generic, instead of specific to any particular field. This has been done so as to standardize the function of recorded items independently of the field of interest. These descriptions fall into both general ontologies useful across domains, e.g. species names, terms for parameter types, dimensions/units; and those that are specific to each tissue or organ system to which Q x DB might be applied, e.g. anatomical details and specific functions.

Q x DB is an open source, multi-platform project, built using software tools of proven reliability and speed. Computational particularities are the ability to easily produce or accept XML output/input or to migrate later to an all-XML framework. Moreover, Q x DB takes advantage of the straightforward and seamless integration of PHP with HTML, and easy learning curve for newcomers wanting to adopt this generic application. Specially designed for physiological and pathophysiological modelling, Q x DB includes checks on data quality, level of evidence, as well as experimental and observation protocols related to the curated data.

To illustrate these original features, we will present two customized databases in different fields of modelling, both built from the skeleton Q x DB package. In the first example, we set up Q x DB for mathematical modelling applied to cancer (this will be called QCDB). Mathematical models of cancer have been extensively developed this last decade, with computation-intensive studies aimed at predicting tumour growth and therapeutic effectiveness (Tracqui 1995; Alarcón *et al.* 2004; Ribba *et al.* 2005). There is real interest in such an integrative approach. Indeed, integrative methods become inevitable as the amount of data provided by the new technologies steadily increases. This argument has also gained importance in therapeutics, since it is increasingly recognized that treatment design requires a rational basis (Boissel *et al.* 2003).

In a second example, we set up *QxDB* for data on cell and tissue mechanical properties (this will be called *QBmDB*), which are increasingly recognized as regulating factors of many biological processes ranging from gene transcription to tissue remodelling. Thus, cell elasticity is a key parameter for mechanical signal transduction (Huang *et al.* 2004; Janmey & Weitz 2004), while extracellular matrix stiffness regulates cell adhesion and migration (Gray *et al.* 2003; Engler *et al.* 2004). In addition, databases gathering mechanical properties of biological tissues are critical in computer-assisted surgery, including surgical simulation (Okamura *et al.* 2004) and preoperative planning using imaging elastic properties of biological tissues, as well as for predicting rupture of pathological structures like the coronary plaque (Finet *et al.* 2004).

To develop comprehensive models of such integrated and multi-level processes, supervised knowledge management is an absolute requirement for handling the increasing amount of data, especially considering that they originate from different fields, i.e. biology, physics or biomedical imaging.

After a presentation of generic *QxDB* in §2, this point will be highlighted in §3, together with the exemplified customization of the database for cancer modelling and cellular and tissue mechanics.

2. *QxDB*

(a) *QxDB* reliability

Usually, data and annotations used to evaluate the model parameters are drawn piecemeal from the literature during model development. Owing to the diversity of experimental and observational settings, values of a given parameter may vary over a wide range. In the field of cell biomechanics, this has been quite well illustrated in a publication of Maksym *et al.* (2000, fig. 12), which highlighted the dispersion of elastic properties of different cell types by six different cell micromanipulation techniques: reported values of cell shear elastic moduli ranged over five orders of magnitude, from 1 to 100 000 Pa. Such variability, which differs from the experimental variance, is easily seen when the results are all collected in a database, and this constitutes one of the best justifications for *QxDB*. Indeed, besides this variability, the varying relevance of study design and researcher experience and skill may induce biases in the estimates of the parameter values. Thus, each item of data or annotation in the database should be scored both by its variability and strength of evidence. Nonetheless, the question of how to achieve such scoring remains open for biochemical and genetic data. In other scientific domains, this issue has been addressed by adoption of a statistical approach (meta-analysis) and a conceptualization of the fundamentals of the empirical process by which the parameter values are determined (Boissel *et al.* 1988; Schulz *et al.* 1994; Bossard *et al.* 2004). Until international standards are agreed upon for scoring variability and strength of evidence, we will adopt the following procedure. For a given parameter, all published values are entered in the database with a short description of the observational or experimental setting. The level of confidence is indicated by an adjective on a short scale, i.e. very good, fair, acceptable, moderate, low, questionable; the level being selected by the contributor by comparison with a series of standardized example cases.

