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The Amine System Project: Systems Biology in Practice

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Summary. In this chapter we present an architecture for the development of Semantic Web applications, and the way it is applied to build an application for Systems Biology. Our working plan is designed to built an ontology-based system with connected biomodules that could be globally analysed, as far as possible. Supported by the advantages of the Semantic Web, we can keep the objective to work on the way to obtain an automated form to integrate both information and tools in our system.

Key words: Semantic Web, Systems Biology, Semantic Mediation, Amine

12.1 Introduction: Problem Statement and Development of a Systems Biology Pilot Project

A living organism is an open system that keeps a continuous interchange of chemical compounds, energy and information with its environment. This interchange involves a high number of elements (molecules) related among them in a dynamic hierarchical and modular way. Modules can be identified from the analysis of the interaction patterns. At molecular level, interacting networks include protein-protein interactions, metabolic pathways, and the different biosignalling pathways controlling intercellular cross-talk and regulation of gene expression [1]. These different local networks are also related among them. From the previous analysis, it is easily deduced that the integration of both structural and functional data concerning all of the involved elements, their spatial locations and their interrelationship patterns is an essential (but still a dawning) task for an efficient advance in biological knowledge. From the beginning of this century, new systemic approaches to the study of living organisms were proposed [2]. They are essential to let come into view the general rules that, as it also occurs in Physics, must govern the biological behaviour. It is our understanding that Systems Biology should include both the relationships among the elements

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of a biological system in a given steady- state and the responses of the system against any endogenous or exogenous perturbation, with the final aim to know not only the system itself but also its dynamics.

The available information required to get more holistic views of Molecular Biology problems increases daily, due to a large amount of data provided by Genome Projects and high-throughput technologies. Obviously, this is a great advantage for (and makes a great deal of) this scientific field. However, the required information is dispersed among different information repositories, which offer redundant, and sometimes ambiguous and/or controversial data. These facts can induce that processes of information retrieval lose both efficiency and fidelity. Another worthmentioning disadvantage of the present trends and tools is the continuous overlapping of new information strata that frequently lead to cover up the previous information.

To sum up, it is clear that the development and support of intelligent integration methods for data searching, screening and analysis are absolutely required. These new tools should accomplish the following properties: i) to be in favour of reaching a consensus among the scientific community; ii) to be able to discriminate among redundant and/or wrong information; iii) to gain the possibility to access to information partially hidden for the web (a remarkable example of it, is for instance the access to data contained in printed papers); iv) to be able to grow towards augmented capabilities to be interconnected to other tools developed by the scientific community. Working in this sense, the discovery of new emergent properties of the systems will be allowed.

Under the name of "Amine System Project" (ASP), we have started working to construct a pilot system for the integration of biological information related to Biochemistry, Molecular Biology and Physiopathology of a group of compounds known as biogenic amines (http://asp.uma.es). Two general objectives can be distinguished in this project: i) development of new and more efficient tools for the integration of information stored in databases, with the aim to detect new emergent properties of this system; and ii) generation of in silico predictive models at different levels of complexity. It is being carried out by a multi-disciplinary group joining biochemists, molecular biologists and informaticians. In the following paragraphs, we present the biological context defined as our "system" and the reasons for this choice. Nevertheless, once the outcoming tools become validated, many of them could be easily adapted to study many other biological systems and to be compatible with many other bioinformatics tools and repositories.

Biogenic amines are low-molecular-weight compounds derived from amino acids. Members of the group have been working for the last 18 years on the different aspects of the amine metabolism and the molecular bases of the physiological effects caused by these compounds in different eukaryotic models, mainly mammalian cells [3–10]. Thus, the experience on the biological topic, as well as tools and facilities available for experimental validation of the in silico-derived hypotheses were important to define our system. We have been mainly devoted to those amines synthetised from cationic amino acids in mammalian organisms. These are: histamine (derived form histidine), and the polyamines putrescine, spermidine