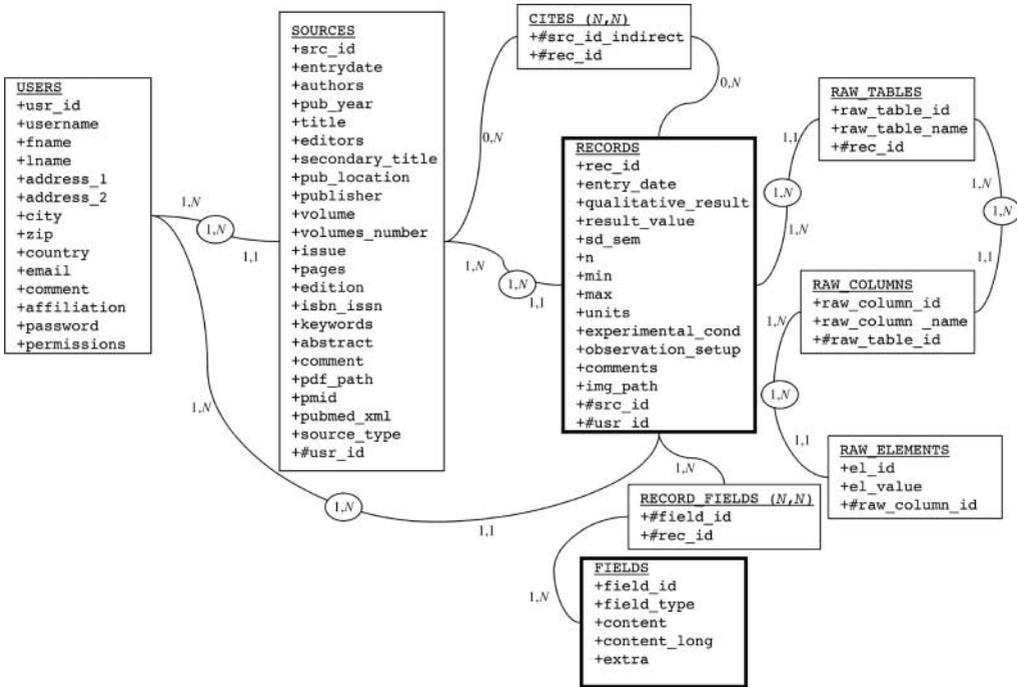


Figure 1. Entity-relation model of QxDB. The main tables are RECORDS, SOURCES and FIELDS.

(b) QxDB genericity

QxDB can be easily customized and applied to different research domains. The package consists of a file dump of the skeletal QxDB MySQL database and a compressed file archive containing the PHP code for the web interface. The skeletal QxDB database file-dump is installed in the server’s MySQL, and the directory of PHP code is copied to the root directory of the server’s Apache installation. Three main tables comprise the core of the database, namely: ‘RECORDS’, ‘SOURCES’, and ‘FIELDS’ (see figure 1). For each data record, the SOURCES table describes the literature reference and, via the RECORD_FIELDS table, the entries of the FIELDS table characterize the record according to defined descriptors by means of field-names.

The FIELDS table also contains a common core, i.e. descriptors that are common to several research domains. Examples of such descriptors are provided in table 1 and may allow two different QxDB databases, i.e. with different descriptors, to interact.

(c) QxDB structure

Three levels of user profiles have been implemented, as summarized in table 2. *Simple* users may freely browse the curated data via dynamic, roll-down lists in a ‘Query’ page. In addition to browsing the database, users with *contributor* privileges may also enter new results and associated literature references into the database. At frequent intervals, these new results will be examined and validated

Table 1. Common core of ‘field_type’ entries of the FIELDS table: retained generic descriptors, this limited number is often enough to account for different research domains. (These lists will be extended as appropriate to adapt Q_xDB for each field of application.)

| field_type | contents |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| biological context | biological or physical process which constitutes the background and support of the reported data |
| traced component | list of chemical species, organelles, etc., depending on domain of application |
| species | indicates the animal or plant species on which the experiment was performed |
| cell type | cell type or cell line involved in the experiment |
| substrate or tissue type | type of substrate or tissue, e.g. dermis, epithelium, tumour stroma used in the experiment |
| parameter | type of parameter or parameter list, e.g. diffusion coefficient, permeability, rate of transport, etc. |
| experimental design | protocol or instrumentation technique used to generate the experimental raw data |
| method for raw data analysis | method used to obtain the actual, second generation data, derived from primary raw data; this ranges from standard mathematical method, e.g. period estimation from Fourier transforms to more involved theoretical models, e.g. nonlinear stress–strain constitutive of tissues |
| confidence level | confidence given to the data, possibly self-generated through an internal procedure |

Table 2. Authorized operations for the three types of users.

| | |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------|
| simple user | browse/retrieve data records browse/retrieve references submit bug reports or comments modify user profile (if registered) |
| contributor | add data records add articles/references modify user profile |
| administrator | validate, modify or delete data records validate, modify or delete literature references accept or reject new user candidates |

by the small administrative committee. *Administrators* may also modify or delete data records or literature references and all associated records, and they examine new requests for *contributor* status, assigning passwords to those who meet the requirements. Figure 1 depicts the database entity-relation model. A detailed description can be found in Dzodic *et al.* (2004). We briefly summarize the main features here.

The central item is an individual data record, placed in the RECORDS table. The rest of the tables serve merely to qualify and identify the record and indicate who contributed it. This table contains fields for a numerical value and its mean, range and the units of measurement, but there is also provision (the result_string

field) for a qualitative result or the name of an image file (stored as a blob or whose path/url is indicated) in the `img_path` field. Finally, the fields ‘comments’, ‘experimental_conditions’ and ‘observation_setup’ contain all-important annotations from the contributor relevant to the individual record. These annotations represent an important part of the database, since the contributors will be established researchers and are expected to indicate relevant experimental conditions, notes about technical limitations, and the like.

Since only published data will be included, each record is associated with a literature reference, given in the `SOURCES` table. As mentioned above, provision is also made for indirect citations, such as may appear in review articles, via an indexing table (`CITES`), since this is possibly a many-to-many relationship. The `SOURCES` table includes fields for standard `PUBMED` style literature references, which may be entered by hand (via a web-form) or by uploading a citation file supplied by reference managing software such as `ENDNOTE`, `REFERENCE MANAGER`, or `BIBTEX`, or in the form of an XML file containing the relevant fields. There is also a comment field for annotations from the contributor about the reference as a whole, and a field for the pdf version of the article for cases where its inclusion is feasible and poses no copyright problem. The `USERS` table contains fields for identification of the contributor of data items, including his/her password and the level of permission to which she/he is authorized. Finally, the `FIELDS` table, along with the many-to-many relation with the `RECORDS` table, through the indexing `RECORD_FIELDS` table, is the heart of this data model’s flexibility and ready extensibility.

(d) *QxDB and applied modelling*

`QxDB` aims to provide a generic structure designed to facilitate development of mathematical models. In the interest of genericity, the database has not been coupled directly to any particular modelling tools. Nonetheless, several of the database characteristics may be particularly useful in modelling applications. Although `QxDB` contains only numerical parameters from the experimental literature, each record may also be linked to one or several modelling articles or review articles as secondary citations (via the `CITES` table for indirect citations). This allows `QxDB` users to explore the modelling applications which have used the data of interest, with the aim of helping them in the design of their modelling framework.

Data descriptors include the ‘Biological context’, which gives an indication of how the data record has been used in previous models (see the examples below).

As additional information, the `QxDB` interface includes a page where users may suggest links to modelling resources such as journals, conferences, and other events, and also to scientific communities, consortia, or funding opportunities.

3. `QxDB` demo

We strove to make the graphical user interface (GUI) of `QxDB` convivial for elementary database operations, such as database exploration and querying, contribution to the database and user identification. We present here a demonstration of `QxDB` through two examples: cancer modelling and cell–extracellular matrix interactions modelling. In these two examples, access

to quantitative parameter values is crucial, especially because they deal with multi-scale and integrated processes.

In the first context, mathematical models of cancer growth often focus on excessive cell proliferation monitored by available nutrient. Thus, nutrient diffusion from blood vessels to cancer cells is taken as a limiting factor in the modelling of tumour growth. In such situations, a parameter such as the rate of glucose uptake must be known in order to compute the rate of diffusion of nutrient in the tissue. In their model of non-Hodgkin's lymphoma growth, Ribba *et al.* (2005) used numerical values from a study aimed at determining the relation between high rate of glucose metabolism and a high grade of malignancy (Lapela *et al.* 1995). In this section, we demonstrate the use of a QCDB for storage of the parameters relevant to this type of model.