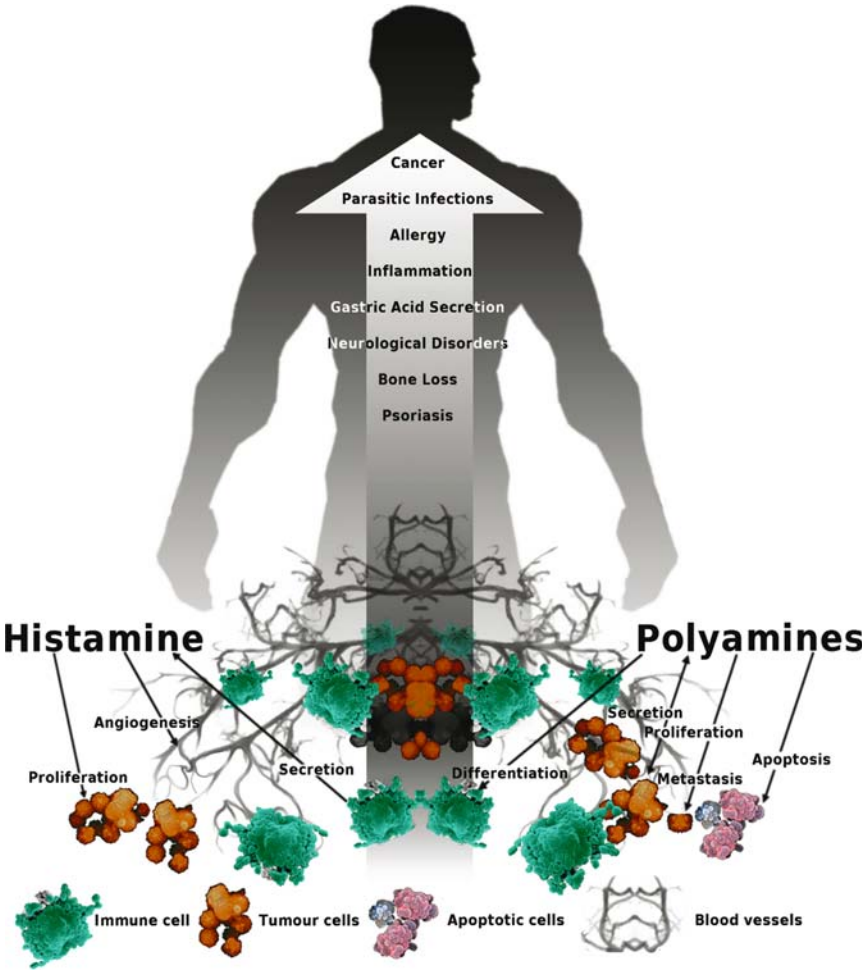

Fig. 12.1. Scheme of the most relevant biological processes modulated by histamine and polyamines at cellular level and their physiopathological consequences on the whole organism

and spermine (derived from arginine/ornithine and methionine). The biological processes modulated by histamine and polyamines in different human cell types and their physiopathological consequences on a human organism were recently reviewed by our group [11] and summarized in Figure 12.1.

Polyamines are essential polycations for every living cells known so far and play their major roles as modulators of the central mechanisms of cell life, growth and death [12]. Histamine is considered as an intercellular mediator of pleiotropic (and sometimes antagonic) effects elicited through different signalling pathways in different target cells: anaphylactic reactions and other inflammatory responses, gastric secretion, neurotransmission, bone-loss, fertility, angiogenesis and tumour growth.

This short summary of the molecular pathways and physiopathological processes related to histamine is enough to show how many biomolecular interactions are involved in its biological missions and how dispersed the amine-related information can be among many different repositories of specialised bibliography and databanks of many different biomedical areas. In some human cell types (for instance, mast cells or macrophages), both polyamines and histamine are essential elements for their specific physiological roles and it is proven that their metabolic pathways keep a molecular cross-talk at different levels [11]. In any case, pathological conditions associated to both polyamine and histamine affect an important percentage of the humanity at any stage of our lives. These circumstances guarantee the fruitfulness of any effort towards a more integrated analysis of the huge quantity of dispersed biochemical and phenomenological information that is required to generate new strategies for a better control of the polyamine/histamine-related diseases.

During the second part of the 20^{th} century, an impressive quantity of high quality work was released from reductionistic approaches. It has provided information about almost every element involved in polyamine metabolism in different cell types. However, most of the attempts to use this information to drive intervention strategies has failed, since evolution has selected robust and sophisticated mechanisms to compensate alterations in the most essential pathways. Consequently, the scientific community will not fully profit from all these efforts until a more systemic view of the regulatory mechanisms associated to amine biochemistry is reached. The application of Systems Biology technologies could allow us to obtain a more extended, dynamics and fruitful level of knowledge on the causes and consequences of alterations in the amine-related pathways, that is, in the highly relevant physiopathological processes related to amine metabolism. Some examples of this assessment are the following examples of the application of our system, which are considered among our present aims: a) to obtain predictions on the structural and functional alterations of a given molecule produced by its interactions with others (protein, nucleic acid, metabolite or drug); b) to locate dynamic bifurcation points and putative hysteretical behaviour of the involved metabolic pathways being altered under pathological conditions or treatments; c) to determine the molecular structural and functional relationships among the amine-related biomolecules and the other cellular components. This emergent knowledge could suggest new strategies for their control and intervention, as explained in [13].

12.2 The Semantic Web: Practical Usage in Systems Biology

As mentioned before, retrieval of the impressive quantity of information disperse in different growing databases is essential for efficient use of the research investments and for advance of knowledge, not only in the amine field, but also in any biological/biomedical problem. The rapid increase in both volume and diversity of "omic" data further stress the necessity for development and adoption of data standards. A recent trend in data standard development has been to use eXtensible Markup Language (XML, http://www.w3.org/XML/) as the preferred mechanism to

define data representations. However, XML cannot provide the necessary elements to achieve the level of interoperability required by the highly dynamic and integrated bioinformatics applications.

To solve this problem, an explicit description of the semantics in biological databases is required. This can be achieved by ontologies describing the biological systems. Ontologies provide a formal representation of the real world, shared by a sufficient amount of users, by defining concepts and relationships between them. In order to provide semantics to web resources, instances of such concepts and relationships are used to annotate them. These annotations over the resources, which are based on ontologies, are the foundation of the Semantic Web [14]. Given the size of the web, we have to deal with large amounts of knowledge. All this information must be represented and managed efficiently to guarantee the feasibility of the Semantic Web.

Knowledge representation and reasoning about this knowledge is a well-known problem for artificial intelligence researchers. Explicit semantics is defined by means of formal languages. Description Logics [15] is a family of logical formalisms for representing and reasoning about complex classes of individuals (called concepts) and their relationships (expressed by binary relations called roles). Description Logics are intended for formal knowledge representation and are based on a structured, decidable fragment of FOL (first Order Logic). The combination of formal knowledge representation altogether with the definition of formal but efficient reasoning mechanism is crucial for reasoning in Description Logics. Description Logics formalism allows the description of concepts, relationships and individuals (i.e. the knowledge base), and all of them together with complex concept formation and concept retrieval and realization provide a query/reasoning language for the knowledge base. Research in Description Logics deals with new ways to query a knowledge base efficiently.

The ongoing standards of current web-based ontology definition languages (such as OWL, http://www.w3.org/TR/owl-features/) are based on Description Logics. These languages provide mechanisms to define classes and properties and their instances. Web Ontology Language (OWL) is a markup language for publishing and sharing data using ontologies on the Internet. OWL is a vocabulary extension of the Resource Description Framework (RDF, http://www.w3.org/RDF/) and is derived from the DAML + OIL Web Ontology Language (http://www.w3.org/Submission/2001/12/). Together with RDF and other components, these tools make up the Semantic Web project. OWL was developed mainly because it has more facilities for expressing meaning and semantics than XML, RDF, and RDF-S, and thus OWL goes beyond these languages in its ability to represent machine interpretable contents on the web and perform reasoning over this knowledge.

OWL is seen as a major technology for the future implementation of a Semantic Web. OWL was designed specifically to provide a common way to process the content of web information. The language is intended to be read by computer applications instead of humans. Since OWL is written in XML, OWL information can be easily exchanged between different types of computers using different operating systems, and application languages. OWL's main purpose will be to provide

standards that provide a framework for asset management, enterprise integration and the share and reuse of data on the Web (taking advantage of the reasoning capabilities that it provides being based on Description Logics).

Semantic Web technologies provide a natural and flexible solution for integrating and combining two levels of abstraction, the data level and the knowledge level, which are related by means of metadata. The information is annotated with semantic contents/metadata that commit with a domain ontology. The semantic interoperability among applications depends on their matching capability between information and knowledge schemas. Generally, this task is carried out at the implementation level, building a syntactic model shared among applications. Ontologies make possible to attain this objective by adding a semantic layer on the syntactic model with knowledge of what the information represents. In this way, some research areas are making a big effort to represent the knowledge they have by means of big ontologies that tend to become standards for representing information. However, these ontologies describe usually generic terms that explain the basis of the domain, and cannot be directly applied to annotate the data of common databases.

Thus, Bioinformatics researchers are developing several domain ontologies, representing big subjects in biology: protein ontology [16], sequence ontology [17] and gene ontology [18]. The main reasons to use an ontology are: to share common understanding of the structure of information among people or software agents, to enable reuse of domain knowledge, to make domain assumptions explicit, to separate domain knowledge from the operational knowledge and to analyze domain knowledge. If the available ontologies does not fulfill these requirements, then it is necessary to start the development of a new one.

12.3 Architecture and Future Prospects

As stated in the introduction of the "Amine System Project" we have started the building of a pilot system for the integration of biological information related to Biochemistry, Molecular Biology and Physiopathology (focusing our main interest on a group of compounds known as biogenic amines). This section introduces the architecture used to build this pilot system, and the way it will help researchers in the project context.

12.3.1 The Pilot: AMine Metabolism Ontology and the Semantic Directory Core

This section presents the Pilot developed for integrating dispersed resources, such as online databases, web services and data transformation tools.

This Pilot is based on a generic infrastructure (Semantic Directory Core, SD-Core), which is mainly used for registering and managing ontologies and their relationships with distributed resources (online databases, web services and data transformation tools).

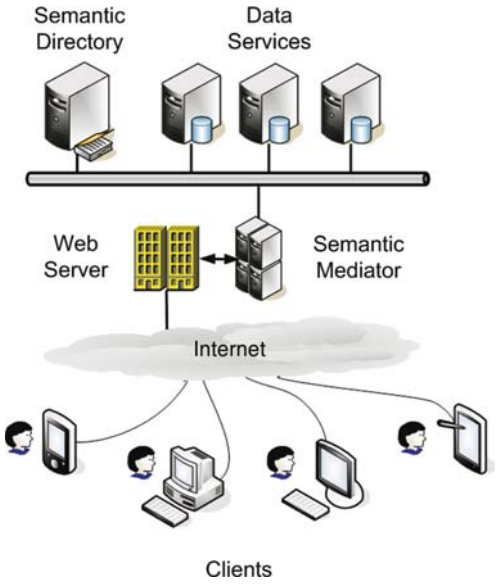

Fig. 12.2. Conceptual architecture of the Amine System Project. The kernel of the system is composed of a Semantic Directory and several Data Services. The Mediator and its Web interface provide an integrated access to the information

Previous works [19, 20] have allowed us to identify the minimum elements that can be useful for building Semantic Web applications, and they are the core of the proposed infrastructure (Figure 12.2). The internal elements of the SD-Core (Figure 12.3) are composed of a set of inter-related ontologies, which describe its semantics, and tools for taking advantage of this semantics. These ontologies include an ontology to manage metadata about ontologies registered in the SD-Core (Ontology Metadata Vocabulary, OMV), and an ontology to manage the metadata of registered resources and their relationships with registered ontologies (SD-Core Metadata Ontology, SDMO).