Modelling cell-extracellular matrix mechanical interactions is another field in which access to quantitative parameter values is crucial. Let us consider as an example the research field of angiogenesis (Carmeliet 2003), a major biological process involved in wound healing or tumour vascularization. More precisely, we will focus on an experimental model of this phenomenon, called *in vitro* angiogenesis, in which *in vitro* morphogenesis of tubular cell networks is observed when endothelial cells are cultured on extracellular matrix (Vailhé *et al.* 2001). Even in its *in vitro* reduction, this multi-factorial process is rather complex, since it results from the interactions of cellular forces, cell migration, extracellular matrix proteolysis and depends on matrix stiffness (Lafleur *et al.* 2002; Sieminski *et al.* 2004). Thus, a quantitative modelling approach of this phenomenon (Tranqui & Tracqui 2000; Namy *et al.* 2004) must consider many different quantitative parameters related to cellular traction forces. This is especially crucial in the context of model-driven acquisition and experiments, where critical thresholds on matrix stiffness and cellular force amplitude have to be fulfilled in order to initiate this morphogenetic process (Namy *et al.* 2004). Since these parameters are obtained from different kinds of experiments, a query procedure applied to QBmDB is clearly the more efficient way to get the required information. This point will be illustrated in the following QxDB query section.

(a) QxDB user-identification

Registered contributors must login to enter new references and data records into the database. An unregistered user may request contributor status by filling out an online form, which will be reviewed by the database administrators. The basic requirement is that contributors be active researchers in the target field.

(b) QxDB contribution

Users with contributor status may add data records and their associated references to the database. A new literature reference may be added manually or by uploading a citation file in the format of ENDNOTE or BIBTEX, or an appropriately structured XML file (ENDNOTE or PUBMED XML formats, at present). Quantitative and qualitative records with associated comments, e.g. level of confidence, are entered from roll-down lists of descriptors (see above), which can be extended as necessary. For further details, please refer to Dzodic *et al.* (2004).

Table 3. Entry of the value of a data record and associated comments for QCDB, according to numerical values drawn from Lapela *et al.* (1995).

| record fields | entries |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| median numerical value | 22.7 |
| range | 9.0–124.3 |
| units | $\mu\text{mol } 100 \text{ g}^{-1} \text{ min}^{-1}$ |
| qualitative result | a high glucose uptake was associated with high histological degree of malignancy |
| comments | glucose uptake is indexed by regional metabolic rate |
| experimental conditions | study of <i>in vivo</i> glucose metabolism in 22 patients with untreated non-Hodgkin’s lymphoma with fluorine-18-fluorodeoxyglucose (FDG) and positron emission tomography (pet); FDG is an analogue of D-glucose that competes with glucose for facilitated intracellular transport and phosphorylation by hexokinase; the phosphorylated FDG is unable to enter the subsequent glycolytic steps and accumulates in cells with low phosphatase activity; note that 15 (68%) of the patients were women, and the median age was 58 years (range 43–78 years); the body mass index, calculated as weight in kilograms divided by the square of height in metres varied from 21.3 to 43.3 kg m^{-2} (median 25.1 kg m^{-2}) |
| observational setup | based on the simple uptake kinetics of FDG, models for quantification of glucose utilization in tissue have been developed; see Phelps <i>et al. Ann. Neurol.</i> (1979) and Reivich <i>et al. J. Cereb. Blood Flow Metab.</i> (1985) |

One should note that a chart indicating explicitly the criteria for reporting data in *QBmDB* can be added to the list of the *FIELDS* items. For example, in the editorial of a special issue of the *Journal of Biomechanics*, Guilak *et al.* (2000) suggested some guidelines which help to facilitate quantitative comparisons among different studies in cell mechanics papers.

Table 3 shows the entries made in the contribution form for a single item of data related to the cancer modelling example; these values get saved in the *RECORDS* table of the underlying database. Table 4 shows the contributor’s choices of descriptors for this data item, chosen from the roll-down lists, which, as mentioned above, are built on-the-fly from the contents of the underlying *FIELDS* table at the time the contribution-page is called.