Tools to manage metadata represented as ontologies include from a simple OWL parser to a complex ontology reasoner. We make use of Jena (http://jena.sourceforge.net/) to access this knowledge in a first version that does not require the installation of any additional elements as a reasoner. However, the reasoning capabilities of Jena are limited, and it is not possible to infer new knowledge from the information registered in the system. For this reason, we have developed a version including the use of a reasoner, Racer [21], to improve the query results by taking advantage of the reasoning mechanisms it uses (concepts classification, concepts subsumption, complex concepts, etc.). However, Racer requires a license for being used, so the addition of this reasoner to the system has been carried out through the DIG API (http://dl.kr.org/dig/) (that provides Racer). In this way, the SD-Core can be changed for using another DIG compliant reasoner by installing and replacing Racer for other

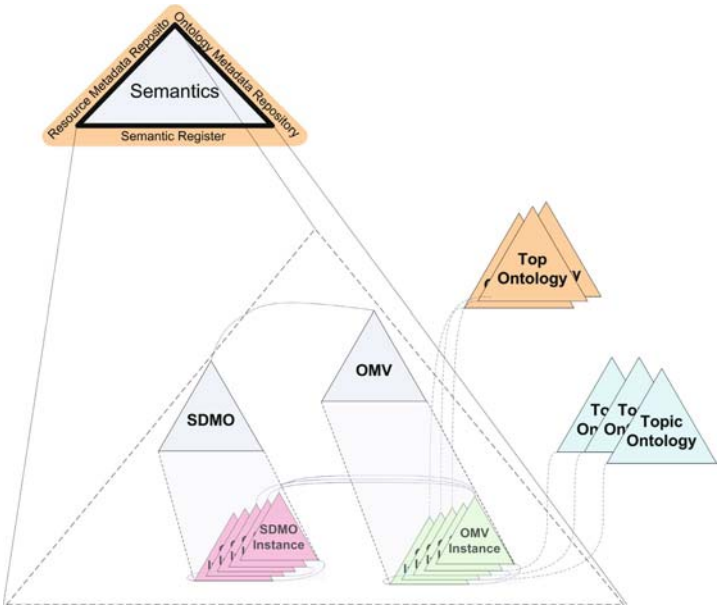

Fig. 12.3. Internal Elements of the SD-Core. The metadata used by SD-Core is represented as ontologies and managed by an ontology parser. The metadata about resources and ontologies is modified and accessed through three components. (Abbreviations are defined in the text)

Reasoner. Thus, the users interested in our proposal and who are not able to acquire a Racer license can make use of it.

When using any reasoner, for enhanced -DL based - reasoning mechanisms, it usually implies that the Web Server will have an overhead because of the reasoner activities. Thus, the way in which it has been included is by means of its installation in a remote machine thereby avoiding to overhead the server.

12.3.2 Ontology-Based Mediation

SD-Core provides necessary elements to deal with ontologies (and reasoning with them if a reasoner is included), but cannot fulfill all the requirements of the ASP project itself. The integration of information is a key requirement in Systems Biology and also in our project. For this reason we have adopted a mediator-based approach.

The main goal of mediation systems is to allow users to perform queries over heterogeneous databases, as if they were only one, using an integration schema. Mediators offer interfaces in order to query the system in terms of the integration schema. Thus, software developers can build applications that make use of distributed and heterogeneous databases as if they were a centralized database.

Internally, mediators transform user queries into a set of sub-queries that other software components (the wrappers), which encapsulate data sources' capabilities,

will solve. Recently, the research has been devoted to the problem of Semantic Mediation, because it introduces the possibility of taking advantage of explicit semantics and reasoning mechanisms to provide better solutions.

Semantic mediation adds a few additional considerations to the logical information integration problems. In this scenario, sources not only export their logical schema, but also their conceptual model to the mediator, thus exposing their concepts, roles, classification hierarchies, and other high-level semantic constructs to the mediator. Semantic Mediation allows information sources to export their schema at an appropriate level of abstraction to the mediator. Mediators are applications that offer a transparent access to the data in distributed resources, being considered for the users as a single database. In this way, a Semantic Mediation system is a system that offers transparent access to the knowledge in distributed resources, being considered as a single knowledge-base. In this context Semantic Mediation systems are those in which the integrated resources are knowledge-bases (or resources enveloped to enable their access as a knowledge-base).

In our pilot, we focus on a intermediate kind of systems, Ontology-Based Mediation, in which data resources are kept unmodified and are registered to make their semantics explicit. The mediator takes advantage of this knowledge about the resources in order to better integrate the information (taking advantage of the semantics and reasoning mechanisms), but the resources do not change their interface allowing existing applications to keep using them.

The mediator can be developed from scratch, building all the required components to obtain the semantics and then use it to solve the integration problem. Nevertheless, the pilot uses the SD-Core for building the Ontology-Based Mediation System, thus avoiding the development of specific tools to deal with semantics.

In the pilot the sources' query capabilities are published as Web Services (called in our proposal Data Services). The goal of Data Services is to allow applications to access data repositories and data providing service functionalities by means of Web Services. The presented infrastructure (SD-Core) is used to register these services, defining their semantics with respect to previously registered ontologies.

The architecture of the proposed Ontology-Bases Mediator is composed of four main components, that can be provided as distributed components. The main advantage of this proposal is that the extension or modification of any part of the mediator will involve the modification of a single component, keeping the other components unchanged. The components are described as follows (see Figure 12.4):

- Controller: this component has as main task the interaction with the user interface, providing solutions as ontology instances for user queries (described in terms of one of the ontologies registered in the semantic directory). The queries are received as conjunctive queries in terms of one of the ontologies registered in the SD-Core.
- Query Planner: the task of this component is to find a query plan (QP), using the SD-Core, for a query described in terms of one of the ontologies registered in the Semantic Directory (O). The use of the SD-Core in combination with a reasoner will provide the mediator with the possibility of improving the results.

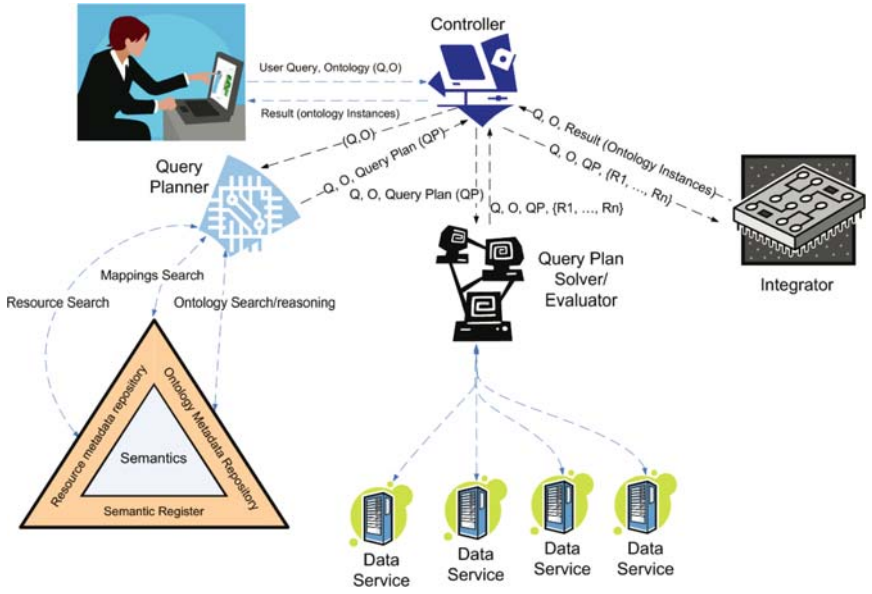

Fig. 12.4. Web Interface to make use of the mediator. The start point of this interface allows the user to search the protein for which he/she wants to know the 3D structure. Below the query for this first step is shown

Thus, when a query includes a concept, but it is not present in the resources, any of its sub-concepts could be used to solve de query.

- Query Solver: this component analyzes the query plan (QP), and performs the corresponding call to the data services implied in solving the sub-queries (SQ1, ..., SQn) of the query plan (R1, ..., Rn).
- Integrator: The results sent by data services (R1, ..., Rn) are composed by this component, obtaining a set of instances representing the result to the user query.

As far as any of the existing ontologies do not cope exactly with the requirements of our project we have started the development of a new ontology, the AMine Metabolism Ontology (AMMO). AMMO represents the minimum number of connections that can allow us to collect and to connect information from the different local biomodules considered in an eukaryotic cell. In practical terms, it is an ambitious information flow network, that would require many biocomputational efforts to be functional on the different Databases and Services associated to each of these concepts, as well as many validation efforts on experimental amine-related biological data (as expressed among our aims in the Introduction). At present, we are generating more specific ontologies, that can be considered as "local ontologies" (to keep a nomenclature in parallel to the situation *in vivo*). Of course, these local ontologies will be progressively integrated in AMMO.

Our present on-going efforts are focused on local ontologies recruiting information from Databases and Services on protein structures and interactions with other

proteins or ligands. As it can be deduced from these lines, once the tools have been validated on the amine system, these resources could be applied to any other molecular biology topic. New information concerning predictive models, the AMMO evolution and validated tools and services generated from it will be available in the web page (http://asp.uma.es).

The mediator provides methods in order to send queries and retrieve the information. However, end-users will not have to implement an application to make use of the mediator and discover the advantages of our proposal. For this reason we have provided a first implementation of a front-end to test the mediator from a Web browser. This Web interface provides several use cases of biological interest in the ASP project. The queries (described in terms of the AMMO ontology) deal by the mediator in each use case are shown for expert users with knowledge in ontologies and conjunctive queries. Other users can run the application in order to get the result without getting intermediate results (see Figure 12.5).