In tables 5–8, examples are provided for *QBmDB*, considering contributions from one experimental and one theoretical paper. In the first case (tables 5 and 6), the quoted paper concerns quantification of traction forces of isolated cells suspended over flexible arrays of beams. In *QBmDB*, quantification obtained by this micro-device can be compared to quantification made at the cell population level, when thousands of cells contract a suspended extracellular matrix (Shreiber *et al.* 2003). Thus, *QBmDB* will provide a direct manner to compare different evaluations of the same mechanobiological parameter, considering simultaneously the level of confidence associated with this comparison according to the experimental design, e.g. same type of cells, same substrate, same experimental conditions. The second example (tables 7 and 8)

Table 4. Contribution to Q CDB descriptors for the numerical data record of the previous table, drawn from Lapela *et al.* (1995).

| descriptors | entries |
|------------------------------|------------------------------|
| biological context | cellular proliferation |
| traced component | glucose |
| species | human |
| cell type | lymphoma B cells |
| substrate or tissue type | untreated patients |
| parameter | uptake rate |
| experimental design | radiochemical tracer |
| method for raw data analysis | positron emission tomography |
| confidence level | good |

Table 5. Contribution to Q $BmDB$ fields according to the experimental work of Tan *et al.* (2003).

| record fields | entries |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| median numerical value | 15 |
| range | 10–60 |
| units | nN (nanonewtons) |
| qualitative result | force increases almost linearly with the area of focal adhesions |
| experimental conditions | microarrays of elastomeric microneedle posts (Young’s modulus of 2.5 MPa) with varying size cell adhesion is ensured by coating with fibronectin for collagen IV; areas of focal adhesion were imaged and measured using immunofluorescence microscopy |
| observational setup | force vectors are obtained directly from the deflections of the post; the control of the post-geometry enables one to demonstrate the coexistence of two types of correlation between the size of focal adhesions and the force generation at those adhesions (negative for area less than 1 μm^2 , positive above) |
| comments | contractile force exerted by a cell on the underlying post; the median numerical value is 10 or 20 nN, depending on the cell spreading |

illustrates the inclusion of a theoretical paper, in which the key parameter is the strain-energy function proposed to describe the elastic response of adherent cells probed by the rotation of microbeads bound to cell surface receptors. The parameter field is now the cell apparent elasticity modulus, derived from the analytical expression of the strain-energy function, and computed for the function coefficient values identified from the experimental data.

(c) Q xDB querying

Any visitor to the Q xDB web site can specify search criteria and retrieve the matching records as a sortable table with detail links. Search queries are formulated using roll-down lists of descriptors constructed dynamically from the contents of the FIELDS table.

Table 6. Contribution to *QBmDB* descriptors according to the experimental work of Tan *et al.* (2003).

| descriptors | entries |
|------------------------------|---------------------------------------------------------------|
| biological context | cellular traction |
| traced component | force amplitude |
| species | bovine |
| cell type | pulmonary artery smooth muscle cells |
| substrate or tissue type | elastomeric microneedle |
| parameter | contractile force |
| experimental design | microarrays of elastomeric vertical microneedle posts (mPADs) |
| method for raw data analysis | beam deflection model; fluorescent staining of focal adhesion |
| confidence level | good |

Table 7. Contribution to *QBmDB* fields according to the theoretical work of Ohayon *et al.* (2004).

| record fields | entries |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| median numerical value | 13.5 |
| range | 6–27 |
| units | Pa (pascals) |
| qualitative result | the cell elastic response to microbead rotation is nonlinear in the large deformation regime; it depends on geometrical parameters (bead embedding angle, cell thickness) |
| experimental conditions | magnetic beads coated with a peptidic arginine–glycine–aspartate (RGD) sequence peptide are twisted by a magnetic torque |
| observational setup | the analysis of the cell monolayer response reduces to a single cell study when considering a homogenization approach for the finite element modelling |
| comments | the nonlinear, strain-hardening response, is established as an intrinsic property of the cell cytoskeleton the Young modulus is derived from the Yeoh strain-energy function: $W = a_1(I_1 - 3) + a_2(I_1 - 3)^2$, with $a_1 = 2.25$ Pa and $a_2 = 50$ Pa |

Considering, for example, the modelling work of Namy *et al.* (2004) on the *in vitro* morphogenesis of endothelial cell networks within fibrin biogels, queries submitted to the *QBmDB* basis will aim to retrieve:

- constitutive stress–strain relationship describing the viscoelastic behaviour of the considered extracellular matrix;
- values of Young’s and Poisson’s elastic moduli for fibrin biogels of the experimentally used fibrin concentration;
- values of the two viscous moduli of the extracellular matrix;
- amplitude of the cell traction force of the type of endothelial cells used in the *in vitro* experiments;
- information regarding potential control of biological processes, e.g. cell migration, cell proliferation, extracellular matrix proteolysis, by mechanical factors.