12.3.3 Conclusion

As stated in the first section, any biological system presents several local biomolecular interaction networks that can be studied *in silico* by using different technologies, so that emergent information and a more dynamic picture of it can be obtained. Macromolecular interactions involved in gene regulation and signal transduction, intercellular communication and metabolic complexes can be studied by applying Graph Theory [22–25] on the results obtained from data mining from interaction databases, such as DIP (http://dip.doe-mbi.ucla.edu/), PPI (http://fantom21.gsc.riken.go.jp/PPI/), Transfac (http://www.gene-regulation.com/pub/databases.html) and others. The information provided by this technology is essential to detect elements having the major regulatory weight on the system (module hubs or connectors among different modules). The development of better tools able to join, screen and score the pre-existing information in databases is required in order to increase fidelity and efficiency of the emergent information from these approaches.

On the other hand, the behaviour of the different metabolic pathways, responsible for the interchange of compounds and energy with the environment, and their responses to different alterations (external stimuli, genetic changes and/or drug treatments) can be modelled *in silico* by following the rules of Enzymology for mathemathical formalization of enzyme kinetic and turn-over and Flux Control Theory [26, 27]. These technologies make possible a dynamic view of the evolution of the systems from an initial steady-state to the next, and provide information on the reactions with a major incidence on the flux of the pathway, which can change under different circumstances.

Even a single element (an enzyme, nucleic acid or others) can be considered as an interactive system, having a three-dimensional (3D) structure responsible for the information concerning its biological function. The 3D structure of a single macromolecule can be obtained by biophysical methods applied on purified versions of the molecule. However, these experimental approaches (for instance,

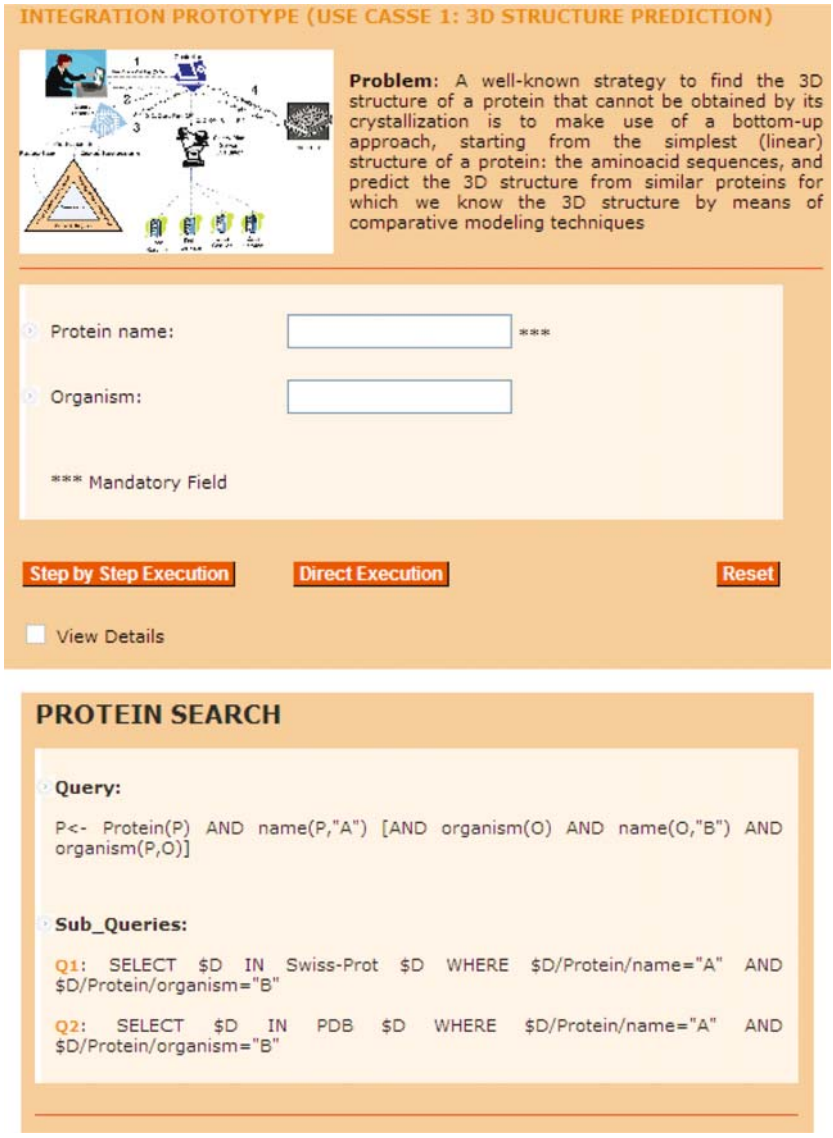

Fig. 12.5. Web Interface to make use of the mediator. The start point of this interface allows the user to search the protein for which he/she wants to know the 3D structure. Below the query for this first step is shown

X-ray crystallography, NMR, and other spectroscopical techniques) frequently provide us just a static view of the molecule, losing information about conformational changes that are behind any biological function. Protein Data Bank (http://www.rcsb.org/pdb/home/home.do) stores information on the macromolecular 3D structures characterized so far. Molecular dynamics calculations applied to macromolecules can overcome this restriction, and it is considered nowadays a very promising technology for the characterization of biomolecular interactions and drug design. Even more, when the 3D structure of a given macromolecule cannot be obtained experimentally, biocomputational tools can allow us to predict its structure, under certain restrictions, with high-accuracy (for instance, ModWeb Database and Services, http://alto.compbio.ucsf.edu/modweb-cgi/main.cgi). Then, Molecular dynamics calculations can also be applied on these predicted structures to obtain information about dynamics during and after interactions/reactions with different ligands [28].