Table 8. Contribution to *QBmDB* descriptors according to the theoretical work of Ohayon *et al.* (2004).

| descriptors | entries |
|------------------------------|-----------------------------------------------------|
| biological context | cell rheology |
| traced component | magnetic torque |
| species | human |
| cell type | alveolar epithelial cells (A549) |
| substrate or tissue type | plastic coated with type-I collagen |
| parameter | elasticity modulus |
| experimental design | magnetic twisting cytometry |
| method for raw data analysis | finite elements simulation; homogenization approach |
| confidence level | good |

Table 9. Search criteria to retrieve the elasticity moduli.

| descriptors | entries |
|------------------------------|--------------------------------------|
| biological context | cell rheology |
| traced component | mechanical stimulation |
| species | any |
| cell type | any |
| substrate or tissue type | any |
| parameter | elasticity moduli |
| experimental design | any |
| method for raw data analysis | theoretical model: rheological model |
| confidence level | any |

Among the hits corresponding to the search query of table 9 could be:

Weisel JW, The mechanical properties of fibrin for basic scientists and clinicians. *Biophys Chem.* 2004 Dec 20;112(2–3):267–76.

Benkherourou M, Gumery PY, Tranqui L, Tracqui P. Quantification and macroscopic modeling of the nonlinear viscoelastic behaviour of strained gels with varying fibrin concentrations. *IEEE Trans Biomed Eng.* 2000 Nov;47(11):1465–75.

Among the hits corresponding to the search criteria shown in table 10 could be:

Sieminski AL, Hebbel RP, Gooch KJ. The relative magnitudes of endothelial force generation and matrix stiffness modulate capillary morphogenesis *in vitro*. *Exp Cell Res.* 2004 Jul 15;297(2):574–84.

Shiu YT, Li S, Marganski WA, Usami S, Schwartz MA, Wang YL, Dembo M, Chien S. Rho mediates the shear-enhancement of endothelial cell migration and traction force generation, *Biophys J.* 2004 Apr;86(4):2558–65.

Among the hits corresponding to the query table 11 will be:

Ross JJ, Tranquillo RT. ECM gene expression correlates with *in vitro* tissue growth and development in fibrin gel remodeled by neonatal smooth muscle cells. *Matrix Biol.* 2003 Nov;22(6):477–90.

Table 10. Search criteria to retrieve the amplitude of cell traction forces.

| descriptors | entries |
|------------------------------|-------------------|
| modelling context | cellular traction |
| model component | any |
| species | any |
| cell type | endothelial |
| substrate or tissue type | any |
| parameter | force traction |
| experimental design | any |
| method for raw data analysis | any |
| confidence level | any |

Table 11. Search criteria to retrieve fibrin gel degradation and mechanical factors.

| descriptors | entries |
|------------------------------|---------------------------------------------|
| biological context | mechanotransduction |
| traced component | fibrin |
| species | any |
| cell type | any |
| substrate or tissue type | any |
| parameter | proteolysis rate |
| experimental design | any |
| method for raw data analysis | any (or Michaelis–Menten theoretical model) |
| confidence level | any |

Deroanne CF, Lapiere CM, Nusgens BV. *In vitro* tubulogenesis of endothelial cells by relaxation of the coupling extracellular matrix-cytoskeleton. *Cardiovasc Res.* 2001 Feb 16;49(3):647–58.

Vailhe B, Lecomte M, Wiernsperger N, Tranqui L. The formation of tubular structures by endothelial cells is under the control of fibrinolysis and mechanical factors. *Angiogenesis.* 1998;2(4):331–44.

(d) *QxDB interactions*

Environmental mechanical forces are known to affect many cellular functions, such as cell growth, proliferation, protein synthesis and gene expression. Thus, any quantitative modelling undertaken in this research field would have to point to different data structures, designed for, for example, cell proliferation data, genetic data, or biomechanical data. We will briefly illustrate how we can benefit from such a common architecture when using *QCDB* and *QBmDB*.