In our group, we have developed models at the 3 different levels mentioned above. For instance, a human transcription factor network model has been obtained, which clearly shows connectors between inflammation and cancer (two of the processes related to amine-metabolism) [29]. We have also developed predictive models on metabolic pathways related to polyamine metabolism in mammalian (including human) tissues, that can explain some of the phenomenological results obtained with transgenic animals and with different drug-treated models *in vivo* and *in vitro* [30, 31]. Finally, by applying protein modelling techniques, the first 3D model for the enzyme responsible of histamine synthesis in animals and humans was obtained, which has opened the possibility to design new and more specific anti-histaminic compounds [32].

All of these technologies involve capture and organization of information coming from different databases and services. Following our own interpretation of Systems Biology (see first section), we notice that all local biomodules of a system are connected and should be globally analysed, as far as possible. Reaching this goal is a long-term project that overpasses the activity of a single working group. Nevertheless, supported by the advantages of the Semantic Web (Section 12.2), we can keep the objective to work on the way to obtain an automated form to integrate both information and tools in our system. For this purpose, we have designed the presented architecture.

12.4 Acknowledgements

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References

1. Rodríguez-Caso, C. and Solé, R. (2006) Networks in cell biology, Fundamentals of Data Mining in Genomics and Proteomics, W. Dubitzky, M. Granzow, and D. Berrar, Eds. Kluwer Academic Publishers, vol. in press.
2. Kitano, H. (2002) Systems biology: a brief overview, Science, vol. 295, no. 5560, pp. 1662–1664, 1095–9203 (Electronic) Journal Article Review.
3. Medina, M.A, Urdiales, J.L., Matés, J.M., Núñez de Castro, I. and Sánchez- Jiménez, F. (1991) Diamines interfere with the transport of l-ornithine in ehrlich-cell plasma-membrane vesicles, Biochem J, vol. 280 (Pt 3), pp. 825–827, 0264- 6021 (Print) Journal Article.
4. Engel, N., Olmo, M.T., Coleman, C.S., Medina, M.A., Pegg, A.E. and Sánchez-Jiménez, F. (1996) Experimental evidence for structure-activity features in common between mammalian histidine decarboxylase and ornithine decarboxy- lase, Biochem J, vol. 320 (Pt 2), pp. 365–368, 0264-6021 (Print) Journal Article.
5. Fajardo, I., Urdiales, J.L., Medina, M.A. and Sánchez-Jiménez, F. (2001) Effects of phorbol ester and dexamethasone treatment on histidine decarboxylase and ornithine decarboxylase in basophilic cells, Biochem Pharmacol, vol. 61, no. 9, pp. 1101–1106, 0006-2952 (Print) Journal Article.
6. Fajardo, I., Urdiales, J.L., Paz, J.C., Chavarría, T., Sánchez-Jiménez, F. and Medina, M.A. (2001) Histamine prevents polyamine accumulation in mouse c57.1 mast cell cultures, Eur J Biochem, vol. 268, no. 3, pp. 768–773, 0014-2956 (Print) Journal Article.
7. Rodríguez-Caso, C., Rodríguez-Agudo, D., Sánchez-Jiménez, F. and Medina, M.A. (2003) Green tea epigallocatechin-3-gallate is an inhibitor of mammalian histidine decarboxylase, Cell Mol Life Sci, vol. 60, no. 8, pp. 1760–1763, 1420-682X (Print) Journal Article.
8. Rodríguez-Caso, C., Rodríguez-Agudo, D., Moya-García, A.A., Fajardo, I., Medina, M.A., Subramaniam, V. and Sánchez-Jiménez, F. (2993) Local changes in the catalytic site of mammalian histidine decarboxylase can affect its global conformation and stability, Eur J Biochem, vol. 270, no. 21, pp. 4376–4387, 0014-2956 (Print) Journal Article.
9. Fleming, J.V., Fajardo, I., Langlois, M.R., Sánchez-Jiménez, F. and Wang, T.C. (2004) The c-terminus of rat l-histidine decarboxylase specifically inhibits enzymic activity and disrupts pyridoxal phosphate-dependent interactions with l-histidine substrate analogues, Biochem J, vol. 381, no. Pt 3, pp. 769–778, 1470-8728 (Electronic) Journal Article.
10. Fleming, J.V., Sánchez-Jiménez, F., Moya-García, A.A., Langlois, M.R. and Wang, T.C. (2004) Mapping of catalytically important residues in the rat l-histidine decarboxylase enzyme using bioinformatic and site-directed mutagenesis approaches, Biochem J, vol. 379, no. Pt 2, pp. 253–261, 1470-8728 (Electronic) Journal Article.
11. Medina, M.A., Urdiales, J.L., Rodríguez-Caso, C., Ramírez, F.J. and Sánchez- Jiménez, F. (2003) Biogenic amines and polyamines: similar biochemistry for different physiological missions and biomedical applications, Crit Rev Biochem Mol Biol, vol. 38, no. 1, pp. 23–59, 1040-9238 (Print) Journal Article Review.
12. Cohen, S.S. (1998) A Guide to the Polyamines. New York: Oxford University Press.