Optimal therapy of tumours requires delivery of a sufficient amount of therapeutic drugs to the cancer cells. These agents have to penetrate the tumour matrix, which constitutes a significant barrier to drug delivery. In addition, proliferating cancer cells induce intra-tumoural vessels to compress and collapse (Padera *et al.* 2004). It thus appears clearly that a better understanding of tumour mechanical properties may be important for the development of improved drug

Table 12. Contribution to *QCDB* of the paper by Netti *et al.* (2000).

| descriptors | entries |
|------------------------------|----------------------------------------------------------------------------------------------------|
| biological context | drug delivery in solid tumour |
| traced component | immunoglobulin G (IgG) |
| species | human cells xenografted in mice |
| cell type | LS174T; U87; HSTS26T; MCaIV |
| substrate or tissue type | skin |
| parameter | diffusion rate |
| experimental design | xenograft; dorsal skinfold chambers; fluorescence recovery after photobleaching (FRAP) experiments |
| method for raw data analysis | mechanical model |
| confidence level | good |

Table 13. Contribution to *QBmDB* of the paper by Netti *et al.* (2000).

| descriptors | entries |
|------------------------------|--------------------------------------------|
| biological context | mechanical properties of solid tumours |
| traced component | stress-strain curves of compressed sarcoma |
| species | human |
| cell type | solid tumour |
| substrate or tissue type | skin |
| parameter | elasticity modulus |
| experimental design | uniaxial loading |
| method for raw data analysis | theoretical model: linear viscoelastic |
| confidence level | good |

delivery strategies. Such strategies are really multifactorial since they involve cell and tissue mechanical characterization, quantification of the ways environmental mechanical forces affect many cellular functions (cell growth and proliferation, protein synthesis, gene expression), designs of therapeutic agents acting on the target cancer cells by direct or indirect modulation of mechanical pressure within the tumour or at the tumour margin. In this context, the use of a common skeleton and contributing/query procedures will greatly help the efficient use and facilitate relevant correlations between databases reporting such data. We will briefly illustrate how we can benefit from such a common architecture when using *QCDB* and *QBmDB* bases, by considering the paper of Netti *et al.* (2000). The contribution of this paper to the *QCDB* basis is presented in table 12, and its contribution to the *QBmDB* basis is presented in table 13.

If we now consider a query from the mechanical field, i.e. a scientist looking for quantitative data on solid tumour elasticity, the above reference, published in a medical journal, i.e. *Cancer Research*, will certainly not be found by a general keyword search. Thanks to the field ‘Method for raw data analysis’, a query like ‘mechanical or elastic’ as keywords makes the connection to this reference possible. In addition, the trace toward images will make accessible a complete set

of incremental step compression curves on different solid tumours (fig. 1 in Netti *et al.* 2000), which are of great help to derive tumour elasticity moduli.

Conversely, studies on anti-angiogenic therapies based on the modelling of tumour growth control by endothelial cells at the tumour periphery (Stoll *et al.* 2003) may be found by querying the *QxDB* for quantitative data on endothelial cell traction forces, which could be taken into account to improve the model's relevance. In addition, this query will reveal connected references, e.g. between traction forces and tumour invasion (Rabinowitz *et al.* 2001), or between tumour growth and the stress fields at the tumour periphery (Gordon *et al.* 2003).

4. Discussion and conclusions

QxDB is an open source web-based generic database package developed using PHP (<http://www.php.net>) and MySQL (<http://www.mysql.com>). The basic version of *QxDB* may be viewed at <http://www.lami.univ-evry.fr/~srthomas/qxdb>, where it may also be downloaded for local installation and customization for a particular field of interest.

The web-GUI allows visitors to browse the database to retrieve the qualitative and quantitative results culled from the literature and entered by the contributors, who must be researchers in the field. *QxDB* offers the usual possibilities of user identification, record querying and contribution traceability. The originality of *QxDB* lies in its adaptable genericity and with its inclusion of the possibility for contributors to score the quality or level of confidence of data items they contribute, in addition to specifying the experimental and observational conditions. We anticipate that future extensions to the *QxDB* package will enable communication and sharing among the closely related daughter databases derived from *QxDB*, thus constituting clusters of interacting modelling databases.

As with any database project, content is everything. *QxDB* and its offspring will be useful only to the extent that researchers in the various target domains of application take the time to contribute to the curated data. The energy for initial seeding of new implementations can reasonably be expected to come from the people who take the initiative to install the database, presumably because of a felt need. Subsequent contributions will depend on motivating the relevant research community. In our experience with *QKDB*, which is still in the early stages, this has not presented a problem. On the contrary, the general community of experimental researchers is all too impatient to see the resource seeded and running, so they can profit from the centralized repository instead of delving into the voluminous and often difficult-to-navigate literature of quantitative experimental studies that often span several decades. Once the database is launched, individual laboratories have been very interested in making sure their own results are included.

Editor's note

Please see also related communications in this focussed issue by Pinter & Shohet (2006) and Welsh *et al.* (2006).

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