13. Medina, M.A., Correa-Fiz, F., Rodríguez-Caso, C. and Sánchez-Jiménez, F. (2005) A comprehensive view of polyamine and histamine metabolism to the light of new technologies, J Cell Mol Med, vol. 9, no. 4, pp. 854–864, 1582-1838 (Print) Journal Article Review.
14. Berners-Lee, T., Hendler, J. and Lassila, O. (2001) The Semantic Web, Scientific American.
15. Baader, F., Calvanese, D., McGuinness, D.L., Nardi, D. and Patel-Schneider, P.F. (2003) The Description Logic Handbook: Theory, Implementation, and Applications. Cambridge University Press.
16. Hussain, F.K., Sidhu, A.S., Dillon, T.S. and Chang, E. (2006) Engineering trustworthy ontologies: Case study of protein ontology, CBMS'06: Proceedings of the 19th IEEE Symposium on Computer-Based Medical Systems. Washington, DC, USA: IEEE Computer Society, pp. 617–622.
17. Eilbeck, K., Lewis, S.E., Mungall, C.J., Yandell, M., Stein, L., Durbin, R. and Ashburner, M. (2006) The sequence ontology: a tool for the unification of genome annotations, Genome Biology, vol. 6, p. R44.
18. Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., Harris, M.A., Hill, D.P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J.C., Richardson, J.E., Ring-wald, M., Rubin, G.M. and Sherlock, G. (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet, vol. 25, no. 1, pp. 25–29.
19. Navas-Delgado, I. and Aldana-Montes, J.F. (2004) A distributed semantic mediation architecture, Journal of Information and Organizational Sciences, vol. 28, no. 1–2, pp. 135–150.
20. Aldana-Montes, J.F., Navas-Delgado, I. and Roldan-Garcia, M.M. (2004) Solving Queries over Semantically Integrated Biological Data Sources, Int. Conf. on Web-Age Information Management (WAIM 2004). LNCS 3129.
21. Haarslev, V. and Möller, R. (2001) The Description Logic ALCNHR+ Extended with Concrete Domains: A Practically Motivated Approach, R. Goré, A. Leitsch, and T. Nipkow, editors, International Joint Conference on Automated Reasoning, IJCAR2001, June 18–23, Siena, Italy, pp. 29–44, Springer-Verlag.
22. Barabasi, A.L. (2002) Linked: The New Science of Networks. Cambridge: Perseus Books Group.
23. Lehner, B., Crombie, C., Tischler, J., Fortunato, A. and Fraser, A.G. (2006) Systematic mapping of genetic interactions in caenorhabditis elegans identifies common modifiers of diverse signaling pathways, Nat Genet, vol. 38, no. 8, pp. 896–903, 1061-4036 (Print) Journal Article.
24. Basso, K., Margolin, A.A., Stolovitzky, G., Klein, U., Dalla-Favera, R. and Califano, A. (2005) Reverse engineering of regulatory networks in human b cells, Nat Genet, vol. 37, no. 4, pp. 382–90, 1061-4036 (Print) Journal Article.
25. Vázquez, A., Dobrin, R., Sergi, D., Eckmann, J.P., Oltvai, Z.N. and Barabasi, A.L. (2004) The topological relationship between the large-scale attributes and local interaction patterns of complex networks, Proc Natl Acad Sci U S A, vol. 101, no. 52, pp. 17 940–945, 0027-8424 (Print) Journal Article.
26. Fell, D. (1996) Understanding the Control of Metabolism, ser. Frontiers in Metabolism. Ashgate Publishing.
27. JM, L., EP, G. and JA, P. (1991) Flux balance analysis in the era of metabolomics, Brief Bioinform, vol. 7, no. 2, pp. 140–150.

28. Garcia-Viloca, M., Gao, J., Karplus, M. and Truhlar, D.G. (2004) How enzymes work: analysis by modern rate theory and computer simulations. Science, vol. 303, no. 5655, pp. 186–195.
29. Rodríguez-Caso, C., Medina, M.A. and Solé, R.V. (2005) Topology, tinkering and evolution of the human transcription factor network, Febs J, vol. 272, no. 24, pp. 6423–6434, 1742-464X (Print) Journal Article.
30. Rodríguez-Caso, C., Montañez, R., Cascante, M., Sánchez-Jiménez, F. and Medina, M.A. (2007) Mathematical modeling of polyamine metabolism in mammals, J Biol Chem, vol. 281, no. 31, pp. 21 799–812, 0021-9258 (Print) Journal Article.
31. Montañez, R., Rodríguez-Caso, C., Sánchez-Jiménez, F. and Medina, M.A. (2007) In silico analysis if arginine catabolism as a source of nitric oxide or polyamines in endothelian cells, Amino Acids, in press.
32. Moya-García, A.A., Pino-Ángeles, A. and Sánchez-Jiménez, F. (2006) New structural insights to help in the search for selective inhibitors of mammalian pyridoxal 5'-phosphate-dependent histidine decarboxylase, Inflammation Res., vol. 55, Supplement 1, pp. S55–S56.